

A Jordanian Multidisciplinary Consensus Statement on Chronic Kidney Disease Screening, Diagnosis, and Management

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Abstract: *Background:* Chronic kidney disease (CKD) is a global public health concern, affecting millions of people worldwide and Jordan is no exception to this growing problem. CKD can be prevented or delayed through effective primary healthcare practices. However, lack of awareness among both the general population and healthcare providers (HCPs) contributes to delayed diagnosis and suboptimal management of CKD. *Aims:* The aims of the expert panel were to raise awareness and provide a multidisciplinary consensus approach to screening, diagnosis, and management of CKD, including identifying and controlling risk factors associated with this chronic condition. In addition, the aim was to develop treatment recommendations and algorithms to HCPs to ease the decision-making process and standardize management protocols. *Methods:* The multidisciplinary panel of experts from different specialties representing several medical societies met to discuss and review the challenges and barriers of CKD in Jordan. The experts also reviewed the relevant publications associated with CKD, including the outcome data trials and the international clinical practice guidelines on CKD. The multidisciplinary panel developed a comprehensive understanding of the current state of CKD in Jordan and the measures being taken to address it.

Results: The multidisciplinary team of experts developed a consensus statement that is tailored to the local situation in Jordan. The panel provided standard recommendations and algorithms, addressing screening, diagnosis, referrals, and treatment of CKD. **Conclusion:** Early screening and interventional programs are crucial to delaying the progression nature of CKD and reducing its complications. Future follow-up is important to measure the impact of these recommendations and educational programs to HCPs on CKD detection and management and improving patients' outcomes.

Keywords: Chronic Kidney Disease, Screening, Diagnosis, Management, Consensus, Multidisciplinary, Jordan

1. Introduction

CKD is a progressive and irreversible disease, resulting in a decrease in kidney function over time and it is considered one of the leading causes of mortality worldwide [1-3]. CKD can have deleterious consequences if not properly managed, including progression to advanced stage 5 CKD, which may require dialysis or kidney transplantation. It is well established that diminished kidney function is associated with adverse clinical outcomes and increased cardiovascular disease (CVD) morbidity and mortality [4]. CKD is a major health concern, affecting more than 12-15% of the overall global population while it is often unrecognized by physicians and patients [5]. The prevalence of CKD is increasing on a global level, reaching an estimated almost 850 million individuals worldwide and it is projected to become the fifth most non-communicable chronic disease by 2040 [3]. CKD is more prevalent due to increased risk factors such as diabetes, hypertension, CVD, and obesity [3, 6].

In Jordan, there are currently no data on the prevalence of CKD in the general population. However, a cross-sectional study reported a 30% CKD prevalence among patients with high-risk for CKD [7]. Another study revealed 50% diabetic kidney disease (DKD) in patients with T2D [8]. According to the most recent Jordanian Ministry of Health report, the most common causes of stage 5 CKD were diabetes and hypertension or both [9]. The center of disease control listed CKD as the sixth most common cause of death in Jordan [10].

Therefore, it was important for a multidisciplinary team of experts to provide guidance and practical considerations to the HCPs, including general practitioners (GPs) regarding the screening, risk factors, diagnosis, and proper treatment to delay the progression of CKD and reduce CVD complications.

2. Objectives

The main objectives of the expert panel were to raise awareness and provide guidance by educating HCPs on the optimal screening, diagnosis, risk factors, and comorbidities in patients with CKD. In addition, the objective was to provide a consensus statement on the treatment and management of CKD in Jordan, utilizing a multidisciplinary team approach, to guide local HCPs and to delay the progression of CKD and reduce CVD outcomes in patients with CKD.

3. Methods

A panel of experts with different specialties, representing

different societies undertook the initiative to discuss the challenges with the screening, diagnosis, and management of CKD in Jordan and provide recommendations and treatment protocols and algorithm, considering local factors. The panel was comprised of endocrinologists/diabetologists, nephrologists, and internists, including general practitioners. The experts represented Jordanian Society of Endocrinology, Diabetes & Metabolism, Jordan Society of Nephrology and Renal Transplantation, the Jordanian Atherosclerosis and Hypertension Society, the Jordanian Society of Internal Medicine, and the Jordanian General Practitioner Society. The local panel of experts also conducted a comprehensive review of the literature, utilizing databases such as Medline and PubMed using key terms such as "chronic kidney disease", "risk factors", "screening", "management", "clinical practice guidelines", "cardiovascular outcome", "multidisciplinary approach", "patient education" and "awareness". The panel reviewed the international practice guidelines on CKD and the relevant literature to provide a multidisciplinary approach and tailor easy to use recommendations to the HCPs in Jordan on the screening and management of patients with CKD.

