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Chronic Kidney Disease: a practical guide (ACT-NAU)

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Concept, study design, methodology, and writing the original draft of the manuscript [ACR and LLD]; all other authors participated in the writing and critical review of the manuscript. All authors read and agreed with the final version of the manuscript.

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ABBREVIATION INDEX

ABPM – Ambulatory Blood Pressure Monitoring
ACE – Angiotensin-Converting Enzyme
ACE-i – Angiotensin-Converting Enzyme inhibitor
ACR – Albumin Creatinine Ratio
ADA – American Diabetes Association
ADPKD – Autosomal Dominant Polycystic Kidney Disease
AER – Albumin Excretion Rate
AKI – Acute Kidney Injury
ARB – Angiotensin Receptor Blockers
ARM – Mineralocorticoid Receptor Antagonist
ASCVD – Atherosclerotic Cardiovascular Disease
BMI – Body Mass Index
BP – Blood Pressure
CCBs – Calcium Channel Blockers
GFR – Glomerular Filtration Rate
CGM – Continuous Glucose Monitoring
CHBs – Calcium Channel Blockers
CKD – Chronic Kidney Disease
CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration
CREDENCE – Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CVD – Cardiovascular Disease
CT – Computerized Tomography
DAPA-CKD – Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DBP – Diastolic Blood Pressure
DRI – Direct Renin Inhibitor
eGFR – Estimated Glomerular Filtration Rate
ESRD – End-Stage Renal Disease
GN – Glomerulonephritis
KDIGO – Kidney Disease Improving Global Outcomes
HBPM – Home Blood Pressure Monitoring
HIV – Human Immunodeficiency Virus
ICA – Intracranial Aneurysms
LDL – Low-Density Lipoprotein
MRAS – Aldosterone receptor antagonists
MRI – Magnetic Resonance Imaging
PCR – Protein-creatinine Ratio
PROPKD – Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease
RAAS – Renin-Angiotensin-Aldosterone System
RBC – Red Blood Cells
RVD – Renovascular Disease
SBP – Systolic Blood Pressure
T1D – Type 1 Diabetes
T2D – Type 2 Diabetes
US – Ultrasonography

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Introduction

Chronic kidney disease (CKD) is a major public health problem that is associated with increased global morbidity and mortality and is a major risk factor for cardiovascular disease.[1-3] The prevalence of CKD is increasing exponentially worldwide.[2] Its prevalence in Portugal is 20.9% in CKD stages 1 to 5, and 9.8% for CKD stage ≥ G3a/A1,[4-5] so it is of utmost importance that this health problem be properly addressed in primary health care.

The most common causes of CKD are hypertension and diabetes, and regular screening for CKD in these patients is recommended.[6-9] Other contributing factors to CKD include acute kidney injury, obesity, smoking, infectious diseases, nephrotoxic drugs and, less frequently, contaminants in food or drinking water, heavy metals, industrial and agricultural chemicals, and high ambient temperatures.[2,10-15]

CKD is a major burden on health care systems with a propensity to increase due not only to the increasing prevalence of hypertension and diabetes but also to the aging population. This will result in greater demand for the healthcare system, greater consumption of resources, and greater economic expenditures on healthcare.[16] Thus, it is of uttermost importance to develop awareness among physicians to prevent CKD and its risk factors, to properly screen for early diagnosis, and to correctly treat and refer to secondary health care facilities.[4-5,16-19]

To improve the care of patients with CKD and strengthen communication between healthcare providers, we present a document with the backbone guidelines for diagnosing CKD, its management according to its various etiologies, and referral criteria to hospital care.

Chronic Kidney Disease

Andreia Nunes; Carolina Belino; Cristina Outerelo; Gilberto Guimarães; Ivan Luz; Zélia Lopes

DEFINITION OF CHRONIC KIDNEY DISEASE

CKD is defined as a set of abnormalities in kidney structure or function that persist for >3 months and can lead to cardiovascular, metabolic, endocrine, and xenobiotic toxicity-related complications.[20]

CKD is classified based on its cause, glomerular filtration rate (GFR) category, and albuminuria category. It has a variable clinical presentation, partly related to etiology, severity, and rate of progression, but is often characterized by its irreversibility, and slow and progressive evolution.[5,20-21]

DIAGNOSIS

The criteria for CKD include the presence for more than three months of indicators of kidney damage and/or decreased GFR (GFR <60 ml/min/1.73 m^2) (Figure 1). Indicators of kidney damage are albuminuria (defined by the presence of ≥ 30 mg of albumin in the 24-hour urine or albumin/creatinine ratio ≥30 mg/g in an isolate urine sample), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormal renal imaging findings, abnormalities in renal histology and previous kidney transplantation.[20-21]

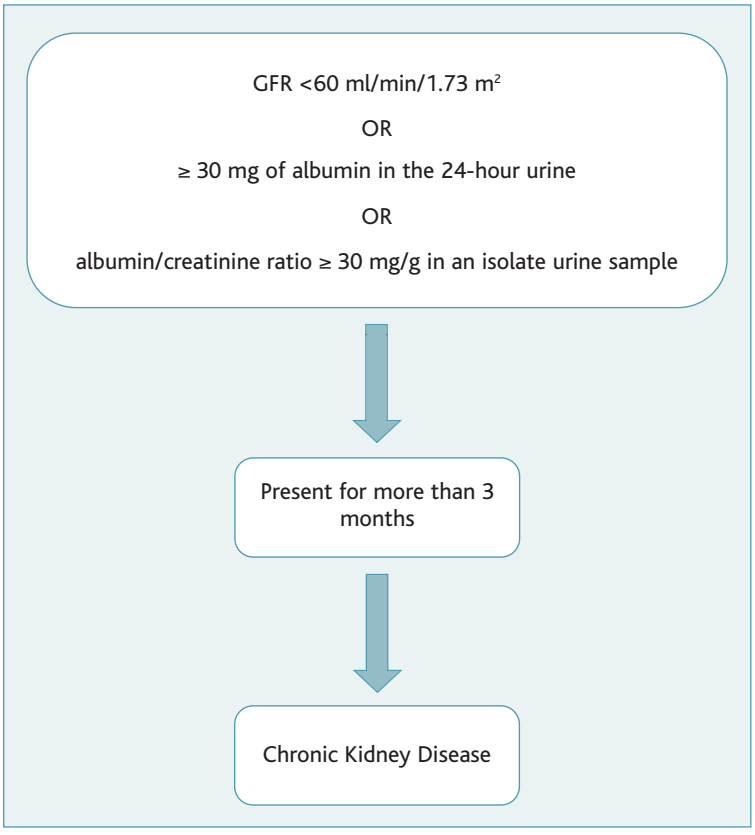

Figure 1. Diagnostic algorithm for chronic kidney disease.[20-21]

If the criteria for CKD are present for less than three months or are of uncertain duration, CKD and/or acute kidney disease may be present and testing should be repeated.[20]

STAGING OF CHRONIC KIDNEY DISEASE

The stages of CKD indicate the prognosis, assessment, and management of the disease.[22] CKD is divided into five GFR categories, and three albuminuria categories, as shown in Tables 1 and 2.[20]

The Kidney Failure Risk Equation predicts the 2- and 5-year risk of end-stage renal disease (ESRD) in patients with CKD stages 3a-5.[23]

SCREENING INDICATIONS

The timing of initiation of CKD screening should be based on comorbidities and individualized risk assessment, rather than at a specific chronologic age. The frequency of testing must be individualized and could range from 1 to 10 years.[24] Screening is for high-risk individuals and not for the general public.[25]

Adults should be screened for CKD in the presence of the following:[7-8,21-22,26-27]

- Diabetes;
- Hypertension;
- Cardiovascular disease (chronic heart failure, ischaemic heart disease, cerebral vascular disease or peripheral vascular disease),
- Previous episode of acute kidney injury;
- Structural renal tract disease, nephrolithiasis, recurrent urinary tract infections or prostatic hypertrophy;
- Gout;
- Multisystem diseases with potential kidney involvement, such as systemic lupus erythematosus;
- Haematuria or proteinuria;
- Human immunodeficiency virus (HIV) or hepatitis C virus infection;
- Malignancy;
- Family history of CKD or hereditary kidney disease;
- > 60 years of age.

Children, young people, and adults taking medications that can impair kidney function, for example, cal-

TABLE 1. Glomerular Filtration Rate categories in chronic kidney disease

GFR Categories	GFR (ml/min/1.73 m²)	Classification
1	>90	Normal or high
2	60 - 89	Mildly decreased
3a	45 - 59	Mildly to moderately decreased
3b	30 - 44	Moderately to severely decreased
4	15 - 29	Severely decreased
5	<15	Kidney failure

TABLE 2. Albuminuria categories in chronic kidney disease

Albuminuria Categories	24-hour Albuminuria (mg/24h)	Albumin/creatinine ratio (mg/g)	Classification
A1	<30	<30	Normal to mildly increased
A2	30 - 300	30 - 300	Moderately increased (previously referred as microalbuminuria)
A3	>300	>300	Severely increased (previously referred as macroalbuminuria)

cineurin inhibitors, lithium, or non-steroidal anti-inflammatory drugs for the long-term, should be monitored at least annually for GFR. Children and young people should be screened for CKD in case of solitary functioning kidney or previous episodes of acute kidney injury.[27]

SCREENING TESTS

Screening tests for CKD include:[21-22,27]

- Measurement of serum creatinine and estimation of GFR by mathematical formulae;
- Determination of albuminuria by measurement of the urine albumin/creatinine ratio in the urine of an isolated urine sample, preferably the first in the morning (the preferred method, due to its ease and good correlation with the excretion in the 24-hour urine);
- Urinalysis;
- Imaging exam (ultrasound of the kidneys and urinary tract).

