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Diabetic kidney disease in type 2 diabetes: a consensus statement from the Swiss Societies of Diabetes and Nephrology

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Summary

Diabetic kidney disease is highly prevalent in patients with type 2 diabetes and is a major cause of end-stage renal disease in Switzerland. Patients with diabetic kidney disease are among the most complex patients in diabetes care. They require a multifactorial and multidisciplinary approach with the goal to slow the decline in glomerular filtration rate (GFR) and cardiovascular morbidity. With this consensus we propose an evidence-based guidance to health care providers involved in the care of type 2 diabetic patients with diabetic kidney disease.

First, there is a need to increase physician awareness and improve screening for diabetic kidney disease as early intervention may improve clinical outcomes and the financial burden. Evaluation of estimated GFR (eGFR) and spot urine albumin/creatinine ratio is recommended at least annually.

Once it is diagnosed, glucose control and optimisation of blood pressure control with renin-angiotensin system blockers have been recommended as mainstay management of diabetic kidney disease for more than 20 years. Recent, high quality randomised controlled trials have shown that sodium-glucose cotransporter-2 (SGLT2) inhibition slows eGFR decline and cardiovascular events beyond glucose control. Likewise, mineralocorticoid receptor antagonism with finerenone has cardiorenal protective effects in diabetic kidney disease. Glucagon-like peptide-1 (GLP1) receptor agonists improve weight loss if needed, and decrease albuminuria and cardiovascular morbidity. Lipid control is also important to decrease cardiovascular events. All these therapies are included in the treatment algorithms proposed in this consensus.

With advancing kidney failure, other challenges may rise, such as hyperkalaemia, anaemia and metabolic acidosis, as well as chronic kidney disease-mineral and bone disorder. These different topics and treatment strategies are discussed in this consensus. Finally, an update on diabetes management in renal replacement therapy such as haemodialysis, peritoneal dialysis and renal transplantation is provided.

With the recent developments of efficient therapies for diabetic kidney disease, it has become evident that a consensus document is necessary. We are optimistic that it will significantly contribute to a high-quality care for patients with diabetic kidney disease in Switzerland in the future.

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Introduction

For more than 20 years, the standard therapy of patients at risk of or with diabetic kidney disease included efficient glucose and blood pressure control and the use of renin-angiotensin system inhibitors. Although these therapies slow the decline in renal function, the number of patients with end-stage renal disease secondary to diabetes is still on the rise all around the world due to the high prevalence of diabetes, obesity and an aging population. Recently, large studies have demonstrated remarkable renal protective properties of new classes of drugs in type 2 diabetes. For this reason, prior recommendations published in this journal in 2014 need an update.

Patients with diabetic kidney disease are among the most complex patients in diabetes care. Their care is multifactorial and multidisciplinary, involving different groups of healthcare providers. The primary care physician, the diabetologist, the nephrologist, the nutritionist and the specialised nurse, among others, need to rely on a common view while treating these patients.

It has become evident that a consensus document is necessary to help all healthcare providers involved in the care of patients with diabetic kidney disease. With this consensus, we propose a concise document summarizing the important topics around diabetic kidney disease. It includes

therapies with proven efficacy and which are available in Switzerland. It largely extends the document in 2014 endorsed by the Swiss Society of Endocrinology and Diabetes (SGED/SSED). This consensus will be updated yearly on its digital platform (diabetic kidney disease SSED/SGED (www.sgedssed.ch) and Swiss society of Nephrology (SSN) (www.swissnephrology.ch) guidelines; www.guidelines.ch).

The working group included diabetologists and nephrologists across Switzerland and extended between 2019 and 2022. Those participating in the workshop are co-authors of the consensus. Before its publication, it was reviewed by the Swiss Society of Endocrinology and Diabetes and by the Swiss Society of Nephrology.

Definition of and screening for diabetic kidney disease

References for this section: [1–11]

Screening for diabetic kidney disease (DKD) is important because it is a silent disease and symptoms develop only at very late stages. Primary care physicians and endocrinologists remain central to the screening process. The yearly recommended screening of creatinine-based estimated glomerular filtration rate (eGFR) and urine albumin/-creatinine ratio has not changed for many decades and will identify patients with significant kidney disease. Yet the urine albumin/creatinine ratio is often lacking in the annual workup, as is the calculation of creatinine-based eGFR. Therefore, there is a constant need to improve physician awareness of diabetic kidney disease by implementing systematic screening and clear classification of patients with diabetes and nephropathy. New biomarkers identifying patients with early renal function decline are actively being investigated (such as tumour necrosis factor [TNF] receptors 1 and 2, kidney injury molecule-1 [KIM-1]). They will hopefully provide a tool for better stratification of patients and intervention in the early stages of diabetic kidney disease.

Epidemiology of diabetic kidney disease

- Present in ≈30% of patients with type 2 diabetes.
- Major cause of chronic kidney disease and end-stage renal disease in Switzerland.
- Higher risk with longer duration of diabetes or early onset of diabetes.

Definitions

Diabetic kidney disease

- Diabetes of any cause.
- eGFR <60 ml/min/1.73 m^2 (KDIGO stage G3–5) and/or
- urinary albumin/creatinine ratio >3 mg/mmol (KDIGO stage A2–3). *30% of patients with an eGFR <60 ml/min/1.73 m^2 don't have albuminuria.* (KDIGO: Kidney Disease: Improving Global Outcomes).
- Persisting for more than 3 months.

Diabetic nephropathy

- Renal biopsy with typical lesions of diabetic nephropathy.

Screening and KDIGO classification

Yearly screening in all (table 1).

- Creatinine-based eGFR calculated with the chronic kidney disease-epidemiology collaboration (CKD-EPI) formula recommended by KDIGO.
- Random urinary albumin/creatinine ratio: *In the absence of intense exercise, urinary tract infection, severely uncontrolled diabetes / hypertension / congestive heart failure. Repeat if abnormal for confirmation.*
- Dipstick and sediment if eGFR <60 ml/min/1.73 m^2 or albumine/creatinine ratio >3 mg/mmol

Classification: KDIGO G1–5, A1–3 (table 1).

Expert opinion: dynamics over time are important to document as:

- Progressive albuminuria.
- eGFR decline: *rapid decline if ≥5 ml/min/year (the average estimated yearly GFR decline in type 2 diabetes in Switzerland was –1.03 ml/min/year in women and –1.15 ml/min/year in men in 2014).*

Limitations of eGFR formulas

- Valid only with stable renal function
- eGFR underestimated by creatinine-based formulas if increased creatinine production: *high muscle mass / meat consumption / creatine supplements*

Table 1:
KDIGO 2012 classification and recommended frequency of monitoring per annum (modified from: Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020 Oct;98(4S):S1-S115 [1]).

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category				**Persistent albuminuria categories. Description and range**		
				A1	**A2**	**A3**
				Normal to mildly increased	**Moderately increased**	**Severely increased**
				<3 mg/mmol	**3–30 mg/mmol**	**>30 mg/mmol**
GFR categories (ml/min/1.73 m^2): description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR: glomerular filtration rate

– eGFR overestimated by creatinine-based formulas if low creatinine production: *low muscle mass, sarcopenia, amputation / liver cirrhosis / vegetarian diet*
– → in these patients, the cystatin C-based formula can be used, taking advantages and pitfalls into consideration. *eGFR_cys correlates better with outcomes and eGFR_cys_creat correlates better with measured GFR. Higher cystatin levels are associated with male sex, greater height, obesity, higher lean body mass, diabetes, markers of inflammation, corticosteroid use, hypo- or hyperthyroidism, increasing age.*

—Twenty-four-hour urine collection is only recommended in situations where creatinine values are less accurate in the estimation of GFR (see above). However it has several caveats (errors in urine collection, tubular creatinine secretion with declining renal function).

Search for non-diabetic causes of nephropathy and criteria for referral to nephrologist

– Non-diabetic causes of nephropathy may be present in 20% of cases.
– Persistent haematuria / active sediment (dysmorphic red blood cells, red blood cell casts).
– Rapid and sustained eGFR decline.
– Inappropriately low eGFR for age (age <40 years: eGFR <75 ml/min/1.73 m^2, age 40–65 years eGFR <60 ml/min/1.73 m^2, age >65 years <45 ml/min/1.73 m^2).
– Rapidly increasing proteinuria and/or proteinuria >0.5 g/g creatinine (0.05 g/mmol) or albuminuria >300 mg/g creatinine (30 mg/mmol) (KDIGO 2012).
– Nephrotic syndrome (nephrotic range proteinuria, hypoalbuminaemia, oedema, hypercholesterolaemia).
– The presence of retinopathy is a strong indicator of diabetic nephropathy and its absence may suggest other causes.
– Family history of hereditary renal disease.
– Signs or symptoms of other systemic diseases.
– Resistant hypertension (blood pressure >140/90 mm Hg with triple antihypertensive therapy including diuretic, renin-angiotensin system (RAS) blocker and calcium antagonist).
– >30% eGFR reduction following initiation of angiotensin-converting enzyme (ACE) inhibitor or sartan (search for reno-vascular disease).

Blood glucose control and antidiabetic drugs in diabetic kidney disease

References for this section: [1, 2, 12–32]

The 1990s demonstrated that tight glycaemic control prevents the early stages of diabetic kidney disease in type 1 diabetes (DCCT, EDIC), which was confirmed in type 2 diabetes later on. Recently, new classes of antidiabetic drugs have been proven to have powerful renal protective effects in type 2 diabetes, particularly the sodium-glucose cotransporter-2 (SGLT2) inhibitor class. Their effects are beyond glucose control, opening an exciting period in the field of chronic kidney disease. This section highlights the important facts around glycaemic control and antidiabetic drugs in diabetic kidney disease. For general information on antidiabetic therapy in type 2 diabetes, we refer to www.sgedssed.ch. Only frequently prescribed antidiabetic drugs are discussed.

Blood glucose control and diabetic kidney disease

– Hyperglycaemia is a main driver for the development of typical lesions of diabetic nephropathy.
– Tight glycaemic control is the most efficient therapy for primary prevention (glycated haemoglobin [HbA1c] <7%).
– The role of glycaemic control in secondary prevention is less clear.
– There is an increased risk of hypoglycaemia with an eGFR <60 ml/min/1.73 m^2 in patients treated with sulphonylureas/glinides/insulin. For this reason, tight glycaemic control needs to be implemented with caution and an HbA1c <8% is reasonable when using these drugs in patients with comorbidities.
– HbA1c validity may be affected by severe anaemia (falsely low) or severe chronic kidney disease (variable effects). Mild to moderate chronic kidney disease and anaemia do not seem to influence significantly the glycaemia-HbA1C relationship.
– Continuous glucose monitoring can be used to evaluate glucose excursions and estimate HbA1c if blood HbA1c validity is questioned. However, further studies are needed to test the accuracy in chronic kidney disease.

