Screening for chronic kidney disease in emerging countries: feasibility and hurdles*

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The burden of chronic kidney diseases

Chronic kidney disease (CKD) is a worldwide threat to public health, but the dimension of the problem is probably not fully appreciated. There are ∼1.8 million people in the world who are alive simply because they have access to one form or another of renal replacement therapy [1]. Ninety percent of those live in high-income countries, where the average gross income is in excess of US $10000 per capita. However, the prevalence rate of renal replacement therapy varies among countries particularly in the emerging world, and this is related to the capacity of the health system to provide such a costly treatment rather than a true difference in epidemiology of renal disease [2]. Although data on the prevalence of predialysis CKD in low- and middle-income countries are sparse, we would expect that there are at least comparable numbers of patients with CKD in poor countries as in developed nations. Some examples indicate that the overall prevalence of CKD is 21%, 10.6% and 11% in urban areas, respectively, of Moldova [3], Nepal [4] and China [5]. Data from India also suggest that in a developing country the prevalence rate of CKD could vary almost 5-fold between rural and city populations [6,7]. These observations imply that CKD would affect not only very many people in the developing world, but preferentially the poor within these countries who usually have no information about disease and risk factors and cannot have access to health care.

It is also increasingly recognized that the burden of CKD is not limited to its implications on demands for renal replacement therapy (dialysis or kidney transplantation), but has major impact on the overall population health. Indeed, patients with reduced kidney function portend a population not only at risk for progression of renal disease and development of end-stage renal disease (ESRD), but also at far greater likelihood for cardiovascular disease (CVD) [8]. However, human resources and financial support of medical programmes by local governments are very limited in many developing nations, which are major hurdles for effective interventions to control non-communicable chronic diseases.

Screening for CKD and risk factors

The objective of early diagnosis is the early detection of asymptomatic diseases when intervention has a reasonable potential to have a positive impact on outcome. Chronic care has tended to screen high-risk individuals for chronic disease. Currently, screening for CKD is accepted practice only in patients with hypertension or diabetes [9,10]. However, recent evidence from a survey in Norway on 65604 people indicates that a high-risk screening model targeting only those with diabetes or hypertension would identify less than half of those with CKD [11]. Moreover, particularly in developing countries, many individuals are not aware that they have diabetes, hypertension or proteinuria. For example, among 1243 subjects with high blood pressure in Dharan, Nepal, 47% were newly detected during the screening [4]. These findings raise doubt whether we should limit our screening strategies to those with known risk factors or preferably should screen the general population. Thus, more widespread screening for CKD is increasingly proposed [1].

In limited, although extremely important, experiences aimed to reduce the burden of CKD, it has been shown that community-based screening programmes are feasible in poor countries. The Kidney Help Trust of Chennai, India [6], has embark on a screening programme in an area of 25000 people. Trained social and health workers have recorded blood pressure, checked for abnormal glucose levels and for the presence of protein in the urine. This survey
Fig. 1. Early detection and intervention programmes ongoing or planned to start in 2009 in low- and middle-income countries, based on the template proposed by the ISN-COMGAN Research and Prevention Committee.

showed hypertension in 5.2%, diabetes in 3.6%, kidney disease without renal dysfunction in 0.68% and chronic renal failure in 0.16% of the screened population [6]. CKD and risk factors for CKD has been screened at community level in Dharan, Nepal, in more than 3000 apparently healthy subjects [12]. The burden of CKD risk factors such as diabetes (9.3%), hypertension (27%), overweight (25%) and smoking (35%) was high. In a subset group, CKD was detected in 10.6% of screened subjects.

Other screening strategies may also be considered for emerging countries according to the local facilities, which may include a screening test applied to people attending the doctor or medical facilities for another reason. This strategy has been adopted in La Paz, Bolivia, and in Chisinau, Moldova, as part of a screening aimed at early detection of hypertension, diabetes, obesity and CKD. Overall, however, studies are scant and there is no strong evidence to favour one or the other of the screening approaches in developing countries.