4. Results

4.1. Screening, Risk Factors, Diagnosis, and Stratification of CKD

Early detection and screening of CKD are essential in preventing disease progression and reducing the risk of complication, especially in high-risk individuals. According to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, individuals who are at high-risk for developing CKD have comorbid conditions such as hypertension, diabetes, and cardiovascular disease (CVD). Other risk factors, including obesity, age more than 60 years of age, family history, acute kidney injury, and environmental or genetic risk factors can cause CKD [11-13].

Diagnosis of CKD is confirmed when there is evidence of kidney damage (such as persistent albuminuria or structural abnormalities) and/or decreased kidney function (eGFR less than 60 mL/min/1.73m²) for a duration of at least 3 months [11].

The best dual assessment tools for initial screening and diagnosis of CKD are the estimated glomerular filtration rate (eGFR), which is calculated by measuring serum creatinine or cystatin C level (if affordable) or both and the albuminuria measurement through quantitative spot urine sample testing of urine albumin- to- creatinine ratio (UACR). Both lower eGFR and higher UACR are strongly associated with increased risk of kidney

failure, cardiovascular events, and mortality [11, 14]. Therefore, the dual assessment tools are crucial for risk stratification. The risk stratification is delineated by a color scheme in figure 1, which denotes green for low risk, yellow for moderate risk, red for high risk, and dark red for very high risk. The risk stratification is useful for prognosis and to guide treatment intervention and modification

to prevent kidney and CV complications. In addition, it is helpful in providing guidance to the HCPs on how closely to monitor patients and measure UACR and assess eGFR per year. CKD classification is done according to eGFR and UACR status as shown in figure 1 [11, 14].

Colors indicates risk				Persistent albuminuria categories		
Description and Range				Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mol	>300 mg/g 3-30 mg/mol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	Low (1/yr if CKD)	Moderate (1/yr) Treat	High (Refer* & 2/yr)
	G2	Mildly decreased	60-89	Low (1/yr if CKD)	Moderate (1/yr) Treat	High (Refer* & 2/yr)
	G3a	Mildly to moderately decreased	45-59	Moderate (1/yr) Treat	High (2/yr) Treat	Very High (Refer* & 4/yr)
	G3b	Moderately to severely decreased	30-44	High (2/yr) Treat	Very High (Refer* & 3/yr) Treat	Very High (Refer* & 4/yr)
	G4	Severely decreased	15-29	Very High (Refer* & 3/yr)	Very High (Refer* & 3/yr)	Very High (Refer* & 4+/yr)
	G5	Kidney failure	<15	Very High (Refer* & 4+/yr)	Very High (Refer* & 4+/yr)	Very High (Refer* & 4+/yr)

CKD and urine albumin excretion of 30-300 mg/24 hours or equivalent [15].

Despite the benefits of RAAS inhibitors, the vast majority of the clinical trials conducted in CKD have focused on T2D populations and there was no effect on all-cause mortality [18-21]. However, the residual risk of CV events remained high in patients with CKD despite treatment with ACEi/ARBs [20, 21]. Moreover, RAAS inhibitors can cause hyperkalemia and may cause temporary decline in eGFR. Therefore, dose modification and even discontinuation may be required in certain situations. Therefore, proper monitoring of potassium levels should be exercised. Binding agents can be used concomitantly to reduce the hyperkalemia incidence associated with RAAS inhibitors use in CKD patients [15].

Hyperlipidemia control:

Hyperlipidemia is a major contributing factor for the development of CVD in patients with CKD. The KDIGO [26, 27] and the ACC/AHA [28] guidelines do not use specific LDL-C targets and recommend focusing on statin treatment with or without ezetimibe for managing dyslipidemia regardless of eGFR in all adult patients ≥ 50 years of age. These patients are considered high risk as they confer a 10- year coronary heart disease risk of $>10\%$. In CKD patients <50 years of age, the recommendation is to use statin therapy in those patients who have known coronary disease, diabetes, prior ischemic stroke, or in those who have $> 10\%$ estimated 10-year risk of coronary death or non-fatal myocardial infarction [26, 27].

