Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes

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Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. There is now convincing evidence that CKD can be detected using simple laboratory tests, and that treatment can prevent or delay complications of decreased kidney function, slow the progression of kidney disease, and reduce the risk of cardiovascular disease (CVD). Translating these advances to simple and applicable public health measures must be adopted as a goal worldwide. Understanding the relationship between CKD and other chronic diseases is important to developing a public health policy to improve outcomes. The 2004 Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on 'Definition and Classification of Chronic Kidney Disease' represented an important endorsement of the Kidney Disease Outcome Quality Initiative definition and classification of CKD by the international community. The 2006 KDIGO Controversies Conference on CKD was convened to consider six major topics: (1) CKD classification, (2) CKD screening and surveillance, (3) public policy for CKD, (4) CVD and CVD risk factors as risk factors for development and progression of CKD, (5) association of CKD with chronic infections, and (6) association of CKD with cancer. This report contains the recommendations from the meeting. It has been reviewed by the conference participants and approved as position statement by the KDIGO Board of Directors. KDIGO will work in collaboration with international and national public health organizations to facilitate implementation of these recommendations.

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Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. The declaration of World Kidney Day to be observed annually beginning in March 2006 sends a clear message to the public, government health officials, physicians, allied health professionals, patients, and families that 'CKD is common, harmful, and treatable'.[1] The recognition of CKD as a public health problem has evolved, in part, from the acceptance of the conceptual model, definition, and classification of CKD proposed by the National Kidney Foundation Kidney Disease Outcome Quality Initiative in 2002 and modified by Kidney Disease Improving Global Outcomes (KDIGO) in 2004[2–4] (Figure 1; Tables 1 and 2). As a result, physicians, investigators, and public health officials across the world can now more easily ascertain CKD irrespective of cause, study its antecedents and outcomes, determine risk factors for its development and progression, and develop strategies for its detection, evaluation, and treatment.

In the US, 9.6% of non-institutionalized adults are estimated to have CKD.[5,6] Studies from Europe, Australia, and Asia confirm the high prevalence of CKD.[7–10] Outcomes of CKD include not only progression to kidney failure but also complications of reduced kidney function and increased risk of cardiovascular disease (CVD). Patients with CKD are far more likely to die, principally from CVD, than to develop kidney failure.[11] There is now convincing evidence that CKD can be detected using simple laboratory tests, and that certain

treatments can prevent or delay complications of decreased kidney function, slow the progression of kidney disease, and reduce its associated CVD risk.[2,12–18] Translating these advances to simple and applicable public health measures must be adopted as a goal worldwide. Although there is still much to learn about the impact of treatments and their optimal combinations for CKD, it is not too early to begin implementation.

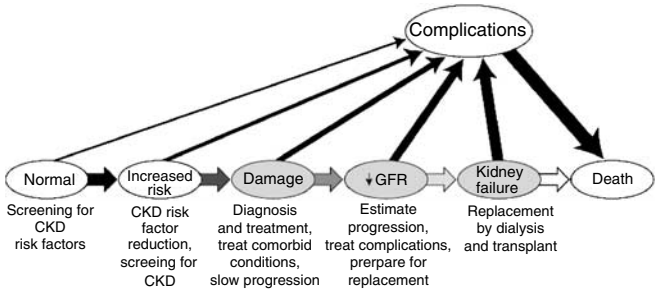

Figure 1 | Conceptual model of the course of chronic kidney disease and therapeutic strategies. Shaded ellipses represent stages of CKD; unshaded ellipses represent potential antecedents or consequences of chronic kidney disease. Thick arrows between ellipses represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions. Interventions for each stage are given beneath the stage. 'Complications' refer to all complications of chronic kidney disease and its treatment, including complications of decreased GFR (hypertension, anemia, malnutrition, bone, and mineral disease) and cardiovascular disease. Increasing thickness of arrows connecting later stages to complications represents the increased risk of complications as kidney disease progresses. Modified and reprinted with permission.[2–4]

Table 1 | KDIGO definition of CKD

Structural or functional abnormalities of the kidneys for ⩾3 months, as manifested by
1. **Kidney damage**, with or without decreased GFR, as defined by
Pathologic abnormalities
Markers of kidney damage
Urinary abnormalities (proteinuria)
Blood abnormalities (renal tubular syndromes)
Imaging abnormalities
Kidney transplantation
2. **GFR** <60 **ml/min/1.73 m^2**, with or without kidney damage

CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

Chronic diseases are now the leading causes of death worldwide. The World Health Organization (WHO) estimates that there were approximately 58 million deaths worldwide in 2005, with 35 million attributed to chronic disease.[19,20] In developed countries and lower-middle-income developing nations, CVD and cancer were the leading causes of death. In low-income developing countries, infections remained the leading cause of death, but chronic non-communicable diseases were on the rise. The WHO report called for governments to provide leadership in addressing the projected continued increase in deaths due to chronic diseases.

While CKD is not mentioned in the 2005 WHO report,[19] it is now recognized that CKD is common in people with CVD and with CVD risk factors, and that CKD multiplies the risk for adverse outcomes in these conditions.[17] CKD is also reported to be a risk factor for adverse outcomes in other chronic diseases such as infections and cancer,[21] and should be studied in more detail. Understanding the relationship between CKD and other chronic diseases is important to develop a public health policy to improve outcomes (Figure 2).

SCOPE

KDIGO is an independent non-profit foundation governed by an international Board of Directors with the stated mission to 'improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines'.[22] The KDIGO Controversies Conference on 'Definition and Classification of Chronic Kidney Disease' was held in Amsterdam in November 2004, attended by an international group of experts, represented an important endorsement of the Kidney Disease Outcome Quality Initiative definition and classification of CKD by the international community.[4] In 2006, KDIGO convened another Controversies Conference to build on and extend the recommendations of the 2004 conference. The agenda, selected presentations, and abstracts of the meeting are posted on the KDIGO website (http://www.kdigo.org/content-cconf.htm#Public%20Health). Specifically, the conference addressed two major topics.

