Renal transplantation in developing world

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Introduction
Renal transplantation is the most acceptable therapeutic option for most patients with irreversible renal failure in developing countries. The high cost of dialysis limits this form of treatment to a privileged groups only, making successful renal transplant a greater necessity in developing country than elsewhere. It is argued that transplantation should be encouraged because it is the most cost-effective form of renal replacement therapy with the best promise of improved quality of life and an excellent chance of rehabilitation.

Incidence of end-stage renal disease is 48 to 240 per million populations in developing countries. The incidence of ESRD is steadily increasing in the United States since 1987; it has increased at a rate of 6% per year. There is no clear explanation for this growth, although the increase in the incidence of diabetes mellitus may be a major contributing factor. A marked difference exists in the mean age of patients initiated on renal replacement therapy in developing countries compared with Europe and the United States. In 1997 the mean age of a patient starting renal replacement therapy in the United States was 61 years, whereas in some developing countries, the mean age is 30 years. A possible explanation for the younger presentation in developing countries is that inadequate preventive and curative medical care allows more rapid development of ESRD. In Bangladesh, approximately 100-110 new patients per million of the population develop ESRD yearly, only 2-3% of these patients can able to avail the facility for dialysis and transplantation.

Another important difference that has emerged is the marked male predominance in the incidence of renal replacement therapy compared with industrialized countries. In the United States, men account for 53% of patients started on treatment. In developing countries, men account for 93% of patients receiving treatment. The incidence of chronic renal failure is unlikely to be considerably higher in men, and the marked discrepancies probably reflect social and cultural factors that favor men.

Renal replacement therapy options in developing countries
The management of ESRD poses complex medical, social, moral and economic challenges for patients and communities in developing nations. Life saving therapy entails the institution of dialysis and or transplantation. In developing countries, most patients with ESRD are offered only conservative treatment because of the lack of access to dialysis and transplantation. In Latin America, a report from Sao Paulo, Brazil, showed that 26% of patients did not receive any form of renal replacement therapy, report sindicate that most of sub-Saharan Africa has no effective renal replacement therapy program. In Egypt, Southern India, Pakistan, Bangladesh of the incident ESRD population do not receive any form of renal replacement therapy. On the other hand acceptance rates for renal replacement therapy in the developed world are 61 to 99%

Haemodialysis
In developed countries, 56 to 60% of ESRD patients receive dialysis. In some countries the figure is higher. The situation in developing countries is different. The problems facing the initiation of such programs includes the following:

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- Prohibitive capital expenses of setting up dialysis units
- Lack of trained staff to care for patients
- Technical problems including erratic power supply, unreliable water supply and mechanical breakdowns
- Shortage of reagents and spares
- Access of patients to long term dialysis. With almost two thirds of the population in developing countries situated in rural areas and treatment centers almost exclusively in urban areas, patients have to travel great distance, which essentially precludes their inclusion in long term dialysis programs.

The long term outcome of maintenance dialysis as the treatment modality of choice shows patients survival to range from 10-15% at 3 yrs in India, 25-52% at 5 years in Egypt and South Africa and in Bangladesh two and five years survival were 68% and 50% respectively. In the absence of an established renal transplant program, it is not viable economically to maintain large number of patients on a maintenance haemodialysis program in a developing country. In South Africa, national guide lines set by the department of Health preclude patients from the renal replacement therapy program if they are not suitable transplant candidates for any reason.

Peritoneal dialysis
Peritoneal dialysis is an efficient form of renal replacement therapy that does not require the capital expenses of hemodialysis. In most instances it is less expensive than haemodialysis. Other advantages of peritoneal dialysis are that it is more physiological than intermittent hemodialysis and requires less stringent dietary and fluid restrictions. It is more appropriate for certain classes of patients, such as diabetics and children. But in most of the developing countries peritoneal dialysis is grossly underused. In India less than 1% of ESRD patients receive peritoneal dialysis. This under use in developing countries is partly due to physician bias. Other reasons are as follows:

- Patients are less educated and less compliant.
- The risk of peritoneal infection is high in the hot, humid climate and poor sanitary conditions that prevail.
- Lack of skilled personnel results in high rates of infection.
- Cost of antibiotics are high.

Recurrence peritonitis and other technical problems were major limitations to the use of peritoneal dialysis in the management of uraemic patients in developing countries.

