

Preventing CKD in Low- and Middle-Income Countries: A Call for Urgent Action



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The epidemiologic transition occurring in low- and middle-income countries (LMICs) has led to a surge in chronic kidney disease (CKD) prevalence because of a combination of highly prevalent chronic non-communicable diseases (NCDs) and communicable diseases (CDs). The progressive rise in CKD prevalence in LMICs threatens the existing weak health systems in these countries as care for advanced CKD remains largely unavailable and unaffordable. An interplay of low literacy levels, poor health-seeking behavior, inadequate health care funding, weak health systems, and lack of skilled nephrology workforce has made it difficult for adequate CKD preventive measures to be implemented. Primary, secondary, and tertiary prevention measures need to be instituted in LMICs by a collaboration of governmental and nongovernmental organizations to stem this tide and help prevent deaths from other NCDs that share similar risk factors with CKD. For these to be effective, locally relevant knowledge is needed to contextualize existing prevention and control solutions, or to develop novel and more appropriate solutions for LMICs.

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CKD is defined as the presence of functional (estimated glomerular filtration rate [GFR] <60 mL/min per 1.73 m²) or structural abnormalities of the kidney persisting beyond 3 months.¹ CKD has long become, and persistently remains, an NCD of public health dimensions and importance that cannot be overstated. Although in 1990, CKD was the 27th leading global cause of death² accounting for a mean age-standardized death rate of 11.1 per 100,000 population, it rapidly gained prominence as a global cause of death by becoming the 18th cause-specific cause of death 2 decades later. Relentlessly still, between 2007 and 2017, it remained the 16th leading cause of premature death, accounting for a mean of 359.4 years of life lost per 100,000 population globally in 2017.³ According to recently published Global Burden of Disease data, CKD accounted for as high as 369.6 per 100,000 age-standardized years of life lost in 2017. To contextualize the magnitude of this statistic, HIV/AIDS and drug-susceptible tuberculosis coinfection accounted for a maximum of 180.0 per 100,000 age-standardized years

of life lost in the same year.³ These dismal figures reflect a global average of the burden of CKD, however, and it must be noted that national and regional epidemiologic differences exist; these differences reveal disproportionate ramifications of the burden of CKD, with LMICs most affected.⁴ The United States Renal Data System data indicate that the prevalence of CKD has remained stable in the United States in the last 2 decades, with prevalence rates of all stages of CKD being 14.8% between 2013 and 2016.⁵ Similarly, across Europe,⁶ prevalence rates of stages 3–5 of CKD have been demonstrated to be between 4.1% and 25.3%. This review discusses the peculiarities of CKD in LMICs and various preventive measures to reduce the prevalence of CKD in these regions.

CKD in LMICs

Though an NCD by its very nature, CKD occurs as a chronic complication of either other NCDs such as systemic hypertension, diabetes mellitus, or a complication of CDs such as HIV, hepatitis B, hepatitis C, and schistosomiasis. Race and ethnicity are also established nonmodifiable determinants of CKD.⁷ The epidemiologic transition plaguing LMICs presents a precarious position in which NCDs such as diabetes mellitus and systemic hypertension are the most frequent causes of CKD and end-stage renal disease (ESRD) in developed

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nations, whereas a distinctive mélange of non-modifiable risk factors, NCDs, and CDs are at play in LMICs. Unlike in high-income countries where prevalence rates are relatively homogeneous, rates are rather heterogeneous in LMICs, varying as widely as between 5.5% in Bolivia and 29.9% in China.⁸ Although variability in prevalence can be explained by different sample population characteristics as well as a nonuniform definition of CKD, it also possibly reflects the differing contributions of the various CKD risk factors to disease occurrence across different countries and regions. Globally, for example, HIV-related CKD is most prevalent in Africa, with prevalence rates of 7.9%.⁹ Furthermore, within the African continent, the prevalence of HIV-related CKD is highest within the West African subregion at 14.6% compared with Southern Africa, which has estimated rates of 3.2%.⁹