Table 2 | Current CKD classification based on severity and therapy

Stage	Description	GFR (ml/min/1.73 m^2)	ICD-9 CM code	Treatment
1	Kidney damage with normal or ↑ GFR	⩾90	585.1	
2	Kidney damage with mild ↓ GFR	60–89	585.2	1–5 T if kidney transplant recipient
3	Moderate ↓ GFR	30–59	585.3	
4	Severe ↓ GFR	15–29	585.4	
5	Kidney failure	<15 (or dialysis)	585.5	
			585.6 (if ESRD) V codes for dialysis or transplantation	5D if dialysis (HD or PD)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

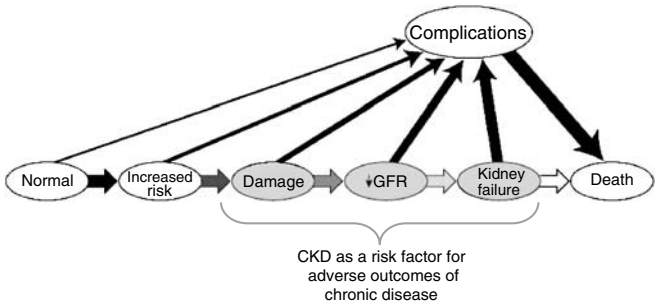

Figure 2 | Relationship of chronic kidney disease to chronic diseases. Among patients with chronic diseases, for example, cardiovascular disease, infectious diseases, or cancer, presence of chronic kidney disease is associated with an increased risk of complications related to those diseases.

Classification, surveillance, and public policy for CKD

The plenary session included presentations on CKD screening and surveillance, standardization of creatinine measurement, experience in measuring and reporting the estimated glomerular filtration rate (eGFR), implementation of albuminuria testing, revisions to the ninth International Classification of Disease, and public policy initiatives. Breakout sessions focused on CKD classification (group 1), CKD screening and surveillance (group 2), CKD, and public policy (group 3).

Associations of CKD with chronic diseases

The plenary session included presentations on the WHO perspective on chronic disease, and on associations of CKD with other chronic diseases: CVD, infections, and cancer. The model for assembling evidence to evaluate and classify CKD as a risk factor for CVD (Table 3) was the paradigm used for evaluating the association of CKD with other chronic diseases. Breakout groups focused on CVD risk factors and CVD as risk factors for CKD development and progression (group 4), and CKD as a risk factor for adverse outcomes of chronic infections (group 5) and of cancer (group 6).

Each breakout group was asked to formulate both clinical and research recommendations based on evidence and opinion. The groups did not perform a systematic review or grading of available evidence. This report contains the recommendations made at the meeting and has been reviewed by the conference participants (Appendix) and approved as position statement by the KDIGO Board of Directors. These recommendations will be pursued by the KDIGO Board with the World Health Organization and other international and national public health organizations.

RECOMMENDATIONS FROM THE BREAKOUT GROUPS

Group 1: Classification of CKD

CKD is a heterogeneous condition, whose clinical manifestations and course depend on the cause and type (pathology), severity, rate of progression, and comorbid conditions. The group examined the need to refine the CKD classification to include additional clinical information, to evaluate the utility of adopting a coding system, which subdivides CKD by presumed cause, and to identify key research questions that would facilitate or improve the understanding and application of the CKD classifications system worldwide. The rationale for the recommendations is that development and adoption of a consistent framework for classification of CKD will facilitate international collaborations and allow for scientific discoveries to be more readily adopted worldwide.

Table 3 | Approach to evaluation of CKD as a risk factor for CVD in CVD risk factor conditions

CVD risk factor	CKD prevalence	CKD as a risk factor for CVD morbidity	CKD as a risk factor for CVD mortality
Hypertension	↑	↑	↑
Diabetes	↑	↑	↑
Dyslipidemia	↑	↑	↑

CKD, chronic kidney disease; CVD, cardiovascular disease; ↑, increased.

Recommendations

- *KDIGO should not change the existing classification at this time*. The classification system endorsed by KDIGO in 2004 includes severity and modality of treatment for kidney failure (Table 2). It is acknowledged that additional clinical information (Table 4) is required for the evaluation and management of individual cases of CKD. However, the potential benefits of adding information was thought to be outweighed by the disadvantages of increased complexity and incomplete description of an essentially heterogeneous condition. The current classification system was deemed to be clear, simple, and useful, as evidenced by its ongoing endorsement and adoption worldwide. Moreover, there was concern that further additions would detract from the attempt to maintain a simple message applicable across various disciplines and communities. There was discussion of whether albuminuria is a marker of kidney damage in non-diabetic as well as diabetic kidney disease. Data from the Heart Outcomes and Prevention Evaluation Study indicate that 'microalbuminuria' was associated with same relative risk for progression to 'clinical proteinuria' in non-diabetic and diabetic kidney diseases,[23] suggesting that the current threshold for albuminuria as a marker of kidney damage (a spot urine albumin-to-creatinine ratio >30 mg/g) is applicable to diabetic and non-diabetic kidney diseases.
- *KDIGO should work with the WHO to adopt the USA modifications to ICD-9 CM and in updates to ICD-10 and subsequent revisions*. It is important that coding systems capture the elements of the current classification system. The ninth version of the International Classification of Disease in the USA (ICD-9 CM) has adopted a revised coding system that incorporates the current CKD staging system. There was consensus that current (version 10) and future (version 11) iterations of ICD should incorporate and maintain this coding system so that