Glycemia control:

Diabetes is the leading cause of CKD and ESKD. Therefore, it is crucial to optimize diabetes control to help delay the progression of CKD. The most recent KDIGO guidelines recommend that the target hemoglobin A1c (HbA1c) target goal is to be individualized according to comorbidities, life expectancy, and the risk of hypoglycemia [12, 29, 30]. The target goal HbA1c could range from $<6.5-8\%$ [29]. Anti-hyperglycemia treatment with metformin and

sodium-glucose cotransporter 2 inhibitors (SGLT-2is) should be included along with lifestyle modifications for all patients with CKD and T2D, as a first-line therapy [30]. Therapy with additional agents, including insulin can be considered if patients do not meet their HbA1c target goal with the initial therapy. The SGLT-2is have been shown to have cardio-renal protection [31-35]. The clinical benefits of both cardiovascular and renal protective effects were independent of glycemic control. In double-blind randomized placebo controlled cardiovascular outcome clinical trials (CVOTs) with the SGLT-2is in T2D patients with established ASCVD or with high risk for ASCVD demonstrated significant reduction in Major Adverse Cardiovascular Events (MACE) by 14% [32, 33] heart failure hospitalization (HHF) by 27-35% [31-35], composite renal outcomes by 40-47% [31-33] and some demonstrated significant reduction in all-cause mortality by 32% [31], CV death by 38% [31], CV death/HHF by 17% [33], CV death/HHF/urgent HF visits by 26% [35] (table 1.). In patients with CKD, clinical trials with SGLT-2i demonstrated significant reduction by 28-39% in the primary composite outcome and showed 34-44% reduction in hard renal specific endpoints (see table 2) [36-38]. CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial) included CKD patients with T2D [36]. However, both DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) [37] and EMPA-KIDNEY (EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease) [38] enrolled CKD patients with and without T2D and the benefit of the SGLT-2i was demonstrated in both diabetics and non-diabetics with CKD as an add-on over RAASi. As a result of these landmark trials, the SGLT-2is were included in the most recent guidelines as a first-line standard treatment in the management of CKD patients with eGFR of 20-75 ml/min/1.73m² and albuminuria [12, 30, 39].

Table 1. SGLTis CVOTs in T2D patients with established ASCVD or with multiple risk factors for ASCVD.

Study	Drug (dose)	Study population	N	Significant Endpoints (RRR; p value)
EMPA-REG [31]	Empagliflozin (10 mg or 25 mg)	T2D and preexisting CVD (MI, multivessel CAD, CAD with ischemia/UA, stroke, or PAD)	7,020	1 ^o endpoint: 3-point MACE 14%; p <0.04 for superiority Sig. 2 ^o endpoint: CV death 38%; p <0.001 HHF 35%; p <0.002 All-cause mortality 32%; p <0.001 Composite renal outcomes: 46%; p <0.001
CANVAS [32]	Canagliflozin (100 mg)	T2D and preexisting CVD at ≥ 30 years of age or >2 CV risk factors at ≥ 50 years of age	10,142	1 ^o endpoint: 3-point MACE 14%; p <0.001 Sig. 2 ^o endpoint: HHF 33%; p <0.02 Composite renal outcomes: 40%; p <0.001 1 ^o endpoint: 3-point MACE 7%; p=0.17 CV death or HHF 17%; p <0.005 Sig. 2 ^o endpoints: Renal composite ($\geq 40\%$ decrease in eGFR rate to <60 mL/min/1.73 m ² , new ESRD, or death from renal or CV causes 24%; p <0.001 HHF 27%; p <0.0008 Composite renal outcomes 47%; p <0.001
DECLARE-TIMI 58 [33]	Dapagliflozin (10 mg)	T2D and established ASCVD or multiple risk factors for ASCVD	17,160	1 ^o endpoint: 3-point MACE 14%; p <0.001 Sig. 2 ^o endpoint: HHF 30%
VERTIS CV [34]	Ertugliflozin	T2D and ASCVD	8,246	1 ^o endpoint: 3-point MACE 3% Sig. 2 ^o endpoint: HHF 30%

Study	Drug (dose)	Study population	N	Significant Endpoints (RRR; p value)
SCORED [35]	*Sotagliflozin	T2D and CKD (eGFR 25 to 60 ml per minute per 1.73 m ²) and at risk for CVD	19,188	1o endpoint: Deaths from CV causes, HHF, and urgent visits for HF 26%, <0.001

EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (Canagliflozin Cardiovascular Assessment Study), DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events trial), VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial), SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk)

RRR: Relative Risk Reduction

Table 2. Clinical trials of SGLT-2 inhibitors in patients with CKD.