Simple and cheap screenings are feasible

Screening for CKD has relied on measurement of albumin or protein in the urine for the detection of patients with, or at risk of developing CKD [13]. Both albuminuria and proteinuria are associated with an increased risk of progressive kidney disease and ESRD [14–16], and an increased risk of myocardial infarction, stroke and premature death in the general population [17–23]. Some have questioned the value of mass population screening for proteinuria, reasoning that its yield of treatable diseases, especially in young adults, is too low to be justifiable [24]. Dipstick urine analysis has imperfect accuracy in the diagnosis of persistent proteinuria, but can be performed in most medical settings [25], including the low-resource environment. However, the dipstick test for proteinuria is semi-quantitative, and insensitive to detect reliably albumin concentrations in ranges <300 mg/day albumin. Various antibody-based methods are used to measure lower levels of urinary albumin, including RIA, nephelometry, immunoturbidimetry and ELISA, but all require costly laboratory facilities not easily affordable in poor countries [26]. There are also antibody-based dipstick tests for microalbuminuria [27]. Although only semi-quantitative, these tests have the advantage that they can be used easily by the general practitioners and health workers in large screening programmes. However, the cost of the tests is still too high for low-resource settings (~€1.6 per test), making this approach unsuitable, at least for community screening. An alternatively possibility is now provided in this issue of the Journal by Lundimu Tugirimana and Delanghe [28]. They have developed a single spot urine test that allows us to quantify microalbuminuria without the use of antibodies, by spotting few microlitres of urine on cellulose acetate strips and staining them with a sensitive protein-binding dye such as Coomassie Blue R-250. Besides being sensitive enough to detect albumin in the urine, the test is technically simple and very cheap with an estimated cost of ~€0.02 per test. This makes the proposed method potentially suited for screening programmes, in particular in poor countries.

Thus, screening in developing countries can be implemented with simple, cheap and reliable tests, such as
measurement of body weight, blood pressure and multistick urine analysis for protein or albumin, glucose and blood. These simple parameters can be used to identify people at higher risk of CKD and progression to ESRD not only in populations with established risks such as those with obesity, hypertension or diabetes, but also as in those developing countries where ESRD is apparently uncommon due to premature mortality. Moreover, with this approach risk factor parameters for CKD and ESRD can be easily measured using only a scale for body weight, a sphygmomanometer for blood pressure and a dipstick for urinalysis.

This would remarkably reduce the cost for screening programmes and would increase the feasibility, particularly when the resources are limited.

An additional open issue is whether screening translates into effective benefit for the health system in a given country. Studies in developed countries on cost-effectiveness of tertiary prevention of CKD by treatment of hypertension, albuminuria and the use of renin–angiotensin system inhibitors have shown that early intervention appears to be more cost-effective than late intervention. Unfortunately, in the emerging world, information about cost-effectiveness of screening and intervention programmes targeted on hypertension, diabetes and proteinuria are lacking or very incomplete, warranting further research.

Conclusion

Medicine is developing evidence for non-communicable chronic disease, including cardiovascular and kidney diseases, but has no equity plan. A more concerted, strategic and multisectorial approach, underpinned by solid research is essential to help reverse the negative trends in incidence of these chronic diseases, not just for few beneficiaries but on a global health equity programme.

For that, well-defined population screening and intervention programmes have to be initiated in developing countries. Along these lines, the Research and Prevention Committee of the International Society of Nephrology (ISN)-COMGAN has developed a global early detection and intervention programme for emerging countries that can be implemented according to the peculiar needs and organization facilities of the given country (Figure 1). It is expected that this kind of population screening can increase health awareness, particularly in countries with less sophisticated health systems and help detect a significant proportion of under diagnosed individuals with chronic renal and/or CVs.

Overall, the emphasis is on a model to promote and foster autonomous prevention programmes in regions where they are most needed.

The hope is to help reverse the negative trend in the incidence of those chronic diseases in emerging countries and overcome the cost and complexity of renal replacement therapy out of reach for these low-income environments.

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Taking aim at targets*

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Since the mid-1990s, many studies showing increased mortality with higher serum calcium [1], phosphorus [2] and parathyroid hormone (PTH) [3] levels in dialysis-dependent patients have been reported. By 2003, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) released guidelines for mineral metabolism for all stages of chronic kidney disease (CKD) that have been influential in determining practice patterns [4]. For stage 5 CKD (estimated GFR <15 ml/min/1.73 m²), these guidelines prescribed serum targets of 16.5–33 pmol/l (150–300 pg/ml) for PTH, 1.1–1.8 mmol/l (3.5–5.5 mg/dl) for phosphorus and 2.1–2.4 mmol/l (8.4–9.5 mg/dl) for calcium. Target ranges for serum calcium, phosphorus and PTH were developed by K/DOQI based on the available literature of the time and have been both standard practice for clinical care [5,6] and primary outcomes for research [7,8] ever since. While the majority of early reports linking mineral metabolism to survival were related to dialysis patients, subsequent observational analyses confirmed similar associations in all CKD stages [9–15], kidney transplant recipients [16] and other populations [17,18]. Given the apparent link between mineral metabolism and patient-level outcomes in CKD, an expanding pharmaceutical armamentarium (vitamin D compounds, phosphate binders and calcimimetics) has become available; since publication of the K/DOQI guidelines on bone and mineral metabolism the use of these drugs has increased significantly, as have the related costs [19].

That altered mineral metabolism in CKD causes cardiovascular disease is biologically plausible. An osteoblastic phenotype in human vascular tissue [20] is actively up-regulated by altered levels of phosphorus [21], PTH [22] and other stimulatory factors in uraemic serum, resulting in vascular calcification [23] and potentially accelerated...