Renal transplantation
The most striking feature of renal transplantation in developing countries is the emphasis and in some cases exclusive reliance on living related donor transplantation. There is worldwide shortage of organs and the gap between supply and demand grows inexorably. Lack of resources, cultural factors and ignorance all contribute to the ongoing shortage of organs. The number of transplants performed per million population correlates with the socioeconomic status of the country. Of all renal transplants that have been performed around the world, most (>90%) have been in developed countries, which perform on average 20-40 transplants per million population per year. This figure compares with 1-5 per million populations in most developing countries, where only 2% of the estimated need for renal transplantation are met. Under these circumstances, the purchase of kidneys from living non-related donors has flourished.

Donors
The incidence of ESRD is estimated at anywhere from 100-200 per million population per year. The maximum yield of cadaver donors (Spain) is about 30 per million populations and is considerably less in most countries. It appears that all countries need to use living donors. Daar and colleagues for the purpose simplifying the
discussion of the ethical issues involved have classified living donation into six categories: genetically related, emotionally related, altruistic strangers, gray basket, rampant commercialism and criminally coerced\textsuperscript{15,16,17}.

**Living related donors**

In the absence of long term dialysis and cadaver donor programs, living related donor transplantation is the only option available to patients in most developing countries\textsuperscript{14,18}. In a report from Pakistan\textsuperscript{41} some of the problems of living related donors experienced in a developing country were highlighted. Although the average number of potential donors per recipient was six, this advantage was dissipated quickly. The structure of most Pakistani society is feudal and tribal in rural areas. Communities live in extended family setups under the patronage of single elder making the number of potential family donors quite large; medical problems excluded 40% of potential donors, however, hypertension was the commonest usually undetected problem. Other problems included urological ones, renal calculi, diabetes mellitus, ischemic heart diseases and hepatitis. This array of problems reflects the limited access to health information and care common in developing countries. Approximately 25% of potential donors refused to donate for social reasons; as a result of ignorance and misconceptions. Families refused to allow a breadwinner from donating for fear of incapacity and loss of family income. There was the perception that the donation would leave the male breadwinner permanently disabled. In the case of women, the perception was that the operation reduced her fertility and compromised her capacity to run a household.

**Spousal donor**

Spousal organ donation can be an extremely rewarding form of treatment, with most donors expressing satisfaction with their decision and improvement in family relationships. Results of spousal transplants could be improved by if recipient had received donor specific blood transfusions previously\textsuperscript{7,56}. Spousal donations are an important source of kidneys in developing countries as well\textsuperscript{41}.

**Emotionally related donors**

In the absence of a suitable relative, an altruistic living donation by a close friend generally would be acceptable today, provided that the donor is motivated by genuine concern for the welfare of the patient. But in fear of commercialization it is not accepted by law in Bangladesh.

**Cadaver donors**

Ignorance appears to be the major limiting factor inhibiting the institution and growth of cadaver organ donation programs in many developing countries\textsuperscript{10}. Most religious commentators including Islamic, Christian, Hindu, Judaic and Buddhist support transplantation\textsuperscript{16}. Saudi Arabia is an excellent example of conservative Muslim country that has implemented a cadaver donor program successfully. The success of such a program require several factors to be addressed\textsuperscript{14}.

**Education**

An integrated education campaign is necessary to increase public awareness of the need for organ donation. In developing countries low adult literacy rates hinder education drives.

**Attitude**

The attitude of indifferent health care professionals has been identified as a major limiting factor.

**Legal aspects**

Recognition of the concept of brain death and the enactment of laws that allow the use of organs from cadaveric donors are important. Many developing countries do not have such laws. Bangladesh has passed the Human Organ Transplantation Act (HOTA) which banned trade in organs, recognized brain death and
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simultaneously promoted cadaver organ donation.

**Resources**
Access to intensive care facilities is required to allow the ventilation of donors. The severe shortage of intensive care unit beds in developing countries can be a major limitation. A reliable tissue typing laboratory is also essential.

**Transplant activity**
No country in the world can claim to have enough donors for its transplantation needs. At best 45-50% of the prevalent ESRD population have functioning grafts in developed countries. In developing countries, the situation is much worse, with renal replacement therapy and transplant activity being well below the need. The number of transplant centers throughout the developing world has continued to increase, however, since the 1980.