The calculation of GFR allows a more accurate assessment of kidney function than serum creatinine alone. The EPI-CKD (Chronic Kidney Disease Epidemiology Collaboration) formula provides a more accurate prediction of prognostic renal outcomes and has fewer biases than the MDRD (Chronic Kidney Disease Epidemiology Collaboration) formula.[21]

The presence of albuminuria, tubular proteinuria, dysmorphic erythrocytes or casts, and renal tubular cell components are pathognomonic of kidney injury. Albuminuria is the major component of urinary protein and therefore, the albumin/creatinine ratio in urine from a single sample is a more sensitive and specific marker of CKD than the protein/creatinine ratio.[21,28] Albuminuria between 30-300 mg/g used to be termed "microalbuminuria," and greater than 300 mg/g, "macroalbuminuria".[21]

RISK FACTORS AND MAIN CAUSES

CKD is a complex disease, involving both non-modifiable risk factors, such as age, family history, and ethnicity, and modifiable factors, such as diabetes, hypertension, and dyslipidemia.[20]

To determine the cause of kidney disease, it is important to assess the patient's clinical background, personal and family history, social and environmental risk factors, and pharmacological therapy, and then perform a physical examination to order appropriate analytical and imaging tests.[20]

Major causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis (often related to nephrolithiasis in adults), autoimmune diseases, polycystic kidney disease, hereditary diseases, congenital malformations, and prolonged acute kidney disease.[21] Other causes include obesity, smoking, infectious diseases, contaminated food or drinking water, heavy metals, industrial and agricultural chemicals, high ambient temperature, and nephrotoxic drugs.[2,10-15,21]

Most causes of CKD are irreversible, and treatment's main goal is slowing the progression to kidney failure. Because of the long natural course of most CKD cases, patients are more likely to have one or more episodes of acute kidney injury (AKI), overlapping with CKD.[20]

COMPLICATIONS

Many disorders can develop as a consequence of the loss of kidney function, as it affects all organ systems. CKD is an independent risk factor for cardiovascular disease, which is the leading cause of mortality in patients with CKD.[14,20,29-31] As mentioned above, all people with CKD are at increased risk of AKI.[20] CKD predisposes to disorders of fluid and electrolyte balance, such as hyperkalemia, hyperphosphatemia, volume overload, metabolic acidosis, and to other systemic and hormonal dysfunctions, such as bone disease, hypertension, hyperlipidemia, anorexia, malnutrition, fatigue, and anemia.[20,22,32] In patients with stage 3 CKD, hemoglobin should be measured at least annually, and more frequently as renal function declines.[20,32] Serum phosphorus, calcium, parathyroid hormone, 25-hydroxyvitamin D, and alkaline phosphatase levels should be checked regularly in patients with stage 3 to 5 CKD, as abnormal levels may indicate renal mineral and bone disorders.[20,22,33]

Infectious diseases are an important cause of morbidity and mortality in CKD patients, being the second leading cause of death after cardiovascular diseases, since decreased kidney function impairs innate and adaptive immune system responses, leading to an increased risk of bacterial infections (particularly pulmonary and genitourinary), virus-associated cancers and diminish vaccine response.[20,34-37]

Therefore, all adults with CKD should be vaccinated annually with influenza vaccine unless contraindicated, and adults with GFR in CKD stages 4 and 5 and who are at high risk for CKD progression should be immunized against hepatitis B and the response confirmed by serologic testing. Adults with GFR in stages 4 and 5 and who are at high risk for pneumococcal infection (e.g., diabetes, nephrotic syndrome, or those on immunosuppressive therapy) should be vaccinated with polyvalent pneumococcal vaccine unless contraindicated, and revaccination should be offered within five years.[20]

In addition, CKD is associated with an increased risk of adverse effects from medications, intravascular radiocontrast administration, surgery, and other invasive procedures.[20]

All these complications cause increased morbidity, mortality, and cost. Thus, early diagnosis of CKD combined with appropriate medical interventions has proven to delay CKD progression to kidney failure and prevent the development of its complications.[20]

MANAGEMENT

CKD is a complex disease and requires a multidisciplinary approach. In addition to pharmacological treatment with antihypertensives and antihyperglycemic agents, diet and exercise are essential for the prevention and control of cardiovascular disease (CVD) risk factors, such as blood pressure (BP) control, and other metabolic parameters like blood sugar, uric acid and dyslipidemia.[20,38-39]

Non-pharmacological measures

The non-pharmacological strategies used to reduce the progression of CKD are:[20-21]

- Specialized dietary advice and information tailored to the severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake when indicated;
- Avoidance of high protein intake in adults with CKD at risk of progression (recommended 0.6-0.8 g/ /kg/day protein intake of at least 50% high biological value);
- Lowering salt intake to <2 g per day of sodium in adults;
- Smoking cessation;
- Regular physical activity (at least 30 minutes five times a week);
- Healthy weight (body mass index [BMI] 20 to 25, according to country-specific demographics).

Pharmacological measures

In general, the pharmacological strategies used to reduce the progression of CKD are:[20-21]

- Use of an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitors (ACE-I) titrated to the highest licensed dose that they can tolerate, in adults or children with CKD and urine albumin excretion of more than 300 mg/24 hours and albumin: creatinine ratio (ACR) is 700 mg/g or more;[39]
- Use of an ARB or ACE-I in adults with CKD and albumin excretion >30 mg/24 hours with blood pressure >130/80 mmHg;
- Achievement of glycosylated hemoglobin levels below 7% for diabetic patients;
- Use of sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as dapagliflozin, as an add-on to optimized standard care with ACE-I or ARBs or for those who cannot tolerate renin-angiotensin-aldosterone system (RAAS) inhibitors;[38]
- Correction of metabolic acidosis;
- In early CKD stages 1 and 2, statins are recommended for all patients over 50 years of age, whilst in stage 3 and advanced stages of the disease, stage 4–5 (eGFR 60 mL/min per 1.73 m^2), a combination of statins and ezetimibe is advised.[40]

It is important to regularly evaluate postural hypotension when treating patients with CKD on antihypertensives and to adapt therapy in elderly patients to more "permissive" blood pressure targets, carefully considering age, comorbidities, other therapies, and potential adverse effects such as electrolyte disturbances and acute deterioration of renal function.[20]

eGFR and albuminuria should be assessed at least annually and more frequently in individuals at higher risk of progression, and/or when their assessment will impact therapeutic decisions.[20]

REFERRAL TO HOSPITAL CARE

Referral of patients with CKD to hospital care varies according to the characteristics of each country's healthcare system, which are often heterogeneous. Ho-

TABLE 3. Referral to nephrology[20,24,39]

Consider referral to nephrology if any of the following situations are present

- AKI or abrupt sustained fall in eGFR;
- GFR <30 ml/min/1.73 m2 (GFR categories G4-G5);
- A decrease in eGFR ≥ 25%;
- A sustained decrease in the GFR of more than 5 mL/min per year;
- A consistent finding of significant albuminuria (ACR >300 mg/g or albumin excretion rate [AER] >300 mg/24 hours, approximately equivalent to the protein-creatinine ratio (PCR) 500 mg/g or PER 500 mg/24 hours);
- Urinary red cell casts, dysmorphic RBC, RBC 420 per high power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with four or more antihypertensive agents;
- Persistent abnormalities of serum potassium;
- Recurrent or extensive nephrolithiasis;
- Hereditary kidney disease or unknown cause of CKD;
- Persistent unexplained hematuria;
- Secondary hyperparathyroidism, persistent metabolic acidosis, anemia due to an erythropoietin deficiency;
- Suspected renal artery stenosis;
- Multiple bilateral renal cysts, especially when hepatic concomitantly;
- ≥ 2 asymptomatic angiomyolipomas bilaterally.

wever, the following characteristics generally indicate the need for hospital follow-up (Table 3):[20,24,39]

- AKI or abrupt sustained fall in eGFR;
- GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5);
- A decrease in eGFR >= 25%;
- A sustained decrease in the GRF of more than 5 mL/min per year;
- A consistent finding of significant albuminuria (ACR >300 mg/g or albumin excretion rate [AER] >300 mg/24 hours, approximately equivalent to PCR 500 mg/g or PER 500 mg/24 hours);
- Urinary red cell casts, dysmorphic red blood cells (RBC), RBC 420 per high power field sustained and not readily explained;
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- Suspected renal artery stenosis;
- Multiple bilateral renal cysts, especially when hepatic concomitantly;
- ≥ 2 asymptomatic angiomyolipomas bilaterally.

Timely referral for renal replacement therapy planning is essential in people with progressive CKD in whom the risk of renal failure within one year is 10-20% or greater.

Referral of children and young people with CKD for hospital care if they have any of the following:[39]

- An ACR of 300 mg/g or more, confirmed on a repeat early morning urine sample;
- "Glomerular Haematuria" (presence of dysmorphic RBC in urinary sediment);
- Any decrease in GFR;
- Hypertension;
- Known or suspected rare or genetic causes of CKD;
- Suspected renal artery stenosis.

CONSIDERATIONS WHEN COMMUNICATING WITH A PATIENT WITH CHRONIC KIDNEY DISEASE

After the diagnosis of CKD, the physician should consider the following aspects when communicating, with the patient:

- CKD is a chronic disease associated with increased morbidity, such as increased risk of cardiovascular disease, and mortality;
- There are several causes of CKD, most irreversible, such as diabetes and hypertension;
- The study of its etiology is very important, to make a directed treatment, whose main goal is slowing the progression to kidney failure;
- Patients with CKD can have episodes of AKI;
- In addition to pharmacological treatment, BP, blood glucose, uric acid, and dyslipidemia control are essential, as well as diet and exercise;
- Lifestyle modification is recommended: smoking cessation, regular exercise (at least 30 minutes five times a week), adequate diet (avoid excessive protein intake, limit sodium intake <2 g/day, avoid processed food);
- CKD should be regularly monitored by the family physician and, if necessary, referred to a nephrologist.

Diabetes in Chronic Kidney Disease

Ana Isabel Rodrigues; Inês Aires; Luís Mendonça; Paulo Subtil; Susana Heitor

INTRODUCTION

The prevalence of diabetes has been increasing worldwide. According to the International Diabetes Federation, in 2021, 537 million adults were living with diabetes worldwide, and this number is expected to increase to 784 million by 2045.[41] Approximately 20-40% of people with diabetes develop CKD, the prevalence of which is increasing in association with the increasing prevalence of diabetes.[42-46]

Diabetes is the leading cause of kidney failure, dialysis, and kidney transplantation worldwide,[46] and usually, CKD that appears in people with diabetes is attributed to diabetes, unless other causes are readily apparent.[45] CKD may be present at diagnosis in type 2 diabetes (T2D), and develops after 10 years in type 1 diabetes (T1D).[7] Data from Relatório Anual do Observatório Nacional da Diabetes (edited in 2023), reveals a 33.2% prevalence of diabetes in new cases of CRF – Global.[7]

The presence of CKD in patients with diabetes markedly increases the risk of cardiovascular disease, heart failure, cardiovascular death, and all-cause mortality.[47-48]

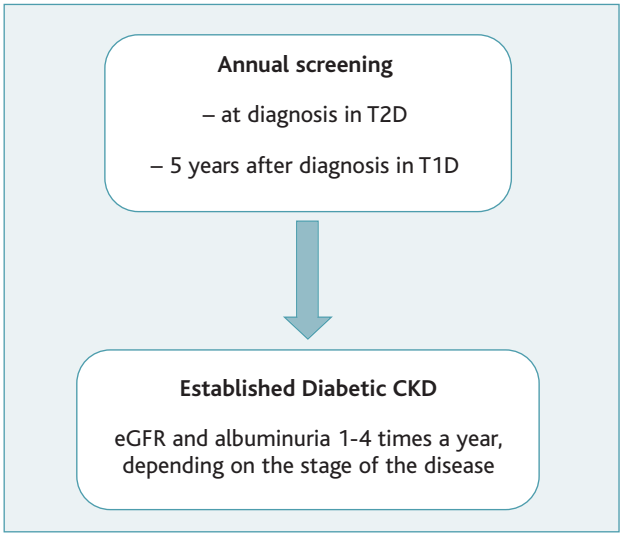

Figure 2. Screening for Diabetic Chronic Kidney Disease.

TABLE 4. Red flags for another etiology of CKD[50]

Consider other etiologies for CKD if one of the following is present

- Absence of retinopathy
- Large and abrupt changes in eGFR or albuminuria
- Abnormal serological tests

Timely screening, diagnosis, and treatment are extremely important, in addition to promoting the active role of the patient, to limit the worst outcomes.