CKD in LMICs tends to occur earlier and appears to be more severe. This is not unrelated to genetic and CD factors. The frequent occurrence of *APOL1* renal risk variants in West Africa may be a primary reason for the disproportionately high prevalence of CKD in this region.^{10,11} This genetic risk has been complicated by the high prevalence of HIV in Sub-Saharan Africa, which acts as a “second hit,” initiating and facilitating the progression of CKD.¹² It is possible that other CDs also act as factors modulating CKD progression in the milieu of genetic risk. Rural agricultural communities in Sri Lanka,¹³ India,¹⁴ and Central America^{15,16} have frequent occurrences of CKD of unknown etiology. The renal disadvantage of indigenes of LMICs occurs early in fetal life as maternal protein malnutrition is linked with reduced fetal nephron numbers and subsequent increased risk of CKD.¹⁷ Another peculiarity of CKD in LMICs includes the widespread use of herbal medications that cause chronic interstitial nephritis.¹⁸ Also, the high prevalence of fake and counterfeit medicines (as much as 10%–60%) in LMICs^{19,20} may be a significant cause of CKD though not well quantified. The relatively high incidence of hematologic disorders like sickle cell anaemia^{21,22} and the sickle cell trait^{23,24} and other hemoglobinopathies²⁴ in West African communities may also contribute to the higher CKD prevalence and increased variability regarding CKD in LMICs. An understanding of these peculiarities of CKD in LMICs underscores the need for appropriate and targeted CKD preventive strategies at all levels (primary, secondary, and tertiary) if the current burden in LMICs is to be mitigated. Stemming the tide of CKD in these regions and its ensuing complications should thus become a global health priority. These figures underscore, in addition, the urgent call to action against CKD, especially in LMICs that bear the disproportionate burden of disease.

Prevention of CKD

Preventive approaches to CKD and its attendant complications can be primary, secondary, or tertiary—the appropriate level at which to deploy a strategy being determined by CKD severity, that is, CKD staging (Figure 1). CKD is classified into 5 stages, 1 through 5, with the progression from stages 1 to 5 representing the worsening renal function and increasing morbidity (such as cardiovascular disease [CVD], anaemia, and mineral bone disease) and mortality. The epidemiologic spectrum of CKD can be described as an inverted pyramid in which an inordinately larger proportion of patients are represented in the earlier stages of CKD 1–3 relative to the later stages of 4 and 5.²⁵ Additionally, the earlier stages of CKD are usually asymptomatic, with ESRD—CKD stage 5—representing the end of the spectrum. Renal replacement therapies must be instituted in ESRD; otherwise, mortality is inevitable. The disproportionately top-heavy range of disease is accounted for by the fact that patients in the earlier stages of CKD are more likely to die from the disease than progress to ESRD.

Nevertheless, both CKD and ESRD are associated with enormous health care costs as previously highlighted. Increasing the awareness of CKD risk factors before the onset of CKD in at-risk cohorts and the general population is the objective of primary preventive efforts whereas early detection and diagnosis is the objective of secondary efforts. In those already known with CKD, tertiary prevention focuses on retarding the progression of CKD; specifically, tertiary prevention modifies the natural history of CKD.

Primary Prevention of CKD

There are shared risk factors between CKD and CVD, with CKD equally being a risk factor for CVD. This makes preventive strategies for CVD quite relevant and applicable to CKD prevention, especially at the level of primary prevention. CKD primary prevention aims at reducing the incidence of CKD risk factors such as hypertension, diabetes, and smoking in the general population²⁶ as well as lowering CKD occurrence as a complication in at-risk groups. Preventive measures to obviate the occurrence of CKD risk factors are directed at influencing predisposing behavioral patterns and include the promotion of healthy lifestyle choices, such as dietary salt restriction for hypertension prevention²⁷; abstinence from smoking and alcohol; and increased physical activity and adoption of low-calorie, low-fat diets to reduce the risk of obesity and diabetes. A 58% reduction in the incidence of type 2 diabetes with intense lifestyle intervention over 3 years was demonstrated in the Diabetes Prevention Program^{28,29}; the US Diabetes Prevention Program Outcomes Study

