THE GROWING GLOBAL BURDEN OF END STAGE RENAL DISEASE (ESRD)

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ABSTRACT
The incidence and prevalence of renal replacement therapies (RRT) is increasing worldwide. As well as being a large and growing clinical problem, it consumes a considerable proportion of health care resources in both developed and developing countries. Ideally, every ESRD patient should have access to dialysis. The reality is that there is not enough money for healthcare in the developing world, particularly for expensive and chronic treatment such as RRT. Efforts should be made to have the cost of peritoneal dialysis fluids reduced and to increase the availability of transplantation.

Keyword: End stage renal disease, Epidemiology. Costs

1.Epidemiology of End-Stage Renal Disease (ESRD)

1.1. Definition
Incidence refers to new cases of ESRD during a given year and is a key population measure of kidney disease and access to renal replacement therapy. Prevalence refers to all causes of ESRD during a given year and is a population measure of disease burden and resource requirements. Prevalence is determined by incidence and patient life expectancy.

Patients who return to dialysis after a failed transplant are counted as incident ESRD patients; this situation is viewed as a modality change. Similarly, patients who stop chronic dialysis and then restart are counted as prevalent, not incident patients. Incidence and prevalence are expressed in terms of absolute counts as well as rates (ie, number per million population). Technically, incidence is expressed as a rate (number/ million population/year), while prevalence is expressed as a proportion (number/ million population).

1.2. Epidemiology of ESRD in the Developed World
1.2.1. Incidence and prevalence of ESRD
There are about 1 million people in the world alive just because they have access to one
form or another of renal replacement therapy (RRT). Ninety percent of them live in the developed countries or, as defined by the World Bank (WB), high-income countries where the average gross income is in excess of $10,000 per capita.

In the epidemiological data of treated end-stage renal failure in the European Union (EU) during the year 1995, the mean incidence of new patients was 120 pmp with values ranging from 68 in Finland to 163 in Germany. These numbers are much higher in USA with 262 pmp and Japan (210), but lower in Canada (140) during the same year.

During 1996, 283,932 patients were treated for ESRD and 73,091 new patients started ESRD treatment in the USA. Incidence and prevalence rates tend to increase with age. The largest group of patients falls in the 45 to 64-year age group. The disease was more common in men than women. Black race constituted 30% to 32% of treated ESRD patients in contrast to 12.6% of the US population. In 1998, the incidence of treated ESRD in Europe ranged from 110 pmp in the Netherlands to 192 pmp in Germany. Even higher incidence rates were recorded in the same year in countries outside Europe, such as the USA (>300 pmp) and Japan (200 pmp). In 1998, the prevalence of treated ESRD in Europe ranged from 498 pmp in the UK to 854 pmp in Italy. Again, Japan and the USA recorded higher rates than European countries, with prevalences of >1400 pmp and almost 1200 pmp, respectively.

A total of 1764 people commenced RRT in Australia in 2000, a rate of 92 pmp, in New Zealand, 417 people commenced RRT in 2000 (107 pmp). The Australian and New Zealand rates are substantially lower than the USA (311 pmp) and Japanese (240 pmp) but similar to the rates reported from England (89 pmp) and most European countries.

The incidence and prevalence of RRT for ESRD has continued to increase through the world, but at rates that vary considerably between countries. Reasons for this increase are likely to be an actual increase in the occurrence of chronic kidney disease: improved survival from other diseases (so-called competitive risk) and wider acceptance criteria for RRT, more elderly patients, patients with diabetes, and patients with several other co-morbidities (malignancies, systemic diseases etc) requiring RRT. The most obvious trends are the rapid increase in RRT incidence in the older patients and in patients with diabetes mellitus. These changes are due in large part to an increase in these population groups in the community. However, improved access to RRT will also have contributed to the increase in incidence observed.

According to analysed data from nine countries participating in the ERA-EDTA registry (Austria, Belgium, Denmark, Finland, Greece, The Netherlands, Norway, Spain, UK (Scotland)), the adjusted incidence rate of RRT increased from 79.4 pmp (range: 58.4-101.0) in 1990-1991 to 117.1 pmp (range: 91.6-114.8) in 1998-1999, ie 4.8% (3.1-6.4) each year in Europe. This increase was greater in men than in women, 5.2 vs 4.0%/year. In most countries, the incidence rate remained stable for those younger than 45 years, rose by 2.2% on average in the 45-64 years age group and by 7.0% among those 65-74 years and tripled over the decade in those 75 years old or older. The mean age of the ESRD population increased 3.5% between 1995 and 1998, to 62.2, in US.

