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Dialysis and Transplantation News

Renal transplantation in Iran

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Introduction

Iran—formerly called Persia—is located in the Middle East between the Caspian Sea and the Persian Gulf. It covers 1648000 km^2 and has 60 million inhabitants. The prevalence of end-stage renal disease (ESRD) patients in Iran is about 15000 and the annual incidence of new ESRD patients is 3175 or 53 patients per million populations per year. Iran has the most successful renal transplant programme in the region. The renal transplant activity of the country has reached 24 renal transplants per million per year. There are two periods in the evolution of the renal transplantation programme in Iran. During the first period (1967–1988) all transplants were from living related donors (LRD) and the number of renal transplants performed was much lower than the national demand. In the beginning of the second period (1988–2000) by careful attention to the country's cultural, religious, and socioeconomic backgrounds a controlled living unrelated donor (LURD) renal transplant programme was adopted. As a result, in the last 12 years more than 10000 renal transplants were performed and the renal transplant waiting list was eliminated by the end of 1999.

In this article, I will first review the history of renal transplantation in Iran from 1967 to 2000 and describe the practice of renal transplantation emphasizing the characteristics of our LURD renal transplantation programme.

Then I will report the results of 1420 consecutive renal transplants from LRD and LURD that have been carried out in our centre. Finally, I will discuss the necessity for and the ethical issues involved with our LURD renal transplantation programme.

History of renal transplantation in Iran (1967–2000)

The first renal transplantation was performed in Shiraz, Iran in 1967 [1]. During 1967–1988, the number of patients on dialysis steadily increased but the renal transplantation programme of the country severely lagged in growth in comparison with haemodialysis [2]. Between 1967 and 1985 only about 100 renal transplants were performed. Since 1980, due to very limited renal transplant activity in the country, the Ministry of Health started allowing dialysis patients to be transplanted abroad with governmental funds. Any dialysis patient who had a letter of acceptance from a transplantation unit abroad was accepted and all travel and transplant expenses were paid. As a result a large number of dialysis patients who were ready to be transplanted created a long transplant waiting list at the Ministry of Health. Between 1980 and 1985, over 400 of these patients travelled to European countries and the US using government funds and received a renal transplant. The majority of these transplants were performed in the UK from LRDs [3].

In 1985, the high expense of renal transplantation abroad and the increasing number of patients on the renal transplant waiting list prompted our health authorities to establish renal transplantation in the country. Two renal transplant teams were organized between 1985 and 1987, and 274 LRD renal transplants were performed.

A large number of dialysis patients had no potential LRD, but needed renal transplantation and no cadaveric organ donation programme had been established. The latter did not seem likely to become a reality in the near future. Therefore, a controlled LURD renal transplantation programme was adopted in 1988 [4]. As a result, the number of transplant teams gradually increased from two to 23 and by the end of 2000 a total of 10957 renal transplants (2468 LRD, 8405 LURD and 84 cadaveric) were performed. In 1999, the renal transplant waiting list of the country was eliminated. Figure 1 shows the annual number of renal transplants performed in Iran from 1984 to 2000. The renal transplant activity in the country has reached 24 renal transplants per million per year. Over 76% of all renal transplants have been from LURD (Figure 2).

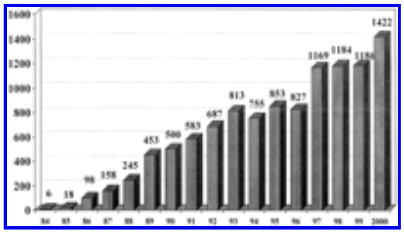

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Fig. 1. The number of renal transplantations performed in Iran from 1984 to 2000.

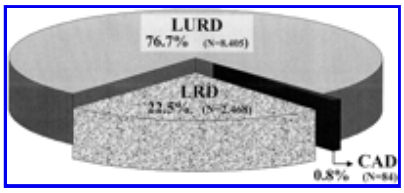

Fig. 2. Sources of kidney donation in Iran from 1984 to 2000.

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Since 1989, several decrees (fatwas) from religious leaders of the country allowing cadaveric organ donation have been obtained. In April 2000, legislation was passed by our parliament accepting brain death and cadaveric organ transplantation. But, due to strong cultural and religious barriers, cadaveric organ transplantation has not been successful in Iran, and only a total of 84 cadaveric renal transplants had been performed by the end of the year 2000. I expect that due to strong cultural barriers along with inadequate administrative efforts, cadaveric organ transplantation in Iran will start to grow very slowly and only a small proportion of ESRD patients will benefit from cadaveric renal transplantation in the coming years.

