

# CHRONIC KIDNEY DISEASE PREVENTION IN INDIA: WHERE ARE WE NOW AND WHERE DO WE GO FROM HERE?

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**Abstract:** Chronic kidney disease has emerged as a worldwide public health problem in recent years. Data from advanced countries suggest that 10-15% of general population suffers from CKD, and population on RRT represents but the tip of an iceberg of CKD population. Even early stages of CKD increase cardiovascular disease risk and reduce quality of life. The CVD risk in non-ESRD CKD patients is 10-30 times that of people without kidney disease. The annual crude and age-adjusted ESRD incidence rates in India have been estimated at 151 and 232 per million population respectively. ESRD patients belonging to the disadvantaged strata of the society often present for the first time with advanced renal failure, over two-thirds have not had prior medical care, and 75% present with complications that necessitate dialysis within 48 hours of arrival. Early detection of CKD entails screening high risk population such as those with diabetes, hypertension, cardiovascular disease and a family history of CKD by urinalysis and estimation of GFR using any prediction equation. Appropriate preventive strategies include a good blood pressure control to values lower than previously recommended (<120/75-80) and reduction of proteinuria to the lowest possible values (preferably <1 g/day). Drugs that block the rennin-angiotensin-aldosterone axis are preferred antihypertensive and antiproteinuric agents both for prevention of CKD progression and minimizing CVD risk. Additional measures include maintaining careful glycemic control in individuals with diabetes, treating dyslipidemia, losing weight, quitting smoking, and managing anemia. There is also evidence that outcomes can be improved by providing these individuals with specialist nephrology care early in disease. CKD incidence would continue to rise in the foreseeable future unless public health policies are altered to deal with this increasing menace.

## INTRODUCTION

The last few decades have been characterized by significant demographic changes in India. The life expectancy has risen from 41.2 years in 1951-1961 to 64.7 years in 2006, and the population growth rate has declined to 1.38%. About 65% Indians are in the age range of 15-65 years (<https://cia.gov/cia/publications/factbook/geos/in.html>). This has been the result of advances in medical practice and technology, eradication of communicable diseases, reduction of nutritional deficiency states and maternal and infant mortality, urbanization and economic improvement. As in the rest of the world, the increasing longevity has led to an increase in the risk of non-communicable chronic diseases related to adoption of an urban lifestyle, unhealthy diet, lack of physical activity and tobacco and alcohol abuse<sup>1</sup>. The list encompasses entities such as diabetes, hypertension, obesity, cardiovascular disease (CVD) and cancer. Chronic kidney disease (CKD), neglected until recently by medical professionals, is now recognized as central player in the network of major chronic diseases. The initial realization came from registry data from industrialized nations where dramatic and unexpected increases in the incident and prevalent end-stage renal disease (ESRD) cases entering dialysis programs were observed. In 1984, Eggers et al<sup>2</sup> estimated that 117,200 patients would be receiving renal replacement therapy (RRT) in USA by 2000. However, these projections were overtaken by reality: the United States Renal Data System recorded a total of 378,862, with a point prevalence rate of 1367 patients per million population in 2000<sup>3</sup>. More recently, it has been recognized that RRT represents the tip of an iceberg of CKD population, with the number of those with CKD not yet requiring RRT being much greater. According to the Third National Health and Nutrition Evaluation Survey of the USA (NHANES III), the prevalence of CKD in the US adult population was estimated as 10.8%. A total of 4.98% of the male population and 1.55% of the female population had serum creatinine values above 1.5 mg/dl; and 0.64 and 0.33% respectively, had creatinine > 2.0

mg/dl. Older age and male sex were associated with higher creatinine levels<sup>4</sup>.

## MAGNITUDE OF CKD IN INDIA

Until recently, no data existed on the incidence or prevalence of CKD in India. Recently, however, some figures have become available. In a population-based study from Bhopal where over 5.7 lakh people are served by a hospital set up to take care of individuals potentially exposed to the methyl-isocyanate gas in the Union Carbide Tragedy of 1984, Modi and Jha<sup>5</sup> determined the annual crude and age-adjusted ESRD incidence rates at 151 and 232 per million populations respectively. The rate was consistent over a 4-year period. If these figures are validated in other parts of the country, it will place India in one of the top 10 nations in the world in terms of ESRD incidence, and mean that every year over 150,000 new patients would need RRT.