1.2.2. Etiology of ESRD

The major causes of ESRD in North America and in many developed countries are diabetes and hypertension, which together account for almost 60% of dialysis patients. In the USA, diabetes is the most common attributed cause of ESRD, followed by hypertension, glomerulonephritis, others (interstitial nephritis, vasculitis, eg), unknown, cystic diseases and urological diseases. In the youngest group (<20 years), the most common diagnoses are glomerulonephritis (31.7%) and cystic/hereditary/congenital diseases (24.4%), whereas diabetes is rare. For the oldest age group (64 years) the most common attributed causes of ESRD are
hypertension (36.8%) and diabetes (35.9%). Diabetes is relatively more common in women and hypertension is relatively more common in men.

Racial differences exist in the distribution of patients by primary renal disease. Diabetes is especially common among Native Americans (63.2%) and, to a lesser extent, Asians/Pacific Islanders (41.6%). Hypertension is notable high among blacks (35.9%) and glomerulonephritis is disproportionately high for Asians-Pacific Islanders (17.8%) that is twice as frequent as in black patients.

In 1998, the incidence of ESRD was 133 pmp for diabetes, 71 pmp for hypertension, 38 pmp for glomerulonephritis, 15 pmp for urological disease, 9 pmp for cystic kidney disease in the USA12. In 1994-1998, the primary disease ratio of the total of dialysis patients was 39.5% for diabetes, 25.2% for hypertension/large vessel disease, 9.1% for glomerulonephritis, 3.8% for interstitial nephritis/pyelonephritis, 2.8% for cystic/hereditary/congenital diseases and 12.5% for uncertain etiology/missing cases. For renal Tx patients, these ratios were 16.1%, 4.2%, 14%, 4.5%, 13.8%, 42.6%, respectively12.

In the EU countries, the incidence of ESRD due to diabetes, hypertension and renal vascular disease nearly doubled over 10 years in 1998-1999: it varied between countries from 10.2 to 39.3 pmp for diabetes, from 5.8 to 21.0 for hypertension and 1.0 to 15.5 for renal vascular disease11. The incidence of RRT in diabetic patients in Europe is only a quarter that of the US white population, which was 94.8 pmp in 199913. The cause of this geographic variation is probably multifactorial, including variation in the diabetes and/or in the management of patients (secondary prevention) differences in mortality and also the persistence in some countries of limited access to RRT for these patients. While there is a wide range in the incidence of RRT for ESRD attributed to hypertension, from 5.8 pmp in Finland to 21 pmp in Norway, all European countries studied reported a much lower incidence than has been reported for the white population of the US (41.8 pmp) (11). Diabetes was a cause of ESRD in 28.8% of German patients who survived more than 90 days on HD. The percentage was considerably lower in Italy, Spain, and the UK (between 20.1 and 21.7%) and only 15.3% in France14.

It is unclear why the rate of diabetes continues to increase even when adjusted for age, gender, and race, while rates of non-diabetic incidence remain steady. While low protein diets, blood pressure control, and ACE inhibitors have all been available for some time, they do not appear to have influenced the diabetic populations. The dramatic rise in the incident dialysis population may be related to advancing obesity, carbohydrate intolerance and insulin resistance12.

1.2.3. Treatment Modalities of ESRD

Since 1990, the number of patients on haemodialysis has almost doubled and the number of patients with transplants has increased more than 90% in the USA12. Peritoneal dialysis has also increased, though this modality still accounts for only 13.5% of the ESRD population. In 1998, the number of dialysis patients was 243.524 in US and the number of point prevalent patients was 211.800 for haemodialysis, 25.300 for peritoneal dialysis, and 99.840 for transplantation. Growth in the prevalent dialysis population is a reflection both of growth in incident rates and of declining death rates. Projections for 2010 suggest that the number of both dialysis and transplant patients will reach levels double those in 1997, while the number of patients on the transplant waiting list will grow almost two and a half times during the same period12.

