Perspective

Treatment of end-stage renal disease in the 21st century: Wide gap between access and demand

Healthcare delivery across the globe and especially in low- and middle-income countries (LMICs) will be put to test in the 21st century. A recent report examined the worldwide access to renal replacement therapy (RRT) in the form of maintenance dialysis and kidney transplantation. RRT is the treatment of end-stage renal disease (ESRD) in the form of maintenance haemodialysis, peritoneal dialysis or kidney transplantation. It is disquieting to note that in the year 2010 more patients might have died prematurely in the absence of RRT than the total number of patients who actually received RRT. And, this figure was a conservative estimate.[1]

Worldwide access to RRT

The data from the above-mentioned report revealed glaring disparities in the utilization of RRT across the world. The patients receiving RRT were as low as <50 per million population (pmp) in much of Africa and South Asia including India. This contrasted with RRT in >2000 pmp in Japan and 1840 pmp in North America. Most recipients of RRT (92.8%) were in high-income (1.628 million) and upper-middle income (0.803 million) countries, with only 7.2% of recipients of RRT living in LMICs. Essentially, almost half of the world's total RRT is delivered in five countries (US, Japan, Germany, Brazil and Italy) that constitute only 12% of the world population. On the contrary, only 20% of recipients of RRT live in about 100 developing countries that make up over 50% of the world population. There is no reason to believe that the variation in prevalence of RRT is attributable to a difference in the incidence of ESRD. In reality, a large majority of individuals never receive RRT and die. The investigators meticulously assorted the best available data representing most of the world population. It was calculated that worldwide in 2010, 2.618 million people received RRT. However, a rigorous methodology estimated that if all ESRD patients in the world were to receive RRT, the actual need was much more. Between 4.902 million and 9.701 million patients would have needed RRT using conservative and liberal estimates of the prevalence of ESRD, respectively; thereby implying that at least 2.284 million people might have died for want of RRT. Worldwide the use of RRT is projected to more than double to 5.439 million (3.899–7.640 million) people by 2030. The analysis showed that gross national income (GNI) and life expectancy were the only predictors of the prevalence of RRT and not diseases such as diabetes or hypertension that cause ESRD. Technically, Asia due to its population base had the highest number of people needing RRT but only 17%–34% actually received it. The access to RRT was abysmal in middle and eastern Africa. It was pegged at 1%–3% of those needing it.[1]

Global burden of chronic kidney disease (CKD) and ESRD

The core issue in the inequitable access to RRT is the mismatch between burden of ESRD (demand) and the capacity of healthcare systems to provide for it (supply). CKD is now a major worldwide medical problem. According to the 2010 Global Burden of Disease study, CKD was ranked 18th in the list of causes of total number of global deaths (age-standardized annual death rate of 16.3 per 100 000). This is a substantial upward movement from the 27th rank in 1990. This is paralleled by an 82% increase in years of life lost due to premature mortality.[2] ESRD is the natural but not inevitable consequence of progression of CKD.

TABLE I. Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g creatinine [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	<60 ml/minute/1.73 m^2 (GFR categories G3a-G5)

AER albumin excretion ratio ACR albumin-to-creatinine ratio GFR glomerular filtration rate

Note: This table is reproduced with permission from 'Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, KDIGO (2012). Clinical practice guidelines for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3:**1–150', Copyright Elsevier 2016.

The burden of CKD received the much-needed attention after the development of a uniformly acceptable definition of CKD (Table I).[3] Approximately 13% of the US population has evidence of renal damage or renal insufficiency, and about 6% have a glomerular filtration rate (GFR) <60 ml/minute. The prevalence increases to 15%–30% in the elderly and rises to ≥50% in subjects affected by cardiovascular (CV) and metabolic diseases.[4] These figures on burden of CKD have been replicated in many countries. With such large numbers at risk, the burden of ESRD is also substantial. In most kidney registries almost half or more than half the patients with ESRD develop it in the setting of diabetes and hypertension. These two diseases are driving the non-communicable disease (NCD) burden of the 21st century. Over the next two decades, the prevalence of hypertension and diabetes is projected to rise by 80%–100% in economically developing countries, and by 20%–50% in developed countries. India, with the highest incidences of diabetes and hypertension in the world, is likely to face a catastrophic CKD/ESRD burden.[5]

In parallel, the prevalence of ESRD is increasing worldwide and more so in the developing economies. For instance, in a report from Latin America the prevalence of people with ESRD receiving RRT increased from 119 patients pmp in 1991 to 660 patients pmp in 2010.[6] Similarly, in a population-based study from India the age-adjusted incidence of ESRD was estimated as 232 patients pmp, unlike the figure of 100 patients pmp that was previously believed.[7] In Hong Kong, the annual incidence of ESRD in 1996 was pegged at 100 patients pmp. This increased to 122 patients and 140 patients pmp in the years 2000 and 2003, respectively.[8]