Antidiabetic therapy and diabetic kidney disease

– Doses of some antidiabetic drugs need to be adjusted with an eGFR <60/min/1.73 m^2 (fig. 1).
– Because of a low hypoglycaemic risk, weight control, low cost and possible cardio-protection, metformin remains as first line therapy (adjusted to eGFR; fig. 2). However, there is a lack of evidence for a clear renal protective effect in DKD.
– SGLT2 inhibitors have cardio-renal protective properties beyond glucose control and should be considered as first line therapy in type 2 diabetes with kidney disease (fig. 2). – *Chronic kidney disease and type 2 diabetes:* They decrease albuminuria progression and slow eGFR decline in chronic kidney disease (canagliflozin CREDENCE, extrapolated time to dialysis delayed by 15.1 years in patients with stages G1–3A3; dapagliflozin DAPA-CKD in patients with eGFR 25–75 ml/min, albumin/creatinine ratio 200–5000 mg/g; empagliflozin EMPA-KIDNEY in patients with eGFR 20–45 ml/min or stage G2–3a and albumin/creatinine ratio >200 mg/g). – *HFrEF and HFpEF (heart failure with reduced and preserved ejection fraction) with type 2 diabetes:* They slow the eGFR decline in patients with HFrEF and HFpEF but have a positive effect on composite renal outcomes only in HFrEF (empagliflozin, EMPEROR). They decrease hospitalisation for heart failure across stages of chronic kidney disease in patients with HFrEF and HFpEF (dapagliflozin DAPA-HF and DELIVER: eGFR >25–30 ml/min; empagliflozin EMPEROR: eGFR >25 ml/min). – *High cardiovascular risk in type 2 diabetes:* They decrease the risk of acute kidney

injury in cardiovascular outcome trials (dapagliflozin, DECLARE-TIMI, empagliflozin, EMPA-REG) and decrease renal outcomes even in patients with preserved eGFR or normoalbuminuria. – *Real world clinical practice with type 2 diabetes:* They slow renal function decline (CVD-REAL3, mean eGFR at inclusion: 90.7 ml/min/1.73 m^2).

– Glucagon-like peptide-1 (GLP1) receptor agonists decrease the progression of albuminuria and decrease major cardiovascular events (liraglutide LEADER; semaglutide SUSTAIN-6; dulaglutide REWIND) and cardiovascular death (liraglutide LEADER) in high cardiovascular risk patients. This class is the most potent antidiabetic class for weight reduction. If compared with dipeptidyl peptidase 4 (DPP-IV) inhibitors, which also have an incretin effect, GLP1 agonists are clearly superior in terms of glucose control, weight reduction and cardio-renal protection. This class should be considered as second line therapy in type 2 diabetes with diabetic kidney disease (fig. 2).

SGLT2 inhibitor prescription in diabetic kidney disease

– Swissmedic: Initiation approved for improved glycaemic control in patients with an eGFR >45 ml/min/1.73 m^2 (empagliflozin, dapagliflozin, canagliflozin). In the case of a urinary albumin/creatinine ratio >30 mg/mmol, canagliflozin can be initiated if the eGFR is >30 ml/min/1.73 m^2 and maintained until dialysis or transplantation. In the case of chronic kidney disease or HFrEF (ejection fraction ≤40%) dapagliflozin can be initiated if the eGFR is >25 ml/min and maintained until dialysis or renal transplantation. In the case of symptomatic left ventricular heart failure, empagliflozin can be initiated until an eGFR of 20 ml/min/1.73 m^2.

– American diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) / KDIGO: In type 2 diabetes with diabetic kidney disease, consider starting an SGLT2 inhibitor until an eGFR of 25 ml/min/1.73 m^2 (ADA/EASD) or 20 ml/min/1.73 m^2 (ADA-KDIGO 2022 [113]).

– Adjust dose when eGFR <60 ml/min/1.73 m^2 (canagliflozin).

– Caution if recurrent mycotic genital infection.

– Personal history of recurrent urinary tract infections should be considered and the issue discussed with the patient before initiating SGLT2 inhibitors.

– Patient education (genitourinary hygiene, prescribe a topical antifungal medication if needed, hydration, avoid nonsteroidal anti-inflammatory drugs, inform if unusual symptoms, discontinue transiently if at risk for hypovolaemia, e.g., vomiting and diarrhoea, or if fasting, sick day management).

– Consider adjusting antihypertensive and diuretic treatment based on the volume status in view of the antihypertensive and diuretic properties of SGLT2 inhibitors.

– Routine monitoring of kidney function or electrolytes within 1–2 weeks (as with RAS blockers) is not mandatory after SGLT2 inhibitor initiation. It should be considered, however, if there is concern about volume depletion, such as in patients with blood pressure <120/70

Figure 1: Adjustment of dosages according to eGFR (Swissmedic [Switzerland], for other countries refer to local restrictions).

CKD stage	1–2	3a	3b	4	5
	eGFR >60 ml/min/1.73 m^2	eGFR 45–60 ml/min/1.73 m^2	eGFR 30–45 ml/min/1.73 m^2	eGFR 15–30 ml/min/1.73 m^2	Haemodialysis
Insulins		Decrease dose			
Glinides					
Novonorm® Repaglinide	0.5–12 mg/d				
Starlix® Nateglinide	60–360 mg/d		60 mg/dose		
DPP-IV inhibitors					
Januvia® Sitagliptin	50–100 mg/d	50 mg/d		25 mg/d	
Trajenta® Linagliptin	5 mg/d				
Galvus® Vildagliptin	2 x 50 mg/d	1 x 50 mg/d			
Vipidia® Alogliptin	25 mg/d	12.5 mg/d		6.25 mg/d	
Onglyza® Saxagliptin	5 mg/d		2.5 mg/d		
GLP1R agonists					
Byetta® Exenatide	10 µg 2x/d		5 µg 2x/d		
Bydureon® Exenatide	2 mg/w				
Victoza® Liraglutide	0.6–1.8 mg/d				
Lyxumia® Lixisenatide	10–20 µg/d				
Trulicity® Dulaglutide	0.75–1.5 mg/w				
Rybelsus® Semaglutide	3–14 mg/d				
Ozempic® Semaglutide	0.25–1 mg/w				
Thiazolidinediones					
Actos® Pioglitazone	15–45 mg/d				
Metformin					
Glucophage® Metformin	500–2550 mg/d	500–1500 mg/d	500–1000 mg/d do not initiate		
SGLT2 inhibitors					
Invokana® Canagliflozin	100–300 mg/d	100 mg/d	Initiation only if ACR >30 mg/mmol	OK until dialysis if ACR >30 mg/mmol. Do not initiate	
Jardiance® Empagliflozin	10 mg/d		If symptomatic LV HF	If symptomatic LV HF →20 ml/min/1.73 m^2	
Forxiga® Dapagliflozin	5–10 mg/d		If HFrEF or CKD	If CKD initiation →25 ml/min/1.73 m^2 OK until dialysis	
Ertugliflozin® Steglatro	5 mg/d				
Sulfonylureas					
Diamicron® Gliclazide	30–120 mg/d				
Daonil® Glibenclamide	2.5–10 mg/d				
Amaryl® Glimepiride	1–6 mg/d				

mm Hg, current evidence of volume depletion (orthostatic symptoms), in patients taking high-dose loop diuretics, and maybe in frail elderly patients. Monitoring of kidney function and electrolytes might also be considered in individuals with significantly reduced kidney function or if one wants to distinguish between an eGFR dip caused by SGLT2 inhibitor initiation and declining of kidney function due to progression of the underlying kidney disease.

- Examine feet regularly. Increased risk of amputation reported in CANVAS (canagliflozin), discontinue if condition at risk of ulcer or amputation.
- Rare but severe adverse effects: *Euglycaemic diabetic ketoacidosis* (in latent autoimmune diabetes misdiagnosed as type 2 diabetes, beta-cell failure in long-standing type 2 diabetes, stress, surgery, decreasing basal insulin, low carbohydrate intake, excessive alcohol intake, hypovolaemia); risk increased 10-fold with canagliflozin (2.2/1000 patient-years) vs control in chronic kidney disease stage G1–3A3 (CREDENCE). *Fournier gangrene*.
- Combination therapy possible with a GLP1 receptor agonist.
- Unaddressed safety: SGLT2 inhibitors in kidney transplantation and in type 1 diabetes with diabetic kidney disease. Ongoing trials.

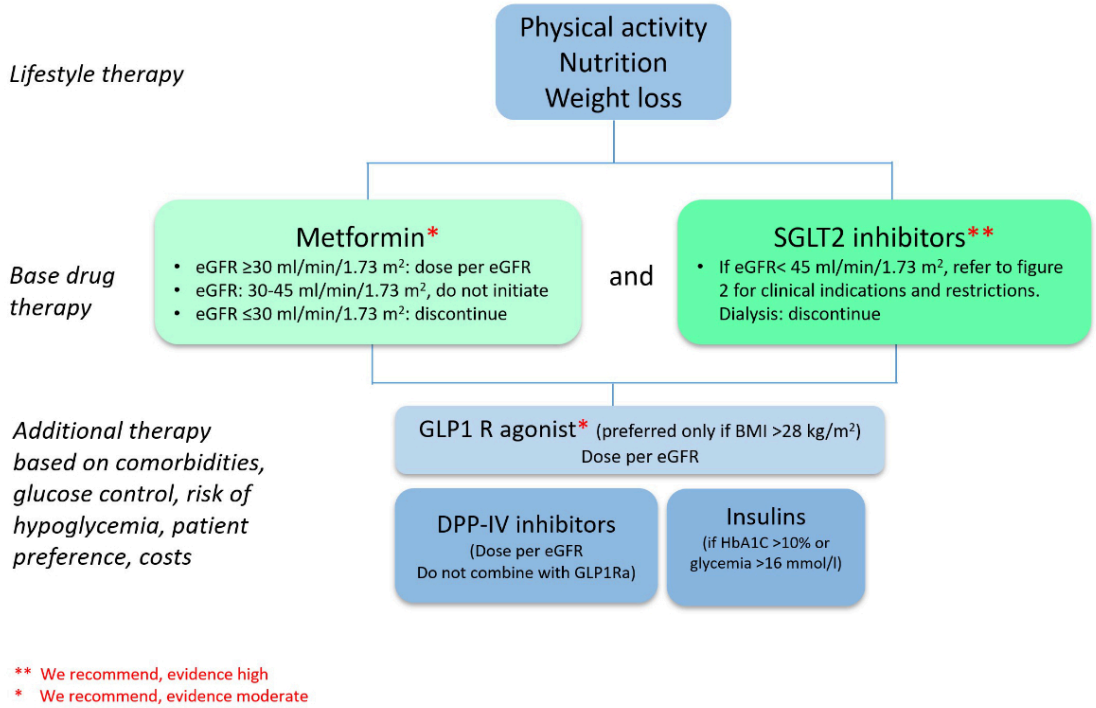
GLP1 receptor agonist prescription in diabetic kidney disease

- Reimbursement only in patients with a body mass index (BMI) >28 kg/m^2.
- Mainly injectable except for Rybelsus® (oral semaglutide).
- Avoid if history of pancreatitis or medullary carcinoma of the thyroid (personal or familial) or active proliferative retinopathy (semaglutide).
- To be considered as first injectable therapy before insulin unless HbA1c >10%, evidence of catabolism or symptoms of hyperglycaemia.
- Patient education (injections, generally transient gastrointestinal symptoms at initiation, reduce doses or discontinue transiently in the case of vomiting, diarrhoea).
- Titrate dose according to tolerability. Side effects may be higher in more advanced chronic kidney disease.
- May increase heart rate.
- Increased risk of gallbladder or biliary disease.

Metformin prescription in diabetic kidney disease

- Adjust dose when eGFR <60 ml/min/1.73 m^2, discontinue if eGFR <30 ml/min/1.73 m^2.
- Avoid metformin initiation if eGFR <45 ml/min, or only in selected patients with regular monitoring of kidney function.
- Patient education (discontinue transiently if at risk of hypovolaemia, vomiting, diarrhoea, sick day management).
- Discontinue metformin before or at the time of an imaging procedure using intravenous or intra-arterial iodinated contrast in patients with an eGFR between 30 and 60 ml/minute/1.73 m^2. Reevaluate eGFR 48 hours after

Figure 2: Antidiabetic therapy in chronic kidney disease stage G1–3 A2–3 (modified from: Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020 Oct;98(4S):S1-S115 [1]). Per eGFR see figure 1. Comment: dual SGLT2 inhibitor – GLP1 agonist therapy is under investigation. Preliminary results demonstrate additional effects on weight, blood glucose and blood pressure control.



the imaging procedure; restart metformin if renal function is stable.