SCREENING AND DIAGNOSIS

Annual screening for kidney disease in diabetics is recommended by the American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Figure 2).[45,49] In T2D, screening for CKD should start at diagnosis, and in T1D, it should start five years after diagnosis.[7] In people with established diabetic kidney disease, albuminuria and filtration rate should be monitored 1-4 times a year, depending on the stage of the disease.[7] Other possible causes of CKD in diabetic patients should always be excluded, especially when retinopathy is not present (particularly in T1D) or with signs of CKD uncommon in diabetes, such as large and abrupt changes in eGFR or albuminuria and abnormal serological tests (Table 4).[50]

LIFESTYLE

To achieve adequate control of blood glucose, lipids, and blood pressure in diabetic patients with CKD, treatment must include, in addition to pharmacological therapy, smoking cessation, nutritional counseling, including proper hydration, quality sleep, and exercise plan (Table 5).[50]

Besides decreasing hemoglobin A1C (HbA1c) levels, a healthy diet has shown numerous health benefits.[45,51] Patients with diabetes and CKD should be advised to adopt a diet rich in fiber, fruits, vegetables, whole grains,

plant-based proteins, nuts, and unsaturated fats, as well as avoid refined carbohydrates, sugary drinks, and processed meats.[45]

It is recommended a protein intake of 0.8 g/kg (weight)/day for patients with diabetes and CKD not treated with dialysis.[7,45,52] Patients treated with dialysis, due to their catabolic response and increased risk of malnutrition, should be recommended to consume between 1.0 and 1.2 g protein/kg (weight)/day.[45,53] Intake of higher amounts of protein (>1.3 g/kg/day) should be avoided since it has been associated with increased albuminuria, faster loss of renal function, and CVD mortality.[7,54]

Regarding sodium consumption, patients with diabetes and CKD should take <2 g of sodium per day[45] or 1500 to <2300 mg/day, according to the ADA.[50] This may reduce blood pressure and the cardiovascular risk.[55]

Additionally, moderate to intense physical activity with a cumulative duration of at least 150 minutes per week, or to a level compatible with the patient's physical and cardiovascular tolerance, is recommended.[7,45] Obesity is an independent risk factor for kidney disease progression and cardiovascular disease,[56] so patients with diabetes, obesity, and CKD should be encouraged to lose weight.[45]

GLYCEMIC MONITORING AND CONTROL

In diabetics, it is reasonable to monitor long-term glycemic control by using hemoglobin A1c (HbA1c) twice a year. In case of uncontrolled glycemia or after a change in therapy, HbA1c can be measured up to 4 times a year.[45,50]

However, the accuracy of HbA1c measurements decreases with advanced CKD (G4-G5), especially in dialysis-treated patients, in whom HbA1c measurements have low reliability. In individuals for whom HbA1c is inaccurate or at risk for hypoglycemia, continuous glucose monitoring (CGM) can be used. Self-monitoring of blood glucose and CGM may prevent hypoglycemia and help improve glycemic control when therapies with a risk of hypoglycemia are used.[45,50] Thus, in some patients, CGM metrics (e.g., time in range and time in hypoglycemia) may be alternatives to HbA1c to define glycemic targets.[45]

Intensive blood glucose reduction can delay the onset and progression of albuminuria and reduce eGFR in people with T1D and T2D.[57-62] In patients with diabetes and CKD not in dialysis, the KDIGO recommends an HbA1c target ranging from <6.5% to <8.0%. When the prevention of complications is the primary goal, there may be defined a lower HbA1c target, such as <6.5% or <7.0%; for patients with multiple comorbidities or increased hypoglycemic burden, may be defined a higher HbA1c target, such as <7.5% or <8.0%.[45] Similarly, the ADA recommends an initial HbA1c target of <7.0% and higher values, such as <8.0% for patients with limited life expectancy and in whom the harms of the treatment may outweigh the benefits.[50]

TREATMENT

An early start of metformin with SGLT2i is recommended in most patients with T2D and CKD. Other drugs can be added to achieve target glycemic values, always with an appropriate dose adjustment based on eGFR.[7,45]

Metformin is recommended in most patients with T2D and CKD who have eGFR ≥ 30 ml/min/1.73 m^2, and eGFR should be monitored at least annually, and every 3-6 months when eGFR is <60 ml/min/1.73 m^2. The dose of metformin should be reduced to 1000 mg daily in patients with eGFR between 30 and 44 ml/min/ /1.73 m^2, and in patients with eGFR of 45-59 ml/min/ /1.73 m^2 if they have an increased risk of lactic acidosis due to hypoperfusion and hypoxemia. When patients are treated with metformin for more than four years, vitamin B12 should be monitored annually.[45]

SGLT2i are recommended in most patients with T2D and CKD with eGFR ≥ 20 ml/min/1.73 m^2 regardless of HbA1c, as they reduce CKD progression, heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD) risk. They can be used without metformin in patients with lower eGFR, who cannot tolerate metformin, or who do not need metformin to achieve glycemic goals.[7,45] In patients with eGFR <30 ml/min, iSGLT2 loses its ability to lower blood sugar, so it provides renal benefits, not metabolic. To maintain glucose control, other therapies should be considered, such as insulin and a-GLP1, although stopping therapy to start insulin should be a last resort.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE] and Dapagliflozin and Prevention of Adverse

Outcomes in Chronic Kidney Disease [DAPA-CKD] clinical trials demonstrated significant benefits in eGFR decline, renal failure, and mortality. However, they suggest that renal and cardiovascular benefits are consistent regardless of baseline albuminuria, including in patients with normal albumin excretion, as reflected in the KDIGO recommendation and consensus statement.[63-65]

The threshold for starting an SGLT2i for patients with T2D and CKD was extended to ≥20 ml/min/1.73 m^2.[7,45] The introduction of SGLT2i is associated with a reversible decline in eGFR, but this does not usually require its discontinuation, as it appears to protect patients against AKI.[66] Thus, it is acceptable to continue therapy if the eGFR falls below the initial threshold, unless the patient is not tolerating treatment or kidney replacement therapy (KRT) is initiated.[45]

For patients with T2D and CKD who require additional glycemic reduction, a long-acting GLP-1 receptor agonist is preferred.[45] GLP-1 receptor agonists reduce albuminuria and slow the decline in eGFR, and are safe with an eGFR of 15-59 ml/min/1.73 m^2. GLP-1 receptor agonists have proven cardiovascular benefits and are recommended when patients with T2D and CKD have not yet reached their glycemic target with metformin and iSGLT2 or are unable to use these drugs. the GLP-1 receptor agonists that have proven cardiovascular and renal benefits (i.e., liraglutide, semaglutide [injectable], and dulaglutide) should be prioritized.[7,45]

GLYCEMIC MANAGEMENT IN ADVANCED CHRONIC KIDNEY DISEASE (eGFR <30 ml/min/1.73 m^2 WITH OR WITHOUT KRT)

Metformin is contraindicated with eGFR <30 ml/min/1.73 m^2 and in patients on dialysis. SGLT2i can be started with eGFR 20-29 ml/min/1.73 m^2 and continued with a lower eGFR if previously started and well tolerated. However, they have minimal effects on blood glucose in this eGFR range and are used for their renal and cardiovascular benefits. GLP-1 receptor agonists have been studied with eGFR as low as 15 ml/min/1.73 m^2 and retain their glycemic lowering ability across the range of patients with eGFR and on dialysis. Selected dipeptidyl peptidase four inhibitors can be used with eGFR <30 ml/min/1.73 m^2 and in dialysis, such as linagliptin.[7,45]

BLOOD PRESSURE CONTROL

For patients with diabetes and hypertension, and a very high cardiovascular risk, a BP target of <130/80 mmHg is advised if this target can be achieved safely. For patients with diabetes, hypertension, and a high cardiovascular risk, the ADA recommends a BP target of <140/90 mm Hg.[67]

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION

ACEi or ARB are first-line in the treatment of BP among patients with diabetes, hypertension, and ACR ≥300 mg/g due to their benefits in preventing CKD progression and are therefore recommended for patients with T1D or T2D with hypertension and albuminuria, titrated to the maximum antihypertensive dose or the highest tolerated dose.[7,45] An ACEi or ARB is not recommended as primary prevention of CKD in people with diabetes who have normal blood pressure, normal albuminuria, normal albumin/creatinine ratio, and normal GFR.[7] However, they may be considered for patients with diabetes, albuminuria, and normal blood pressure. BP, serum creatinine, and serum potassium should be monitored for 2-4 weeks after starting or increasing the dose.[45]

Spironolactone, a steroidal mineralocorticoid receptor antagonist, is effective in the treatment of resistant hypertension and primary hyperaldosteronism, but causes hyperkalemia, particularly with reduced renal function (i.e., eGFR <45 ml/min/1.73 m^2). A new class of nonsteroidal Aldosterone receptor antagonists (MRAs), such as eplerenone and finerenone, has been added to RAS inhibition in patients with CKD and diabetes.[68] Finerenone has been approved for slowing CKD progression and reducing cardiovascular events as FIDELIO-DKD and FIGARO-DKD demonstrated cardiovascular and renal benefits for finerenone among people with T2D.[69-70] It can be initiated with eGFR ≥25 ml/min/1.73 m^2.

LIPID MANAGEMENT

Dyslipidemia is an important risk factor for both CVD and CKD.[71] Although all patients with T1D or T2D and CKD should take statins, not all statins have the same effect on kidney function.[7,45] Atorvastatin showed a greater improvement in eGFR than pravastatin and

TABLE 5. Therapeutic approach in diabetic Chronic Kidney Disease (CKD)

Therapeutic approach in diabetic CKD	
Lifestyle changes	• Smoking cessation • Nutritional advice • Regular exercise
Pharmacological therapy	• Metformin + iSGLT2 • ACEI or ARB • Finerone • Statins

simvastatin, due to its greater effect in reducing low--density lipoprotein (LDL) cholesterol. Treatment with a high dose of atorvastatin (80 mg/day) was significantly associated with an increase in eGFR and a reduction in CVD events.[72-73]

CONSIDERATIONS WHEN COMMUNICATING WITH A PATIENT WITH DIABETIC CHRONIC KIDNEY DISEASE

After the diagnosis of diabetic CKD, the physician should consider the following aspects when communicating with the patient:

- Approximately 20-40% of people with diabetes develop CKD and diabetes is the leading cause of kidney failure, dialysis, and kidney transplantation worldwide;
- CKD may be present at diagnosis in type 2 diabetes, and develops after ten years in type 1 diabetes;
- The presence of CKD in patients with diabetes markedly increases the risk of cardiovascular disease, heart failure, cardiovascular death, and all-cause mortality;
- CKD treatment's main goal is slowing the progression to kidney failure;
- Patients with CKD can have episodes of AKI;
- In addition to pharmacological treatment of Diabetes, BP, uric acid and dyslipidemia control are essential, as well as diet and exercise;
- Lifestyle modification is recommended: smoking cessation, regular exercise (at least 30 minutes five times a week), adequate diet (avoid excessive protein intake [protein intake of 0.8 g/kg(weight)/day for patients with diabetes and CKD not treated with dialysis], limit sodium intake <2 g/day, avoid processed food);
- CKD should be regularly monitored by the family physician and, if necessary, referred to a nephrologist.