A couple of studies have reported on the CKD prevalence in different Indian communities. Mani<sup>6</sup> reported a prevalence of chronic renal failure of 0.16% and other renal diseases (short of CRF) in 0.7% amongst a rural population of 25,000 near Chennai who are served by the a prevention program. Agarwal et al<sup>7</sup> screened over 4900 individuals in urban communities of Delhi, and found a 0.79% point prevalence of individuals with serum creatinine over 1.8 mg/dl. These figures are substantially less than the NHANES data, but because of the sheer population base, represent a staggering load for the Indian medical community.

## CKS IMPOSES A HIGH MEDICAL AND ECONOMIC BURDEN

Yearly death rates of ESRD patients are approximately 20%. However, only about 10% of all CKD patients end up on RRT. What about the rest? It is now increasingly recognized that besides its implication on demands for RRT, CKD has major impact on overall population health by substantially increasing the risk for CVD. Large population based-studies have shown that progressive decreases in the glomerular filtration rate (GFR) are associated with increased risks of death, cardiovascular events, and hospitalization<sup>8-11</sup>. CKD lowers quality of life, and is expensive to treat. In approximately 4 lakh Medicare patients with diabetes and CKD in the USA, the risk

of death for cardiovascular diseases was 32% over two years, about 6-fold higher than that for development of ESRD. [12] The CVD risk in non-ESRD CKD patients is 10-30 times that of people without kidney disease<sup>11</sup>. These findings suggest that CKD patients who are advancing toward ESRD carry the heaviest burden of cardiovascular disease (CVD) and that this frequently leads to death before ESRD is reached.

ESRD treatment consumes a disproportionate piece of the healthcare budget pie. Constituting < 1% of the US Medicare population, their care consumes 6.4% of the health care expenditures<sup>13</sup>. This economic burden of ESRD care is even more stark in India. It bears to keep in mind that the minimum annual expenditure for a patient on regular dialysis is Rs 1 lakh, a figure that stands out in sharp contrast to the national annual per capita income of approx Rs 2,000, and where only 3% of the population earns over Rs 50,000/year. The national per capita expenditure on health is Rs 40 per year.

### THE SUBOPTIMAL CKD CARE IN INDIA

Data from around the world suggests an epidemic of CKD among certain ethnic groups. These populations include Aborigines in Australia's Northern Territory, and some native Indian communities in the USA, who carry upto 20-fold higher risk than local Caucasians<sup>13</sup>. Especially important are data from certain hospitals and dialysis units from areas in UK where ethnic south Asians form over 50% of the local population. Lightstone and colleagues<sup>14</sup> documented a 4-fold higher ESRD take-on rates amongst south Asians compared to Caucasians. Data from within India is scarce, but in our own center, a major public sector tertiary care hospital, ESRD patients belonging to the disadvantaged strata of the society are over-represented; these individuals often present for the first time with advanced renal failure, over two-thirds have not had prior medical care, and 75% present with complications that necessitate dialysis within 48 hours of arrival. We found a clear impact of patients' socioeconomic status on the access to nephrological care and late presentation with advanced renal failure. Children in Pakistan, which has a population similar to that in India in terms of ethnicity and socio-economic development, have higher blood pressure levels adjusted for body-mass index, than their seen in white children in the United States<sup>15</sup>, and childhood levels have been shown to predict levels in adulthood.

CKD patients continue to receive suboptimal care around the world<sup>13, 16-21</sup>, including developing countries like India. The reasons for this suboptimal care are likely complex, but people at risk because of diabetes or hypertension are often unaware that CKD can be caused by these conditions. In addition, quantitation of albuminuria with sensitive methods is inadequately performed in patients with diabetes. The reasons behind high CKD risk in poorer populations and certain ethnic groups have been under investigation recently. In addition to possible contribution of genes, the role of intrauterine origin of chronic disease in adult age, particularly systemic arterial hypertension and CKD, has come to the fore. It is suggested that lower nephron numbers acquired *in utero* can increase susceptibility to kidney damage from diseases such as hypertension and diabetes, and also cause *de novo* hypertension and renal damage.<sup>22</sup> Whether nephrogenesis is influenced by intrauterine malnutrition and/or any adverse intrauterine environment is a matter of speculation. A link between low birth weight and early malnutrition followed by over nutrition in adult life and ultimate development of metabolic syndrome, diabetes and diabetic nephropathy has been suggested and could emerge as a central theme.<sup>23</sup>

### CKD CAN BE PREVENTED

The debate regarding the issue of upstream preventive strategies has

largely been settled. Other than treatment of the primary disease, it is now generally accepted that a good blood pressure control to values lower than previously recommended (<120/75-80) and reduction of proteinuria to the lowest possible values (preferably <1 g/day), are the most effective preventive strategies<sup>24</sup>. Initial data came from diabetics with micro- and normoalbuminuria. The Irbesartan in patients with type 2 diabetes and microalbuminuria (IRMA) trial showed that the angiotensin II receptor blocker could prevent the progression from micro- to macroalbuminuria<sup>25</sup> and the Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) study showed that an ACE inhibitor may prevent the progression from normo- to microalbuminuria.<sup>26</sup>