– Annual monitoring for vitamin B12 deficiency.

DPP-IV inhibitor prescription in diabetic kidney disease

– Adjust dose when eGFR <60 ml/min/1.73 m^2 with most DPP-IV inhibitors, but not linagliptin.
– No proven cardiorenal benefit.
– Avoid saxagliptin: increased risk of hospitalisation for congestive heart failure.
– Avoid if history of pancreatitis.
– Do not combine with GLP1 receptor agonist.

Sulphonylurea/glinide prescription in diabetic kidney disease

– Avoid if possible at eGFR <60 ml/min/1.73 m^2 because of the increased risk of hypoglycaemia.
– If eGFR <60 ml/min/1.73 m^2, gliclazide is the only sulphonylurea allowed, withdraw if eGFR <30 ml/min/1.73 m^2.
– Do not combine with insulin as this combination greatly increases the risk for hypoglycaemia.

Insulin prescription in diabetic kidney disease

– Adjust dose when eGFR <60 ml/min/1.73 m^2.
– Consider increased risk of hypoglycaemia and do not combine with a sulphonylurea.
– Blood glucose monitoring before driving in the case of eGFR <45 ml/min/1.73 m^2 or basal bolus insulin therapy
– Continuous glucose monitoring recommended with basal bolus insulin therapy.

Blood glucose targets in chronic kidney disease

– Tight glycaemic control in primary prevention if not at risk of hypoglycemia or with cardiovascular co-morbidities (HbA1c <7%, preprandial plasma glucose 5–7 mmol/l; 2-hour postprandial capillary plasma glucose <10 mmol/l).
– Loosen goals in prevalent chronic kidney disease (HbA1c <8%) because of the risk of hypoglycaemia.
– Consider continous blood glucose measurement (CGM) devices, ideally with alarm functions for hypoglycaemia in patients on basal bolus insulin therapy.

Blood pressure control and diabetic kidney disease

References for this section: [33–40]

Hypertension and diabetes coexist in a vast majority of patients with type 2 diabetes. Antihypertensive therapy is beneficial for both cardiovascular and renal outcomes in patients with type 2 diabetes and is central to the standard of care in this population. The exact goal of blood pressure control remains unclear as studies with specific blood pressure goals in diabetic kidney disease are lacking. The UKPDS, HOT and ADVANCE BP trials, dedicated to patients with type 2 diabetes, failed to achieve a systolic blood pressure goal of <130 mm Hg. The ACCORD BP study showed no clear evidence that a systolic blood pressure goal of <120 mm Hg is beneficial for cardiovascular endpoints, except for stroke reduction and albuminuria progression with, however, more serious adverse events such as hypotension and hyperkalaemia. Thus, proposed goals are based on consensus statements and may differ from each other. A goal of <140/90 mm Hg has a high level of evidence for cardiac and renal protection whereas a goal <130 mm Hg has a high level of evidence for stroke reduction. The ADA 2021 guidelines recommend targets of <140/90 mm Hg in all or <130/80 mm Hg in those at higher cardiovascular risk (established or 10-year atherosclerotic cardiovascular disease [ASCVD] risk >15%). KDIGO 2021 guidelines recommend a systolic blood pressure goal of <120 mm Hg using standardized office blood pressure measurement in patients with chronic kidney disease, with or without diabetes, not undergoing dialysis. However, KDIGO acknowledge that the evidence supporting such a goal is less certain in diabetes.

Both angiotensin converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the progression of albuminuria in diabetic kidney disease more effectively than other drug classes. The renal protective effects are beyond the blood pressure lowering effects. They are recommended as first line therapy (fig. 3).

Diagnosis of hypertension in diabetic kidney disease

– We recommend out-of-office blood pressure measurements, i.e., ambulatory blood pressure measurement (ABPM, at least once) and home blood pressure measurements with validated blood pressure devices (www.swisshypertension.ch, www.validatebp.org, www.bihsoc.ord, www.stridebp.org).

Comments on blood pressure control in diabetic kidney disease

– Observational studies suggest that targeting a decrease in albuminuria is also important, including in patients with a systolic blood pressure between 130 and 140 mm Hg. If full-dose RAS blockade is present, adding an SGLT2 inhibitor and/or finerenone is an option to further decrease albuminuria.
– Only ABPM will identify masked nocturnal hypertension (30% of normotensive patients with type 2 diabetes).
– Screening for postural hypotension in all, particularly frail diabetic patients (elderly, long-standing diabetes) is important before and after starting and intensifying of therapy.
– Do not combine an ARB with an ACE inhibitor or renin inhibitor because there is no proven benefit (increased risk of hyperkalaemia, acute kidney injury).
– After starting or increasing the dosage of an ARB/ACEI in diabetic patients with chronic kidney disease or high potassium, careful monitoring of blood electrolytes and eGFR after 1 to 2 weeks is mandatory. If eGFR declines by more than 30%, treatment should be stopped and

renovascular disease investigated. Refer to nephrologist if renal artery stenosis is present.

– Warning for small risk of non-melanoma skin cancer (1/16,000 patient per year), particularly with long-term use of hydrochlorothiazide and in immunosuppression (11/2018). Patients should continue treatment but protect their skin from the increased photosensitivity with hydrocholothiazide.
– Chlortalidone can be prescribed even at an eGFR of <30 ml/min/m^2.
– Consider reducing antihypertensive therapy and diuretic when introducing a SGLT2 inhibitor.
– Preconception counselling: ARBs / ACE inhibitors and spironolactone are contraindicated. A diuretic (furosemide) to be used only during late pregnancy for volume control. Labetolol, long-acting nifedipine and methyldopa are safe in pregnancy.

Mineralocorticoid receptor antagonism in diabetic kidney disease

References for this section: [41–45]

The mineraolcorticoid receptor is an important contributor to the development of diabetic kidney disease. Mineralocorticoid receptor overactivation is assumed to promote kidney inflammation and fibrosis in diabetic individuals. The steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone reduce albuminuria either as monotherapy or on top of ACE inhibitor or ARB treatment in diabetic kidney disease. They are also indicated for the treatment of HFrEF and refractory arterial hypertension. However, no studies examine the impact of steroidal MRA treatment on hard endpoints in diabetic kidney disease.

Finerenone, a specific and nonsteroidal MRA improves renal (–18%, number needed to treat [NNT] 29, p = 0.001) and cardiovascular outcomes (3PMACE+HHF, –14%, NNT 42, p = 0.03) if given in addition to maximum tolerated RAS blockade, with only a modest effect on blood pressure in patients with type two diabetes, proteinuric diabetic kidney disease and an eGFR of 25–75 ml/min/1.73m^2. Treatment doubles the risk of hyperkalaemia. Only 4.6% of the patients were on an SGLT2 inhibitor, therefore the exact treatment effect of combination therapy is unclear. Also, no head-to-head comparisons of the cost-effectivenes of different MRAs exist. Post-hoc analyses suggest that the addition of finerenone to a SGLT2 inhibitor further reduces albuminuria. In addition, cardiorenal protection with finerenone appears to be independent of SGLT2 inhibitor use. Finally, the risk of hyperkalaemia was significantly lower with the SGLT2 inhibitor + finerenone combination.

– We recommend considering adding an MRA (e.g. finerenone) in albuminuric diabetic kidney disease with a potassium ≤4.8 mmol/l, for individuals on RAS blockade with or without an SGLT2 inhibitor. Monitoring potassium is required regularly after starting therapy with finerenone (at 1 and 4 weeks and at least every 4 months thereafter). Withhold treatment if potassium is >5.5 mmol/l. Because supported by more extensive data, SGLT2 inhibitors remain the first option before con-

Table 2:
Classification of office blood pressure* and definition of hypertension grade** (modified from: Williams B, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens. 2018;36(10):1953–2041 [36]).

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

* Blood pressure category is defined according to seated clinic measurement and by the highest level, whether systolic or diastolic.

** The same classification is used for all ages from 16 years.

Table 3:
Definition of hypertension according to office, ambulatory and home blood pressure levels (modified from Williams et al. J Hypertens. 2018;36:1953-2041 [36]).

	Category	Systolic (mm Hg)		Diastolic (mm Hg)
	Office blood pressure*	≥140	and/or	≥90
Ambulatory blood pressure	Daytime (or awake) mean	≥135	and/or	≥85
	Night-time (or asleep) mean	≥120	and/or	≥70
	24-hour mean	≥130	and/or	≥80
Home blood pressure mean		≥135	and/or	≥85

* Refers to conventional office blood pressure rather than unattended office blood pressure

Table 4:
Office blood pressure treatment target ranges (modified from Williams et al. J Hypertens. 2018;36:1953-2041 [36]).

		Diabetes	CKD
SBP	Age 18–65	Target to 130 *or lower if tolerated, not <120*	Target 130–139 *if tolerated*
	Age ≥65	Target to 130–139 *if tolerated*	Target 130–139 *if tolerated*
DBP		70–79	70–79

CKD: chronic kidney disease; DBP: diastolic blood pressure; SBP: systolic blood pressure

sidering finerenone in albuminuric diabetic kidney disease.

Lipid control and diabetic kidney disease

References for this section: [46–57]

Metabolic factors, among them dyslipidaemia and diabetes, are the most important modifiable cardiovascular risk factors and cardiovascular diseases are the most important causes of death in both patients with diabetes and patients with chronic kidney disease. Therefore, lipid-lowering treatment is among the cornerstones of cardiovascular disease prevention in both diabetes and chronic kidney disease. This has been adopted in recent guidelines, which uniformly advocate the use of lipid-lowering treatment, mostly statins, in patients with diabetes and chronic kidney disease not requiring dialysis.