Blood pressure in Chronic Kidney Disease

Diogo Ramos; Luís Rodrigues; Paula Felgueiras; Sofia Homem de Melo

INTRODUCTION

Hypertension is not only a major risk factor for CKD and its progression, but also an effect of CKD.[74-79] The incidence and severity of hypertension increase as GFR decreases.[80] Furthermore, as hypertension and CKD are independent risk factors for cardiovascular disease (CVD), their coexistence substantially increases cardiovascular morbidity and mortality.[81]

Hypertension is one of the leading causes of CKD and renal function should be assessed regularly in all hypertensive patients, through serum creatinine, with calculation of GFR and urinary albumin/creatinine ratio.[82]

Although CKD can lead to the development of resistant hypertension, a possible cause of secondary hypertension should always be ruled out in these cases.[83] Renovascular disease (RVD) is a major cause of secondary hypertension and accounts for 1-5% of hypertension in the general population.[84-87] Atherosclerotic stenosis of the renal artery is the most common type of RVD (90%), followed by fibromuscular dysplasia (9%).[88-89]

Blood pressure control has been shown to reduce proteinuria and delay GFR decline.[90-92] Although BP remains a major determinant of CKD progression, current BP targets are not being met in a large proportion of patients.[93]

Several mechanisms contribute to the development of hypertension in CKD (Figure 3).[79] As eGFR decreases, there is an upregulation of the RAAS which promotes salt and water retention, which is aggravated by an increase in BP sensitivity to salt. Afferent signals generated by functionally declining kidneys cause an increase in sympathetic tone, which also contributes to the development of hypertension in CKD. Other mechanisms implicated in the development of hypertension are endothelial dysfunction, characteristic of advanced CKD (eGFR <30 mL/min/1.73 m^2), as well as increased arterial stiffness, observed throughout the CKD spectrum.[79]

Thus, treatment of hypertension is of most importance in patients with CKD to protect against progressive decline in kidney function and cardiovascular disease. Awareness of the importance of risk factor management in primary care includes stricter management of systolic BP (SBP), along with smoking cessation, and reduction of overweight and obesity to prevent the development of CKD and its slow progression.[93] It is essential to implement public health strategies, to educate about CKD and thus decrease its morbidity and mortality.[94]

BLOOD PRESSURE TARGET VALUES

In patients with CKD, there is uncertainty about the optimal target BP for preventing CVD and slowing the decline in renal function.[95]

Some randomized trials that compared intensive and standard BP reduction in patients with CKD without diabetes showed no overall benefit of intensive BP treatment on their primary renal outcomes.[54,96] On the other hand, in the SPRINT (Systolic Blood Pressure Intervention Trial) study, intensive BP reduction resulted in lower rates of the primary composite outcome of CVD

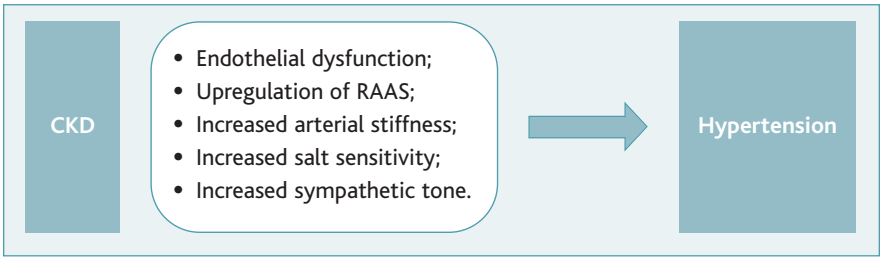

Figure 3. Development of hypertension in chronic kidney disease.

and all-cause death,[97] including in patients >75 years old at baseline.[98] Although in a variety of renal outcomes, no benefit was found from an intensive reduction of SBP, there was also no adverse effect on the main composite kidney outcome.[97]

However, intensive SBP reduction also resulted in a slightly higher rate of eGFR decline during the initial six months of therapy in those with and without CKD and higher rates of hypokalemia, hyperkalemia, and acute renal failure,[95,97,99] likely related to more frequent use of diuretics and renin-angiotensin system inhibitors.[96,100] These complications can be prevented by changing therapy or decreasing its intensity.[96,100] This acute decline in eGFR in patients under intensive care has been attributed to a reversible hemodynamic effect of antihypertensive drugs on renal microcirculation.[101]

In another study, intensive BP treatment proved beneficial in patients with significant proteinuria,[102] since lowering BP reduces proteinuria, which slows the decline in eGFR and decreases CVD.[79] This study showed that in patients with significant proteinuria (>1 g/day; ACR >70 mg/mmol, CRP >100 mg/mmol) there is greater renoprotection from a target SBP <120 mmHg than in those without proteinuria.[102]

In patients with mild to moderate CKD and hypertension without diabetes, intensive SBP reduction resulted in substantial reductions in CVD and all-cause mortality, without an effect on increasing the decline in eGFR or ESRD.[100,103]

The balance of pros and cons seems to favor the intensive reduction of SBP in this population.[96,100] The rationale for the low SBP target values is their survival, cardiovascular, and cognitive benefits. Although there has been scarce data on the renal protection benefits of SBP <120 mmHg, these are more substantiated for CKD patients with proteinuria and long-term follow-up.[104] However, in people with advanced CKD (G4 and G5), diabetes, significant proteinuria, "white coat" hypertension, very low diastolic BP (DBP), and at extreme ages (younger or older), the benefits of SBP <120 mmHg are more uncertain.[104]

According to the KDIGO guidelines, the BP target values in CKD patients are:[104]

- SBP <120 mmHg, for most patients not receiving dialysis, when tolerated;
- SBP <130 mmHg and DBP <80 mmHg, for adult kidney transplant recipients;
- Mean arterial pressure (calculated as DBP + 1/3 x pulse pressure) ≤50th percentile for age, sex, and height, for children.

The optimal levels at which BP should be targeted in the treatment of hypertension in CKD remain controversial, and the 2018 ESH/ESC guidelines and the eighth report of the Joint National Committee recommend a uniform BP target of <140/90 mmHg, regardless of the level of albuminuria, while the 2017 American College of Cardiology/American Heart Association guideline, based largely on the SPRINT study, recommended a tighter BP goal of <130/80 mmHg for most adults with a high cardiovascular risk profile, including patients with CKD.[8,82,105]

BLOOD PRESSURE MEASUREMENT

For measuring BP among adults with CKD, standardized office BP measurement is recommended. The standardized office BP measurement is the one that is obtained according to the following procedures:[104]

- Patient relaxed, sitting in a chair with feet on the floor and back supported for more than five minutes;
- Measurements with the patient on an examining table do not fulfill these criteria;
- For at least 30 minutes before measurement the patient should not have consumed caffeine, exercised, or smoked;
- Patient should have his/her bladder emptied;
- Clothes covering the location of cuff placement should be removed;
- During the rest period or measurement no one should talk;
- The BP measurement device must have been validated and calibrated periodically;
- The correct cuff size should be used so that it covers 80% of the arm;
- The patient's arm must be supported, e.g., resting on a desk;
- The middle of the cuff should be positioned on the patient's upper arm at the level of the right atrium (midpoint of the sternum);
- In the first visit the BP should be evaluated in both arms, using the following readings the arm with the higher reading;
- Repeated measurements should be separated by 1-2 min;

- For auscultatory readings the stethoscope or bell should be used;
- For auscultatory readings, a palpated estimate of the radial pulse obliteration pressure should be used to estimate the SBP. For auscultatory BP determination, the cuff should be inflated 20-30 mmHg above this level;
- For auscultatory determinations, deflate the cuff pressure to 2 mmHg per second, and listen for Korotkoff sounds;
- Note the time of most recent BP medication taken before measurements;
- Record SBP and DBP. In the auscultatory technique, record SBP and DBP as the onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number;
- To estimate the individual's BP level use an average of at least two readings taken on at least two occasions;
- Give patients the SBP/DBP readings verbally and in writing.

Auscultatory or oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring BP in the doctor's office.[8] An oscillometric BP device may be preferable to a manual BP device since it minimizes potential sources of inaccuracies in BP measurements.[104,106] Unattended office blood pressure measurement, automatically providing a period of rest followed by multiple BP readings with a single activation, may be the preferred method of BP measurement if available and the conditions allow for its use.[104] In patients with atrial fibrillation, oscillometric devices can be used to measure BP.[103,107]

Out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) can complement standardized BP readings in the office.[104] Patients who do HBPM have better BP control than those who do not.[108] HBPM is the average of all BP readings performed with a semiautomatic validated BP monitor, preferably for 6-7 consecutive days before each clinic visit, at least three days, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements within 1-2 min apart should be taken at each measurement session.[8] 24-hour ABPM allows a more accurate description of the BP profile and is a better predictor of CVD events in CKD patients than in-office readings.[109] In addition, the reverse-dipper pattern of BP in ABPM may be independently associated with type 2 diabetes in patients with hypertension.[110]

LIFESTYLE INTERVENTIONS IN CHRONIC KIDNEY DISEASE PATIENTS NOT IN DIALYSIS

CKD patients have high salt sensitivity and sodium restriction results in important reductions in BP in these patients.[111,112] A sodium intake of <2 g per day (or <90 mmol, or <5 g sodium chloride) is recommended.[104] In CKD patients on RAAS blockade medication, such as ARB and ACE-I, reducing dietary sodium intake to <50 mmol/day (~ 3 g/day salt) decreased SBP by an additional ~ 10 mmHg.[113]

Patients with hypertension and CKD should perform moderate-intensity physical activity at least 150 minutes per week, or at a level adapted to their cardiovascular characteristics and physical tolerance,[104] since physical activity lowers BP, may improve eGFR,[114] decreases weight, improves quality of life[115] and lowers the risk of mortality in CKD patients.[116] Weight loss allows a reduction in BP, and proteinuria, and may even slow the progression of CKD.[117] In overweight patients with a body mass index >27 kg/m2 with CKD and proteinuria, an average weight loss of ~ 4% can reduce proteinuria by ~ 30%.[118]

TREATMENT

In regards to the pharmacological therapies available, these aim to provide a renoprotective and/or cardioprotective action, often independent of their effects on BP lowering.[96]

The class of antihypertensive drugs known as RAAS blockade are currently recommended for proteinuric CKD and non-proteinuric CKD in patients with hypertension,[39] although they are not always sufficient to reach therapeutic targets.[119-120] ACE-I and ARB have both cardioprotective and renoprotective properties and offer a BP-independent reduction in proteinuria,[121] in both diabetic and non-diabetic CKD.[122]

In people with non-proteinuric CKD, the superior renoprotective effect of RAAS blockade is associated with the effect on BP lowering and therefore can be replaced by other antihypertensives with the same effect.[123]

However, it may be reasonable to treat people with CKD and high BP and no albuminuria with RAAS blockade because of its cardiovascular protection.[104,124-125]

Combination therapy with an ACE-I and ARB should be avoided, as it leads to an increase in adverse events without a significant reduction in the progression of the primary CKD endpoint, ESRD, or death.[79]

The main adverse events associated with RAAS blockade include hyperkalaemia and the development of AKI. After initiation or dose increase of an ACE-I or ARB, BP should be checked, serum creatinine and serum potassium within 2-4 weeks.[104] The increase in serum creatinine should stabilize in this period,[126] and therapy must be continued unless serum creatinine rises more than 30% in one month.[104] In case of hyperkalemia, instead of decreasing the dose or stopping RAAS blockade, measures to decrease serum potassium should be tried, after ruling out pseudo-hyperkalemia, such as: discontinuation potassium supplements, hyperkalemic drugs or salt substitutes; dietary potassium restriction; adding potassium-wasting diuretics or oral potassium binders and treat metabolic acidosis.[104,127]

According to the KDIGO guidelines, it is recommended to start ACE-I or ARB in CKD G1-G4 A2-A3 irrespective of diabetes.[104]

ACE-I or ARB should be given at the maximum approved and tolerated dose to obtain the benefits described.[104]