Clinical trial	Drug (dose)	(n)study population (median follow-up)	Baseline Characteristics	Primary Endpoints RRR, p value
CREDENCE [36]	Canagliflozin (100 mg)	(4601) patients with T2D and albuminuric CKD-eGFR 30-<90 ml/min/1.73m ² UACR ≥30 mg/mmol (2.6 years follow-up)	T2D: 100%T2D duration: 15.8 years CVD: 50.4% HbA1c: 8.3% *eGFR: 56.2±18.2 §UACR: 927 mg/gm *Age: 61.8±12.1	1° endpoint: A composite of doubling of serum creatinine, ESKD, death from renal or CV causes: 30% 2° endpoint (renal specific): ESKD, doubling of serum creatinine, or renal death: 44%; p<0.001)
DAPA-CKD [37]	Dapagliflozin (10 mg)	4304 CKD patients with or without T2D (2.4 years follow-up period)	T2D: 68% CVD: 38% HbA1c: 7.1% overall and T2D patients 7.8% *eGFR: 43±12.3 §UACR: 965 (472-19.3)	1° endpoint: A composite of decline in eGFR of ≥50%, ESKD, renal or CV death: 39%, p<0.001) 2° endpoint (renal specific): Composite of decline in eGFR of ≥50%, ESKD, or death from renal causes: 44%; p<0.001)
EMPA-KIDNEY [38]	Empagliflozin (10 mg)	6609 CKD patients with or without T2D and eGFR of at least 20-<45 ml/min/ 1.73 m ² (irrespective of level of albuminuria); or an eGFR of 45 <90 ml/min/ 1.73 m ² with a UACR of at least 200 mg/g (2 years follow-up period)	Age: 63.9±13.9 T2D: 44% CVD: 26% *eGFR: 37.4±14.5 §UACR: 331 (46-1061)	1° endpoint: A composite of progression of kidney disease (ESKD, a sustained decrease in eGFR to <10 ml per minute per 1.73 m ² , a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes: 18%; p<0.001)

CREDENCE: (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial); DAPA-CKD: (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease); EMPA-KIDNEY (EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease)

*Age and eGFR values are expressed in mean ±SD

§The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine in grams.

The glucagon-like peptide receptor agonists (GLP-1 RAs) are another class of drugs to consider that can be added to the first-line treatment of metformin and SGLT-2is in patients who do not achieve their HbA1c target goals [12, 30, 39]. They have been shown to reduce CV events and provide favorable renal benefits in terms of reducing albuminuria, improving glycemic control, reducing weight, and lowering blood pressure [40-48]. However, they do not have favorable effect on slowing down the eGFR decline [42, 43].

More recently, finerenone (the nonsteroidal selective mineralocorticoid receptor antagonist) has been added to the guidelines as a second-line treatment after maximum tolerated dose of ACEi/ARBs for patients with DKD following two randomized placebo controlled clinical trials, which demonstrated favorable kidney and CV outcomes [49, 50].