It is likely that the actual burden of ESRD is similar across most countries. The differences among various regions are mostly attributable to the poor access to ESRD care in LMICs and developing economies. This was borne out in the report from Latin America. In areas with 100% access to RRT, the prevalent RRT burden matched that in the developed world.[6]

The other major factor that affects the burden of CKD and ESRD is the age composition of the population. It is well known that the prevalence of CKD rises with age and communities with more elderly people have a higher burden of ESRD. In Europe, as per the European Renal Association–European Dialysis and Transplant Association (ERA-ETDA) registry data, the proportion of incident dialysis patients ≥75 years of age varied from 15% to 44% between countries and the mean age at the start of RRT across Europe was 62 years. In this context, demographic and epidemiological transitions of the LMICs and developing economies such as South Asian nations assume great importance. The former refers to the shift in the average composition of population to higher age groups, thereby increasing the exposure to NCDs (and consequently CKD). This combined with overall economic development leads to epidemiological transition that is characterized by a shift in the composition of the disease burden to lifestyle diseases and NCDs. NCDs accounted for 60% of the 58 million deaths worldwide in 2005. Of these, 4 out of 5 deaths occurred in LMICs. In South Asia, the disease burden attributable to NCDs exceeds the cumulative effect of communicable diseases, maternal and child health issues, and nutritional causes combined.[5]

Poverty has a bidirectional association with CKD. Besides affecting access to medical care, an analysis of the National Health and Nutrition Examination Survey (NHANES)

data from the USA showed that poverty is associated with increased risk of microalbuminuria (odds ratio [OR] 1.35) and macroalbuminuria (OR 1.78). The effect multiplies because people in the lowest socioeconomic quartile are at 60% greater risk of progressive CKD.[9]

Global availability of RRT: Resources and manpower

On the supply side, the access to RRT is determined by the capacity and type of healthcare systems that are in turn driven by capital and human resources. About 2%–3% of healthcare expenditure in developed nations is spent on the treatment of ESRD even though patients with ESRD comprise just 0.1%–0.2% of the total population. In 2010, treatment costs for ESRD accounted for 6.3% of the Medicare budget in the USA, 4.1% of the total healthcare budget in Japan in 1996, and 3.24% of the national health expenditure in South Korea in 2004.[10]

The lack of health insurance for the large majority of people in developing countries makes RRT practically unaffordable. A session of haemodialysis costs US$ 100 in Nigeria. This amount is twice the minimum monthly wage paid to federal government workers. In India, the cost of a dialysis session varies from US$ 20 to 60. Government-supported insurance schemes for the poor have been started in some states in India, but coverage remains limited. As of now, the annual expense in these schemes is capped at approximately US$ 500. Compare this to the annual dialysis expense of approximately US$ 5000 in India, which makes long-term haemodialysis impossible. Thus, patients are forced to pay out-of-pocket, and get pushed into poverty. In one Indian study, the cost of dialysis resulted in catastrophic healthcare expenditures for 70% of patients.[10] Similarly, the Chinese government has a variety of insurance schemes for rural and urban populations. However, patients have to make co-payment, which is 35%–45% of the cost, and is particularly hard for those in rural areas.

In LMICs, public healthcare systems receive only 0.8%–4% of the gross domestic product (GDP), as opposed to 10%–15% in developed countries. Two developing regions—Latin America and Caribbean, and Middle East and North Africa—provide RRT for a comparatively larger proportion of patients. However, resources allocated to RRT in these regions are not likely to be sustainable, and may be unrealistic targets for other regions. The Brazilian Ministry of Health spent US$ 500 million on RRT in 2004; in Egypt 28% (US$ 100 million) of the healthcare budget was spent on government-sponsored RRT in 2008.[11]

Moreover, manpower resources are scarce for the prevalent burden of CKD. Nephrologists, renal nurses and dialysis technicians are in short supply even in the developed world. In Latin America, the number of nephrologists varies from 1.7 per million population in Honduras to 53.9 per million population in Uruguay. In Asia, the range is from 0.2 per million population in Myanmar and Indonesia to 5.0 per million population in Thailand. India with a population of >1.25 billion has just over 1000 nephrologists.[10]

How to achieve equitable access to RRT?