The practice of renal transplantation in Iran

Growth of the chronic haemodialysis programme (1967–2000)

Between 1967 and 1976, small chronic dialysis units were gradually established at several university and private hospitals in Tehran. In 1976, an ESRD office was established at the Ministry of Health for evaluation and registration of all new patients, training of dialysis staff, expansion of dialysis facilities throughout the country and reimbursement of all dialysis expenses. As a result the total number of dialysis patients and dialysis centres of the country steadily increased (Figure 3). At the end of 1980, a total of 701 patients were being dialysed in 40 centres throughout the country, increasing progressively the total case load: 2445 patients in 62 centres by the end of 1988, 6450 patients in 128 centres by 1996 and 8300 patients in 232 centres by the end of 2000, respectively. This increase in the number of dialysis patients in Iran has been due to improved awareness of the physicians and the public about the availability of full government paid dialysis therapy and a more liberal patient selection policy in the country.

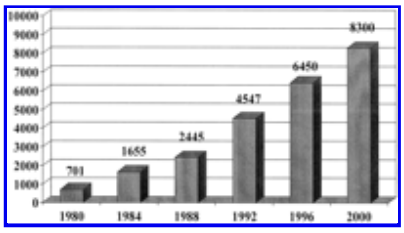

Fig. 3. Total number of patients on dialysis in Iran from 1980 to 2000.

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Sources of kidney donation in Iran

Living related kidney donation

In the last 16 years, 2468 renal transplants from LRDs have been performed. LRD was the only source of kidney donation until 1988. In spite of the usually large family size in Iran, which gives most dialysis patients the opportunity of having one or more potential kidney donors, unfortunately due to cultural reasons many potential family donors refuse kidney donation. Until 1988, LRD transplantation has been performed on a limited scale only, i.e. less than three LRD renal transplants per million per year. Since 1988, when a controlled LURD renal transplant programme was started, the total number of renal transplants performed each year steadily increased. This significant growth in renal transplantation was due to a continuous rise in the number of LURD renal transplants. The number of LRD renal transplants performed annually remained unchanged (two to three per million per year). As a result, the ratio of LURD to LRD renal transplants in the country has steadily increased.

Cadaveric kidney donation

During the last two decades, considerable efforts have been made repeatedly by renal physicians, surgeons, and patients to start an effective cadaveric renal transplantation programme in Iran. Unfortunately due to strong cultural and religious barriers as well as inadequate knowledge and expertise of health authorities in establishing cadaveric transplant programmes, only 84 cadaveric renal transplants have been performed by the end of year 2000 (less than 0.8% of total). It is expected that the cadaveric renal transplant programme of the country will continue on a limited scale in the coming years and many ESRD patients will have to remain on chronic dialysis or still receive a renal transplant from a live donor.

Living unrelated kidney donation

In 1988, a controlled LURD renal transplant programme was started because a large number of dialysis patients had no LRD or their potential LRDs were refusing to donate a kidney and because an effective cadaveric renal transplant programme was not established in the country nor did it seem likely to become a reality in the coming years. As a result, more than 8400 renal transplants from LURD were performed (76% of total) and the renal transplant waiting list of the country was eliminated by the end of 1999.

As part of the adopted LURD renal transplant programme during the evaluation of the renal transplant candidate, the transplant physician emphasizes the advantages of LRD compared with LURD transplantation (such as longer graft survival rates and fewer acute rejection episodes) and recommends transplantation from an LRD. If the patient has no LRD or the potential donor is not willing to donate a kidney, the patient is referred to the Dialysis and Transplant Patients Association (DATPA) to find a suitable LURD. Those who wish to volunteer as LURDs also contact DATPA. All the members of DATPA are ESRD patients and they receive no financial incentives for finding a LURD or for referring the patient and donor to a transplant team. There is no role for a middle-man or agency in this programme. All transplant teams belong to the university hospitals and the government pays all of the hospital expenses of transplantation. After transplantation, the LURD receives an award from the government and a majority of the LURDs also receive a rewarding gift (or arranged payment by DATPA) from the recipient. Transplant teams receive no incentives from the rewarding gifts or the governmental awards. The rewarding gifts have been limited to a range that the majority of patients of a poor socioeconomic class are able to afford. This programme is under the close observation of the Iranian Society of Organ Transplantation for ethical issues. Foreigners are not allowed to undergo renal transplantation from Iranian LURDs.