**Asia Pacific region**
Combining the registry report of 12 Asian developing countries with individual country reports shows that a total of 29,027 kidney transplants were performed in the period 1993-1997. The Peoples Republic of China is exceptional in undertaking the greatest number of cadaver donor transplants in the region - its main source of organs is reported to be from judicially executed prisoners. Excluding China’s controversial contribution, living related donor transplantation accounts for 90% of transplants in the region. India undertakes the greatest number of living donor transplants. Of the 7,742 living donor transplants undertaken in Asia in the 2-year period 1996-1997, 83% were living related donor transplants and 17% were living unrelated donor transplants. Cadaver donation is underdeveloped in most of Asia, where brain death has not yet been generally accepted. Many of these countries do not have organ procurement organizations that are supported by the necessary legislation. Singapore was one of the earliest Asian countries to introduce legislation on organ transplantation. Human organ transplant Act (HOTA) made provision for the procurement of organs form cadavers, defined death to include brain death criteria and banned commercialism. Despite this program, a donor shortage persists, owing to a lack of awareness by the public and particularly by health professional as well as cultural and religious factors. Taiwan has had a significant cadaver donor program resulting from active organ procurement using brain-death criteria, although the laws were enacted only in 1987.

Commercialism had earned India a poor reputation, but in 1995, it passed the HOTA which banned trade in organs and simultaneously legalized brain-death criteria and cadaver organ donation. Since then, there has been a slow but steady increase in cadaver donation, including the occasional donation of hearts and livers.

The annual number of renal transplants has increased over the years in Asia, but great potential remains for further growth. This growth can be achieved through legal and social acceptance of the brain death concept, the establishment of organ procurement organizations and most important, education of the public and health care providers through systematic support from the authorities.

**Middle East and Afro-Arab region**
Progress continues to be made in the Middle East and Afro-Arab region where most countries now have kidney transplant programs. Similar to most developing countries, living related donors account for most transplants. The data from 16 countries showed that 6,408 renal transplants were performed by 1997. Countries with cadaver programs include Saudi Arabia, Oman, Jordan, Kuwait, Turkey, Lebanon and Tunisia. This active cadaver program was achieved through intensive public education.
The lack of cadaver donor programs has persisted despite support from religious authorities\textsuperscript{16}. As a result, many patients against the wishes of their local transplant teams, have gone abroad to obtain living non-related donor kidneys through commerce in India, Egypt, Iraq and possibly Iran\textsuperscript{2,14, 16}\textsuperscript{51}.

Africa and Indian Ocean Islands
Africa has a population of nearly 700 million. There is little available information because there are no reliable registries\textsuperscript{60}. Except for North Africa, the Indian Ocean Island and South Africa, there is no significant renal replacement therapy in Africa\textsuperscript{6}.

Central and Eastern Europe
After the collapse of communism, many countries suffered adverse socioeconomic conditions and this was reflected in the effective renal replacement therapy rates\textsuperscript{50}. The former Soviet Union\textsuperscript{30}, Poland\textsuperscript{39}, Romania\textsuperscript{57} and Albania\textsuperscript{29} had renal replacement therapy rates comparable to developing countries. Central and Eastern Europe provides renal replacement therapy predominantly dialysis\textsuperscript{49}. In Poland, reflecting the regional experience, transplantation accounted for 8\% of the renal replacement therapy population\textsuperscript{49}.

Latin America
Latin America has experienced a phenomenal increase in transplant activity. This region is the fastest growing in terms of number of transplants; new units established and progress with cadaver organ donation. What makes the achievement more remarkable is that it occurred during a decade of economic recession in the region. The Latin American registry includes 21 countries, a regional population of 470 million, representing approximately 10\% of the world transplant activity\textsuperscript{52}. Another important development has been an increase in the number of cadaver donors, which by 1990 accounted for 42\% of all transplants\textsuperscript{35}. Currently cadaver and living donor transplants are approaching parity in Latin America.

Transplant outcome
Patient survival
Egypt\textsuperscript{8}, India\textsuperscript{19}, United Arab Emirates\textsuperscript{36}, Turkey\textsuperscript{2}, Iran, Saudi Arabia\textsuperscript{4}, Tunisia\textsuperscript{9}, Pakistan\textsuperscript{41}, Taiwan\textsuperscript{32} and Korea\textsuperscript{45} reported living donor transplantation patient survival ranging from 72 to 100\% at 5 yrs. The survival decreased to 62 to 86\% at 10 yrs in reports from Saudi Arabia\textsuperscript{4} and Korea\textsuperscript{45}. Patient survival with cadaver donor transplants was 71-94\% at 5 years in reports from South Africa\textsuperscript{20} Cyprus\textsuperscript{31} Saudi Arabia\textsuperscript{4}, Taiwan\textsuperscript{12} and Korea\textsuperscript{49}. This rate decreased to 29-90\% at 10 years in reports from South Africa\textsuperscript{34} and Saudi Arabia\textsuperscript{4}.