Diuretics are often used as adjunctive therapy because they offer antihypertensive and cardioprotective effects, reducing volume expansion and improving left ventricular mass index and arterial stiffness in people with CKD.[128-129]

Mineralocorticoid receptor antagonists may also be considered in patients with albuminuria, resistant hypertension, or heart failure with reduced ejection fraction,[82,130] but run the risk of exacerbating hyperkalaemia[131] and may cause a rise in creatinine, particularly in patients with eGFR <45 ml/min per 1.73 m^2.[132-133]

Both dihydropyridine and non-dihydropyridine calcium channel blockers (CCBs) are useful in the management of hypertension in CKD. Dihydropyridine CCBs, such as amlodipine, can be used as first-line treatment in non-proteinuric CKD, either alone or in combination. Although in proteinuric CKD, their effect is inferior to RAAS blockade,[102] their combination in proteinuric patients improves BP control without worsening proteinuria.[134] Its main adverse event is peripheral edema, which can be particularly problematic for those with CKD.[135]

β-Blockers offer lower renoprotection than ACE-I but have cardioprotective benefits and effectively reduce BP.[136] β^2-Blockers should be considered particularly when overt CVDs coexist, in combination with established RAAS blockade.[79]

CONSIDERATIONS WHEN COMMUNICATING WITH A PATIENT WITH HYPERTENSIVE CHRONIC KIDNEY DISEASE

After the diagnosis of hypertensive CKD, the physician should consider the following aspects when communicating with the patient:

- Hypertension is a major risk factor for CKD and its progression, and is also a consequence of CKD;
- CKD is a chronic disease associated with increased morbidity, such as increased risk of CVD, and mortality;
- CKD treatment's main goal is slowing progression to kidney failure, and BP control has been shown to reduce CKD progression and to protect against cardiovascular diseases;
- The BP target values in CKD patients are SBP <120 mmHg, for most patients not receiving dialysis, when tolerated, and SBP <130 mmHg and DBP <80 mmHg, for adult kidney transplant recipients;
- The BP target values in CKD patients with Diabetes are <140/90 mmHg in patients with high cardiovascular risk and <130/80 mmHg in patients with very high cardiovascular risk
- It is important to measure BP correctly and out-of--office BP measurements complement standardized BP readings in the office;
- In addition to BP control, blood glucose, and dyslipidemia control are essential, as well as diet and exercise;
- Lifestyle modification is recommended: smoking cessation, regular exercise (at least 30 minutes five times a week), adequate diet (avoid excessive protein intake, limit sodium intake <2 g/day, avoid processed food);
- CKD should be regularly monitored by the attending physician and, if necessary, referred to a nephrologist.

Glomerular Diseases in Chronic Kidney Disease

João Nobre; Gil Silva; Manuel Amoedo; Henrique Sousa

INTRODUCTION

Glomerular diseases affect people of all ages and can occur from infections, systemic autoimmune diseases, drugs, or malignant diseases. Excluding diabetic nephropathy, these diseases cause about 25% of CKD cases worldwide. In younger age groups (children, adolescents, and young adults), glomerular disease is a major cause of irreversible kidney damage.[137] Risk factors for glomerular disease are present in Table 6.

Considering that glomerular diseases often manifest at a young age, they present long-term morbidity, which leads to high healthcare costs. Thus, early and effective diagnosis is essential, as well as their appropriate management, to slow the progression of kidney disease.

TABLE 6. Risk factors for Glomerular Disease

Risk factors for Glomerular Disease
• Diabetes
• Autoimmune diseases
• Family history of glomerular diseases
• Recent infections
• Abuse of nephrotoxic drugs

DIAGNOSTIC EVALUATION

The diagnosis of glomerular diseases is often made during opportunistic screening for kidney disease in the general population or by symptoms associated with systemic diseases with renal manifestations, through blood pressure, urine analysis, and renal function (Figure 4). The gold standard for the diagnostic evaluation of glomerular diseases is kidney biopsy. However, in some clinical conditions, the treatment may be considered without a kidney biopsy, such as Alport disease, Fabry disease, systemic lupus erythematosus, children with post-streptococcal glomerulonephritis (GN) or minimal change disease, among others.[137]

ASSESSMENT OF KIDNEY FUNCTION

Proteinuria

Significant proteinuria is present in most glomerular diseases and its quantification has specific relevance for treatment decisions and prognosis.[137-138] However, the spot albumin/creatinine ratio and protein-creatinine ratio (PCR) are not accurate enough for therapeutic decisions on high-risk drug use based on small changes in proteinuria.[139,140] A random "spot" urine collection is associated with variation over time in protein and creatinine excretion and is not ideal for PCR, and first-morning urine collections may underestimate 24-hour protein excretion.[137]

Thus, a 24-hour urine collection should be obtained to determine total protein excretion. If this is not possible, an alternative method can be to determine PCR on an aliquot of an attempted 12-24-hour urine collection on a first-morning void or at first presentation. In children, it is recommended to monitor the first-morning PCR, as 24-hour urine collection is not ideal.[137-138] Note that PCR of a 24-hour urine collection that is at least 50% complete, accurately reflects 24-hour proteinuria.[141]

Glomerular Filtration Rate

The *gold standard* for estimating renal excretory function is inulin or isotopic clearance techniques, which require operator expertise and are expensive.[137-138]

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR creatinine equation is used instead and is the preferred equation for estimating GFR in adult patients.[137-138,142] In children, the modified Schwartz equation is preferred, and the Full Age Spectrum equation can be used in adults and children.[137]

Nevertheless, there are some limitations: eGFR equations have not been validated for glomerular diseases and/or nephrotic syndrome;[137-138] hypoalbuminemia may cause overestimation of GFR in creatinine-based formulas, due to increased tubular creatinine secretion;[145] in creatinine-based formulas, low muscle mass overestimates eGFR;[146] glucocorticoids potentially underestimates eGFR due to increase in serum cystatin

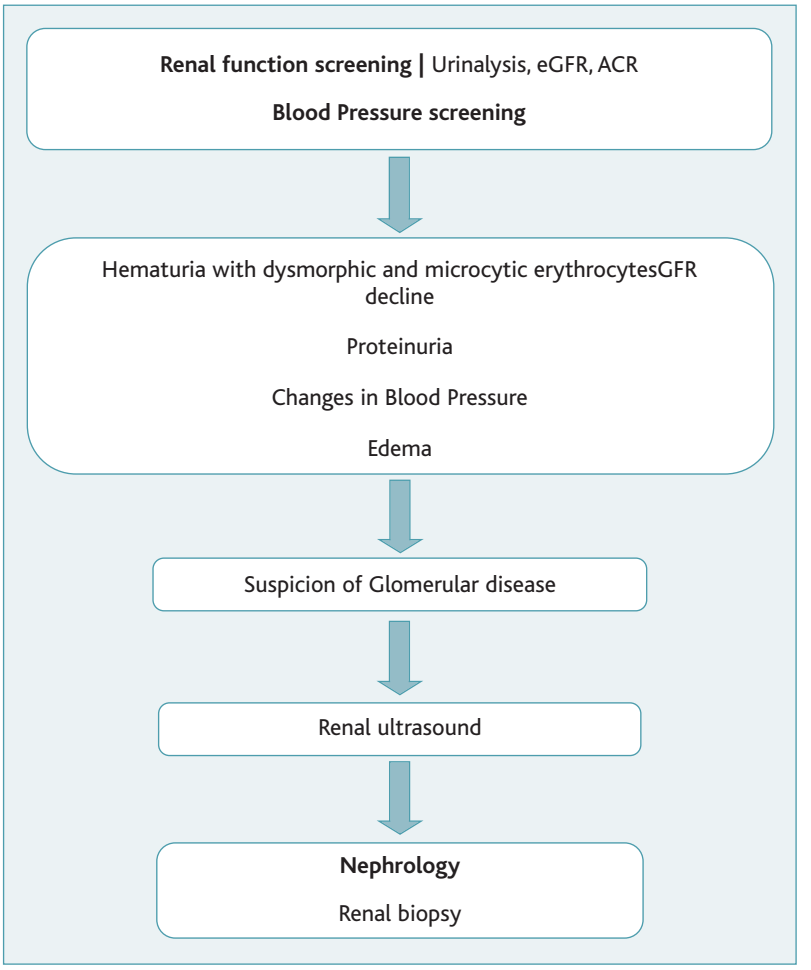

Figure 4. Diagnostic algorithm for Glomerular Diseases.

TABLE 7. eGFR creatinine equations

CKD-EPI eGFR creatinine equation[143]

GFR = 141 × min (Scr/κ, 1) α × max (Scr/κ, 1) – 1.209 × 0.993 Age × 1.018 [if female] OR 1.159 [if black]

Where:
Scr is serum creatinine;
κ is 0.7 for females and 0.9 for males;
α is -0.329 for females and -0.411 for males;
min indicates the minimum of Scr/κ or 1;
max indicates the maximum of Scr/κ or 1

Modified Schwartz equation[144]

eGFR(mL/min/1.73m^2) = (K x Height in cm) / Serum creatinine in mg/dL

Where "k" is a constant representative of the function of urinary creatinine per unit of body size. For this formula k = 0.413

C;[147] eGFR is only valid in steady-state and can be confounded in AKI, which denotes a sudden and often reversible reduction in kidney function, as measured by glomerular filtration rate (GFR).[137,148]

Hematuria

Hematuria (micro or macro) is one of the main manifestations of glomerular disease.[137,138]

Hematuria is usually detected by dipstick analysis of a random urine sample, which is very sensitive for the detection of urinary hemoglobin, with false positives in case of hemoglobinuria or myoglobinuria, and with very few false negatives (ingestion of large amounts of vitamin C). Hematuria in GN is not associated with clots or urinary tract symptoms and urologic diseases should always be excluded. When a dipstick test detects hematuria, it should be confirmed by a microscopical examination of fresh, centrifuged urine sediment. In GN, the erythrocytes are often dysmorphic and microcytic, and the presence of red cell casts or acanthocytes indicates inflammatory glomerular disease. Of note, all of the erythrocytes seen in properly collected urine are of a glomerular/dysmorphic type.[137]

In glomerular disease, it is indicated periodic evaluation of urine sediment (erythrocyte morphology and presence of casts or acanthocytes) and monitorization of hematuria (magnitude and persistence), as it has a prognostic value and is a "biomarker" of progression in many forms of glomerular disease.[137,149-151]

MANAGEMENT OF COMPLICATIONS OF GLOMERULAR DISEASE

Hypertension

As with all diseases, lifestyle modification is essential to reduce BP. Salt restriction, weight normalization, regular exercise, reduction of alcohol consumption, and smoking cessation cut across all patients, whereas antihypertensive therapy may not be necessary in all patients with glomerular disease.[137]

There is still some controversy regarding target BP values. In the GN patient with proteinuria >1 g/d, a BP of 125/75 mmHg is recommended. In most adult patients, the target systolic BP value is <120 mmHg using standardized office BP measurement, and in children it is <= 50th percentile for age, sex and height using ambulatory BP measurement.[104,138]

Proteinuria reduction

The reduction in proteinuria reflects control of the primary disease, reduction in glomerular hypertension, and podocyte injury, an important factor in glomerular scar formation.[137] Proteinuria goal is variable and disease-specific in adults with GN, usually <1 g/d.[137]