Table 4 | Key elements for description of CKD in clinical practice

Domain	Example
Severity	GFR level
Treatment	Therapies for causes of kidney disease Treatment modality for kidney failure
Marker of kidney damage and severity	Pathologic abnormality Magnitude of albuminuria/proteinuria Imaging abnormalities
Cause of kidney disease	Diabetic kidney disease Non-diabetic kidney disease Glomerular diseases Tubulointerstitial diseases Vascular diseases Cystic diseases Disease in the kidney transplant recipient
Presence and severity of complications	Hypertension Anemia Malnutrition Bone and mineral disease
Presence and severity of comorbid conditions	Diabetes Cardiovascular disease Chronic infections Cancer
Prognosis	Past history or risk factors for fast progression Risk factors for cardiovascular disease

more epidemiologic information could be gained from administrative data. Healthcare providers in different countries have variable familiarity with these codes. Nonetheless, each country does have a system of coding and variable obligations for reporting. The consistency of evolving iterations of ICD is essential for following trends over time, and potentially for cross country comparisons, as well as providing essential information to regional public health authorities.

- *KDIGO should facilitate the development of a uniform 'essential data set' for description of CKD for coding purposes*. There is a need to describe an essential data set for coding to ensure that a minimal amount of data is obtained on all patients identified as having CKD. Although no final recommendations were made, key elements could include the information provided in Table 4. For research purposes, the inclusion of race, ethnicity, socio-economic status, and level of education would improve understanding the impact of CKD worldwide.

Research recommendations

- *Research recommendations from the 2004 KDIGO conference on definition and classification of CKD remain high priority.*[4]
- *Additional studies are needed to:*
  - *Define the societal and individual implications of over- and underdiagnosis of CKD*. This should include analysis of the impact of health behaviors, and evaluation of the costs of testing, labeling, and resource utilization in different countries.
  - *Systematically analyze the performance of current GFR estimating equations in different populations and their use:*
    - for some specific testing or treatment strategies, such as frequency of testing for complications or for drug dosing
    - in special patient populations such as patients with reductions in kidney mass due to surgery or a past history of acute kidney injury
    - in chronic diseases, due to concerns about muscle wasting and malnutrition (see reports by groups 5 and 6).
- *Identify new markers of kidney damage and new filtration markers (for example cystatin C) and analyze their performance in different patient populations.*

Group 2: Screening and surveillance

The group discussed strategies for implementation of screening and surveillance for CKD in developed and developing countries. Screening is an activity, whereby persons in a defined population who are not aware of CKD are tested to detect the disease and, if present, are subsequently treated to reduce the risk of progression of CKD and its complications. Surveillance refers to an activity to provide key information on CKD, such as time, location, magnitude, and severity, in order to guide implementation of medical and public health measures to control progression of CKD and its complications.

It is not known whether screening the general population would be cost-effective.[24,25] Targeted screening should be directed at subgroups of the population who would derive the most benefit from CKD detection. Among developed and developing nations, the risk for CKD is increased in people with CVD risk factors or established CVD, in whom CKD multiplies the risk for adverse outcomes of CVD. Thus, the 'CKD subgroup' of patients with CVD and CVD risk factors constitutes a high-risk group requiring special attention.[2] As discussed by groups 5 and 6, patients with some chronic infectious diseases and cancers may also be at increased risk. In conditions where the prevalence of CKD is increased and the risk of complications due to preventable factors is high, including adjustment of drug doses to avoid toxicity, screening for CKD may be warranted. In these groups, screening for CKD could be implemented using existing infrastructures for the detection of other chronic conditions.

Many countries have registries for patients treated by dialysis and transplantation. However, these programs overlook people with severe CKD who die before the onset of kidney failure or are not treated with dialysis or transplantation despite the onset of kidney failure. In principle, a

surveillance program for CKD stages 4 and 5 would enable countries to monitor the magnitude and the care of this high-risk, high-cost population, and possibly to reduce both the risk of progression to kidney failure and the cost of dialysis and transplantation.[2] A surveillance program for patients with CKD stage 3 would reach many more people and might be an effective way to lower rates of CVD and death, especially among the elderly with CVD risk factors or CVD. However, such a larger surveillance program would require more resources and the available data to assess the costs and benefits is incomplete.

Recommendations

- *All countries should have a targeted screening program for CKD* (Table 5).
- *Target groups should include patients with hypertension, diabetes and cardiovascular disease*. Other groups might include families of patients with CKD, individuals with hyperlipidemia, obesity, metabolic syndrome, smokers, patients treated with potentially nephrotoxic drugs, some chronic infectious diseases and cancers (see reports from groups 5 and 6), and age >60 years.
- *Tests for CKD screening should include both a urine test for proteinuria and a blood test for creatinine to estimate GFR*. Tests for proteinuria should be selected and performed according to local guidelines. (This article refers to tests for proteinuria as tests for detection of proteinuria, including tests for albumin only; and tests for albuminuria as tests for detection of albumin only.) Verification of proteinuria would require two out of three positive tests.[3] In selected populations with an increased risk for glomerulonephritis, testing for hematuria should also be performed. Equations for estimating GFR should be appropriate for standardization of the serum creatinine assay and application to majority racial and ethnic groups.
- *Frequency of testing should be according to available guidelines and the target group to be tested. In the absence of specific recommendations, testing need not be more frequent than once per year.*
- *All countries should have a surveillance program for CKD stages 4–5 and strive to include earlier stages*. If possible, data on risk factors for development and progression of CKD most relevant for the specific population should be included. Surveillance for CKD could be incorporated into existing surveillance programs (such as those for hypertension, diabetes, cardiovascular diseases, infectious diseases, and cancer) and data from such programs should be used for surveillance of CKD risk factors. Data could be obtained from random samples of the general population or (possibly) populations receiving medical care or (ideally) registries of stages 4 and 5 CKD. Data should be collected at a frequency of every 5–10 years, or more often, depending on disease dynamics, interventional strategies, and regional resources. Additional components of a CKD surveillance program could be: consequences of CKD (mortality), education/awareness (public and professionals), health system capabilities (primary and specialty care), quality of care markers (appropriate treatment/referrals), and health policy goals.