PRIMARY PREVENTION	SECONDARY PREVENTION	TERTIARY PREVENTION
<p><u>Aim:</u> obviate or minimize the risk of CKD occurrence</p> <p><u>Strategy/strategies:</u></p> <ul style="list-style-type: none"> • Promote healthy lifestyle choices such as increased physical activity and dietary salt restriction • Influence predisposing behavioral patterns, e.g., smoking cessation, abstinence from alcohol, and restrict the use of over-the-counter medications and herbal preparations • Health education about CKD and its risk factors <ul style="list-style-type: none"> • World Kidney Day 	<p><u>Aim:</u> Early detection and treatment of CKD</p> <p><u>Strategy/strategies:</u></p> <ul style="list-style-type: none"> • Screening for risk factors for kidney disease as well as the presence of CKD <p>Two-staged approach to screening in LMICs:</p> <ol style="list-style-type: none"> 1. Screen to identify individuals unaware of the presence of hypertension, diabetes 2. Identified individuals screened for the presence of CKD and appropriate treatment instituted 	<p><u>Aim:</u> Prevent the progression of CKD</p> <p><u>Strategy/strategies:</u></p> <ul style="list-style-type: none"> • Effective control of blood pressure <ul style="list-style-type: none"> • <140/90 mm Hg • <130/80 mm Hg if UA >30 mg/24 h • Effective control of albuminuria/proteinuria <ul style="list-style-type: none"> • Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

Figure 1. Overview of chronic kidney disease (CKD) prevention strategies in low- and middle-income countries (LMICs). UA, urine albumin.

similarly showed a 27% reduction over 15 years. A population strategy influences collective behavior, which in turn improves the health outcomes of a population while also improving the distribution of these outcomes within the population. As seminally highlighted by Rose,³⁰ the determinants of the incidence or prevalence rates of disease are a product of population characteristics rather than that of individual traits. If the disease burden of CKD is to be significantly diminished, population-based strategies cannot be overemphasized. Population-focused, life-style-directed plans, however, affect long-term changes that are only prospectively appreciated and not instantaneously. Integration into public health policies together with long-term government support is, therefore, a necessity for this strategy.

Health education to increase awareness about CKD and its risk factors is an equally important strategy in the primary prevention of CKD at the population level. Increased awareness potentially improves health-seeking behavior and utilization of health services among individuals as well as health care providers at the primary care level. A heightened level of awareness is especially applicable in LMICs, where the knowledge of CKD and determinants is low.³¹ The vehicle of the World Kidney Day has been a most useful tool for raising and spreading awareness about CKD, including screening for CKD and its risk factors in LMICs. In LMICs, the screening programs associated with the World Kidney Day may be the only opportunity to have a free assessment of renal function as many cannot afford the cost of screening or the basic screening tests are not routinely available in these regions. Governments, nongovernmental organizations, and private entities could use the World Kidney Day vehicle for

early identification of CKD and institution of adequate treatment modalities to prevent CKD progression even in difficult-to-reach and underserved communities. We suggest a World Kidney Day theme that focuses on the rural populace in LMICs, which would encourage channeling of funds to these disadvantaged populations.