The antiproteinuric agents of choice are ACE-I or angiotensin II receptor blockers (ARB), which can reduce proteinuria by up to 40%-50% in a dose-dependent manner.[137] ACE-I and/or ARBs decrease GFR and can increase SCr by 10%-20%, even on monotherapy. If a patient's GFR is worsening rapidly, an ACE-I or ARB may further contribute to renal failure and should be discontinued. If clinically significant hyperkalemia is seen, this can be counteracted by the use of potassium-sparing diuretics, correction of metabolic acidosis, or oral potassium-binding agents.[137]

Alternatively, if the patient cannot tolerate an ACE-I or ARB a mineralocorticoid receptor antagonist (ARM) can be used.[132] The absolute risk-benefit ratio of aldosterone blockade in GN remains uncertain. However, it is known to reduce cardiovascular mortality in patients with heart failure and also reduce albuminuria.[152-154]

In patients unable to tolerate even low doses of ACE--I, ARB, ARM, or Direct renin inhibitor (DRI), other antihypertensives are recommended for BP control and increased urine protein excretion. Non-dihydropyridine calcium channel blockers (CHBs), such as diltiazem and verapamil, modestly reduce proteinuria, and beta--blockers, diuretics, and A-1 blockers also reduce it, but to a lesser degree.[137]

Studies are being conducted on the effect of SGLT2 inhibitors on kidney function and proteinuria. So far, these studies have been primarily in diabetic patients, with positive results. In a recent study, short-term treatment with dapagliflozin did not modify renal function or attenuate proteinuria in non-diabetics with focal segmental glomerulosclerosis, possibly due to the down-regulation of renal SGLT2 expression in focal segmental glomerulosclerosis.[155]

Hyperlipidemia

Hyperlipidemia in patients with glomerular disease may be the result of several causes, such as diet, genetic predisposition, the presence of nephrotic syndrome, and complications of glomerular disease treatment,

including glucocorticoids, mTOR inhibitors (sirolimus and everolimus), and calcineurin inhibitors such as cyclosporin A.[156-157]

All patients with hyperlipidemia and glomerular disease should undergo lifestyle modifications such as a healthy diet, increased physical activity, reduced weight, and stop smoking.[137] Treatment of hyperlipidemia in patients with nephrotic syndrome should be considered particularly in patients with other cardiovascular risk factors, such as hypertension and diabetes.[158]

Statins are the first-line therapy, are well-tolerated and effective, and some data suggest that atorvastatin may reduce albuminuria. The available data on other lipid-lowering agents such as ezetimibe, fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors (e.g., evolocumab, alirocumab) are extremely limited and need to be studied in the GN population.[158-159]

Hypercoagulability

The risk of arterial or venous thrombotic events in nephrotic syndrome in both children and adults is higher than in the general population, especially in the first six months after diagnosis. Deep vein thrombosis and renal vein thrombosis are the most common and events differ in frequency according to the underlying histopathology. Pulmonary embolism is relatively common and can occur without symptoms.[137] The best predictors of thrombotic risk are histologic diagnosis, degree of proteinuria, and serum albumin <2.5 g/dL. A low serum albumin level may increase the risk of thrombotic events, regardless of the degree of proteinuria. Other risk factors include genetic predisposition to thrombosis, previous thrombosis, antiphospholipid antibodies, immobility, obesity, malignancy, pregnancy, or surgery.[137]

Prophylaxis and treatment of venous or arterial thromboembolic events in the context of nephrotic syndrome is with heparin or its derivatives and/or coumarin agents (vitamin K antagonists or warfarin). Direct oral anticoagulants for prophylaxis or treatment of thrombosis have not yet been systematically studied in nephrotic patients.[160-161]

Prophylactic anticoagulation should be considered in patients with nephrotic syndrome when the risk of thromboembolism exceeds the estimated patient-specific risks of anticoagulation induce serious bleeding event when the serum albumin <20-25 g/l and any of the following: proteinuria >10 g/d, body mass index >35 kg/m^2, genetic disposition for thromboembolism, heart failure class III or IV, recent orthopedic or abdominal surgery, prolonged immobilization.[137]

Risk of infection

Patients with glomerular disease on immunosuppressants are at increased risk for infections, including community-acquired pneumonia, sepsis, and other infectious diseases. Diagnosis and treatment of infectious diseases before or concomitantly with initiation of therapy can reduce morbidity and mortality. Adequate screening depends on exposure risk factors related to geographic region and/or occupational activities.[137]

Serologic testing for syphilis, HIV, hepatitis B, and hepatitis C should always be performed, and if identified, treatment should be considered preceding or concurrently with immunosuppressive therapy, depending on the urgency of initiating therapy. Immunosuppressive therapy (glucocorticoids and and/or cytotoxic/immunomodulatory agents, rituximab) may induce a severe exacerbation of hepatitis B viral replication and therefore aggravate the liver disease.[137]

Latent tuberculosis and infection with the helminth *Strongyloides stercoralis* should be screened for and treated in at-risk individuals before immunosuppression, especially with glucocorticoids.[162-163] *Strongyloides* superinfection should be considered in immunosuppressed patients who have lived in tropical endemic environments and present with eosinophilia and elevated serum immunoglobulin E levels.[137]

Adults and children with NG and nephrotic syndrome are at increased risk for invasive pneumococcal infection, so they should receive pneumococcal vaccination and annual influenza vaccination, as should household contacts.[137]

Exposure to chickenpox can be fatal, especially in children. In case of exposure, treatment with immunoglobulin against zoster should be given and antiviral therapy with acyclovir or valacyclovir started at the first sign of varicella lesions. Prevention of herpes zoster is also recommended with vaccination.[137]

The prophylactic use of trimethoprim-sulfamethoxazole should be considered in patients receiving high

doses of prednisone or other immunosuppressive agents, to prevent Pneumocystis infection.[137]

DIETARY MANAGEMENT

In the diet, sodium intake should be <2 g/d (<90 mmol/d), critical for controlling BP and edema, especially in the nephrotic patient, and for improving urinary protein excretion.[137]

An adequate protein intake in the diet of the patient with proteinuria should be ensured (0.8-1.0 g/kg per day) as well as a high carbohydrate intake (35 kcal/kg of ideal body weight, unless obese). In the MDRD study, up to 5 g of dietary protein was added to partially compensate for proteinuria in nephrotic patients, but on the other hand, a very high protein diet in nephrotic syndrome may also worsen proteinuria.[162] Although in patients with GFR <60 ml/min per 1.73 m^2, higher protein restriction may have a positive impact on renal function and metabolic acidosis, a very low protein diet should be avoided because of the risk of malnutrition.[137]

Patients with GFR <60 ml/min per 1.73 m^2 and increased body mass index should reduce weight and have a more restrictive diet (30-35 kcal/kg/d) to prevent CV and renal complications. In addition, fats should be limited to <30% of total calories and saturated fats <10%.[137]

REPRODUCTIVE HEALTH AND PREGNANCY

Contraception in patients with glomerular disease is a relevant topic, as many GN therapies are potentially teratogenic or embryotoxic. After stopping mycophenolate, a pregnancy is not recommended for a minimum of six weeks, and in men treated with this substance, condom use is recommended to avoid a pregnancy, and this should continue for a minimum of 90 days after stopping this therapy. Immunosuppression (e.g., cyclophosphamide) can have an impact on long--term fertility.[137]

The care of pregnant patients with GN should be ideally planned before pregnancy and requires coordination between nephrology and obstetrics. Before planning a pregnancy, glomerular disease and BP should be controlled.[137] Many GN patients presented during pregnancy with complications,[163] and the risk to the mother and fetus varies by glomerular disease type, being higher in systemic lupus erythematosus and antiphospholipid syndrome.[164-166] GFR at the time of conception and during mid-pregnancy is a major predictor of pregnancy outcome.[167-170]

CONSIDERATIONS WHEN COMMUNICATING THE SUSPICION OF GLOMERULAR DISEASES IN CHRONIC KIDNEY DISEASE

Upon suspicion of glomerular disease in CKD, the physician should consider the following aspects when communicating with the patient:

- Glomerular diseases affect people of all ages and can occur from infections, systemic autoimmune diseases, drugs, or malignant diseases;
- CKD is a chronic disease associated with increased morbidity, such as increased risk of cardiovascular disease, and mortality;
- The patient will be referred to a nephrologist, who will evaluate him and confirm or not the diagnosis of glomerular disease;
- CKD treatment's main goal is slowing the progression to kidney failure and, in addition to pharmacological treatment of CKD, BP, blood glucose, uric acid, and dyslipidemia control are essential, as well as diet and exercise;
- Lifestyle modification is recommended: smoking cessation, regular exercise (at least 30 minutes five times a week), adequate diet [limit sodium intake <2 g/day; avoid processed food; adequate protein intake in the diet of the patient with proteinuria should be ensured (0.8-1.0 g/kg per day) as well as a high carbohydrate intake (35 kcal/kg of ideal body weight, unless obese)];
- Adults and children with GN and nephrotic syndrome are at increased risk for invasive pneumococcal infection, so they should receive pneumococcal vaccination and annual influenza vaccination, as should household contacts;
- Exposure to chickenpox can be fatal, especially in children. In case of exposure, treatment with immunoglobulin against zoster should be given and antiviral therapy with acyclovir or valacyclovir started at the first sign of varicella lesions. Prevention of herpes zoster is also recommended with vaccination;
- Pregnancy should always be planned, as many GN therapies are potentially teratogenic or embryotoxic.

Autosomal dominant Polycystic Kidney Disease in Chronic Kidney Disease

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and causes about 10% of ESRD cases. This inherited disease has an estimated prevalence of between one in 1000 and one in 2500 individuals, affecting 12.5 million people worldwide.[171-174]

ADPKD is a progressive kidney disease characterized by the continuous growth of kidney cysts that replace normal renal parenchyma causing kidney enlargement and organ failure.[175] For decades, depurative function has been preserved by compensatory hyperfiltration in surviving glomeruli, despite the ongoing destruction of the renal parenchyma.[176] CKD progresses, frequently without symptoms, until glomerular function starts to decline. The age when the patient reaches ESRD varies depending on the genotype, as exemplified by the median age of renal replacement therapy initiation of 58 years for truncating mutations in the *PKD1* gene.[175,177] In addition, extra-renal cystic and non-cystic involvement plays an important role in morbidity.

Besides CKD and ESRD, renal manifestations of ADPKD include hypertension, abdominal fullness, acute and chronic pain, gross hematuria, cyst infection, and nephrolithiasis.[175,178-179] Extrarenal manifestations include hepatic and pancreatic cysts, intracranial aneurysms, cardiac valvular lesions, and abdominal hernias.[175]

ADPKD is caused in 78% of cases by mutations in the *PKD1* gene and in 15% by mutations in the PKD2 gene,[180] although additional genes have been identified in more recent years. Being an autosomal dominant phenotype, the pattern of inheritance in any given family may be confounded by de novo mutations, mosaicism, or biallelic disease. Compared with PKD1, PKD2 mutations confer milder renal disease with fewer renal cysts, delayed onset of hypertension and ESRD by two decades, as well as longer survival.[181-182]

ADPKD has changed from an incurable disease a few decades ago to a disease whose quality of life and lifespan can be improved through early detection and treatment of hypertension, renal, and extrarenal complications. The new KDIGO guidelines on ADPKD are currently being revised.