Table 5 | High-risk groups for targeted screening program for CKD

Highest priority
Hypertension
Diabetes
Cardiovascular disease
To be considered
Older age
Family history of kidney disease
Other cardiovascular disease risk factors
Exposure to toxic drugs
Certain chronic infections
Certain cancers

CKD, chronic kidney disease.

Research recommendations

- *Evaluate target groups for screening*
- *Compare specificity and sensitivity of different screening tests in various settings, including verification of proteinuria*
- *Define optimal timing interval for screening and surveillance*
- *Analyze costs, benefits and risks of screening programs*

Group 3: Public policy

The group discussed the need for CKD public policy programs in developed and developing countries, and steps to implement them. In some countries, the incidence of kidney failure due to some types of CKD is stabilizing or declining, possibly reflecting early detection and treatment.[26,27] Although the prevalence of kidney failure varies substantially throughout the world, the number of patients and the cost of providing dialysis and transplantation continue to escalate.[26,27] Few countries have policies for CKD and most are unaware of the high prevalence of CKD, its contribution to other diseases, or its economic burden. Prevention, early detection and intervention are the more cost-effective strategies for CKD.

At the same time, costs for other chronic diseases are increasing. In developed countries, the care of patients with hypertension, diabetes and cardiovascular disease consumes a large fraction of health care resources.[27] The epidemic of obesity is expected to magnify these costs. Developing countries are now also experiencing the burden of these non-communicable diseases, even though communicable diseases are not yet under control. CKD is especially common in people with other chronic diseases and multiplies the risk for adverse outcomes and costs. Thus, public health policies for CKD must be coordinated with existing policies for other chronic diseases.

Recommendations

- *Governments should adopt a public health policy for CKD.* CKD is a key component of a cluster of chronic diseases,

including hypertension, diabetes, and cardiovascular disease. Within each of these groups, the CKD population is the group at highest risk and thus, highest priority for intensive care and close monitoring. Governments should partner with non-governmental organizations and industry (at the regional, national, and international levels) to support the incorporation of CKD into public health agendas.

- *Governments should support programs for screening and surveillance of CKD.* The program would document the prevalence, incidence, outcomes, care and education of the public and health care providers. Specific recommendations for screening and surveillance are contained in the report by group 2.
- *Governments should support a public awareness program for CKD.* The public awareness program should present a simple message: CKD is common, harmful, and treatable, and individuals should 'know their A, B, Cs:' **A**lbuminuria, **B**lood Pressure, **C**igarette Smoking and **C**holesterol, **D**iabetes, **E**stimated GFR, …'

Group 4: CVD risk factors as risk factors for initiation and progression of CKD

The group acknowledged the strong evidence that CKD itself is a risk factor for CVD. The group addressed development and progression of CKD as an outcome of exposure to CVD risk factors or the presence of CVD. Treatment recommendations for lowering CVD risk factor in CKD were not discussed, as many publications have focused on this topic.[12,14,28]

The group reviewed a conceptual model distinguishing risk factors for development of CKD (initiation and susceptibility) and progression of CKD to later stages including kidney failure (Figure 3) and attempted to make terminology more empirical in describing putative risk factors relating both to CKD and its outcomes (Table 6). The concept of a 'clinical intersection' between CKD and CVD was proposed as a 'high risk state' for poor health outcomes.[29] Inter-relationships of CKD and CVD include the following: (1) common risk factors (e.g., older age, diabetes, hypertension), (2) bidirectional effects of one disease process on the progression of the other (e.g., renal artery stenosis, heart failure caused by CKD), (3) adverse effects on one disease process when investigating the other (e.g., contrast-induced acute kidney injury complicating angiography), and (4) treatment biases potentially influenced by both diseases (e.g., angiotensin converting enzyme inhibitors).

The group addressed specific questions related to CVD (myocardial infarction, heart failure, etc) and CVD risk factors (diabetes, hypertension, dyslipidemia, obesity, and smoking) as risk factors for CKD, and attempted to distinguish CVD risk factors that were responsible for susceptibility to CKD from those that might be involved in initiation and progression. Although potentially useful from a conceptual standpoint, it was generally agreed that this distinction is difficult based on existing data. Furthermore,

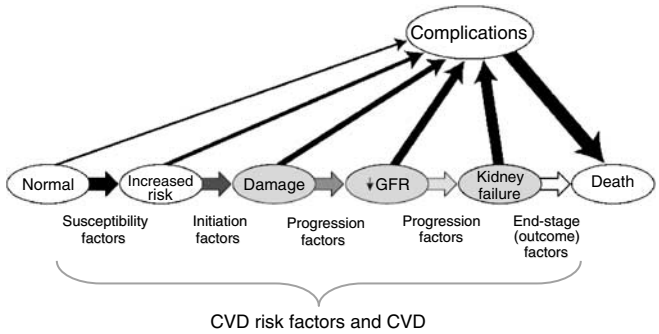

Figure 3 | Risk factors for development and progression of CKD. CVD and CVD risk factors are associated with an increased risk of transitions from one stage of CKD to the next.

some risk factors (e.g., hypertension and diabetes) may operate at all three levels (susceptibility, initiation, progression) with respect to CKD. The ability to distinguish risk factors for development from progression in observational studies has been complicated by the lack of data on albuminuria or other markers of kidney damage at baseline; thus it may be difficult to be confident that patients with an estimated GFR >60 ml/min/1.73 m^2 do not have kidney damage. In order to examine these issues better in future observational studies, it was recommended to classify risk factors as: (1) likely causal mechanism, (2) mechanism uncertain, or (3) likely to reflect non-causal association.