Racial differences are evident across modalities in both incident and prevalent populations. Between 1994 and 1998 the greatest percentage increase in the number of haemodialysis patients has among the Native Americans and Asian populations, 11.2%, 68.5, respectively. Compared to white patients, a lower percentage of minority patients received transplants, and these
patients were more likely than white patients to be on haemodialysis12. In the EU during the 1995, the first RRT was HD in 80.8% (with a range from 61.4% in the UK to 97% in Portugal), was PD in 18.2% with a range from 2.7% in Portugal to 37.5% in the UK) and pre-emptive Tx in only 1.0%.[5] The mean percentage of dialysis patients undergoing a renal transplant during the year was 6.5% ranging from 2.8% in Greece to 23.3% in Ireland.

1.2.4. Survival, Mortality and Causes of Death in ESRD Patients

Despite advances in dialysis and transplantation, the prognosis of kidney failure remains bleak. The USRDS reported more than 60000 deaths of patients with ESRD, and an annual mortality rate of dialysis patients in excess of 20%.[15] Expected remaining lifetimes of patients treated by dialysis were shorter than the age matched general population, varying (depending on race and gender) from 7.1 to 11.5 years for patients aged 40 to 44 years, and from 2.7 to 3.9 years for patients aged 60 to 64 years. Atherosclerotic cardiovascular disease accounts for approximately half of the deaths in ESRD and contributes to the extraordinary high total annual mortality of 23% observed in such patients.[13] Incidence of myocardial infarction and stroke in the dialysis population is 5-to-15-fold higher in ESRD[15]. The second principal cause of death is infections and diabetics have the highest rate of death. Morbidity of kidney failure is also high. The mean number of co-morbid conditions in dialysis patients is approximately 4 per patient. The mean number of hospital days per year is approximately 15, and self-reported quality of life is lower than that of general population.[15] Hypertension and diabetes are the complicating co-morbid conditions found most often in new patients, 73.9% and 64.4% respectively, followed by congestive heart failure (33.4%), and ischemic heart disease (24.6%) in the USA[12].

Cardiovascular disease is responsible for 35-52% of the deaths (greatest in the elderly and diabetics) among Canadians with ESRD[16]. Cardiovascular disease is already well established by the onset of ESRD. Symptomatic ischemic heart disease was present in 38% and heart failure in 35% of the Canadians at first dialysis[17].

In the USA, the number of first year deaths per 100 patient years in 1998, was 29.9 for all dialysis patients, 28.1 for HD, 27.8 for PD and 2.9 for Tx. Five-year survival was approximately %33. Five-year survival curves have shown that female patients live longer than males across most age groups, races, primary diagnosis, and modalities[12].

In the EU during the year 1995, the death rate among treated ESRD patients was 10.4% ranging from 5.4% in Ireland to 12.6% in Denmark[3]. In all fatal cases during 1995, the treatment modality was HD in 75.3% (ranging from 53.9 in the UK to 93.35 in Luxemburg), PD in 17.8% (from 0% in Luxemburg to 29% in Greece) and Tx in 6.9% (ranging from 6.9% in Ireland to 17.2% in Finland). The mean death rate was 13.4% for HD (ranging from 9.6% in Greece to 29.85 in Ireland) as compared to 20.7% for PD (ranging from 6.95 in Ireland to 39.7% in Greece). The mean death rate for patients with transplants was 2.2% with values from 0.5% in Greece to 8.8% in Portugal. The 1995 incidence of death from ESRD was highest in the USA with 191 pmp, while it was 115 in Japan and 64 in Canada, as compared to 67 in the EU.

1.2.5. Economic Costs of ESRD

There is a clear, direct relationship between gross national product and availability of RRT. Dialysis treatment absorbs 0.7 to 1.8% of the health care budget in European countries, while the dialysis population represents 0.02 to 0.05% of the whole population.[2] Consequently, economic costs of ESRD are high; in 1999, more than 400000 Americans required dialysis therapy and/or transplantation for kidney failure, and Medicare medical expenditure for ESRD care was more than $11 billion (KEEP3). With the current rate of growth, there will be 172,667 incident and 661,330 prevalent patients by the year 2010. The Medicare costs for care of
ESRD will increase from $12 billion to 28 billion over this time period. The costs of medication and patient care are also rising. Between 1994 and 1999 spending on recombinant human erythropoetin increased by 100% in the USA, the cost of intravenous (i.v.) iron supplementation increased by 50% and cost for i.v. calcitriol or other vitamin supplements increased by 200% USRDS. Practically everywhere, public chronic HD is the most expensive modality, followed by private and limited care HD. The least expensive modalities are home HD and CAPD, whereas APD costs are in the same range as limited care HD.