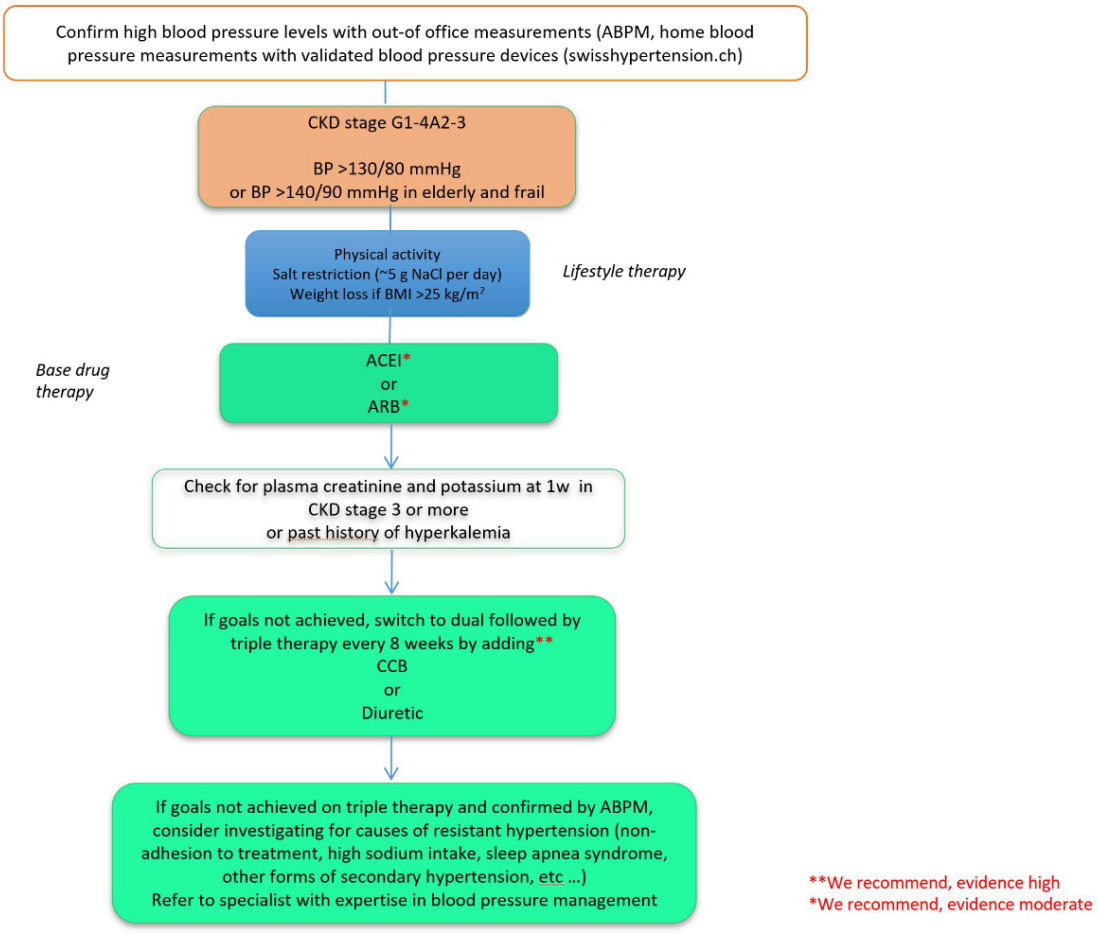
Cardiovascular risk in chronic kidney disease

- Cardiovascular disease is the predominant cause of mortality in chronic kidney disease and accounts for 50% of all deaths in this population. The inverse relation between cardiovascular risk and eGFR is independent of other risk factors, already present in mild renal impairment and highest in patients with end-stage renal disease.
- Patients with diabetes have increased cardiovascular risk. However, in patients with chronic kidney disease at identical eGFR and albuminuria, all-cause and cardiovascular mortality are attributed the same high-risk category.
- Declining eGFR, increasing albuminuria and their combination are among the strongest contributors to improved cardiovascular risk prediction. Patients with albuminuria (urinary albumin/creatinine ratio >3.0 mg/mmol) and/or impaired eGFR (<60 ml/min/1.73 m^2) are unequivocally considered to be at high or very high cardiovascular risk.
- The association of declining eGFR with cardiovascular disease risk and mortality has been appreciated in recent lipid management guidelines, which consider chronic kidney disease as equivalent to cardiovascular disease. However, nonatherosclerotic cardiovascular disease, such as heart failure and arrhythmias, rather than ischaemic, atherosclerotic events may account for the very high cardiovascular risk in patients with end-stage kidney disease.

Dyslipidaemia in diabetic kidney disease

- Both diabetes and chronic kidney disease are associated with distinct changes in lipoprotein metabolism and pattern, favouring a more atherogenic lipid phenotype.

Figure 3: Proposed algorithm of blood pressure target and management in diabetic kidney disease.



– Diabetic dyslipidaemia is characterised by increased concentrations of atherogenic triglyceride-rich lipoproteins, normal concentrations of low-density lipoprotein (LDL) with a shift of its pattern towards more atherogenic particles and low high-density lipoprotein (HDL) concentrations. This is reflected by mild to moderate hypertriglyceridaemia, low HDL cholesterol and normal or mildly increased LDL cholesterol when a standard lipid panel is obtained.
– A very similar lipid phenotype is observed in chronic kidney disease and may significantly contribute to the increased risk of atherosclerotic cardiovascular disease.
– LDL cholesterol significantly contributes to cardiovascular risk in mild to moderate chronic kidney disease with a 14% increased risk per 0.6 mmol/l higher LDL-cholesterol. However, in patients with end-stage renal disease on dialysis, LDL-cholesterol has a negative association with all-cause mortality at below average levels.

Lipid lowering therapy in diabetes and/or chronic kidney disease

Statins

– In primary prevention statin-based therapies reduce the relative risk of a first major vascular event by 19–21% per 1 mmol/l LDL cholesterol reduction and cardiovascular mortality, regardless of the presence of diabetes and the starting LDL cholesterol concentration. This translates to absolute risk reductions of 5.3% and 2.6% per mmol LDL cholesterol reduction for major vascular events in patients with diabetes mellitus with and without preexisting vascular disease.
– This effect, however, is attenuated with chronic kidney disease and declining renal function, and relative risk reductions are 22%, 24%, 15% and 15% in patients with an eGFR >60, 45–60, 30–45 and <30 ml/min/1.73 m^2 not on dialysis, respectively, and no risk reduction is observed in patients undergoing haemodialysis.
– A clear cardiovascular benefit has been demonstrated for high intensity statins (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) in subjects with chronic kidney disease (eGFR <60 ml/min/1.73/m^2) in randomised trials and meta-analyses, and some subsequent guidelines recommend high intensity statins in all patients with diabetes and/or chronic kidney disease at increased cardiovascular risk and not treated with dialysis. The safety and efficacy of this uniform approach has been questioned in patients with more advanced chronic kidney disease (stage ≥G4) and the use of statins specifically studied in these patients (atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg ± ezetimibe 10 mg) has been advocated in the KDIGO guidelines and is supported by authors.
– According to current Swissmedic labelling, rosuvastatin is contraindicated and lower doses are recommended for simvastatin, pravastatin and pitavastatin if eGFR is <30 ml/min/1.73 m^2. For other countries refer to local restrictions.

Ezetimibe

– The addition of ezetimibe in statin treated patients confers an additional 20–25% LDL cholesterol lowering.
– A significant relative 17% risk reduction (2.1% absolute risk reduction) for major cardiovascular events was observed in patients with chronic kidney disease (75% stage G4 and 5) treated with simvastatin plus ezetimibe in the SHARP study, with no clear benefit in those on haemodialysis.
– No dose adjustments are recommended for patients with impaired renal function.

PCSK9 inhibitors

– Addition of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab to statin therapy allows for an additional 50–60% LDL cholesterol lowering.
– In high-risk patients on maximum tolerated statin therapy both compounds reduce major cardiovascular events but not cardiovascular mortality.
– Similar LDL cholesterol lowering and greater absolute risk reductions have been observed with more advanced chronic kidney disease stage ≥G3 in patients treated with evolocumab (2.5%, NNT = 39), whereas alirocumab did not reduce major cardiovascular events in patients with an eGFR <60 ml/min.
– Due to cost-effectiveness issues at current prices, Swiss health authorities have restricted the use of PCSK9 inhibitors to patients with either clinical cardiovascular disease and LDL cholesterol levels >2.6 mmol/l, or heterozygous for familial hypercholesterolaemia and LDL cholesterol levels >5.0 mmol/l (4.5 mmol/l with additional risk factors) despite maximum tolerated statin therapy. For other countries, refer to local restrictions.
– No dose adjustments are recommended for patients with impaired renal function.

Table 5:
Current recommendations on cardiovascular risk stratification in diabetes and chronic kidney disease [51, 58].

EAS/ESC, 2021	Very high risk if	Patients with DM with established ASCVD and/or severe target organ damage	eGFR <45 ml/min/1.73 m^2 irrespective of albuminuria
			eGFR 45–59 ml/min/1.73 m^2 and microalbuminuria (ACR 3–30 mg/mmol)
			ACR >30 mg/mmol
			Presence of microvascular disease in at least 3 sites (i.e., ACR >3 mg/mmol plus retinopathy plus neuropathy)
	High risk if	Patients with DM of >10 years duration or ≥1 CVD risk factor without ASCVD or target organ damage	
	Moderate risk if	Patients with DM and none of the above	

ACR: urinary albumin/creatinine ratio; ASCVD: atherosclerotic cardiovascular disease: DM: diabetes mellitus;

Fibrates

- Fibrates effectively reduce plasma triglycerides (up to 50%) and triglyceride-rich lipoproteins with variable effects on LDL cholesterol.
- Since a reduction of cardiovascular events was observed only in subgroups of patients with hypertriglyceridaemia (>2.3 mmol/l) and low HDL cholesterol (<1.0 mmol/l), mostly in combination with statins, fibrates are not considered first line agents to reduce cardiovascular risk.
- Reversible increases in plasma creatinine / decreases in eGFR are observed and need to be considered.
- Fenofibrate, the most commonly prescribed fibrate, is not recommended if the eGFR is <60 ml/min and contraindicated in patients with an eGFR <30 ml/min.

Dyslipidaemia and cardiovascular risk in renal transplant recipients

- Cardiovascular disease is the leading cause of premature death in most kidney transplant registries and has a multifactorial aetiology.
- Dyslipidaemia is very frequent (>50%) in renal transplant recipients and in part secondary to the use of immunosuppressants, specifically glucocorticoids, calcineurin inhibitors (ciclosporin > tacrolimus) and mechanistic target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus. Therefore, lipid lowering with statins is recommended as part of cardiovascular risk management in patients following kidney transplantation.
- Results of a randomised trial and a Cochrane analysis suggest that the beneficial effects of statins in renal transplant recipients may be comparable to those observed in other populations.
- Interactions of statins with the immunosuppressive regimen need to be considered in renal transplant recipients and low to moderate doses of statins ± ezetimibe are recommended.

Guidelines

- Current recommendations are summarised in table 6 and recommend statins ± ezetimibe in all patients with chronic kidney disease stage G3–5 not on dialysis.
- If dialysis is started in patients already receiving statins ± ezetimibe, continuation of therapy may be considered.
- PCSK9 inhibitors may be considered in patients with chronic kidney disease and clinical cardiovascular disease if LDL cholesterol goals are not achieved with statins ± ezetimibe.

Complications of chronic kidney disease

Hyperkalaemia

References for this section: [59–65]

Diabetes mellitus, chronic kidney disease and treatment with blockers of the renin-angiotensin-aldosterone system (RAAS) are major risk factors for hyperkalaemia. For this reason, patients with diabetic kidney disease are at high risk of hyperkalaemia. Up to now, there are no clinical trials studying relevant clinical outcomes in patients with diabetic kidney disease and chronic hyperkalaemia. Novel molecules are or will soon be available for potassium control in chronic kidney disease, and are briefly discussed here. The recommendations are not specific to diabetic kidney disease.

General recommendations

- Measure potassium at each routine analysis.
- Measure potassium level 1 week after start or dose increase of RAAS blocker (ACE inhibitor, ARB, renin inhibitor).
- Do not combine RAAS blockers.
- A caveat when interpreting potassium values is the difference between serum and plasma or whole blood potassium levels. This has to be taken into account when interpreting and comparing potassium measurements. Both types of samples are used in clinical routine and research settings. Because intracellular potassium can be released during clotting, serum potassium levels were shown to be between 0.5 and 0.9 mmol/l higher than plasma potassium levels.

Treatment of chronic hyperkalaemia

Mild to moderate stable hyperkalaemia (4.5–6 mmol/l)

- Counsel about potassium reduced diet (with specialised dietician).
- Stop potassium supplementation.
- If possible, stop NSAIDs, MRAs, potassium-sparing diuretics, trimethoprim, or other agents that can increase plasma potassium.
- If metabolic acidosis is present (plasma bicarbonate <22 mmol/l), consider oral sodium bicarbonate.
- If there is hypervolaemia consider non-potassium-sparing diuretics (thiazides or loop diuretics).
- Consider reducing or temporarily stopping RAAS blockers and beta-blockers.