Graft survival
Living Related Donors
The graft survival of living donor transplants was 47-95\% at 5 years in reports from South Africa\textsuperscript{20}, Cyprus\textsuperscript{31}, Lebanon\textsuperscript{27}, United Arab Emirates\textsuperscript{36}, Saudi Arabia\textsuperscript{4}, Tunisia\textsuperscript{9}, Pakistan\textsuperscript{48}, Taiwan\textsuperscript{32} and Korea\textsuperscript{45}. The graft survival in HLA-identical donor transplants was 90-95\% at 5 years in reports from Lebanon\textsuperscript{27} and Pakistan\textsuperscript{48}. The graft survival in HLA-haploidentical and poorly matched donor transplants was 47-90\% at 5 years in reports form Lebanon\textsuperscript{21}, Pakistan\textsuperscript{40} and Korea\textsuperscript{45}.

Living non-related donors
In the larger series of living non related donor transplants from developing countries, graft survival ranged from 81 to 88\% at 5 years in reports from Lebanon\textsuperscript{27}, Iran, Korea\textsuperscript{45} and Brazil\textsuperscript{24}. This rate decreased to 47\% at 10 years in reports from Korea\textsuperscript{45}.

Cadaver donors
China has the highest cadaver transplant activity in the Asia-Pacific region, although its unconventional organ source is highly controversial. In 1992 a Chinese report revealed a poor graft survival rate of 26\% at 5 years.
during the precyclosporine era before 1985 but this had improved to 41% at 5 years with cyclosporine immunosuppression. In more recent series in developing countries, cadaver donor graft survival ranged from 55 to 72% at 5 years in reports from South Africa\textsuperscript{20}, Cyprus\textsuperscript{31} and Saudi Arabia\textsuperscript{4}. This rate decreased to 29-58% at 10 years in reports from South Africa\textsuperscript{20} and Saudi Arabia\textsuperscript{4}.

**Economic and social consideration**

*Cost and economic considerations*

Cost has significant implications on the future of renal transplantation in developing countries, where transplantation is constrained heavily by financial resources. There are striking differences in the provision of renal replacement therapy in different regions. The relationship between transplant activity and per capita income of countries in the developing world shows strikingly that cost and economic considerations have a major bearing on delivery. A similar relationship was shown in Latin America\textsuperscript{35}.

The cost of renal replacement therapy depends on the importation of dialysate fluid, disposables and immunosuppressive therapy, specifically cyclosporine, for transplantation. Several reports confirm that transplantation is less expensive than dialysis in the developing world\textsuperscript{8,13,40}.

In Taiwan\textsuperscript{25} the average cost of transplantation in the first year was approximately 70% that of hemodialysis, decreasing to 38% in subsequent years. Another report compared the annual maintenance cost between the different treatment modalities in Nigeria\textsuperscript{37}. Peritoneal dialysis was 70% the cost of haemodialysis, and a living related donor kidney transplant was 50% the cost of haemodialysis in the first year, decreasing to 10% in subsequent years. The distinct advantage of transplantation resulting from prolonged graft survival is improved quality of life\textsuperscript{32,44,45}. Transplantation affords the patient more freedom with rehabilitation to gainful employment. The transplant becomes economically beneficial if the graft survives longer than the break-even cost saving was achieved after 1.5 years on cyclosporine based regimens, whereas in the United States this was achieved after 4.6 years\textsuperscript{21}. Donor selection that offers the best graft survival confers the greatest cost-effectiveness. Genetic and emotionally related living donors offer better graft survival and greater cost-effectiveness than cadaver donors do.

In the case of living donor transplantation, considerable costs can be saved if a patient receives a graft without prior dialysis. For patients with a living donor, early preemptive transplantation is an ideal choice for primary treatment of ESRD in developing countries. Avoiding hemodialysis not only saves costs, but also avoids the inconvenience and discomfort of dialysis and protects the patient from undue exposure to blood products\textsuperscript{25}. The report favored preemptive transplantation as a cost-effective approach for living related transplants. In a study from Vellore, South India, a group of 43 preemptive renal transplant recipients had significantly less morbidity than those transplanted from dialysis\textsuperscript{26}.

Overall, renal transplantation is less expensive than dialysis in developing countries. The absence of government support and the high cost of imported medication make treatment affordable to only a few affluent individuals, however, including those with family support or those with assistance from employers\textsuperscript{13}. Schemes to reduce costs include cyclosporine withdrawal at 3 to 12 months maintaining patients on azathioprine and steroids\textsuperscript{38}. Another strategy has been to combine cyclosporine with ketoconazole or diltiazem, both of which increase cyclosporine levels, allowing dose and cost reduction.
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