Research recommendations

- *Studies of CKD as an outcome should strive to:*
  - Incorporate markers of both kidney damage and function
  - Distinguish risk factors for development of CKD as well as progression to different stages of CKD
  - Study the extent to which risk factors are the same or differ across different kidney diseases
  - Include all ages, including children, and 'special populations'
- *Studies of CKD should include data on CVD risk factors and events.*
- *Studies of CVD should include data on the development and progression of CKD as an important health outcome (endpoint).*
- *Studies evaluating the impact of CVD treatments should include patients with CKD.*

Group 5: CKD as a risk factor for infections

The group focused on two topics: screening for CKD in chronic communicable diseases and vaccination strategies for CKD. Whereas both acute and chronic infections can influence the risk of development and progression of CKD,[30–35] little is known of the compounding impact of CKD on the development and outcome of chronic infections.

Infection is an important cause of morbidity and mortality among patients with kidney failure, and is the second leading cause of death following CVD.[36–39] Death

Table 6 | Approach to classification of risk factors for CKD and its outcomes

Risk factor	Hypothesized mechanism	Observed associations[a]
Development of CKD	Increase susceptibility to kidney damage	Older age, family history of chronic kidney disease, congenital or acquired reduction in kidney mass, primary hyperfiltration states, cardiovascular disease, US and European racial or ethnic minority status, low income or education
	Directly initiate kidney damage	Diabetes, high blood pressure, obesity, metabolic syndrome, dyslipidemia, hypercalcemia, autoimmune diseases, systemic infections, urinary tract infections, nephrolithiasis, urinary tract obstruction, drug toxicity
Progression of CKD	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Types of kidney disease; higher level of proteinuria,
Complications of CKD	Increase risk for complications of decreased GFR	Non-CKD factors related to hypertension, anemia, malnutrition, bone, and mineral disorders
	Accelerate onset or	Traditional CVD risk factors
	Recurrence of CVD	Non-traditional 'CKD-related' risk factors
	Increase morbidity and mortality in kidney failure	Low dialysis dose (Kt/V), fluid overload, temporary vascular access, severe anemia, low serum albumin level, late referral

CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.
[a]For many of the observations, the mechanism underlying their association with CKD is unclear and many of them may be involved at multiple levels in the pathogenesis of kidney disease and its outcomes. Factors that are implicated in the development, progression and complications of kidney disease are listed in the initial category in which they could potentially appear.
Adapted from.[87]

rates due to pneumonia and sepsis are markedly higher in dialysis patients compared with the general population (Figure 4).[40,41] These observations suggest that CKD may be a risk-multiplier for acute infectious disease-associated mortality, as it is for CVD.

The course of chronic infectious diseases might be influenced by coexisting CKD. Five infectious diseases, including the human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), tuberculosis, and malaria, are estimated to affect 873 million people worldwide.[42] Table 7 summarizes the prevalence of CKD in large cohorts of individuals with these chronic infections, and where known, its association with adverse outcomes.[43–51] Several studies, mainly of HIV and HBV infection, have revealed a strong association of CKD with increased morbidity and mortality. CKD may increase risk by adversely affecting the host immune response; alternatively, the development and progression of CKD may be a marker of more severe infection.

Many treatment-related issues have not been addressed. The accuracy of GFR estimating equations has not been studied well in patients with chronic infectious diseases, in whom muscle wasting due to malnutrition may confound estimates based on serum creatinine.[52,53] Clinical trials examining the safety and efficacy of novel anti-infectious drugs traditionally exclude patients with CKD; this is particularly true for HCV and HIV infections.[54–56]

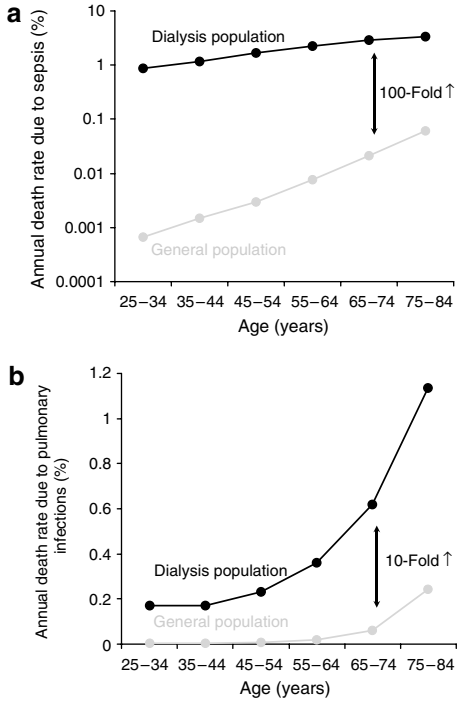

Figure 4 | Annual death rates due to sepsis (a) and pulmonary infections (b) among dialysis patients (black line) compared with the general population (gray line). The data are stratified by age and are shown on a logarithmic (**a**) or an arithmetic (**b**) scale. This figure was reproduced with permission.[37]

Recommendations

- *Screening for CKD in HIV. The guidelines of the Infectious Diseases Society of America for the management of CKD in HIV-infected patients recommend screening for kidney disease at the time of HIV diagnosis.[57] Tests should include (1) a urinalysis (for hematuria and proteinuria) and (2) a measure of kidney function (creatinine to estimate GFR). If there is no initial evidence of kidney disease, screening should be repeated annually. Semi-annual monitoring of*

Table 7 | Proposed approach to CKD as risk factor for adverse outcomes of chronic ID

ID	Measure of CKD prevalence	CKD as a risk factor for ID morbidity	CKD as a risk factor for ID mortality
HIV	HIVAN[43,44,46,47] Proteinuria[44–47] ↓ eGFR[48]	Yes (AIDS defining illness and hospitalization) Proteinuria[45–47] ↓ eGFR[45–47]	Yes Proteinuria[44–47] ↓ eGFR[48]
HCV	Proteinuria[51] ↓ eGFR[50]	Unknown	Unknown
HBV	Proteinuria[51]	Unknown	Probable ↓ eGFR[49]
Malaria	Unknown	Unknown	Unknown
TB	Unknown	Unknown	Unknown