IMAGING DIAGNOSIS FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD is an autosomal dominant Mendelian disease. The most frequently used method for diagnosis of adults at risk for ADPKD is ultrasonography (US), due to its availability, low cost, and non-invasiveness.[175,183] Presymptomatic screening of at-risk children is not currently recommended. In the general population, the prevalence of simple cysts increases with age.[177] Red flags for diagnosis of ADPKD are present in Table 7.

The Ravine Criteria

In at-risk individuals, age-dependent US diagnostic criteria have been developed. Diagnostic confirmation is assured by the presence of a total of three or more kidney cysts (uni or bilateral) between the ages of 15 and 39, two cysts or more in each kidney for ages 40 to 59,[177] while four or more cysts in each kidney are required for individuals over 60 years.[184] On the other hand, the absence of renal cysts in at-risk individuals aged 40 years or older is sufficient for the exclusion of the disease.[184] However, for individuals younger than 40 years, the US is suboptimal, and magnetic resonance imaging (MRI) might be advised for screening purposes, particularly in the evaluation of living-related kidney donors for patients with this disease.

Differential diagnosis

Many other kidney diseases may present with a cystic phenotype. These include recessive entities, like ciliopathies (nephronophthisis and others) and Autosomal Recessive Polycystic Kidney Disease, as well as dominant ones such as the Tuberous Sclerosis Complex, Autosomal Dominant Tubulo-interstitial Kidney Disease (including the renal cysts and diabetes syndrome), von Hippel-Lindau disease or even Autosomal

TABLE 8. Red flags for ADPKD diagnosis

Red flags for ADPKD diagnosis
• Family history
• Enlarged kidneys
• Renal cysts
– > = 3 kidney cysts (uni or bilateral) between the ages of 15 and 39
– >= 2 cysts in each kidney for ages 40 to 59
– >= 4 cysts in each kidney over 60 years of age
• Hypertension, abdominal fullness, acute and chronic pain, gross hematuria, cyst infection, nephrolithiasis
• Hepatic and pancreatic cysts, intracranial aneurysms, cardiac valvular lesions, and abdominal hernias

Dominant Polycystic Liver Disease. Most of these diseases do not present with enlarged kidneys and, as such, an increased total kidney volume is often clarified as the majority of ADPKD patients have enlarged kidneys. A patient with bilaterally enlarged kidneys and numerous cysts, with no other findings suggesting a different cystic disease, most likely has ADPKD. Nevertheless, in ADPKD, the kidney size may be close to normal in some individuals, with a small number of cysts, and a genetic diagnosis may be necessary to confirm the diagnosis.[177]

Molecular diagnosis and genetics testing

As previously mentioned, most ADPKD families segregate with either PKD1 or PKD2. In recent years, however, additional genes have been identified: GANAB, DNAJB11, and IFT140[185-187] to name a few. Although the latter accounts for ~2% of cases, only a very small fraction of patients will harbor GANAB or DNAJB11 mutations. The genes responsible for ADPKD, similar to other genes responsible for inherited cystic phenotypes, all code for proteins that localize to the primary cilia of renal tubular epithelia and therefore emphasize the disruption of this mechano-sensitive organelle in cystic disease initiation and progression. Next Generation Sequencing, or massively parallel sequencing, is the sequencing technology currently in use. Available target gene panels encompass most of the autosomal dominant as well as recessive genes responsible for cystic phenotypes. However, due to the genomic landscape of the PKD1 *locus* (16p13.3), having a centromeric duplication of its first 32 exons, a preliminary step of long--range polymerase chain reaction encompassing the PKD1 is advised before target gene panels. Otherwise, 50% of the mutations risk being missed.[188] Test results can be confounded by *de novo* mutations, mosaicism, and bilinear disease.[189-190]

Most patients with ADPKD do not require molecular genetic testing for diagnosis, but this may be considered in particular cases: i) asymmetric kidney involvement, ii) early severe onset, iii) kidney failure without significant kidney enlargement, iv) markedly discordant disease in the family, v) sporadic cases with ambiguous imaging findings, vi) young living related donors in whom imaging bears limited information and vii) whenever reproductive decisions are pending, as in pre-implantation genetic diagnosis.[177,183,191]

In asymptomatic and normotensive children with an affected parent, screening is not recommended, because of potential problems of insurability and the ethical question of diagnosing a child with an untreatable chronic disease.[177]

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE MANAGEMENT

When considering a patient-centered holistic approach it is recommended that ADPKD-affected individuals, their families, and carers should have access to lifelong and multidisciplinary care.[192-193] Importantly, it is recommended that patients should have a referral to hospital care as soon as the diagnosis is made, ideally when kidney function is not yet impaired.[193]

Patient-centered and multidisciplinary approach

The route map for ADPKD requires a cross-functional team. Besides nephrologists knowledgeable about the disease, there is the requirement for general care (physicians, social workers, and psychologists), radiologists, geneticists, and all the specialties needed for the management of renal and extrarenal complications (liver surgeons, urologists, transplant surgeons, and neurosurgeons/radiologists).[194]

ADPKD affects the biological, physical, and psychological aspects of the patient's quality of life and can cause physical and psychological burdens. Health professionals often underestimate the effect of kidney pain on ADPKD patients, despite its high prevalence, and value other manifestations of the disease that do not affect the patient as much.[195]

Lifestyle interventions

Patients with ADPKD should be recommended to maintain a healthy lifestyle and diet. Maintenance of optimal weight is essential, as overweight and obesity are associated with a decline in estimated glomerular filtration rate (eGFR) and an increase in total kidney volume in early-stage ADPKD.[196] Moreover, caloric restriction might slow disease progression.[197] Regular cardiovascular exercise, smoking avoidance, and limiting use of non-steroidal anti-inflammatory agents are also recommended.[198] Salt intake should be limited to 5 grams per day in ADPKD patients. High water intake should be strongly encouraged not only to prevent nephrolithiasis but also due to its ability to suppress vasopressin activity, which may have beneficial effects on the progression of ADPKD.[175]

Treatment of Hypertension

Compared with the general population, individuals with ADPKD are at increased risk for hypertension, which often presents early in these patients, and cardiovascular events.[175,199] Thus, obtaining optimal blood pressure control is essential in the management of this disease.

The HALT-PKD study enrolling early-stage ADPKD patients, aged 15-49 years; with an eGFR >60 ml/min/1.73 m^2, investigated whether low vs. standard blood pressure control had an impact on kidney outcomes, and if adding telmisartan to lisinopril *vs.* lisinopril alone was advantageous. It showed that in young patients with preserved eGFR without significant cardiovascular comorbidities, a blood pressure of <110/75 mmHg was found to be safe and associated with a modest reduction in total kidney volume.[26,77-78] A reduction in renal vascular resistance, urine albumin excretion, and left ventricular mass index was also documented. No benefits were seen in eGFR, not even with dual blockage.[200-201] Apart from these patients, the target values for blood pressure are similar to those for CKD.

To control blood pressure, some lifestyle strategies and medical treatment may be needed. In combination with a sodium-restricted diet, therapies that block the RAAS are first-line agents.[177]

Considering that cardiovascular manifestations of ADPKD are evident at a young age, it is recommended to screen children with a family history of ADPKD for hypertension from the age of five years onward, with an interval of three years.[175]

Cysts infection and rupture, Nephrolithiasis, Acute and Chronic Pain

Renal and liver cysts may be symptomatic and their infection should be suspected in the presence of fever, abdominal pain, and elevated levels of inflammatory markers.[202-203] Imaging tests may help in the differential diagnosis and in locating the infected cyst, such as 18 F-fluorodeoxyglucose positron emission tomography.[204] Blood and urine cultures may be negative, which makes the diagnosis more difficult, in which case, it would require identification of the cyst, puncture, and a positive culture of the content. High levels of circulating CA19.9 have been found in patients with infected liver cysts, as well as in patients with ADPKD in general.[205-206] The standard of treatment is fluoroquinolones and trimethoprim-sulfamethoxazole, depending on sensitivity, if available.[177]

Renal and liver cysts rupture can lead to bleeding presenting as acute pain and macroscopic hematuria and/or anemia.[203,207] Episodes of cyst hemorrhage or gross hematuria occur frequently in ADPKD and are commonly self-limited, resolving within 2-7 days. If symptoms persist, a neoplasm should be excluded. Gross hematuria may be present in cyst hemorrhage, infection, nephrolithiasis, and renal or urothelial

carcinoma. In an episode of cyst hemorrhage, fever may be present, making differential diagnosis with cyst infection difficult.[177] Treatment of cystic hemorrhage is usually symptomatic and the use of tranexamic acid and an antifibrinolytic agent may improve the symptoms.[208]

Twenty to 36% of ADPKD patients have nephrolithiasis, due to some risk factors such as hypocitraturia, hyperoxaluria, hypercalciuria, hypomagnesuria, possible distal acidification defects, and urinary stasis due to compression of the collecting system by cysts.[209-210] Computerized tomography (CT) is the best imaging technique for the evaluation of nephrolithiasis.[211] The treatment of choice in patients with ADPKD and nephrolithiasis is potassium citrate and Extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, and flexible ureterorenoscopy with laser fragmentation can be used as well.[212-214]

The most common renal manifestation of ADPKD is kidney pain, so a multidisciplinary approach to pain management is of utmost importance.[215-216] The main causes of acute pain are pyelonephritis, cystic infection, cystic hemorrhage, and nephrolithiasis,[217-218] and chronic pain is the increase in size of the kidneys or the liver.

Some interventions to control chronic pain include cyst sclerosis, laparoscopic cyst fenestration, celiac plexus blockade, radiofrequency ablation, spinal cord stimulation, laparoscopic renal denervation, and percutaneous transluminal catheter-based denervation.[177] It is very important to evaluate chronic pain and involve the patient in pain management.[219]

Liver disease

One of the main extrarenal manifestations of ADPKD is liver cysts, present in more than 90% of patients over 35 years of age.[175,220-221] It is defined by at least twenty simple cysts in the liver, which usually vary in size and appear later than kidney cysts. Diagnosis is usually made by CT or MRI.[222-223]

The main risk factors for polycystic liver disease are age, female sex, exposure to exogenous estrogens, and multiple pregnancies.[224-226]

Symptomatic polycystic liver disease affects approximately 20% of ADPKD patients. The main symptoms arise due to hepatomegaly, which can cause extrinsic compression of the thoracic and abdominal organs and lead to abdominal pain, the most frequent manifestation. In addition, they also lead to abdominal distension, gastroesophageal reflux, early satiety, nausea and vomiting, dyspnea, orthopnea, hernias, uterine prolapse, rib fractures, malnutrition, loss of muscle mass, low back pain, venous obstruction (hepatic, inferior vena cava, portal), biliary tract obstruction, and others. Even with massive involvement, liver parenchyma is preserved, and rarely hepatic failure occurs. Bile duct dilation is a serious complication that can occur and has been described in 17-40% of patients.[227] Another complication that may arise is cystic infection, for which positron emission tomography after administration of 18-fluorodeoxyglucose is the most sensitive diagnostic tool.[222-223]

Elevated alkaline phosphatase and gamma-glutamyl transferase may be found, while bilirubin levels are usually normal, but may be elevated due to compression of the bile ducts by a cyst. CA19.9 levels have been proposed as a biomarker of liver cyst infection, as they are elevated in up to 45% of patients and correlate with liver volume.[226]

The treatment aims to reduce the volume of the liver. Hormone replacement therapies and estrogen-containing contraceptives should be avoided in women with severe polycystic liver disease.[175,177] The only drugs that have been shown to modify the natural course of the disease are the somatostatin analogues (octreotide and lanreotide), as they may reduce liver volume by 6% during 1-3 years, and sirolimus, due to its antiproliferative effect.[228-230] The surgical treatment includes aspiration sclerotherapy (cyst aspiration and subsequent administration of a sclerosing agent), fenestration (aspiration with resection of the superficial walls of the cysts), liver resection, and liver transplant when very severe involvement and complications are difficult to treat. Less commonly used methods are combined liver-renal transplant and embolization of hepatic artery branches.