1.3. Epidemiology of ESRD in the Developing World

1.3.1. Incidence and Prevalence of ESRD

The exact number of patients with chronic renal failure requiring RRT in the developing world is not known. Unlike the developed world, most developing countries lack renal registries. Therefore, the exact incidence and prevalence of ESRD in the population, its burden on the health care system, and the outcome of these patients are not known.

The reported annual incidence of patients with ESRD varies widely, from as low as 4 pmp in Bolivia to as high as 254 pmp in Puerto Rico. Incidence rates of 52 pmp and 200 pmp were reported in Turkey and Egypt, respectively. In the rest of the world, the estimated incidence ranges from 100 to 200 pmp. In India, an estimated incidence of ESRD of 100 pmp, approximately 100,000 patients develop ESRD each year. The reasons for such wide variations are likely to be differential racial factors, environmental conditions, the criteria used for diagnosis, and the availability of sophisticated dialysis programs. The number of patients accepted by dialysis programs is about 80 pmp in Egypt, 20 pmp in Malaysia, 3 to 5 pmp in India and China.

In a questionnaire on data addressing epidemiology, etiology and management of ESRD from 10 developing countries reported by Barsoum, the incidence of ESRD varied from 40 pmp in Pakistan to 340 pmp in Mexico. Prevalence was largely dependent on the economic standing of individual countries. It was highest in Mexico, lowest in Pakistan.

The availability of dialysis and transplantation is quite variable in Africa. There is only small number of patients on RRT in southern and sub-Saharan Africa. In comparison, treatment rates in North Africa are 30 to 186.5 pmp in countries with more established programs: Algeria 78.5, Egypt 129.3, Libya 30, Morocco 55.6, Tunisia 186.5 pmp.

1.3.2. Etiology of ESRD

Etiology of ESRD in the developing world also varies between geographic regions and economic conditions. Glomerulonephritis is the most common cause of ESRD in India and Pakistan. It is similar in countries within the same World Bank Low- economy category and less prominent in countries in the Medium-economy category, ranging from about 11% in Egypt and Argentina to 25% in Saudi Arabia. Proliferative glomerulonephritis constituted the major bulk of primary etiology in contrast to its remarkably low frequency in the developed world.

Focal and segmental glomerulosclerosis is the second most common lesion in Africa. In contrast, Ig A nephropathy is uncommon in Africa. On the contrary, the prevalence of Ig A nephropathy is high in Thailand. Amyloidosis was reported as a fairly common glomerulopathy with a prevalence ranging from 6.1% to 10.3% of all glomerular lesions. It may be attributed to chronic infection as tuberculosis in India, schistosomiasis in Egypt, or to familial Mediterranean fever in North Africa. Interstitial nephritis accounted for 2.4% to 20% of reported ESRD: the highest prevalence being encountered in India and Pakistan.

In the developing world, diabetic nephropathy that is increasing over the years, constitutes more than 25% of the dialysis population. It appears to be higher in Latin America and India than in Africa. The reported contribution of diabetes ranged from 9.1% in
Egypt to 29.9% in Thailand. Hypertensive nephrosclerosis accounted for 13% to 21% of reported ESRD. But the range is much wider in other reports, spanning between 4% in the Sudan (29) and 43% in Nigeria. The mean age of ESRD patients requiring dialysis in most developing countries is much lower, 32 to 42 years, than that in the developed world, 60 to 63 years. Among the reasons for this difference are the delay in detecting renal disease and the failure to institute controlling and preventive measures in patients with progressive renal failure, both of which result in faster deterioration of renal function and progression to ESRD. Patients aged under age 18 years constitute about 3% in Egypt and Thailand, 12% in Mexico and South Africa. There is a significant male preponderance in developing countries that varying from about 52% in Thailand to 68% in Egypt and up to 80% in India. This may be partly explained by the increased exposure of men to noxious environmental factors.