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV hepatitis C virus; HIVAN, HIV-associated nephropathy; ID, infectious diseases. ↓, decreased.

kidney function and urinary markers of kidney damage is warranted for those receiving long-term drug therapy with toxicity to the kidney. Table 8 shows the increased risk of adverse outcomes of HIV infection in patients with CKD.[43–48] Among newly diagnosed patients with HIV, positive tests for CKD might reflect HIV-associated nephropathy, other HIV-related glomerular diseases, or drug-related toxicity,[58] but might also be caused by pre-existing hypertension, diabetes mellitus, or CVD. In countries with access to highly active anti-retroviral therapy, the incidence of HIV-associated nephropathy has declined by almost 75-fold.[59] However, in the emerging chronic disease phase of the AIDS epidemic, long-term survivors are likely to develop comorbid conditions including hypertension, diabetes mellitus, and cardiovascular disease. There is also evidence to suggest that the highly active anti-retroviral therapy-associated metabolic syndrome might constitute a novel CVD risk factor, potentially associated with CKD.[60,61]

- *Screening for CKD in HCV. The draft KDIGO clinical practice guidelines for HCV in CKD recommend screening for kidney disease at the time of HCV diagnosis and annually thereafter. Tests should include (1) a urinalysis (for hematuria and proteinuria) and (2) a measure of kidney function (serum creatinine to estimate GFR)*. The occurrence of glomerular disease in association with HCV infection is well established,[62,63] and population-level data are now available. A cross-sectional analysis in the USA demonstrated an association between HCV seropositivity and albuminuria in people over age 40 years.[50] Among individuals older than 60 years, 46% of HCV-seropositive individuals had albuminuria compared with 24% of those who were seronegative, but there was no significant association between HCV seropositivity and low eGFR. In a cross-sectional study from Taiwan, non-diabetic subjects who were HCV seropositive had an 8.3% prevalence of $\geqslant 1+$ dipstick proteinuria compared with 5.1% in the seronegative group.[51] The impact of these abnormalities on outcomes remains to be determined.
- *Screening for CKD in other chronic infections. There are insufficient data to recommend screening for kidney disease at the time of diagnosing HBV, tuberculosis, and malaria, particularly Plasmodium malariae*. It is acknowledged that acute and chronic phases of these infections can cause CKD,[30–33] that there is potential toxicity to the kidneys of drugs used to treat them,[57] and that medication dose and frequency adjustments are necessary for decreased GFR. However, there is insufficient evidence for screening and no published guidelines on the optimal timing, frequency or cost–benefit analysis of screening for CKD in these conditions.
- *Vaccination in CKD. All patients with CKD Stage 5D should be vaccinated for influenza, hepatitis B, and pneumococcus. The influenza vaccine should be offered annually. Hepatitis B vaccine should be administered at the initiation of dialysis and post-vaccine serological testing should be performed. The pneumococcal vaccine should be given at least once*. Patients with CKD stages 1–4 should receive the influenza, hepatitis B, and pneumococcal vaccine if high-risk factors coexist and in accord with regional immunization guidelines. Recommendations for organ transplant candidates and recipients were discussed at a recent KDIGO conference.[64] A compilation of published guidelines from selected countries on the use of these three vaccines is available on the KDIGO website (http://www.kdigo.org/ControConf/content-immunization.htm). The substantial heterogeneity of recommendations for CKD indicates the need to evaluate the evidence basis and harmonize immunization guidelines for CKD worldwide. In the general population, vaccination for these infections is generally safe and effective. The association of CKD with impaired host cellular and humoral immunity can result in suboptimal vaccine-induced immune response.[37,65,66] This calls for the development of a specialized immunization and monitoring program for the CKD population. Early vaccination maximizes the chance of achieving and sustaining immunity,[67,68] which in turn might benefit future kidney transplant recipients. Further research is needed in CKD stages 1–4 to answer these important questions.

Research recommendations

- *Studies to understand the risk of CKD in patients with HIV, HCV, HBV, tuberculosis, and Plasmodium malariae:*
  - Determine the prevalence of CKD.

Table 8 | Summary of studies examining the association of CKD with HIV infection

Author (reference)	Study design	Sample size	CKD predictor variable	Outcome	Results (multivariate analyses)
Lewden C (2002)[43]	Multicenter prospective cohort study (France)	1155 HIV-infected adults	Baseline and post-treatment (4-month) sCr < normal (0.9 (male) or 0.8 (female) mg/dl)	Death	At baseline: HR (95% CI) 2.4 (1.3, 4.3) At 4 months: HR 2.5 (1.0, 6.1)
Gardner LI (2003)[44]	Prospective cohort study (USA)	885 HIV-infected and 425 at-risk HIV-negative women	Baseline proteinuria (⩾2+) and/or sCr⩾1.4 mg/dl	Death	HR 2.5 (1.9, 3.3)
Gardner LI (2003)[45]	Prospective cohort study (USA)	885 HIV-infected adult women	Baseline proteinuria (⩾2+) and/or sCr⩾1.4 mg/dl	Condition-specific hospitalizations	Overall hospitalization: HR 1.5 (1.3, 1.8) Condition-specific hospitalization: AIDS-defining illness: HR 1.7 (1.1, 2.7) Kidney conditions: HR 5.0 (2.3, 11.0) Hepatic conditions: HR 1.8 (1.1, 2.8)
Szczech LA (2004)[46,47]	Prospective cohort study (USA)	2038 HIV-infected women	Proteinuria (⩾1+ on ⩾2 visits); Inverse sCr decrease	New AIDS-defining illness and death before and after widespread use of HAART	AIDS-defining illness Pre-HAART, proteinuria: HR 1.3 (1.1, 1.6) Post-HAART, 1/sCr↓: HR 1.4 (1.0, 2.1) Death Pre-HAART, proteinuria: HR 1.3 (1.1, 1.8) Pre-HAART, 1/sCr↓: HR 1.7 (1.1, 2.7) Post-HAART, proteinuria: HR 2.2 (1.3, 3.7)
Levin A (2006)[48]	Prospective cohort study (Canada)	2629 HIV-infected adults initiating anti-retroviral therapy	eGFR (MDRD 4-variable equation) < 60 ml/min/1.73 m^2	Death	eGFR < 60 ml/min/1.73 m^2: HR 1.65 (1.01, 2.71)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HAART, highly active anti-retroviral therapy; HR, hazard ratio; sCr, serum creatinine.