Table 6:
Current recommendations on lipid lowering treatment in diabetes with chronic kidney disease [51].

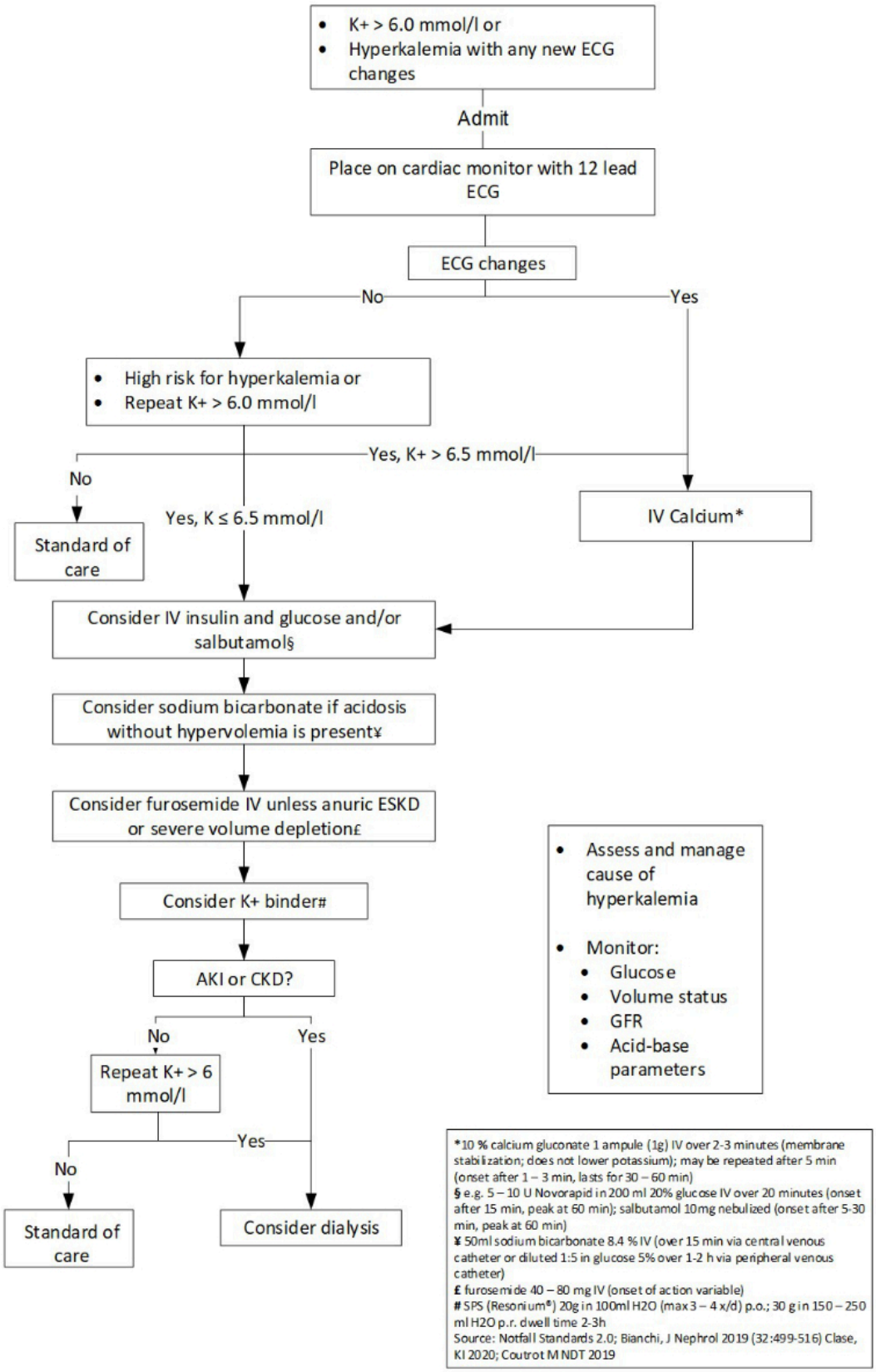
	CKD stage/risk category	Treatment	LDL cholesterol goal
EAS/ESC, 2021	Very high >G3b or G3aA2 or A3	High intensity statin (Class IA) ± ezetimibe (Class IB) / PCSK9 inhibitor (Class IIbC)	Step 1: <1.8 mmol/l and 50% reduction from baseline
			Step 2: <1.4 mmol/l* (if established ASCVD Class IA, if not IIbC)

ASCVD: atherosclerotic cardiovascular disease; LDL: low-density lipoprotein

*Based on residual 10-year cardiovascular risk, lifetime cardiovascular risk and treatment benefit, comorbidities, frailty and patient preferences.

Class IA (recommended, high evidence), IB (recommended, moderate evidence), IIbC (may be considered, low evidence).

Figure 4: Treatment of acute hyperkalaemia. Suggested management algorithm for acute hyperkalaemia in adult patients (adapted from: Clase CM, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020;97(1):42–61 [59]). Depending on the patient and the clinical situation, the sequence of procedures may be adapted.



– Consider concomitant therapy with potassium-binding resin if continuation of RAAS blocker treatment is desired (table 7).
– Combination treatment with a potassium binder and a RAAS blocker could be considered in the following settings: Patient with concomitant heart failure with reduced or mid-ranged ejection fraction (HFrEF or HFmrEF) / treatment of resistant hypertension / chronic kidney disease G1–G3b and albuminuria.
– Potential benefits of combined treatment (potassium binding resin + RAAS blocker): benefit of RAAS blockade / healthy diet (dietary approaches to stop hypertension [DASH]) can be continued (less dietary potassium restriction) / Patiromer was shown to reduce albuminuria, aldosterone levels and blood pressure (OPAL HK).
– (Potential) disadvantages of combined treatment: so far no trials with "hard" outcomes / interference with intestinal absorption of other drugs / additional costs / potential side effects (see table 7).

Severe hyperkalaemia (>6 mmol/l)

– Counsel about potassium reduced diet (with specialised dietician).
– Stop RAAS blocker.
– Additional emergency management strategies (fig. 4).

Management of RAAS blocker therapy in patients at risk for hyperkalaemia

– Start with the lowest possible dose of a RAAS blocker.
– Do not start a RAAS blocking agent if K^+ ≥5 mmol/l.
– We advise against a combination of an ACE inhibitor with an ARB or renin inhibitor because of increased risk of hyperkalaemia and renal failure.
– In combination with an ACE inhibitor, ARB or renin inhibitor the dose of spironolactone should not exceed 25 mg/d.
– Plasma potassium should be checked at baseline and within 1–2 weeks after initiation or titration AND during times of acute illness.
– If K^+ increases significantly from baseline, therapy should be reviewed and creatinine and K^+ levels must be rechecked.

Anaemia

References for this section: [66–72]

Table 7:
Potassium binders (modified from [61–63]).

	Polystyrene sulphonate (Resonium®)	**Patiromer (Veltassa®)**	**SZC (sodium zirconium cyclosilicate)**
Approval in Switzerland	Yes	Yes*	No
Formulation	Dissolvable powder	Dissolvable powder	
Application	Oral or rectal	Oral	Oral
Counterion	Sodium	Calcium	Sodium
Cations bound	K^+, Mg^{2+}, Ca^{2+}	K^+, Mg^{2+}	K^+
Chemical properties	Polymer; sodium salt of polystyrene sulphonic acid	Polymer; patiromer sorbitex calcium	Non-polymer; non-absorbed zirconium silicate
Mechanism of action	Exchanges Na^+ for K^+, Mg^{2+}, Ca^{2+}	Exchanges Ca^{2+} for K^+; also binds Mg^{2+}	Captures K^+ in exchange for hydrogen and Na^+
Counterion content	Na^+: 100 mg/g SPS	Ca^{2+}: 191 mg/g patiromer	Na^+: 80 mg/g SZC
Site of action	Colon/rectum	Distal colon	Entire GI tract
Onset of action	1–2 h	4–7 h	1 h
interactions	Lithium, levothyroxin edigitalis, sorbitol	Reduced systemic exposure of coadministered ciprofloxacin, metformin, and levothyroxine. No interaction when patiromer and these drugs were taken 3 h apart	No significant drug-drug interactions
	Separate from oral medications by at least 3 h before or 3 h after; if gastroparesis, separate other medications by 6 h	Take other oral medications at least 3 h before or 3 h after administration	Take other oral medications with gastric pH-dependent availability at least 2 h before or 2 h after
Side effects	GI: nausea, vomiting, diarrhoea, constipation. Serious GI effects: ileus, intestinal ulcer/necrosis, perforation, haemorrhage, ischaemic colitis. Electrolyte disturbance: hypokalaemia, hypocalcaemia, hypomagnesaemia, oedema and hypertension due to sodium retentionH	Hypomagnesaemia and hypokalaemia; diarrhaea, constipation, nausea, flatulence, abdominal discomfort; potentially calcium overloading	Hypokalaemia, Oedema
Setting	Acute hyperkalaemia	Chronic hyperkalaemia	Acute and chronic hyperkalaemia
Dosage	15–60 g (1–4×/d); Rectal: 30–50 g (1–4×/d)	Initial: 8.4 g qd (max.: 25.2 g orally once daily); dose can be increased by 8.4 g increments at one week intervals	Initial: 10 g orally 3 times daily for 48 h
Maintenance dose	15–60 g once daily	8.4–25.2g once daily	10 g
Cost	+	+++	

* Veltassa® is reimbursed by the health insurance company after consultation with the doctor in charge for adult, non-dialysed patients with CKD (treatment must be started in CKD stage G3 or 4; the glomerular filtration rate must be below 60 ml/min/1.73 m^2), who developed chronic recurrent hyperkalemia during therapy with an inhibitor of the renin-angiotensin-aldosterone system, as determined by repeated measurements, and for whom cation exchange resins must be used because the non-drug measures (diet) and the previous drug measures (e.g. potassium-lowering diuretics) were not sufficient to normalize potassium levels (below 5.5 mmol/l). The *initial prescription* of Veltassa® can only be made by a nephrologist or cardiologists.

Anaemia is a common complication of all types of renal disease, occurring usually in advanced stages. Its pathophysiology is multifactorial, involving deficient erythropoietin production, decreased iron availability and inflammation among others. In patients with type 2 diabetes and chronic kidney disease, anaemia is associated with an increased risk of renal and cardiovascular events. Anaemia is also associated with increased mortality and a higher risk for hospitalisation in chronic kidney disease.

There are no specific recommendations for the management of anaemia in diabetic kidney disease as compared to nondiabetic kidney diseases; therefore, anaemia guidelines for chronic kidney disease apply (KDIGO anaemia guidelines).

Definition of anaemia: <12 g/dl in females, <13 g/dl in males.

Frequency of anaemia monitoring:

- If no anaemia: annually in chronic kidney disease KDIGO stage G3, every 6 months in stages 4 and 5, monthly in dialysis.
- If anaemia present: every three months in non-dialysis patients, monthly in dialysis patients.