Secondary Prevention of CKD

Early detection and treatment of CKD have been demonstrated to impact positively on the morbidity and mortality outcomes and constitute the cornerstone of secondary prevention in CKD. As stated earlier, the early stages of CKD are relatively asymptomatic, and individuals in the general population or individuals with predisposing high-risk conditions, especially in LMICs, are usually unaware of the presence of CKD. Screening as a preventive strategy endeavors to appropriately identify such individuals to institute early treatment. Early management of the asymptomatic stages of CKD is known to have the potential to prevent the progression of CKD. Albuminuria as an attribute of CKD is an integral component of the definition, staging, and prognostication of CKD and is consequently a standard parameter used in CKD screening. Although there is broad consensus on the utility of albuminuria screening of at-risk groups for CKD, no adequate evidence is available to justify screening of the general population, the primary reason being the low yield of treatable cases with albuminuria-based screening, especially in young adults. The average age of onset of CKD in LMICs, however, is the fourth decade of life,⁸ and this reasoning may not hold in this region. An argument against population-based screening strategies may hold in high-income

countries but not in LMICs, where the level of awareness of CKD and its risk factors is low and thus remains undiagnosed in the general population. In a community screen of semiurban and rural people, the prevalence of CKD was 11.4%,³² whereas the age- and gender-adjusted prevalence rate of hypertension was 26.1%. In a community-based CKD screening program in Dharan, Nepal, the prevalence rate of hypertension was 38.7%³³ in the study population with a mean age of 42.9 ± 14.9 years; in approximately 1 in 2 individuals, hypertension was newly diagnosed, and only 51% of patients with known hypertension were receiving treatment. Data by Ulası *et al.*³⁴ show even more staggering figures from a community CKD screening in an urban area of Nigeria in which 7 of 10 individuals who received a diagnosis of hypertension were previously unaware of their condition. Population or community screening is needed in these regions and would require customization to increase the yield of positive cases, minimize screening-related costs, and avoid unwarranted treatment of false positives. A 2-staged screening strategy is proposed, one in which there is a first screening to identify individuals with previously unknown CKD risk factors, with those duly identified then getting screened for CKD. Kengne *et al.*³⁵ had in an earlier review proposed the use of risk scores and questionnaires to identify CKD risk and subsequent biochemical testing such as estimated GFR and albuminuria determination alone or in combination.

Tertiary Prevention of CKD

CKD is a progressive disease, with increasing severity being associated with increased risks of CVD, CVD-related mortality, and all-cause mortality in both the general and at-risk population.³⁶ Matsushita *et al.*³⁷ demonstrated that a GFR of 15–29 ml/min per 1.73 m^2 with clinically significant albuminuria (albumin-to-creatinine ratio 30–299 mg/g) was associated with a 300% increase in the hazard of all-cause mortality relative to a GFR of 90–104 ml/min per 1.73 m^2 in a general population cohort.³⁸ This same trend obtains among high-risk cohorts. Relative to an estimated GFR of 75–89 ml/min per 1.73 m^2 , the hazard for all-cause mortality in CKD stage 4 (estimated GFR 15–29 ml/min per 1.73 m^2) was 300% the hazard for CKD stage 2 (estimated GFR 60–89 ml/min per 1.73 m^2). Tertiary prevention in CKD, therefore, aims at retarding the progression of CKD along its continuum of worsening renal function, which in turn reduces CVD and mortality. Two important modifiable risk factors for CKD progression are hypertension and proteinuria,^{39,40} and their effective treatment should be the target of tertiary prevention. Meta-analytic data⁴¹ show that intensive control of blood pressure (BP) reduces the composite