- Determine the optimal timing of screening for CKD in chronic infections, the frequency of testing, the sensitivity and specificity of screening tests, and the cost–benefit relationship of this approach.
- Evaluate the accuracy of GFR estimating equations in persons with chronic infections, with a particular focus on reducing the influence of confounding factors such as muscle wasting, malnutrition, and extracellular fluid volume expansion, particularly, in the setting of chronic viral liver disease.
- Examine the interaction of coexisting co-infections with CKD on morbidity and mortality, and the impact of coexisting co-infections on progression of CKD.

- *Studies of the risk of infections and the optimal use of vaccines in CKD*
  - Determine the optimal test for the diagnosis of latent tuberculosis, particularly in endemic areas worldwide.
  - Elucidate uremic factors that contribute to impaired immunity in patients with CKD, hampering effective immunization.
  - Determine the efficacy and cost-effectiveness of hepatitis B and pneumococcal vaccine in earlier stages of CKD (e.g., stage 1–4)
  - Examine whether due to impaired immunity CKD patients require a specific immunization program against highly preventable communicable diseases.

Group 6: CKD as risk factor for adverse outcomes of cancer

The group addressed the assessment of kidney function in subjects with cancer, occurrence of CKD in parallel to or secondary to cancer, use of kidney sparing therapies for kidney cancers, occurrence of cancer in subjects with CKD, screening for CKD in cancer, screening for cancer in subjects with CKD, outcomes of cancer treatment in subjects with CKD.

Assessment of kidney function in subjects with cancer is essential for dosage adjustment of chemotherapy and for assessment of treatment toxicities. Even in early stages of cancer, there may be muscle wasting, which could affect GFR estimates based on serum creatinine. GFR estimating equations have been tested with variable results. This variability may have immediate consequence, as shown in a report comparing the use of three creatinine-based formulas in subjects with bladder cancer, in which eligibility for adjuvant chemotherapy varied many fold according to the formula that was used.[69] Use of the abbreviated modification of diet in renal disease (MDRD) Study equation has been recommended by KDIGO, but the US Food and Drug Administration recommends using the Cockcroft and Gault formula.[70] Studies in cancer patients suggest new formulas may be more accurate, but they have not been validated and evaluated adequately.[71,72]

Table 9 summarizes the prevalence of CKD in individuals with cancer, and where known, the association of CKD with adverse outcomes of cancer. Kidney disease occurring in parallel to or secondary to cancer is well described. Paraneoplastic membranous glomerulopathy is an acknowledged complication of cancer, but there is only one quantitative report for this association.[73] Reduced GFR in subjects with cancer has been reported in over half of the

subjects in a study from France, but this study did not clearly distinguish whether reduced GFR was related to the cause or effects of cancer.[74] Kidney disease caused by specific cancers such as multiple myeloma is well known, but accounts for less than 1% of patients treated by dialysis in the USA. Conversely, CKD occurring after chemo- or radiotherapy is known, but has not been quantified. With the improved rates of cure of many cancers, there is a potential for increased numbers of individuals with CKD as a late effect of cancer treatment.

CKD may occur after surgery for kidney cancer. Although radical nephrectomy has been the standard surgery for localized kidney cancer for many decades, partial nephrectomy has been shown to be effective for the treatment kidney tumors less than 4 cm in diameter. Recent data suggest that a significant number of subjects with kidney cancer have CKD before treatment and an even greater number are at risk to develop an eGFR <60 ml/min/1.73 m^2 in long-term follow-up after nephrectomy for cancer.[75] In contrast to kidney donors, patients with kidney cancer are an older patient population, often with coexistent hypertension and other chronic diseases, which may be risk factors for development of CKD following nephrectomy. Consequently, for small, incidentally discovered kidney tumors, partial nephrectomy may be indicated even in patients without CKD.

CKD was also considered as a risk factor for cancer. Occurrence of cancers in subjects with CKD is well documented for kidney and bladder cancer.[76] Acquired cysts and kidney cancers are especially frequent in subjects on long-term dialysis but also occur before the start of dialysis,[77] and the growing number of kidney transplant candidates may require screening for native kidney cancers.[78] Kidney transplantation itself is associated with susceptibility to cancers,[79] mainly skin cancers and lymphomas, which appear to be related to immunosuppression rather than to reduced kidney function.

Data from the USA showed a 30% prevalence of past or present cancer in subjects starting dialysis, which was 50% higher than that of a matched non-dialysis Medicare population, and could not be explained by bladder or kidney cancers alone.[80] It is possible that risk factors common to both cancer and kidney disease, such as smoking, diabetes and obesity, may account for this apparently high prevalence of cancers at the start of dialysis. Screening for cancer in patients with end-stage renal disease has been evaluated using decision analysis. Screening for common cancers, such as breast or colon, had a very low yield and was not recommended.[81] This is likely due to the competing risks for increased mortality in dialysis patients. In subjects with earlier stages of CKD, quantitative analyses of the benefits of cancer screening are not known.