Investigations:

- Complete blood count
- Reticulocytes
- Ferritin, iron, transferrin saturation (TSAT)
- Vitamin B12, folate
- Thyroid stimulating hormone
- C-reactive protein

Consider:

- Serum electrophoresis, serum immunofixation and serum free light chains (once)
- Parathyroid hormone (if erythropoietin-stimulating agent [ESA] resistance)
- Haemolysis workup (lactate dehydrogenase, bilirubin, schistocytes, haptoglobin) depending on clinical situation

Iron therapy in anaemic patients:

- Consider iron supplementation if TSAT is ≤30% and ferritin is ≤500 ng/ml and haemoglobin increase is desired.
- Trial of oral iron can be considered with moderate anaemia in predialysis patients (not with calcium or antacids).
- In haemodialysis patients iron should be given intravenously.
- First dose of intravenous iron sucrose or dextran should be administered in an environment with resuscitative facilities and staff trained to evaluate and treat serious adverse reactions. We recommend monitoring the patient for 60 minutes after the first infusion.
- Iron should not be administered to patients with active systemic infections.
- Reevaluate iron status at least every three months, more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of intravenous iron, and in other circumstances where iron stores may become depleted.

ESA use in anaemic patients

In dialysis and nondialysis patients with chronic kidney disease, several studies have shown that targeting haemoglobin levels ≥13 g/dl increases the risk of adverse outcomes. The TREAT trial was a randomised, double-blind, placebo-controlled study in 4000 nondialysis diabetic patients with chronic kidney disease. Half received darbepoetin alfa to target a haemoglobin level of 13 g/dl, while the other half received placebo and were treated with an ESA only if their hemoglobin fell below 9 g/dl. The group with the higher haemoglobin concentration showed a significant reduction in the need for blood transfusions, but at best a marginal improvement in quality of life. TREAT failed to show a beneficial effect of higher haemoglobin on hard cardiovascular or renal endpoints. In contrast, the risk of venous and arterial thromboembolism increased significantly in the high haemoglobin group, and the risk of stroke was almost double in patients in the higher haemoglobin arm. In the group of patients who had malignant disease at baseline, the number of cancer-related deaths was increased more than tenfold in the higher haemoglobin group.

- ESA treatment should be initiated by a nephrologist.
- Predialysis and dialysis: initiate ESA if haemoglobin <10 g/dl after iron and vitamin repletion.
- Target haemoglobin: 10–11.5 g/dl.
- Follow-up every month after initiation, every three months if stable.
- Dose adjustment according to target.
- Caution in patients with malignancy or post stroke.
- Future: different small molecules inhibiting prolyl hydroxylase enzymes, thus stabilising the hypoxia-inducible factor and promoting erythropoietin production are being tested for efficiency of anaemia correction and security in predialysis and dialysis patients with chronic kidney disease.

Chronic kidney disease-mineral and bone disorder

References for this section: [73–75]

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a universal complication of progressive loss of kidney function. Biochemical abnormalities, vascular calcification and bone fragility constitute the CKD-MBD syndrome. CKD-MBD is associated with increased risks for morbidity and mortality in observational studies.

For diabetic kidney disease, there are no specific guidelines and recommendations for the management of CKD-MBD. The proposed recommendations reflect guidelines for chronic kidney disease irrespective of aetiology.

Laboratory tests for CKD-MBD

The frequency of laboratory tests should consider chronic kidney disease stage and progression, and individual factors to monitor trends and treatment efficacy.

CKD KDIGO stage G3a–G3b:

- Plasma calcium and phosphate: every 6–12 months

– Parathyroid hormone: based on baseline level and chronic kidney disease progression
– 25 (OH) vitamin D: measure at least once per year

CKD KDIGO stage G4:

– Calcium and phosphate: every 3–6 months
– Parathyroid hormone: every 6–12 months
– Alkaline phosphatase: every 12 months, or more frequently in the presence of elevated parathyroid hormone
– 25 (OH) vitamin D: at least once per year

CKD KDIGO stage G5, including G5D:

– Calcium and phosphate: every 1–3 months
– Parathyroid hormone: every 3–6 months
– Alkaline phosphatase: every 12 months, or more frequently in the presence of elevated parathyroid hormone
– 25(OH)-vitamin D: at least once per year

Assessing vascular calcifications

For chronic kidney disease stage G3a–G5D vascular calcifications should be assessed in an individual approach to detect patients at the highest risk for cardiovascular events.

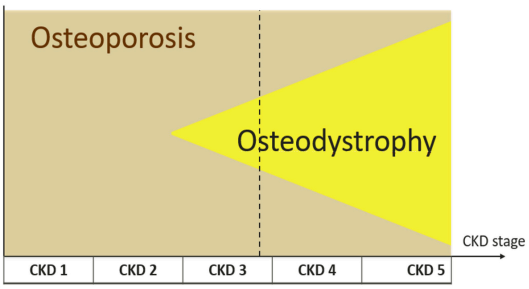
Assessing osteoporosis / renal osteodystrophy

This topic should be managed by an experienced nephrologist as inadequate therapy may do more harm than good. Patients with diabetes and chronic kidney disease are at increased risk for osteoporosis and renal osteodystrophy. Importantly, osteoporosis and renal osteodystrophy are distinct disorders. Their prevalence depends on the disease stage. Osteoporosis can be present alone or in combination with renal osteodystrophy (fig. 5).

The term “renal osteodystrophy” is used to describe alterations in bone morphology connected to chronic kidney disease detected on bone biopsy. It is classified into five distinct forms, which can overlap: osteitis fibrosa, mild hyperparathyroidism, osteomalacia, adynamic bone disease, and mixed uraemic osteodystrophy.

– The risk for clinical osteoporosis should be assessed with, for example, FRAX (fracture risk assessment tool), including a history of previous fractures as well as a family history for clinical and densitometric osteoporosis.

Figure 5: Osteoporosis and osteodystrophy in chronic kidney disease (CKD).



– Evidence of CKD-MBD and/or risk factors for osteoporosis → bone mineral density testing (DXA) if results will impact treatment decisions.
– Some experts recommend a bone biopsy before initiation of therapy.
– For CKD KDIGO stages ≥G3 antiresorptive or anabolic therapy should only be initiated by a physician experienced in CKD-MBD.

Therapy for CKD-MBD: dietary interventions and drugs

– Patients with rising phosphate levels, frank hyperphosphataemia and elevated parathyroid hormone levels need to be seen by specifically trained dieticians. Reduction of phosphate needs to focus on sources with inorganic phosphate used in food additives of ready-to-eat foods, many canned drinks and most processed foods.
– Phosphate intake should be reduced in a way that does not impede adequate protein intake in a population at risk for protein malnutrition. As vegetarian sources of protein have a lower phosphate bioavailability, substituting vegetable protein for animal protein should be considered.
– Do not use phosphate binders routinely. The intention is to lower phosphate toward the normal range (and not in the normal range as suggested by 2009 KDIGO guidelines). Based on the limited data available, use sevelamer-chloride and sevelamer-carbonate preferentially. Limit calcium-based agents, if possible.
– Parathyroid hormone normalisation is not the aim.
– Treat vitamin D deficiency (25OH-vitamin D) as for the general population.

Chronic metabolic acidosis

References for this section: [76–78]

Metabolic acidosis is characterised by a serum bicarbonate level <22 mmol/l in an individual with normal pulmonary function. It is common in chronic kidney disease and represents an independent and modifiable risk factor for progression of the disease. Importantly, even before frank metabolic acidosis occurs, multiple adaptive responses that increase acid excretion are activated. They include activation of pathways, such as the intrakidney RAAS, that mediate the immediate benefit of increased acid excretion, but chronically become maladaptive and promote a decline in kidney function. Importantly, patients with diabetic kidney disease are at increased risk for type IV renal tubular acidosis, with or without hyperkalaemia, caused by hyporeninaemic hypoaldosteronism.

For diabetic kidney disease and chronic metabolic acidosis, there are no specific guidelines. The proposed recommendations reflect current guidelines for chronic kidney disease irrespective of aetiology. This section does not discuss acute metabolic acidosis secondary to SGLT2 inhibitors (euglycaemic ketoacidosis) or metformin (lactic acidosis).

Assessing metabolic acidosis in CKD

Overt metabolic acidosis commonly develops if GFR declines below 40 ml/min/1.73 m^2. Importantly, in individuals with diabetic kidney disease it may manifest earlier due to type IV RTA, which has to be suspected in patients with hyperkalaemia.

Venous blood gas analysis is sufficient to measure bicarbonate concentration.

Suggested monitoring:

CKD KDIGO stage G3a–G3b:

- Potassium: at each routine analysis
- Bicarbonate: every 6–12 months

CKD KDIGO stage G4**:**

- Potassium: at each routine analysis (least every 3–6 months)
- Bicarbonate: every 3–6 months

CKD KDIGO stage G5, including G5D:

- Potassium: every 1–3 months
- Bicarbonate: every 1–3 months

In patients receiving treatments for acidosis or with biochemical abnormalities:

- Increase the frequency of measurements to monitor for trends and treatment efficacy.

Prevention and therapy of metabolic acidosis: dietary interventions and oral alkali supplements

- We suggest that bicarbonate levels are maintained at >22 mmol/l with dietary interventions and/or oral alkali supplements in patients not on dialysis.
- All patients with bicarbonate levels <22 mmol/l should be seen by a specifically trained dietician collaborating with every dialysis unit or nephrology department.The aim is to limit the dietary acid load, which is particularly high in some cheeses, meat products and certain grains, including brown rice. In addition, in individuals not prone to hyperkalaemia, base-producing fruits and vegetables are key to ameliorating metabolic acidosis. This intervention may be considered even before apparent metabolic acidosis (bicarbonate <22 mmol/l) develops, that is, in patients with low normal bicarbonate levels (22–24 mmol/l).
- Alkali supplementation with sodium hydrogencarbonate (Nephrotrans®): the maximum dose corresponds to nine capsules (approximately 50 mmol base equivalent) per day divided in three or four doses. Caution is required in patients with heart failure, oedema and uncontrolled hypertension.
- Alkali supplementation with potassium citrate, potassium hydrogencarbonate (Kalium Effervetten): one tablet corresponds to 30 mmol potassium and 30 mmol base equivalent. This therapy is contraindicated in patients with advanced renal failure, hyperkalaemia, and in combination with RAAS inhibitors.

End-stage renal disease

Blood glucose control in haemodialysis patients

References for this section: [79–84]

There is an increasing prevalence of diabetes in haemodialysis centres, reaching 30–45% of patients. These patients have variable clinical outcomes and life expectancy. On average, the 5-year mortality of patients with diabetes on haemodialysis is over 50%. Goals of glucose control should be individualised to the patient's prognosis. Among patients with more stringent goals such as those on the transplantation list, basal bolus therapy is often proposed with 24-hour glucose monitoring.

Introduction

- The risk of hypoglycaemia is high. Some patients may progress to "burnt-out diabetes" and no longer require antidiabetic medication. The cause is multifactorial, including a decrease in clearance of insulin as well as a state of undernutrition linked to a worse prognosis.
- Blood glucose may considerably vary during haemodialysis sessions, mainly owing to the gradient between the patient's blood glucose concentration and the glucose concentration in dialysates (most often 5.5 mmol/l). With a steep gradient, there may be a significant decrease in blood glucose during the session followed by reactive hyperglycaemia after the session due to various mechanisms (insulin clearance, increase in counter-regulatory hormones, snacks).
- The hyperosmolar hyperglycaemic state is not associated with hypovolaemia; however, it can present with increased thirst and very high blood glucose levels because of impaired glycosuria.

Monitoring glycaemic control

- HbA1c remains the preferred parameter for follow-up because of studies linking values to mortality.
- HbA1c flaws: *Falsely increased values:* vitamin B12 or iron deficiency, increased urea levels, metabolic acidosis. – *Falsely low values:* anaemia, blood transfusion, erythropoietin stimulating agents, shortened red blood cell life span.