outcome of renal failure by 17% (hazard ratio 0.82, 95% confidence interval 0.68–0.98) and progression to ESRD by 18% (hazard ratio 0.79, 95% confidence interval 0.67–0.93). The Kidney Disease: Improving Global Outcomes guideline for BP management in CKD recommends targeting systolic BP <140 mm Hg and diastolic BP <90 mm Hg in both diabetic and nondiabetic CKD patients irrespective of CKD stage. Even lower targets of systolic BP <130 mm Hg and diastolic BP <80 mm Hg are recommended in all CKD patients with clinically significant urine albumin levels, that is, >30 mg per 24 hours. Blood pressure reduction with antihypertensives such as angiotensin-converting enzyme inhibitors, angiotensin aldosterone receptor blockers, non-dihydropyridine calcium channel blockers such as verapamil, or diltiazem is pervasively used clinically. There are, however, no firm recommendations for their use as the antihypertensives of choice for BP control over other agents when albuminuria is between 30 and 300 mg per 24 hours,⁴² as the evidence for their supposedly superior roles in this cohort come from observational data and subgroup and *post hoc* data analysis of clinical trials.^{43–47} Indeed, the Kidney Disease: Improving Global Outcomes guideline only makes a grade level 2D suggestion for their use in this scenario. The evidence is, however, more robust for the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for BP control over other agents when urine albumin is >300 mg per 24 hours in both diabetic and nondiabetic CKD, with Kidney Disease: Improving Global Outcomes recommending their use for BP control in patients when urine albumin >300 mg per 24 hours.^{48–51}

The reduction of proteinuria as a strategy in retarding CKD progression is closely linked with BP control as there are shared pathophysiologic mechanisms⁵² and therapeutic agents, that is, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Agents such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have dual pharmacologic capabilities—BP and albuminuria reduction. These unique abilities are possible because of their actions on both systemic and intrarenal renin–angiotensin–aldosterone system, which result in the lowering of not only systemic hypertension but also intraglomerular hypertension and glomerular hyperfiltration—pathophysiologic processes that are central to the occurrence of proteinuria.⁵³ In the Ramipril Efficacy in Nephropathy study,^{54,55} investigators explored the effect of Ramipril with standard therapy versus placebo with standard treatment in patients with nondiabetic, proteinuric CKD and found Ramipril to significantly slow the decline in GFR (0.53 ml/min [standard error 0.08] vs 0.88 ml/min

[standard error 0.13]; $P = 0.03$). This effect remained statistically significant even after adjusting for BP control. Follow-up data of the subsets with proteinuria between 1–3 g per 24 hours and >3 g per 24 hours showed a continued deceleration in the rate of GFR decline and progression to ESRD.⁴⁸ Among patients with non-nephrotic proteinuria, lower baseline GFR, and higher baseline urine protein levels, a more significant effect of Ramipril on renal endpoints was evident.⁴⁸ The GISEN (Gruppo Italiano di Studi Epidemiologici in Nefrologia) investigators further have been able to also prove the independent role of proteinuria reduction, apart from BP control, in slowing CKD progression and improving outcomes.³⁹

The scarce availability of resources, reduced availability and access to dialytic therapies, few to non-existent kidney transplantation programs, and competing health care-related costs from CDs and other NCDs, emphasize the opinion that promoting tertiary prevention of CKD over primary and secondary level prevention in LMICs may not have the very much desired impact of appreciably changing the epidemiology of CKD in these countries. An understanding of the double-barreled contribution of CDs and NCDs to CKD occurrence underscores the need for appropriate and targeted CKD preventive strategies, as one-size-fits-all preventive approaches may not be of value across the board; prevention programs that have been successfully deployed in high-income countries may not succeed in LMICs. Given the more enormous economic and population health ramifications of CKD and its complications in LMICs, preventive strategies ought to have a more public health and policy thrust.

Hindrances to CKD Prevention in LMICs

Poor Funding of Health Care

Many LMICs have a median health expenditure per capita per annum of between US\$100 and US\$400 compared with US\$2000 in high-income countries.⁵⁶ This is despite having only 20% of the world population living in high-income countries. The competition for the scarce resources is worsened by a double burden of disease caused by the growing epidemiologic transition in LMICs. Policymakers in LMICs must make difficult decisions about the allocation of resources between infectious diseases killing the young and under-5 population and chronic NCDs like CKD, which affect mostly adults and the elderly. The lack of funds will, for a long time, impede progress in CKD prevention and early detection.