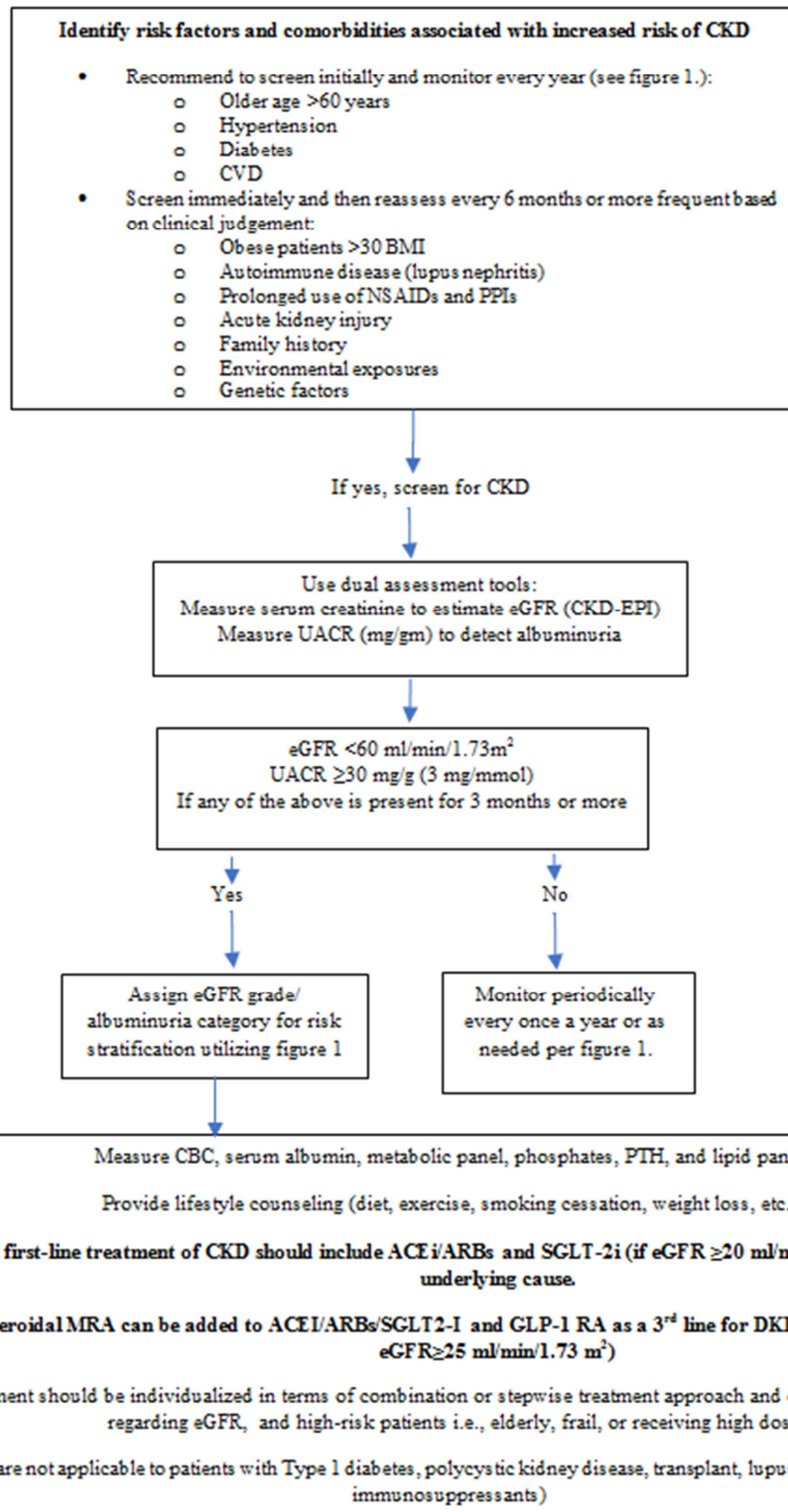
4.3. Local Screening and Treatment Recommendations with Practical Considerations