Would a similar approach work in nondiabetics? The African American Study of Kidney Disease and Hypertension Study Group (AASK) trial compared amlodipine, metoprolol and ramipril in 1094 African-Americans aged 18-70 years with hypertensive renal disease (GFR 20-65 ml/1.73 m<sup>2</sup>); and showed a 22% reduction in the composite end points of GFR slope change, e<sup>+</sup> 50% reduction in GFR and ESRD in the group treated with ramipril<sup>27</sup> over other agents. In a meta-analysis of almost 2000 non-diabetic patients, Jafar et al.<sup>28</sup> found a systolic blood pressure goal of 110-129 mmHg to be beneficial in patients with proteinuria exceeding 1 g/day. With an aggressive blood pressure and proteinuria control in high-risk patients with hypertension, microalbuminuria or overt albuminuria, Hoy et al.<sup>16</sup> were able to cut down the renal and non-renal deaths in half with a goal blood pressure of 125/75 mmHg. In the Prevention of Renal and Vascular End Stage Disease Intervention Trial (PREVEND-IT), an ACE inhibitor lowered the number of cardiovascular events by 44% in microalbuminuric nondiabetics<sup>29</sup>. On the basis of trials conducted in the developed world, it is by and large accepted that drugs that block the rennin-angiotensin-aldosterone axis are preferred antihypertensive and antiproteinuric agents both for prevention of CKD progression and minimizing CVD risk<sup>24</sup>. Doses higher than those used in current-day practice are advocated. Subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study showed that in subjects with higher baseline levels of albuminuria, intervention with an ACE inhibitor is of particular value<sup>30</sup>. A similar observation has been made in the Losartan Intervention for Endpoint Reduction (LIFE) study, which included subjects with hypertension and left ventricular hypertrophy<sup>10</sup>. REIN-2 study showed no additional benefit from intensive blood pressure control when patients were already on an ACEI<sup>31</sup>. Additional measures include maintaining careful glycemic control in individuals with diabetes, treating dyslipidemia, losing weight, quitting smoking, and managing anemia. Some of these recommendations have been based on studies with relatively small number of patients, and should be accepted cautiously<sup>32,33</sup>.

To be acceptable, such programs must also be cost-effective. A health economic analysis of the IRMA and Irbesartan Diabetic Nephropathy Trial (IDNT) trials showed that earlier intervention was associated with substantial cost-savings.<sup>34</sup> The PREVEND group has also shown the cost-effectivity of the approach of screening the general population for microalbuminuria and treatment of those found positive with ACE inhibitors<sup>35</sup>. The cost-benefit in the initial years is more in terms of the prevention of cardiovascular events than postponement of ESRD. Information whether of targeted screening and intervention programs as recommended in the west would also be cost-effective in India are lacking, warranting further research.

The earlier enthusiasm about dietary protein restriction for slowing progression of CKD has become muted following demonstration of only minor benefits of low-protein diets<sup>36</sup>. Coupled with the demands

that adherence to a low-protein diet for several years will place on patients and their families, and the likelihood of development of malnutrition for only a modest benefit, this approach is no longer followed aggressively<sup>37</sup>. Moreover, low-protein diets decrease blood urea levels, may instill a false sense of security in the minds of patients and doctors. This bears emphasis in India, where the basal protein intake is low in a predominantly vegetarian population, and restriction pushes it down to dangerously low levels.

## METHODOLOGICAL ISSUES IN CKD PREVENTION

### *Who should be screened?*

The objective of early diagnosis is the detection of asymptomatic disease at a stage when intervention would have a reasonable potential to have a positive impact on outcome. A key point will be the early identification of *at risk individuals*. The debate here is centered on whether the candidates for screening should be derived from the general population or from certain high-risk groups. Chronic care has tended to screen high-risk individuals. For CKD, these include individuals with diabetes, hypertension, elderly, the obese and those with urolithiasis, recurrent urinary tract infections, and family history of kidney disease. Till date, there is no strong evidence to favor one or the other of the screening approaches [38]. Another suggested approach is to include patients attending the doctor or medical facilities for another reason. In a recent Controversies Conference organized by the Kidney Diseases: Improving Global Outcomes (KDIGO) initiative that was attended by nephrologists and public health personnel from around the world, a targeted approach was preferred over universal screening.