Goals of therapy in haemodialysis

- Mortality is increased if HbA1c <6.5% or >9%.
- Goals: HbA1c 7–8.5% depending on life expectancy
- Threshold for hypoglycaemia is <5 mmol/l, which requires the ingestion of 15 g of glucose.
- A reasonable goal is a blood glucose of 5–10 mmol/l.
- Ideally start the haemodialysis session with a blood glucose <11 mmol/l.

Antidiabetic therapy in haemodialysis patients

See figure 2 for therapies indicated in end-stage renal disease.

Comments:

- Preferred option: DPP-IV inhibitors.
- Insulin therapy: Avoid if possible because of the increased risk of hypoglycaemia. Try to avoid fast-acting insulins; if used, consider continuous glucose monitoring. Blood glucose monitoring is required before driving, with no driving if blood glucose <5 mmol/l. De-

crease preprandial rapid insulin by 10–15% before a haemodialysis session. The goal is to start the session with a blood glucose level <11 mmol/l. Reinforce education for the prevention of hypoglycaemia. In patients with altered cognition and a shortened life expectancy, administration of long-acting degludec 3×/week at the end of the haemodialysis sessions may be an option.

– GLP1 agonists: Under investigation. Increased side effects, accumulation of doses (liraglutide). Improved short-term glycaemic control and decreased insulin requirements and glucose variability (dulaglutide). May be interesting if body weight loss is a goal prior to renal transplantation

Continuous glucose monitoring devices in haemodialysis patients

Continuous glucose monitoring has become the standard of care in patients at high risk of hypoglycaemia and on intensive insulin regimens. However, fluid shifts between interstitial and intravascular spaces that occur during dialysis sessions, uraemia and acidosis have the potential to impact the performance of commercially available continuous glucose monitoring devices. Non-therapeutic continuous glucose monitoring for a short period in both haemodialysis and peritoneal dialysis was shown to improve glycaemic control thanks to more frequent treatment adaptations. There are ongoing studies examining the effectiveness of therapeutic continuous glucose monitoring devices with haemodialysis.

Although not all continuous glucose monitoring sensors are validated for haemodialysis, their use outside haemodialysis sessions is highly recommended. With the approval of the patient, the data collected in a cloud can be viewed at all times by healthcare providers. We review the advantages and disadvantages of systems for haemodialysis.

Flash system Freestyle Libre

– Disadvantages: Possible interference with high doses of vitamin C. Regular scanning required to download previous 8 hours of monitoring (Freestyle Libre 1 and 2). Freestyle Libre 3, available in 2022, is considered as a continuous glucose monitoring device and will not require regular scanning.

– Advantages: No calibration needed. Two-week duration of sensor. Possibility to measure real capillary glucose and ketones (in type 1 diabetes) with reader. Alarm available with second generation sensor (Freestyle Libre 2, 3).

CGMS Dexcom G6

– Disadvantages: Interference with drugs (high doses of paracetamol, vitamin C).

– Advantages: No calibration needed. Alarms. More reliable than the Flash system. Connection possible with closed loop systems (Diabeloop, Tandem).

CGMS Guardian Connect

– Disadvantages: Interference with drugs (paracetamol, vitamin C).

– Advantages: No calibration needed. Alarms. More reliable than the Flash system. Connection available with the Medtronic Insulin pump 640G, 670G,780G (automatic interruption of insulin delivery if hypoglycaemia is predicted within 30 minutes; automatic basal rate adjustment [670G, 780G]; automatic micro-bolus adjustments [780G]).

Implantable sensor Eversense

– Not recommended: Interference with mannitol; transmitter not magnetic resonance imaging (MRI) compatible.

Prevention of hypoglycaemia in haemodialysis patients

– Oral intake of 10–20 g glucose during haemodialysis session to avoid hypoglycaemia in patients on insulin therapy.

– Oral intake of 20–30 g of glucose at beginning of session if blood glucose <7 mmol/l.

– Do not correct hypoglycaemia with potassium- and phosphate-rich drinks.

– Check capillary glucose before leaving the dialysis unit (>5 mmol/l required if driving).

Blood glucose control in peritoneal dialysis patients

References for this section: [85–96]

Introduction

– Peritoneal dialysis is a continuous renal replacement therapy process in which solutes and fluid are exchanged between blood in the peritoneal capillaries and dialysis solution in the peritoneal cavity by crossing the peritoneal membrane. Patient outcomes with peritoneal dialysis are comparable to those with haemodialysis, and peritoneal dialysis is more cost-effective.

– Most diabetic patients with end-stage renal disease have multiple cardiovascular and metabolic complications. In haemodialysis, solutes and water are removed rapidly and intermittently. This can be associated with dialysis-induced hypotension, coronary ischaemia and arrhythmia. On the contrary, peritoneal dialysis avoids aggressive fluid shifts offering better haemodynamic tolerance.

– The most common complication of peritoneal dialysis (1 event every 20–60 patient-months) is peritonitis which is associated with loss of ultrafiltration, hospitalisation, catheter loss, technique failure and transfer to haemodialysis.

– Diabetes mellitus is associated with higher all-cause mortality but not with adverse therapeutic outcome of peritonitis associated peritoneal dialysis.

Modalities of peritoneal dialysis

– Continuous ambulatory peritoneal dialysis (1 to 4 dwells per 24 hours).

– Automated peritoneal dialysis: this method uses a machine (automated cycler) that performs multiple exchanges at night during sleep.

Peritoneal dialysis solutions (dialysates)

– Glucose-based dialysis solutions (dextrose solutions 1.5%, 2.5% or 4.25%) and glucose-sparing solutions in-

cluding high molecular weight glucose polymers such as icodextrin (EXTRANEAL®) are the predominantly used dialysates in peritoneal dialysis patients.

– Glucose polymer solutions offer the possible advantages of decreased absorption of solute and increased ultrafiltration for a longer period of time (up to 12 hours).

Effects of peritoneal dialysis on glycaemic control

– Glucose-based dialysate may worsen glycaemic control and increase insulin requirements in diabetic patients by glucose absorption from the dialysate into the blood stream down its concentration gradient.
– In general, the amount of glucose absorbed by the patient is approximately 60% at the end of a 6-hour dwell and will depend on peritoneal membrane transport characteristics, dwell time, dialysate volume and glucose concentration, and the patient's blood glucose level. Of the total amount of glucose absorbed, 50% occurs during the first 90 minutes of the dwell (continuous ambulatory peritoneal dialysis).
– Poor glycaemic control is associated with higher mortality in peritoneal dialysis patients.
– Compared with automated peritoneal dialysis, continuous ambulatory peritoneal dialysis can be associated with more glycaemic fluctuations on continuous glucose monitoring, although HbA1c and average blood glucose levels do not change significantly.
– New-onset diabetes mellitus is observed in both haemodialysis and peritoneal dialysis patients. The prevalence of new-onset diabetes is slightly higher in dialysis patients than in the general population. Data on diabetes induced by peritoneal dialysis are limited. However, a recent meta-analysis and systematic review has shown that 8% of non-diabetic patients became diabetic after initiating peritoneal dialysis.
– In addition to inducing hyperglycaemia, peritoneal dialysis increases the risk of dyslipidaemia, weight gain and increased visceral fat.

Methods of monitoring glycaemic control

Glycated haemoglobin (HbA1c):

– Less accurate in end-stage renal disease (haemodialysis section).
– Was shown to be weakly correlated (r = 0.4–0.5) to average glucose levels measured by continuous glucose monitoring system.
– Target: 7–8%, should be individualised by age, comorbidities, transplantation plan.

Self-monitoring of blood glucose:

Since icodextrin results in elevated blood levels of maltose, only glucose-specific monitors and test strips that utilise the enzyme glucose dehydrogenase must be used. Pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase test strips are contraindicated because they will give falsely elevated readings leading to insulin misuse and hypoglycaemia events. New test strips have been designed to minimise interference with non-glucose sugars and most glucometers in Switzerland are compatible. Companies providing dialysates have the information on interferences with glucometers.

Continuous glucose monitoring:

Data on the accuracy of therapeutic continuous glucose monitoring in the setting of peritoneal dialysis are still not available.

Suggested antidiabetic treatment regimens for patients on peritoneal dialysis

Indications and contraindications are similar to those discussed in haemodialysis (see above). The main difference relies on the use of antidiabetic drugs to prevent glucose fluctuations induced by peritoneal dialysis solutions. In this respect, insulin regimens offer the most adjustable therapies with a range of duration of action (from 1.5 to 48 hours). Timing of insulin action should take into account the abrupt onset of glucose diffusion at start of dialysis and the abrupt stop when glucose solution is drained.

In most patients on insulin therapy at initiation of peritoneal dialysis, insulin dosages should be increased especially in those receiving hypertonic exchanges. One study showed that diabetic patients receiving a standard 6 l/day dialysis exchange, had a 27% increase in insulin requirements.

Kidney transplantation

References for this section: [97–106]

Solid organ transplantation is an established and routine therapeutic option that has transformed the survival and quality of life of patients with end-organ dysfunction. Post-transplant diabetes mellitus (PTDM), also known as new-onset diabetes after transplantation, is a common and important complication following solid organ transplantation. PTDM in kidney transplant patients is associated with decreased patient and graft survival and other adverse outcomes including increased cardiovascular risk, infection and graft rejection. The reported incidence of PTDM varies from 4% to 25% of kidney transplant recipients. Approximately 50% of kidney transplant recipients need antidiabetic therapy (including pre-existing diabetes and PTDM).

Risk factors for PTDM

– Obesity, age, race, ethnicity, family history, active hepatitis C virus, donor source (deceased vs living), acute rejection, dose of corticosteroids, and type of immunosuppressive agents used to prevent and treat rejection (table 8)
– Solid organ transplant recipients with specific end-organ diagnoses such as end-stage kidney disease due to polycystic kidney disease have been reported to be at increased risk of PTDM.

Pretransplant baseline evaluation

– Patients with risk factors for metabolic syndrome should be screened for diabetes.
– Detection of impaired glucose tolerance by oral glucose tolerance testing prior to heart or pulmonary transplantation is more predictive of diabetes than fasting blood

glucose or HbA1c. Although not studied in renal transplantation, its use is encouraged.

– Patients with evidence of prediabetes can be counselled about lifestyle modifications including dietary modifications, 30 minutes of moderate intensity physical activity, and overall 5–10% weight reduction if overweight.

Early hyperglycaemia after transplantation

– New onset perioperative hyperglycaemia is common and may develop in the context of high-dose corticosteroid therapy and/or because of post-transplant stress hyperglycaemia.
– Patients with early post-transplant hyperglycaemia (defined as hyperglycaemia before 45 days after transplantation) should not be diagnosed as PTDM.
– Clinically stable patients with persistent post-transplant hyperglycaemia for >45 days should be screened for PTDM.

Diagnosis of PTDM

A diagnosis of PTDM is valid in patients on a stable immunosuppressive regimen, in the absence of infection, and at least 46 days after transplantation. Although the criteria for PTDM are based on criteria for diabetes in the general population, it is unclear whether thresholds for diabetes risk are the same. Some data suggest that criteria for prediabetes and diabetes are all associated with mortality risk in kidney transplant patients.