Donor–recipient evaluation and immunosuppression protocols

At present there are 23 active renal transplant teams in Iran. All transplant teams belong to university hospitals. The methods of donor and recipient evaluation as well as the immunosuppression protocols of different transplant teams are very similar but not exactly the same. So I will describe below the donor–recipient evaluation and immunosuppression protocols of the our transplant unit of the Hashemi Nejad Kidney Center—one of the largest and pioneering transplant units of Iran as an example for whole country.

The selection of recipients and suitable donors at our unit is based on complete clinical and psychological evaluation as well as appropriate laboratory tests and imaging methods. Highly sensitized patients who have a positive cross match with the donor or who have high panel cell reactivities are excluded from transplantation. The 'Donor Selection Panel'— consisting of nephrologists, transplant surgeons, and members of the nursing staff—evaluates all LRDs and LURDs to ascertain whether the donation is voluntary in order to exclude the possibility of any outside pressure being exerted for kidney donation.

The immunosuppression protocol consists of: cyclosporin given twice daily at a dose of 5–6 mg/kg/day, prednisolone initiated at a dose of 1 mg/kg/day and tapered gradually to 15 mg/day in 4 weeks and 10 mg/day in 6 weeks and azathioprine at a dose of 1–1.5 mg/kg/day. All patients are also given a prophylactic dose of intravenous (i.v.) methylprednisolone (1 g/day) for the first 3 postoperative days. For high-risk cases, such as those undergoing a second transplant or those with previous high panel cell reactivities, induction therapy with ALG, ATG (and recently in a few cases with Zenapax) is used. Since 1997, mycophenolate moefetil is given instead of azathioprine for maintenance immunosuppression of some high-risk cases. Anti-rejection therapy consists of methylprednisolone (1 g/day) for 3–5 days and ALG or ATG in patients with steroid-resistant rejection. In selecting LRDs, priority is given to the candidate who has the best HLA match with the recipient. For LURD transplant, HLA matching is not practical and any donor who is ABO compatible with the patient is accepted.

Results

Unfortunately there is no national transplant registry in Iran to report the short- and long-term results of all renal transplants carried out in the country. Most renal transplant teams report their own results as single-centre experiences. The annual report of the ESRD office of Iran includes data about the number, dates and types of transplants, but lacks the short- and long-term results of transplants; so the results of our centre (The Hashemi Nejad Kidney Hospital) will be shown and discussed below as an example representation for the country [5].

Between April 1986 and July 2001, a total of 1420 renal transplants were performed at our centre; 478 (33.7%) were from LRDs (146 HLA-identical, 311 one HLA-haplotype matched and 21 zero HLA-haplotype matched) and the remaining 942 (66.3%) were from LURDs. Among these 1420 recipients, 897 were male and 523 were female, and the age range was 8–68 years. Patient and graft survival rates were estimated by the Kaplan–Meier method. Patients who died with a functioning graft were considered to have had graft loss. The overall patient survival rates were 92.8%, 83.7%, and 73.3% and the overall graft survival rates were 87.2%, 66.2%, and 49.8% at one, 5 and 10 years, respectively. The actuarial patient and graft survival rates were also determined in the LRD and LURD transplant groups (Figure 4). The graft survival rates were significantly higher for recipients of LRD transplant compared with LURD transplants ($P<0.05$).

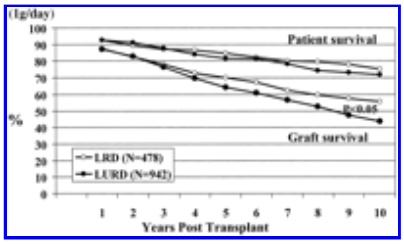

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Fig. 4. Patient and graft survival rates in LRD and LURD renal transplantation in Hashemi Nejad Hospital, Tehran from 1986 to 2000.