What is the most plausible answer to the magnitude of the problem and its hunger for resources? Actually, there is neither a clear answer nor a well-tested strategy. Even the high-income countries are struggling to keep up the funding for universal RRT. Still a host of actions will have to be initiated especially in LMICs.

Prevention of CKD and its progression to ESRD

Realistically, most patients in LMICs will not have access to RRT and thus preventive efforts will be of paramount importance. These could range from prevention of development of lifestyle diseases such as obesity, diabetes and hypertension and prevention of progression of established CKD to ESRD. There is evidence to show that lifestyle changes, renin angiotensin system blockade, blood pressure and diabetes control and cardiovascular risk factor management can achieve these goals. This endeavour can be helped by the availability of cheap generic medicines. The challenge is to deliver this plan on the ground. A commonly cited pilot study of a low-cost intervention has shown success in rural India, achieving blood pressure and diabetes targets, and lowering prevalence of CKD at an annual cost of US$ 0.43 per capita of population. This programme minimized costs by using non-physician health workers and the cheapest available diagnostic tests and drugs.[12] CKD should be an integral part of the integrated national programmes for chronic vascular/cardiovascular disease prevention.[13]

Eventually, the cost-effectiveness for all available interventions needs to be studied locally for different regions since it depends on the local GDP. To illustrate, interventions are classified as highly cost-effective when the cost of the intervention per disease-adjusted life-year saved is less than the GDP/person, cost-effective when it is between 1 and 3 times the GDP/person or not cost-effective (more than three times the GDP/person).[10] Unfortunately, there are no studies from India to give definitive guidance on cost- effectiveness and feasibility of interventions on a population-wide basis.

Increasing access to RRT and financing

Government and policy-making bodies have a major role to play. Allocation of efforts and resources between prevention and treatments will have to be judiciously done. The experience from CVD data suggests that >50% reduction in secular trends in CVD mortality were attributable to population-level risk reduction and the remainder to medical treatment and interventions.

Some countries have invested heavily in prevention, detection and treatment programmes for CKD. Taiwan started a kidney health promotion project and reported a decline in the number of incident ESRD cases since 2009, leading to savings of US$ 36 million per year. The Mexican Ministry of Health has set up a network of health services against chronic renal disease with an outlay of US$ 50 million, with a goal to reduce the number of patients with ESRD by 50% by 2025. In Uruguay, the incidence and prevalence of ESRD declined from 1.6% and 5.4%, respectively, in 1994–2003, to 0.13% and 1.6% in the following decade. In Chile, the annual incidence and prevalence of ESRD reduced from 13.3% and 14.5%, respectively, in 2005–08 to 1.9% and 4.6% in 2009. These official country statistics need to be independently validated and it is crucial that these efforts are sustained over the long term.[10]

There is an urgent need for the development of cost-effective dialysis technologies since the present techniques are too expensive for a large section of the population, particularly over the long term. Innovations are needed in water purification techniques, filter design and pump mechanics. Advances in nanotechnology and fluidics are expected. Indigenous development of dialysis consumables and generic medicines has to be driven with commitment. A national policy on consumables and hardware used for RRT both in terms of indigenization and cost control is needed.

Kidney transplant is the most effective RRT. A massive thrust is required to remove all impediments ranging from creating facilities, training, increasing organ availability and sharing. Streamlining and transparency of the legal system involved in kidney transplantation is also much needed.

The lack of trained manpower will render all endeavours futile. It is clear that reliance on the western physician-centric model of care delivery is unlikely to be successful in LMICs. Judicious task shifting, aided by the use of technology with the help of non-physician healthcare workers (NPHW) to deliver up-to-date guideline-based care in the community will go a long way. Evidence is accumulating that NPHWs can efficiently detect and manage individuals at high risk of CVD.

In India, for that matter in all LMICs, government spending on healthcare will always be short of the demand and thus is likely to be heavily supplemented by external aid and user fees. This will inevitably lead to rationing of RRT. It is imperative that clear guidelines are in place on the selection of patients for RRT. Even though it appears unethical, in the absence of such guidelines the already meagre resources are ill spent.

The final answer for equitable access to RRT lies in appropriate and adequate healthcare spending starting from prevention to provision of RRT. The way forward may be in large-scale low-cost health insurance for all citizens paralleled by low-cost RRT but safe systems that are governed by unambiguous guidelines on delivery and rationing. Till recently, CKD was an orphan chronic disease. It is a mammoth task to tackle CKD and RRT across the world because of the large present burden, rising incidence, disproportionate distribution of wealth across countries, shortage of human resources and governance-related issues. Action will have to occur at many levels in terms of advocacy, healthcare delivery, governance, policy, research and cost-efficacy analyses of potential interventions.

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