– Confirmed fasting plasma glucose ≥7 mmol/l is a diagnosis of diabetes.
– Confirmed random symptomatic plasma glucose ≥11 mmol/l is a diagnosis of diabetes.
– HbA1c ≥6.5% is a diagnosis of diabetes. A normal HbA1c does not exclude the diagnosis of PTDM in the presence of post-transplant anaemia and/or dynamic kidney allograft function.
– Oral glucose tolerance test: diabetes if fasting plasma glucose ≥7 mmol/l, 2-hour plasma glucose ≥11.1 mmol/l after 75 g of anhydrous glucose dissolved in water. – Better predictor of mortality risk in PTDM than HbA1c. – To be considered if fasting plasma glucose ≥5 mmol/l and HbA1c ≥5.7% OGTT. – Half are diagnosed with PTDM solely on the 2-hour criterion.

Table 8:
Risk of post-transplantation diabetes mellitus with different medications.

Medication	Risk of post-transplantation diabetes mellitus
Corticosteroids	Increased
Tacrolimus	Increased
Ciclosporin	Slightly increased
mTOR ihibitor	Increased
Mycophenolic acid	Not diabetogenic
Azathioprine	Not diabetogenic
Belatacept	Not diabetogenic
Basiliximab	Probably increased
Thymoglobulin	Not diabetogenic

– If no diagnosis at screening: repeat HbA1c, fasting and random plasma glucose at 3, 6, 9, 12 months after transplantation, then annually.
– If prediabetes at screening: definition of prediabetes: fasting plasma glucose 5.6–6.9 mmol/l *or* 2-h plasma glucose after 75 g glucose 7.8–11.0 mmol/l *or* HbA1c 5.7–6.4%. Repeat HbA1c, fasting and random plasma glucose at 3, 6, 9, 12 months after transplantation, then twice a year. Counselling on dietary and lifestyle modification.

Prevention and management of early post-transplantation hyperglycaemia and PTDM

Non-pharmacological preventive and management strategies

– Lifestyle modification advice is important because substantial weight gain is often observed after transplantation.

Antidiabetic therapies

– Early antidiabetic therapy will improve glucose control and may decrease PTDM within the first year. Currently, there is no evidence of additional effects on outcomes.
– Insulin tapering or withdrawal and transitioning to a non-insulin-based regimen can be considered after the first 1–3 months.
– Antidiabetic therapies other than insulin to be considered only if stable renal function and stable immunosuppressive therapy. Check for interactions with immunosuppressive therapy and gastrointestinal side effects that may alter the absorption of immunosuppressive drugs. – *Metformin:* dosage to be adjusted according to eGFR. – *DPP-IV inhibitor:* dosage to be adjusted according to eGFR (except for linagliptin). Well tolerated and safe. Ongoing studies to examine the prevention of PTDM with vildaglitpin and sitagliptin. – *GLP1 receptor agonist* (if BMI >28 kg/m^2): not in association with a DPP-IV inhibitor. Limited experience in renal transplantation. The cardio-renal protective effects demonstrated in high cardiovascular risk patients could be beneficial in the transplanted population. Ongoing study on prevention of PTDM with exenatide. – *SGLT2 inhibitors*: limited experience in renal transplantation. Urinary tract infection may increase with SGLT2 inhibition and immunosuppression and alter graft function. The cardio-renal protective effects demonstrated in high cardiovascular risk patients could be beneficial in the transplanted population beyond glucose control. Ongoing study of efficacy and safety of empagliflozin in PTDM. – *Sulphonylureas/glinides:* last choice because of the increased risk of hypoglycaemia

Modification of immunosuppression

– Immunosuppression is the major modifiable risk factor for the development of PTDM. Importantly, risk versus benefit analysis is required to balance risk of developing PTDM versus rejection. – Diabetogenic effects of immunosuppressive drugs vary (table 8). – Immunosuppression regimens should be selected to achieve the

best outcome for patient and graft survival, regardless of PTDM risk (in some selected patients with PTDM or at high risk of PTDM, the nephrologist / transplant team may consider switching immunosuppression to less diabetogenic drugs or discontinuing the steroid (after 6–12 months) if immunologically justifiable.

Glycaemic targets in PTDM

Encourage self-monitoring of glucose early after transplantation.

- Inpatient target blood glucose: 7.8–10 mmol/l.
- Outpatient target blood glucose: fasting blood glucose: 5–7 mmol/l; two-hour post-prandial glucose <10 mmol/l.
- HbA1c monitoring only if clinically stable (>45 days after transplantation). Individualised goal according to comorbidities: HbA1c: 7–8%; HbA1c <7% if no risk of hypoglycaemia.

Life-style management and nutrition

References for this section: [107–111]

Life-style management including individualised nutrition therapy, physical activity and interventions for smoking cessation are cornerstones of diabetes management and cardiovascular disease risk reduction and should be reinforced at any time during the course of diabetes and diabetic kidney disease.

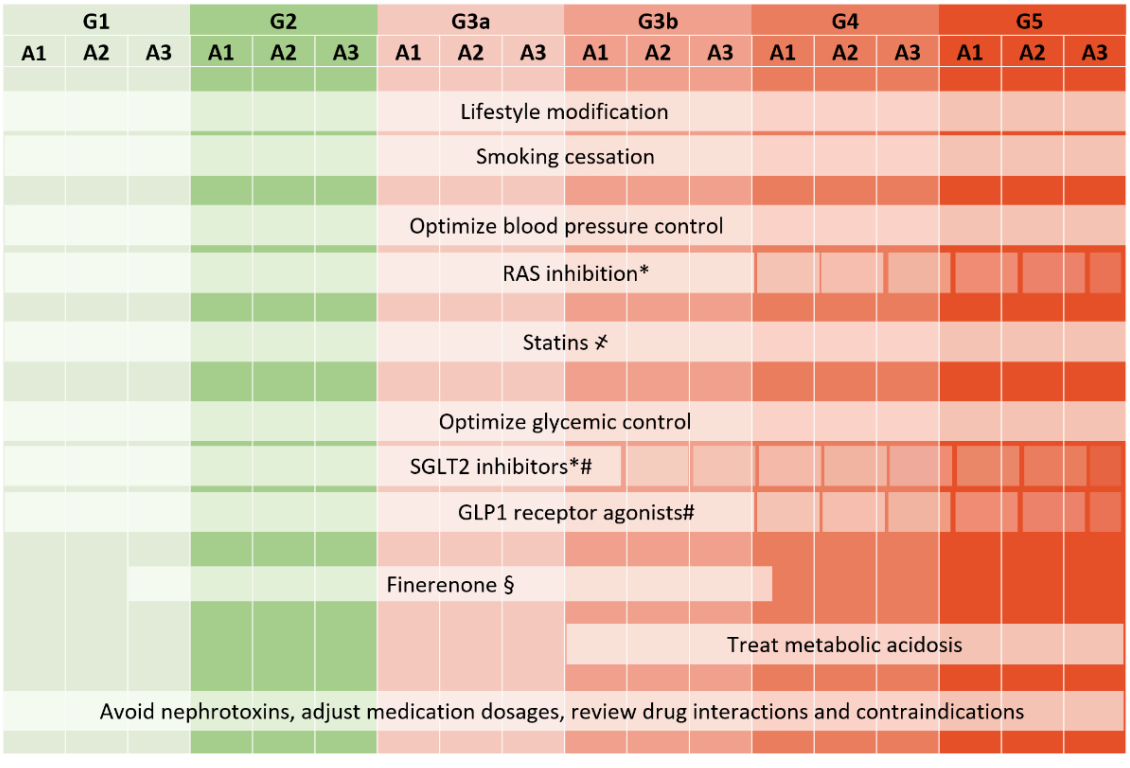
In overweight patients with mild to moderate chronic kidney disease, therapies favouring weight loss as treatment with GLP1 receptor agonists or SGLT2 inhibitors and lifestyle changes reinforced by programmes such as Diafit in Switzerland are highly encouraged. However, in more advanced disease (eGFR <30 ml/min/1.73 m^2), weight loss may lead to muscle wasting and worse outcomes.

Living with diabetes and chronic kidney disease is a huge challenge for dietary adjustments. The combination of these two conditions makes diet more complicated, as restrictions required by the renal diet may conflict with previous dietary recommendations for diabetes. Successful dietary management requires careful planning, regular assessment of nutritional status and of laboratory values. Poor adherence to the diet puts patients at risk for acute complications such as fluid overload, hyperkalaemia, hyperphosphataemia as well as worsening kidney disease. Diet interventions are recommended to improve adherence to diet and to prevent muscle wasting, sarcopenia and cachexia, which contribute to frailty and morbidity. Early, individualised counselling and nutritional intervention in recently hospitalised patients with chronic kidney disease at nutritional risk are highly recommended with the recent demonstration of decreased mortality and complications at 30 days.

Details of dietary interventions are beyond the scope of these recommendations. All recommendations need to be adapted individually.

The general dietary approach we propose is as follows:

Figure 6: Interventions to slow DKD progression and/or reduce cardiovascular disease (adapted from: Shlipak MG, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2021;99:34–47 [112]). RAS blockade, SGLT2i and GLP1Ra use in more advanced CKD to be considered individually and based on drug label and figure 2. ≠ No statin initiation in dialysis. * RAS blockers and SGLT2i slow eGFR decline in albuminuria stage A3. # SGLT2i and GLP1Ra decrease renal and cardiovascular morbidity in high CV risk patients. § Cardiovascular and renal protection with finerenone in albuminuria stage A2 and A3.



– *Indications for referral to a diabetes dietician:* All stages of DKD with a focus on carbohydrate intake and adjustments of insulin regimen.
– *Indications for referral to a renal dietician:* KDIGO stage G3a–5 / accelerated renal function decline (>5 ml/min/y) / plasma albumin <35 g/l / weight loss of undetermined origin >5% / hyperkalaemia / resistant hypertension or >10 g of salt in 24-hour urine / plasma phosphate >1.45 mmol/l.
– *Healthy plate:* half fruit and vegetables, quarter protein (animal or plant), quarter whole grains and starchy vegetables.
– *Protein intake:* 0.8 g/kg KDIGO stage G3–5 / 1.0–1.2 g/kg in haemodialysis or peritoneal dialysis.
– *Sodium intake:* <5 g sodium chloride per day (≤2 g or 90 mmol of sodium per day).

Conclusion

More than 30% of people with diabetes mellitus develop chronic kidney disease. A considerable number of them progress to kidney failure requiring dialysis or transplantation. Hence, there is a great need for efficient evidence-based management of these patients to minimise negative outcomes. Our guidelines address the relevant aspects and provide recommendations for the treatment of diabetic kidney disease and its complications. We also provide advice on screening for and establishing the diagnosis of chronic kidney disease in individuals with type 2 diabetes. Where evidence for diabetic kidney disease is lacking, we have integrated the current recommendations for chronic kidney disease in general.

Developments in recent years have brought effective new therapeutic options such as SGLT2 inhibitors and GLP1 receptor agonists which slow the progression of diabetic kidney disease and/or significantly lower the risk of cardiovascular complications.

Fortunately, the field of diabetic kidney diseases is still rapidly evolving. Several clinical trials of novel agents targeting different pathways in patients with diabetes mellitus are underway. New substances such as nonsteroidal mineralocorticoid receptor antagonists decrease renal and cardiovascular risk in patients with diabetic kidney disease. Endothelin antagonists are in the therapeutic pipeline. These new therapies might be combined with currently available drugs in the future such that an individualised approach can be accomplished. Due to the dynamic development, we plan to publish the guidelines on an electronic platform, so that they can be updated promptly in case of clinically relevant new findings. We are optimistic that our guidelines will significantly contribute to a high-quality multidisciplinary care of patients with diabetic kidney disease in Switzerland in the future.

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