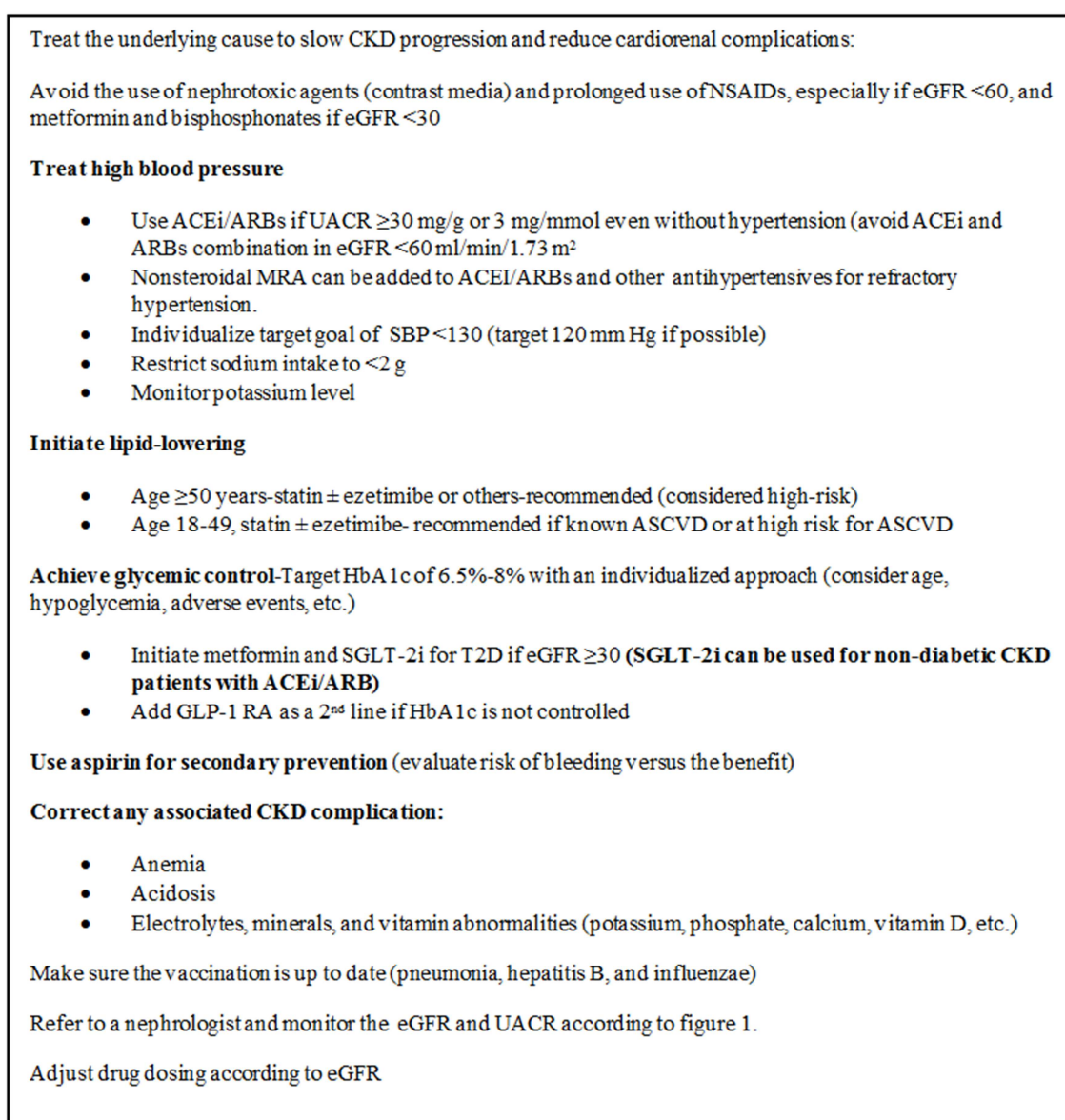
The Jordanian local experts recommend CKD screening for those high-risk individuals who are greater than 60 age or with history of hypertension, diabetes, and/or CVD. In addition, other high-risk groups should be considered for screening if they have a family history of kidney disease, hospitalization for acute kidney injury, autoimmune diseases, history of prolonged

use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs), obesity, genetic factors, and environmental exposures that could potentially harm the kidneys. Repeated screening might be required for early detection of CKD in individuals who test negative initially (see figure 1 and figure 2). Detection of kidney function decline and/or damage should be assessed by utilizing the dual assessment tools, the eGFR and the UACR. The group recommended using the serum creatinine as a measurement to calculate the eGFR because it is cheaper than cystatin C, utilizing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation [51]. Both the urine albumin and the creatinine should be measured quantitatively in milligrams (mg) and in grams (gm), respectively, by obtaining a “spot urine” sample and not a 24-hour urine collection for practical reasons. The quantitative urine albumin measurement is more sensitive than the dipstick to measure proteinuria. The ratio should be expressed in mg/gm by dividing the urine albumin in mg over urine creatinine in gm. The risk stratification should be done according to the eGFR grade and UACR category (figure 1). All identifiable causes and risk factors of CKD should be addressed and treated to prevent further deterioration of the kidney function and reduce complications. Lifestyle modifications and pharmacological

treatment should be deployed to prevent the progression of CKD and also to reduce the CVD, including heart failure, especially with the SGLT-2i (see screening and treatment algorithm figure 1.) [12, 39]. Monitoring and assessment of eGFR and UACR are recommended based on severity of CKD and associated risk. Adjustment of drug dosing should be done according to the eGFR. Patients with moderate to severe CKD

are at risk of developing electrolytes abnormalities, mineral and bone disorders, and anemia [6, 39]. Therefore, screening and frequency of assessment should be commensurate with CKD severity, and it is recommended to have complete blood count, serum albumin, metabolic panel, phosphates, parathyroid hormone (PTH), vitamin D, and lipid panel measurements to manage the patient appropriately [6, 39].