Intracranial aneurysms

The prevalence of intracranial aneurysms (ICA) in patients with ADPKD ranges from 9% to 12% and is five times higher than in the general population.[177,231-235] Intracranial aneurysms are a very

important extrarenal manifestation of ADPKD because they are usually asymptomatic and go unnoticed and because their rupture can be fatal, although they can be cured.

The main risk factor for ICA is a positive family history of ICA and/or subarachnoid hemorrhage (HSA), which is associated with a prevalence of 20-29%.[231-232,234-235] The main complication of ICA is rupture, which correlates with aneurysm size and location, family history of ICA and/or HSA, presence of an aneurysm sac, hypertension, smoking, cocaine, estrogens, or anticoagulants.[233-234,236-238] The main symptom of ACI rupture is a sudden, severe headache, sometimes accompanied by loss of consciousness.[236,239]

The diagnostic test is gadolinium-free MRI since it avoids the iodinated contrast of CT angiography.[234] The treatment of ICA should be evaluated by multidisciplinary teams with neurosurgeons and interventional radiologists, and the available treatment options are surgical clipping, endovascular treatment, or conservative treatment.[240-241]

Early screening for ICA should be performed for people with positive family history, suggestive symptoms, and professional risk.

Renal Replacement Therapy

Being a progressive disease, ~50% of the affected individuals will reach ESRD during their lifetime.[242] For these patients, peritoneal dialysis and hemodialysis are a customary practice in renal replacement therapy. However, the recommended procedure is kidney transplantation.[193] When considering transplantation, it must be taken into account that:

1. Nephrectomy may be necessary if there is a space conflict or risk of severe infection;
2. Simultaneous liver and kidney transplantation can be performed in selected cases.

Nephrectomy is indicated in cases of severe bleeding, recurrent cyst infection, infected stones, intractable pain, suspected renal cancer, and before transplantation if needed to implant the graft due to space conflict.[243] It is associated with substantial morbidity and mortality, as it increases the risk of blood transfusions and allosensitization and may limit patients' access to preventive transplantation. Thus, it should therefore be avoided.[191,244-245]

Reproductive issues

Exposure to exogenous estrogen or progesterone may aggravate polycystic liver disease in women. Normally, pregnancy is expected to proceed favorably in women with ADPKD with normal blood pressure and renal function. However, preterm delivery and preeclampsia occur more often. Multiple pregnancies (>3) are associated with a greater risk of decline in kidney function in ADPKD.[177,246]

In various severe genetic diseases with early manifestations, such as ARPKD and cystic fibrosis, preimplantation genetic diagnosis can be used to select healthy embryos created by in-vitro fertilization for implantation.[247-249] Prenatal genetic diagnosis should be included in the discussion of reproductive choices with ADPKD patients, but it is only available in a few countries, and acceptance of this technique is influenced by personal ideological values and the severity of the disease.[250-253]

Assessing Glomerular Filtration Rate

Despite substantial kidney growth over time, in ADPKD the GFR remains stable or declines slowly. The explanation for this discrepancy is that the GFR is maintained by hyperfiltration of the surviving nephrons.[254]

GFR estimation by the CKD-EPI and MDRD (eGFR) equations is acceptable in patients with ADPKD.

Tolvaptan in Autosomal Dominant Polycystic Kidney Disease at risk of rapid progression

In 2015 tolvaptan (Jinarc®, Otsuka Pharmaceutical SA) was approved by the European Medicines Agency, and in 2018 by the Food and Drug Administration, as the first treatment to slow kidney function decline in adults at risk of rapidly progressing ADPKD. The medication is indicated in CKD stages 1–4 with evidence of rapid progression.[255] This medication is still not commercialized in Portugal.

Two randomized controlled trials were crucial for the agencies' approval. The TEMPO 3:4 study enrolled individuals aged 18-55 years with an eGFR ≥60 ml/min/ /1.73 m^2, showing after three years of follow-up that tolvaptan had a 49% reduction in the growth of total kidney volume, a surrogate marker in ADPKD (see below), and a 26% reduction in kidney function deterioration as assessed by the inverse of plasma creatinine.[256] The

REPRISE study enrolled either individuals aged 18-55 years with an eGFR 25-65 ml/min/1.73 m^2 or 56-65 years with an eGFR 25-44 ml/min/1.73 m^2, randomly assigned to receive either tolvaptan *vs.* placebo. Compared to placebo, individuals treated with tolvaptan by the end of the study had a difference of 1.27 ml/min/1.73 m^2 in the eGFR.[257]

Arginine vasopressin-mediated cAMP is a driver of cyst proliferation and fluid secretion in ADPKD, and various studies using cell and rodent models showed that suppression of vasopressin release by vasopressin V2 receptor antagonism, high water intake, or genetic elimination of vasopressin, resulted in improvement of cyst burden.[258-259] Tolvaptan, a vasopressin V2 receptor antagonist, had previously been approved by the Food and Drug Administration in 2009 for hypervolemic and euvolemic hyponatremia and was therefore re-purposed for the treatment of ADPKD.

Besides the heavy polyuria and risk of hypernatremia, if access to water is limited, there is the risk of idiosyncratic hepatotoxicity. The implementation of a pharmacovigilance program is mandatory, with monthly liver function evaluation for the first 18 months and every three months afterward.

Tolvaptan should be given twice a day, starting at a dose of 45 mg + 15 mg and up-titrated to a maximum of 120 mg/day. It is extensively metabolized by cytochrome CYP3A isoforms and as such, extreme caution is required whenever compounds that are either CYP3A inducers or inhibitors are prescribed. Pregnancy and breastfeeding are formal contra-indications for the use of tolvaptan.

Rapidly progressive Autosomal Dominant Polycystic Kidney Disease

It is generally considered that rapidly progressive ADPKD will lead to ESRD before 55 years of age.[260] In addition, from the TEMPO 3:4 study (and its open-label extension TEMPO 4:4 study.[261] we have learned that benefits are maximized if tolvaptan is initiated earlier in the course of disease and that older individuals tend not to respond to the drug. An increase in kidney volume, in conjunction with age and kidney function, allows for the identification of individuals at the highest risk of progression to advanced CKD and ESRD, as well as those who will most likely never lose kidney function or progress to ESRD.[262-263] In addition, kidney volume is an accurate estimator of renal cyst burden and is associated with many renal manifestations of ADPKD, including pain, hypertension, macroscopic hematuria, and proteinuria or albuminuria.[177] The seminal study by Grantham *et al.*[254] has shown that kidney enlargement resulting from the expansion of cysts in patients with ADPKD is continuous and quantifiable and is associated with the decline of renal function. In the following years, height-adjusted total kidney volume (htTKV) became an established surrogate marker in ADPKD, and the Mayo classes 1A to 1E were recognized as a model for selecting patients for clinical trials.[263] Kidney volume can be measured by various imaging methods, such as US, MRI, and CT. Namely, ellipsoid formulas can readily be applied to assess htTKV in a user-friendly manner.[264]

To identify individuals at risk of ADPKD, the American Society of Nephrology endorsed a strategy based on the Mayo stratification[265] while the European Working Group of Inherited Kidney Diseases mostly focused on eGFR. Both limit treatment for individuals having eGFR of ≥25 ml/min/1.73 m^2 and an age ≤55 years. Several national[193] and regional guidelines[266] for the use of tolvaptan in ADPKD have been implemented in the meantime.

ADPKD bears strong geno-phenotype correlations. Renal survival in PKD2-affected individuals is 20 years longer than for PKD1.[267] In addition, PKD1 truncating mutations have the worst outcome with a mean age for ESRD of 55 years, compared to 67 years in PKD1 with non-truncating (e.g., *missense* alleles). As expected, a correlation between htTKV and genotype was also shown, with PKD1 truncating mutations being most frequently associated with Mayo class 1E and the shortest renal survival.[268] The Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease (PROPKD) score was developed to incorporate genotype information for defining renal prognosis and identifying individuals at risk for rapid progression.[269]

Although tolvaptan remains the sole ADPKD-specific approved medication available, several other compounds are being evaluated.[270] Being an orphan, although prevalent, disease, those compounds consist of mere drug repurposing. Most sadly, recent trials with innovative compounds have deliberately excluded

ADPKD populations, beginning with the DAPA-CKD trial[64] that had a legacy effect not only in other trials with iSGLT2[65] but also with MRA.[271]

CONSIDERATIONS WHEN COMMUNICATING WITH PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Upon diagnosis of ADPKD, the physician should consider the following aspects when communicating with the patients and their families:

- ADPKD is the most common inherited kidney disease and ~50% of affected individuals will progress to ESRD during their lifetime;
- The disease is characterized by the development and progressive growth of renal cysts that replace normal renal parenchyma and cause kidney enlargement and failure. Long before changes in serum creatinine occur, kidney volume and genetics are reliable predictors of renal outcomes;
- ADPKD is inherited as an autosomal dominant disease and the risk of an affected individual transmitting the disease to their offspring varies depending on whether each progenitor is affected. Routine genetic testing is not recommended;
- In ~10% of instances the occurrence of a *de novo* mutation is the most plausible explanation for sporadic cases;
- Although ESRD is the most fearful ADPKD manifestation, patients are also at increased risk of early hypertension, cardiovascular events, and extra-renal manifestations; often complain of abdominal fullness and acute and chronic pain, gross hematuria, cyst infection, nephrolithiasis, hepatic and pancreatic cysts, intracranial aneurysms, cardiac valvular lesions, and abdominal hernias;
- It is recommended early referral to a specialized care center as soon as the diagnosis is made. Patients and families should have access to health professionals having expertise in treating ADPKD manifestations, including dialysis and transplantation (liver and kidney), and in genetic counseling;
- Screening for intracranial aneurysms in selected ADPKD populations is advised as they are associated with high mortality;
- Lifestyle modification is recommended: smoking cessation, regular exercise (at least 30 minutes five times a week), adequate diet (limit sodium intake <5 g/day; avoidance of processed foods; protein intake restriction in patients with proteinuria (0.8--1.0 g/kg per day); a high carbohydrate intake (35 kcal/kg of ideal body weight, unless obese); a high water intake); systolic blood pressure targets are <110/75 mmHg in people younger than 50 years with preserved eGFR and without significant cardiovascular comorbidities;
- Pregnancy should always be planned since preeclampsia is more frequent and multiple pregnancies (>3) are associated with a higher risk of kidney function decline in ADPKD. Preimplantation genetic diagnosis should be discussed with couples seeking genetic counseling.
- Tolvaptan is the only approved specific medication that slows kidney function decline in ADPKD adults at risk of rapid progression. Measured htTKV, genotype information (when available), and eGFR decline enable the identification of individuals at risk that will benefit from disease-modifying therapy;
- Around 50% of affected individuals will reach ESRD in their lifetime. For these patients, peritoneal dialysis and hemodialysis are standard practice for renal replacement therapy. However, the recommended procedure is kidney transplantation.

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DISCLOSURES

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