Weak Health Systems

In many LMICs, especially Sub-Saharan Africa, the health systems have been weakened by lack of human resources and skilled workforce, lack of facilities, and a

nonsustainable structure. Many LMICs have a dysfunctional primary health care system, which is pivotal for the success of the earlier-discussed screening programs. The nonfunctionality of the primary health systems makes the follow-up of individuals with early CKD extremely difficult. One of the primary pillars of primary health care is the encouragement of an integrated approach to health care instead of running parallel programs for specific disease entities. This approach would seem to work very well in LMICs where resources are scarce and there is a double burden of CDs and NCDs.

An example is the integration of diabetes and hypertension care in existing HIV clinic systems in Cambodia.⁵⁷ Another vital principle of primary health care is community participation.⁵⁸ Health promotion activities that ensure primary prevention of CKD may be more easily implemented in LMICs where there is still communal living, especially in the rural communities. One of the guiding principles for screening programs is that case finding should be a continuous process and not a “once and for all” project⁵⁹ as it is being done in many LMICs for CKD. A functional primary health system will ensure that screening the members of the community is a continuous process. Governments of LMICs need to get their primary health care system to function well if there is any hope of tackling the surge of NCDs including CKD.

Cost of Screening Programs

A significant concern about the success of screening programs is the question of who pays for the screening. The Screening and Early Evaluation of Kidney Disease (SEEK) program in Thailand⁶⁰ was partly funded by the government and a big pharmaceutical company. A pharmaceutical company funded a similar screening program in India.⁶¹ Similar large community-based screening programs for CKD are sparse in Sub-Saharan Africa. Out-of-pocket expenditure for CKD screening services will most likely discourage inhabitants of the rural areas of LMICs.

Moreover, there has been little data in LMICs showing the cost-effectiveness of community-based screening programs,³⁴ which makes it difficult for health policy makers in these regions to take well-informed decisions about paying for CKD screening programs. Health policy makers in LMICs should provide funds for these screening programs, especially for the at-risk population. Multinational corporations operating in LMICs should be encouraged to sponsor screening programs as part of their corporate social responsibility.

Lack of Locally Relevant Data

Many LMICs, especially in sub-Saharan Africa, do not have local data that document the burden of CKD and

its traditional risk factors. This limitation makes planning for prevention and treatment programs difficult. The heterogeneity of the different racial groups in LMICs requires local data in various ethnic and language groups. Also, the different GFR estimating equations may have different sensitivities across the various ethnic groups and CKD etiologies, leading to possible CKD classification errors. Local research is therefore vital, not just for the documentation of the prevalence of CKD and its risk factors but also in generating knowledge regarding attitudes and practices that would facilitate the implementation of CKD prevention and treatment programs in LMICs.

Lack of Skilled Workforce

Globally, there is a shortage of skilled nephrology personnel, which is more acute in the developing world.⁶¹ This shortage makes secondary and tertiary prevention programs challenging to see through as the number of persons with CKD requiring prevention of progression may overwhelm the available workforce. The various intervention programs of the International Society of Nephrology, including short- and long-term fellowships and educational ambassador programs, have helped train the different cadre of the nephrology workforce in the LMICs, but there is still a considerable gap that could be filled by long-term training programs instituted by health policy makers in various LMICs. As part of the effective use of health care personnel in LMICs for the prevention of CKD, task-shifting may be most useful in bridging the wide gap caused by a paucity of skilled nephrology workforce.⁶² LMICs can leverage on the various International Society of Nephrology educational programs to train non-nephrology workforce personnel to acquire basic laboratory skills necessary for the various screening programs. Also, with the improvement in penetration of mobile phone and telemedicine systems in LMICs, remote provision of educational resources and early intervention become increasingly possible.

Conclusion

The scourge of CKD in LMICs is likely to increase in severity and possibly weaken further the already faulty health systems in these countries if governments, nongovernmental organizations, and individuals do not evolve cost-effective and functional programs to enhance early identification and prevention of CKD progression.

DISCLOSURE

All the authors declared no competing interests.

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