Ref: 6, 12, 39

Figure 2. CKD screening and treatment algorithm.

4.4. CKD Multidisciplinary Management Approach and Referral to the Nephrologist

In clinical practice, there has been suboptimal adoption and implementation of the clinical practice guidelines by primary care providers to screen and diagnose patients with CKD [52, 53]. Identifying and stratifying risk of individuals with high-risk to developing CKD are important and require education. In addition, collaborative efforts between multi-stakeholders are important to simplify processes of CKD screening and diagnosis. The panel of experts recommend utilizing automated laboratory reporting and using risk-equations tools to evaluate and provide guidance for (re)testing and risk-stratification of patients and subsequently referrals. A multidisciplinary team approach between the primary care provider, the nephrologist,

nutritionist, and the pharmacist optimize care for newly diagnosed CKD patients. Early identification and intervention should be integrated into the existing work environment. The experts' consensus recommendation is that the primary care physicians should be educated to be able to identify reversible causes of CKD and should be aware of when to refer the CKD patient to the specialist for further evaluation and/or intervention. The Jordanian multidisciplinary panel of experts endorses KDIGO guidelines criteria recommendation that patients with CKD to be referred to the nephrologist when they reach severe decline in eGFR grade 4 and/or severe albuminuria category A3 (figure 1) [11]. The frequency of monitoring UACR and eGFR per year is also illustrated (Figure 1). Patients with albuminuria of >2200 mg/ 24 hours should be consulted by a nephrologist to check for nephrotic syndrome. In addition, patients who have hematuria (>20 red blood cells per high-power field) and unidentifiable cause, red

blood cell casts on urine microscopy or other indications of glomerulonephritis, CKD with uncontrolled hypertension (despite 4 or more antihypertensive medications), persistent hypokalemia or hyperkalemia, anemia requiring erythropoietin therapy, kidney stones (recurrent or extensive), hereditary kidney disease, acute kidney injury, and rapid CKD progression (decrease in eGFR $\geq 25\%$ from baseline or sustained decline in eGFR > 5 ml/min/1.73m²). In addition, patients who are high-risk of progressing to ESKD (polycystic kidney disease, certain types of glomerulonephritis, and nephrotic syndrome albuminuria) should be referred to the nephrologist for planning of kidney replacement and transplant evaluation [6, 11]. The primary care physician should collaborate with the nephrologist and have a plan to when to initiate kidney replacement based on both symptoms and eGFR decline. Initiation of dialysis should be individualized and considered when patients have uremic symptoms, electrolytes abnormalities, or fluid overload [11]. Patients should be educated and have an active role in the decision-making process about their options.

4.5. CKD Awareness and Patient Education

In a cross-sectional study involving 12 countries from six world regions demonstrated that only 6% of the general population and 10% of the high-risk population were aware of their CKD [54]. Flinkelstein *et al* reported that one-third of patients who were followed in nephrology clinics had limited or no understanding of their CKD and were not aware of treatment options [55]. This evidence suggests that there are existing gaps in awareness and the lack of education among patients with CKD. More education in patients with CKD and in the general population is needed to raise awareness, especially early on in the CKD continuum.

5. Conclusion

CKD is a progressive disease and has become a public health concern globally and in Jordan. Early screening and intervention are key to delaying the progression of the disease and reducing complications. Prevention should focus on promoting awareness and education among HCPs and patients to be knowledgeable about disease risk factors, screening high-risk individuals, and the treatment options available. A multidisciplinary team care approach would be the ideal setting, integrating different health services to provide patients with CKD the best possible outcome. Future follow-up is recommended to measure the impact of increasing awareness among HCPs on CKD.

Conflicts of Interest

The authors declare that they have no competing interests.

Disclosures

AstraZeneca reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible

for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

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