### *What is the best screening/detection modality?*

The two commonest tests for detecting sub clinical disease are: testing for protein in the urine and measurement of GFR using prediction equations such as the MDRD formula<sup>39</sup>. The latter has not been validated in a primarily vegetarian Indian community that has a significantly different body composition, and is likely to have significantly different rates of creatinine generation. Still, using any formula, even the Cockcroft-Gault equation<sup>40</sup>, is better than not calculating GFR. Standardization and regular validation of the method for estimation of serum creatinine is critical to avoid large variations that are commonly encountered in Indian laboratories.

The Multiple Risk Factor Intervention Trial (MRFIT) investigated the value of a single measurement of dipstick proteinuria and estimated GFR for prediction of end-stage renal disease (ESRD) over a 25-yr period<sup>41</sup>. The presence of a 1-2+ proteinuria was strongly associated with renal risk, whereas a baseline GFR < 60, but not of 60 to 75 ml/min per 1.73 m<sup>2</sup>, indicated a poor renal prognosis. Because only subjects with a baseline serum creatinine < 2.0 mg/dl were included, the risk attributable to impaired baseline GFR may have been underestimated. Iseki et al.<sup>42</sup> in a more general population of Japanese subjects showed that impaired renal function at baseline and dipstick-positivity predicted progression to ESRD. However, testing for an impaired GFR and proteinuria detected only 13% and 19% of the patients who later developed ESRD respectively, whereas the combination of both detected no more than 27%<sup>41</sup>.

This suggests the need to have an alternate approach. One suggestion is to use an integrated renal risk score that would take into account other risk factors, such as age, smoking status, BP, cholesterol, and race<sup>43</sup>. This approach would likely increase the sensitivity and specificity of screening, but at a significantly higher manpower and financial costs. The currently favored approach is to screen for lower

levels of proteinuria (20 to 200 mg/L) using antibody-based techniques as was used in the PREVENT study<sup>9</sup>. Microalbuminuria predicts future CVD, and subjects will therefore benefit from early cardio protective treatment, such as BP lowering and ACEI/ARB use. The cost of this test remains a concern, but can be brought down to as low as Rs 20/test in mass screening. Point-of-care machines are also available, but tests using those cause significantly more (Rs 150-200/test).

Suggestions have been made that the South Asian populations may be especially susceptible to interstitial nephritis. The importance lies in the fact that it has an insidious onset without marked hypertension, proteinuria or hematuria, and hence is likely to be missed if only albuminuria detection strategies are employed<sup>44</sup>. Whether development of new biomarkers, such as markers of tubular damage, would allow earlier detection of this condition remains a research question.

## WHAT TO DO TO THOSE WITH ABNORMALITIES?

### *Primary prevention*

Primary preventive measures can be applied to high-risk patients who have not yet developed any evidence of chronic kidney involvement. Some examples include glycemic control in diabetics, management of elevated blood pressure and appropriate management of primary kidney diseases such as glomerulonephritis, vesicoureteric reflux, stones, urinary tract infection, cessation of smoking, lipid control and weight loss. There is sufficient evidence to suggest that this approach reduces the CKD burden. An important example is the dramatic reduction in the incidence of nephropathy due to type 1 diabetes in Scandinavian countries following adoption of strict glycemic and BP control.

### *Secondary prevention*

This is the stage where the current-day preventive strategies are largely concentrated. The strategy here is to institute appropriate measures at the earliest indication of kidney involvement, such as low-level albuminuria or mildly reduced GFR. As stated above, the management goal of CKD in the conservative phase should also include use of all available therapeutic options aimed at preventing or reducing the development of cardiac abnormalities and vascular disease.

Timely referral to nephrologists is an important issue at this stage. Data from North America suggests that an early referral to nephrology specialist care is associated with decreased morbidity and short-term mortality, improved long-term survival on dialysis and leads to significant cost savings<sup>19</sup>. Despite this evidence, the epidemiological data indicate that late referral has not decreased in recent years even in the west. At our own center, over 85% of all ESRD patients had their first encounter with a nephrologist less than 3 months before going on dialysis. In India, where there is no formal barrier to referral to nephrology specialists, such a gap suggests that economic issues, coupled with a lack of awareness of the potential benefits of early and regular management by a nephrologist continue to be widespread.

## TERTIARY PREVENTION

These measures are aimed at appropriate management of complications related to established CKD, such as correction of anemia, control of abnormal bone mineral metabolism, acidosis, maintenance of growth in children, coronary artery disease and heart failure and preparing patients for renal replacement therapy including addressing the psychological issues. The stress is on improving the quality of life, appropriate education regarding RRT modalities and

suggesting rehabilitation programs. The course of the underlying CKD is not expected to be affected in a big way at this stage.