The potential for CKD as a risk factor for adverse outcomes of cancer and its treatment was also considered. This may be evident in some conditions such as multiple myeloma but is less well established in solid tumors. Analysis of a large database from Japan showed no increase in gastric, lung, or colon cancer mortality for subjects with eGFR <60 ml/min/1.73 m^2 compared with those with higher eGFR.[82] In the Cardiovascular Health Study, a longitudinal study of older people in the USA, a significant trend toward increased mortality from cancer was reported in those subjects in the highest quartile of cystatin *C* values.[21] One intriguing study reported a possible lowering of cancer risk by use of converting-enzyme inhibitors.[83] Proteinuria has been linked with poor outcome in some studies of lymphoproliferative and solid malignancies.[84] Most current phase 3 trials of cancer treatments exclude subjects with impaired kidney function. Thus, comparative data are scarce. In one study, the response rates to capecitabine or 5-fluorouracil in subjects with metastatic colorectal cancer did not differ according to estimated creatinine clearance.[85] In other studies, dose adjustment of carboplatin according to kidney function, and not body surface area, greatly improved prediction of drug levels and toxicity.[86] Newer agents, including biologicals or radionuclides, may have unsuspected kidney toxicity that can only be detected by regular testing. More regular assessment of kidney function is needed in subjects with cancer. In the USA, the National Cancer Institute (NCI) Organ Dysfunction Working Group may facilitate additional studies of cancer in patients with CKD. Communication among physicians, researchers and public health officials could be improved by harmonizing the classification of severity of CKD with the KDIGO classification.

Recommendations

- *All cancer patients should be screened for CKD at diagnosis, at initiation, and change of cancer therapy. Tests for CKD should include (1) a urinalysis (for hematuria and*

Table 9 | Proposed approach to CKD as a risk factor for adverse outcomes of cancer

Cancer type	Measure of CKD prevalence	CKD as a risk factor for cancer morbidity	CKD as a risk factor for cancer mortality
Kidney and urinary tract tumors	Yes: ↓ eGFR[75] ESRD status[76,77]	Probable: Effect on chemotherapy ↓ eGFR[69]	Probable: ↓ eGFR[69] ESRD status[76,77]
Other solid tumors	Possible:[85,88] ↓ eGFR[85] ESRD status[88]	Probable: Effect on chemotherapy ↓ eGFR[85]	Albuminuria[84] Reduced risk with ACE inhibitor treatment for CKD[83]
Hematologic malignancies	Unknown	Likely but unknown	Albuminuria[89]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ↓, decreased.

proteinuria) and (2) a measure of kidney function (serum creatinine to estimate GFR).

- *Kidney sparing interventions should be utilized in patients with kidney and uroepithelial cancers.*
- *Screening for CKD is recommended in subjects cured of cancer who are at risk for CKD, because of the type of cancer, its complications, its treatment, or other risk factors for CKD not related to cancer.*

Research recommendations

- *Cancer institutes and associations should use KDIGO definition and staging of CKD in guidelines and recommendations for detection, evaluation and treatment of cancer.*
- *Evaluate the accuracy of GFR estimating equations in cancer patients, with a particular focus on reducing the influence of confounding factors such as muscle wasting, malnutrition, and extracellular fluid volume expansion.*
- *Include CKD patients in clinical trials of cancer treatment.*

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APPENDIX

Conference participants include:

Sanjay Agarwal, India; Sharon Andreoli, United States; Mustafa Arici, Turkey; Robert Atkins, Australia; Ezequiel Bellorin-Font, Venezuela; Emmanuel Burdmann, Brazil; Rafael Burgos-Calderón, Puerto Rico; Jing Chen, United States; Eric P. Cohen, United States; Allan Collins, United States; Josef Coresh, United States; Bruce Culleton, Canada; Angel Martín De Francisco, Spain; Paul De Jong, Netherlands; Joris Delanghe, Belgium; Santos Depine, Argentina; Natale De Santo, Italy; Kai-Uwe Eckardt, Germany; John Eckfeldt, United States; Garabed Eknoyan, United States; Meguid El Nahas, United Kingdom; Bjørn Odvar Eriksen, Norway; John Gill, Canada; Matthias Girndt,

Germany; Lee Hebert, United States; William Huang, United States; Lawrence Hunsicker, United States; Enyu Imai, Japan; Ólafur Skúli Indriðason, Iceland; Fujiko Irie, Japan; Kunitoshi Iseki, Japan; Corinne Isnard-Bagnis, France; Bertrand Jaber, United States; Michel Jadoul, Belgium; Tazeen Jafar, Pakistan; Robert Jakob, Switzerland; Vivekanand Jha, India; Cynda Ann Johnson, United States; Bertram Kasiske, United States; Ivor Katz, South Africa; Norbert Lameire, Belgium; Vincent Launay-Vacher, France; Andrew Levey, United States; Adeera Levin, Canada; Nathan Levin, United States; Liz Lightstone, United Kingdom; Alison Macleod, Scotland; Seiichi Matsuo, Japan; Peter McCullough, United States; W. Greg Miller, United States; Donal O'Donoghue, United Kingdom; Runólfur Pálsson, Iceland; Neil Powe, United States; Giuseppe Remuzzi, Italy; Miguel Riella, Brazil; Paul Roderick, United Kingdom; Jerome Rossert, France; Boleslaw Rutkowski, Poland; Rajiv Saran, United States; Robert Schrier, United States; David Seccombe, Canada; Faissal Shaheen, Saudi Arabia; Lesley Stevens, United States; Charlie Tomson, United Kingdom; Yusuke Tsukamoto, Japan; Katherine Tuttle, United States; Raymond Vanholder, Belgium; Joseph Vassalotti, United States; Rowan Walker, Australia; Haiyan Wang, People's Republic Of China; Christoph Wanner, Germany; David Warnock, United States; David Wheeler, United Kingdom; Luxia Zhang, People's Republic Of China; Carmine Zocalli, Italy.