1.3.3. Treatment Modalities of ESRD

CAPD is becoming the preferred modality of dialysis in countries with limited resources. The procedure does not require expensive equipment, and after the initial period, the patient no longer requires regular visits to a dialysis centre. These qualities should make CAPD the ideal modality for ESRD patients in developing countries. However, utilization of CAPD varies greatly among developing countries. In some South American countries like Mexico, Venezuela, and Brazil, 50% to 90% of dialysis patients are on CAPD. Its use in other developing countries such as China, Thailand, Saudi Arabia, Egypt, Tunisia, Argentina and India is low. In contrast to that in the developed world, the cost of CAPD is two times higher than that of haemodialysis in developing countries. The main reason for this disparity is the lack of indigenous facilities to manufacture peritoneal dialysis fluid. The number of dialysis units in developing countries is not known, although published figures indicate that the fewest are in the large populated countries: Brazil, 3.3 pmp; Algeria, 0.8 ppm; China, 0.2 pmp; and India, 0.2 pmp. The reported number of haemodialysis units in other developing countries was a gross average of 5.2 pmp. There was an additional small pool of units providing only peritoneal dialysis, the size of which averaged 20% that of the haemodialysis pool. In the absence of adequate dialysis facilities, renal transplantation remains the only hope of survival for ESRD patients in developing countries. In contrast to developed countries, the underdeveloped nations have no organized cadaver transplant program. Utilization of cadaveric kidneys is poorly organized in Asian countries.

Considering the reported incidence of ESRD in different countries, gross diversity can be seen in the priority of offering transplantation as the preferred treatment modality. Sources of kidney donation for transplantation are mainly living donors ranged from almost 0% in Egypt to 28% in South Africa. In contrast, in some developing countries, cadaver donors account for approximately 50% to 60% of transplants such as Argentina and Thailand. About 2500 to 3000 renal transplants are performed in India each year. Of the 3000 transplants, only about 100 are of cadaveric origin. Living unrelated donors account for 50% to 60% of transplants in India, 20% in Egypt, and the rest are from living related donors.

1.3.4. Survival, Mortality and Causes of Death

Intermittent peritoneal dialysis is seldom used as a method of long-term life support with an average annual survival of less than 10%. The mean annual survival on CAPD is 62% ranged from 30% in Egypt to >90% in Tunisia and that on haemodialysis is 73.4% ranged from approximately 10% in India to 90% in Egypt and Tunisia. The principal causes of death are cardiovascular (43% to 51%) and infection (16% to 23%). In underdeveloped countries, a combination of poor living conditions, inadequate dialysis, malnutrition, hypoalbuminemia, and frequent
blood transfusion makes dialysis patients prone to a variety of bacterial, viral, and fungal infections. The incidence of tuberculosis in dialysis patients has been reported to vary between 4% and 15% in tropical countries. The average prevalence of hepatitis B and HCV in a survey was found as 9.4% and 32.8%, respectively. HIV infection has not yet been reported to be a major problem in the dialysis population in developing countries.

Infections complicate the course in 50% to 75% of transplant recipients in developing countries, with mortality ranging from 20% to 60%. In comparison, developed countries have an incidence of infection of about 40%, and advances in diagnosis, prevention, and therapy have reduced mortality to less than 5%.

1.3.5. Economic Cost of ESRD

The items of typical annual direct dialysis cost per capita are essentially the same between countries. It is noteworthy that peritoneal dialysis is the more expensive modality in countries that still import the dialysis solutions. For example, costs of dialysis modalities are approximately $22,644 for haemodialysis, 22,350$ for peritoneal dialysis in Turkey. CAPD is also currently an expensive treatment modality in Africa. On the other hand, countries that could overcome this barrier such as Mexico and South Africa are able to provide this modality at a much lower cost.

In conclusion, the rate of treated ESRD continues to increase globally and the economic burden of RRT is increasing in both developed and developing countries. To reduce the cost of peritoneal dialysis fluids and to increase the rate of transplantation seems the best way to increase the availability of RRT for ESRD patients in the developing world.

REFERENCES