## PREVENTION PROGRAMS IN INDIA

Structured chronic disease prevention programs are lacking in India. The Kidney Help Trust, an organization spearheaded by Dr. MK Mani of Chennai, runs a surveillance and treatment program in an area of approximately 25,000 people. Targeted mainly on hypertension and diabetes, this is mainly based on health workers who are drawn from the local population, and are trained to administer a questionnaire, record blood pressure, check blood glucose levels and protein in the urine by visiting people in their homes. Those who need treatment get cheap drugs such as reserpine and hydrochlorothiazide, metformin and glibenclamide. This approach was effective in bringing down blood pressure to 140/90 or less in 96% of the hypertensives, and in reducing the glycosylated hemoglobin to 7% or less in 52% of the diabetics<sup>6</sup>.

Perhaps there are lessons to be learnt from ongoing programs in South Africa and Cuba. The South African Chronic Disease Outcome Primary Prevention program has been evolved around an integrated chronic illness model focusing on detecting high-risk patients and controlling their hypertension, diabetes, and risk factors and implemented in primary-care clinics in Soweto and nearby areas.<sup>45</sup> The first phase had a surveillance component; it also achieved success with blood pressure control, but less control of diabetes and proteinuria reduction was achieved. Nevertheless, the program has provided a better understanding of renal disease and cardiovascular risk and positive short-term treatment outcome. Cuba has developed a National Chronic Kidney Disease Program based incorporating preventive strategies at all levels of care<sup>46</sup>.

World Health Organization's Innovative Care for Chronic Conditions Framework (<http://www.who.int/mediacentre/factsheets/fs172/en/>) provides a model for redesigning health care systems in accordance with local resources. The framework emphasizes a well-defined care plan, self-care, scheduled follow-up appointments, monitoring of outcomes, adherence, and stepwise treatment protocols delivered mainly by primary care practitioners.

## CHRONIC KIDNEY DISEASE AS A PUBLIC HEALTH PROBLEM

In a recent publication for the Centers for Disease Control, Schoolwerth et al<sup>13</sup> suggested that CKD be treated as a public health problem through a public health action plan. For any condition to be called a public health problem, need to fulfill the following criteria was suggested:

1. The burden of the disease should be high, with evidence of recent increase and likelihood of increase in the future. The disease should impact mortality and morbidity, quality of life and cost to the extent of being perceived as a threat by the public.
2. The problem should be distributed unfairly, i.e., it should affect disadvantaged individuals to a greater extent.
3. There should be evidence that upstream preventive strategies could substantially reduce the burden of the condition, and
4. Evidence that such preventive strategies are not yet in place should be present.

The discussion above clearly underlines the fact that CKD meets all four of these criteria, should be treated as a public health problem and should have a public health plan in India. To this end, researchers in India need to generate more data related to the second and third points, which would then need to be presented to the government and other public sector policymakers.

Institution and implementation of the prevention programs requires not only drugs, but also equipment, creation of research institutions, and education and training of health professionals<sup>1</sup>. So far, the academic response to the challenge of non-communicable diseases in India has been muted; education institutions and teaching program both at school level and more astonishingly, in medical colleges, have paid scant attention to these issues. Current-day Indian medical graduates are ill prepared for the vital roles they need to play in the changing health environment and deal with the increasing chronic disease burden. In addition to a pertinent medical education, awareness and public health education strategies must be introduced at school level in order to prepare students and general public about the growing burden of chronic disease, and to sensitize them about the need to tackle these conditions at an early stage.

Until the public sector develops, individual practitioners will continue to be the frontline caregivers. These physicians should be required, perhaps even mandated, to participate in continuing medical education programs regarding the management of hypertension, diabetes, and chronic kidney disease<sup>47</sup>.

Professional societies, such as the Indian Society of Nephrology, Indian Academy of Nephrology, Indian Academy of Pediatrics and the Association of Physicians of India need to be engaged in developing early detection and intervention programs that suit the needs and organizational facilities of different regions of our country. Failure to act on their part would hand the initiative to outside agencies and the opportunity to deal with our destiny will be missed. Involvement of statutory bodies such as the Medical Council of India and the Indian Council of Medical Research is crucial and would attract the attention of global agencies such as the World Health Organization.

The role of non-governmental organizations (NGOs) that have done so much to raise awareness and provide better care to HIV-infected individuals cannot be overemphasized. There is some evidence that organizations have turned their attention in this direction; I am aware of at least one Indian NGO (Chronic Care Foundation) that has included reduction of CKD burden in the community as one of its core missions.

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