

Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action



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The International Society of Nephrology has adopted a proactive approach to defining the current state of kidney care and unmet needs through a multifaceted Closing the Gaps initiative. As part of this initiative, the International Society of Nephrology convened a meeting of experts to develop an approach to tackle acute kidney injury and chronic kidney disease (CKD). This manuscript expands on the recently published International Society of Nephrology CKD Roadmap and reports on the discussions of the working group assigned to the task of reviewing the global impact of complication of CKD. The working group defined the following goals:

Goal 1: Optimize the management of anemia and endocrine and metabolic abnormalities associated with CKD. The impact of these conditions at a global level is not well understood, particularly in regions where renal replacement therapy is not readily available. Some treatment regimens may be affordable in low- and middle-income countries and if implemented, could have an impact on the burden of suffering associated with CKD.

Goal 2: Improve the prevention and management of cardiovascular complications linked to CKD. Most research on cardiovascular complications of CKD has focused on atherosclerotic diseases (myocardial infarction, ischemic stroke, and peripheral gangrene). There has been growing recognition that other forms of cardiovascular diseases, such as heart failure, valvular disease and arrhythmias, have a major impact on patient outcomes. Much less is

known about the mechanisms and treatment of these non-atherosclerotic complications.

Goal 3: Improve the diagnosis and management of symptoms associated with CKD. Symptom management is one of the greatest challenges in the management of CKD, with limited knowledge about the mechanisms associated with the development of these common problems and how best to characterize them into usable clinical phenotypes.

Improved understanding of the complications of CKD may alleviate suffering and prolong life among millions of people worldwide both in developed countries and in regions where renal replacement therapy is not widely available.

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Chronic kidney disease (CKD) is associated with several adverse clinical outcomes, such as cardiovascular events, kidney failure requiring renal replacement therapy, mortality, and poor quality of life for survivors in general.^{1–6} Kidney disease amplifies the enormous burden and population health impact associated with both communicable and noncommunicable diseases.^{6,7}

CKD has not been included in the major chronic disease control strategies at international, regional, and/or national levels. The progressive nature of CKD, the associated cardiovascular morbidity and mortality, and the ensuing end-stage kidney disease place a considerable burden on global healthcare resources.^{6–8} A better understanding of the nature of CKD-related complications may help to optimize the diagnosis, prevention, and management.

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The International Society of Nephrology Closing the Gaps initiative was established to define the global needs and current state of kidney care building on acute kidney injury initiatives (0by25; www.theisn.org) and focusing on CKD. The goal was to create a “blueprint” to enhance the optimal care globally through research, education, and advocacy. As part of this initiative, the International Society of Nephrology convened the first Global Kidney Health Summit on July 26 to 28, 2016 in Vancouver, Canada. This article expands on the recently published International Society of Nephrology CKD Roadmap,⁹ which is the result of the Summit.

CKD-RELATED COMPLICATIONS: CURRENT STATE

Progressive CKD is linked to several complications with higher prevalence and intensity at lower levels of kidney function, which interact with each other^{8,10,11} (Table 1, Figures 1 and 2). These complications contribute to high morbidity and mortality and poor quality of life. Some of these complications can be readily defined and quantified (cardiovascular disease, hypertension, anemia, mineral bone disorder, volume overload, electrolytes, and acid-base abnormalities) and may require a specific management approach, for example, the prescription of erythropoiesis-stimulating agents to correct anemia. Other less well-defined complications with a less distinct pathogenesis, such as anorexia, fatigue, cachexia, pruritus, nausea, and sexual dysfunction, may manifest as complex symptoms often associated with advanced CKD. The work group identified the following complications of CKD as being relevant to the global burden of poor health caused by CKD.

1. Hypertension: Hypertension remains one of the most damaging complications of CKD and is thought to contribute to the acceleration of progressive decline in

kidney function, cardiovascular diseases (CVD), and related mortality. Both detection and control of high blood pressure is frequently suboptimal and improvements could directly help patients.¹² The Systolic Blood Pressure Intervention Trial provided important information about the effects of a more stringent lowering of systolic blood pressure to a target of <120 mm Hg that may be relevant to CKD patients; although, this trial excluded high-risk subjects with CKD, proteinuria, or diabetes.¹³ Lifestyle modifications, such as weight loss and dietary salt restriction, may also improve the blood pressure control. Such interventions can be lower in cost than pharmacological therapies and have the potential to affect outcomes, such as heart failure and stroke, in both developed health care systems and low- and middle-income countries (LMICs). Since many anti-hypertensive agents are available and affordable in LMICs, one feasible goal would be to improve the control of high blood pressure complications in CKD patients, aiming to achieve target ranges in a proportion of patients. Such a goal can be attained globally, and its impact is easily measurable.

2. Cardiovascular complications: CVD represents the leading cause of mortality in CKD patients, and the prevalence and burden of this complication increases with declining kidney function (Figures 1 and 2).^{8,14} For example, the risk of mortality from CVD is 8.1-fold greater in a patient with CKD stage G5 A3 (eGFR < 15 ml/min per 1.73 m² and urinary albumin-creatinine ratio > 300 mg/g) than in a reference population without kidney disease.⁴ While the risk of conventional atherosclerotic cardiovascular events increases with CKD, the majority of increased risk is

Table 1 | Systematic complications of chronic kidney disease and cross-links

System	Common manifestations	Endocrine and						
		Cardiovascular	metabolic	Gastrointestinal	Hematologic	Neurologic	Musculoskeletal	Integument
Cardiovascular	Atherosclerosis, HTN, cardiomyopathy		X		X	X		
Endocrine and metabolic	Menstrual disorders, sexual dysfunction, infertility, pregnancy disorders, electrolytes, and MBD	X		X	X	X		X
Gastrointestinal	Anorexia, nausea, emesis, weight loss		X					
Hematologic	Anemia, platelets disorders, coagulopathy, low cell count and infection risk	X		X				X
Neurologic	Neuropathy, seizures (with severe uremia), strokes	X	X					X
Musculoskeletal	MBD, fractures, myopathy	x	x			x		x
Integument	Dry skin, dermatitis, pruritus		X		X	X		
Complex symptoms ^a	Fatigue, insomnia, impotence, cachexia	X	X	X	X	X		X

HTN, hypertension; MBD, mineral bone disorder.

^aPoorly defined disorders associated with advanced chronic kidney disease.

X denotes a crosslink between systems, e.g., MBD contributing to cardiovascular system, anemia contributing to cardiovascular system, and interplay of all systemic features causing complex symptoms.

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