The actuarial graft survival rates for recipients of HLA-identical and one HLA-haplotype matched LRD transplants and LURD transplants were compared (Figure 5). The graft survival rates in HLA-identical LRD transplants were 88.9%, 81.7%, and 69.9%; in one HLA-haplotype matched LRD transplants were 86.0%, 68.2%, and 52.7%; and in LURD transplants were 87.1%, 64.2%, and 43.7% at one, 5 and 10 years, respectively. As we have reported previously there was no significant difference in graft survival rates between recipients of one HLA-haplotype matched LRD and LURD renal transplants [6].

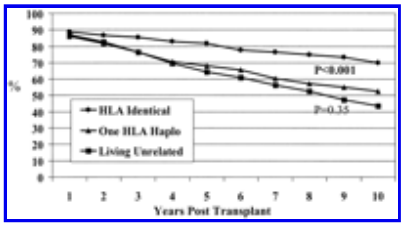

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Fig. 5. Graft survival rates in HLA-identical, one HLA-haplotype match and living unrelated renal transplant in Hahemi Nehad Hospital, Tehran from 1986 to 2000.

Discussion

The results of LURD renal transplants from our unit are comparable with the results reported from transplant centres of other countries [7,8]. The United Network for Organ Sharing (UNOS) Transplant Registry and some individual transplant centres have reported better results with LURD renal transplants [9–12]. I believe that the following factors had an adverse effect on our renal transplant patient and graft survival rates. Due to a limited health care budget and lack of administrative expertise in our health authorities, all transplant units (including our unit) are insufficiently equipped. Some patient deaths and graft losses could have been prevented if our transplant unit were not deficient with respect to laboratory facilities, scientific consulting staff, and necessary drugs. Many dialysis patients from small towns and rural areas are referred to our centre for renal transplantation. These patients have to return home after transplantation where optimal long-term post-transplant care is difficult to achieve. The patient deaths and graft losses have understandably been higher in this

subpopulation of our transplant recipients. Post-transplant complications and delayed graft function were more common in the early years of our transplant programme. The frequency of post-transplant complications and early patient and graft losses has gradually decreased (due to a centre effect) as the experience of our transplant teams has improved [13,14].

At present all countries, including the wealthiest, have adopted a dialysis and renal transplantation programme to best match to their cultural needs and socioeconomic conditions. In most developing countries, starting an effective dialysis and renal transplantation programme as an expensive and modern treatment has always created profound cultural and socioeconomic problems. Developing countries such as Iran must often make adjustments when new technologies are introduced from Western or technologically advanced countries in order to integrate the changes into their own cultural, religious, and socioeconomic conditions. For example, during the last decades the introduction of vaccination and antibiotics in the absence of an effective family planning programme resulted in striking population growth in some developing countries. In China appropriate adjustment was carried out by adoption of a one-child family policy in 1979 to stop the population explosion and its related socioeconomic consequences [15]. This one-child family policy, which might be condemned by Western ethical standards, especially due to some of its uglier aspects such as female infanticide or sex-selective abortion, has been necessary in China for its very important role in prevention of excessive population growth. In the same way, Western dialysis and organ transplantation technologies that have reached developing countries necessitating appropriate adjustments.

Iran has an ancient culture and is an oil producing country, yet it has a limited health care budget and many incapable and malpositioned health authorities. Starting a cadaveric organ transplantation programme similar to the Western model has not been possible in Iran, not only due to strong cultural barriers but also due to inadequate knowledge, effort, and expertise of its health authorities. Haemodialysis is a costly life-saving treatment modality, which has been increasingly used in Iran without any patient selection criteria. This has placed a great burden on our limited financial resources. So in order to reduce the demand for dialysis and to serve the large number of patients who should receive renal transplant, we had to adopt a controlled LURD renal transplantation programme to increase the renal transplant activity of the country (Figure 6).

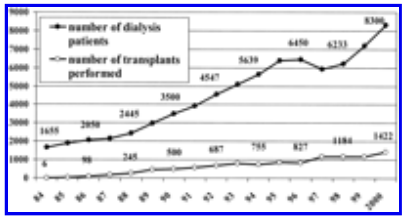

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Fig. 6. The dialysis and renal transplant activity in Iran from 1984 to 2000.

Unfortunately much of the world's experience with LURD renal transplantation is from centres that have approached it with little regard for ethical standards. Prior to 1995, several thousand uncontrolled commercial renal transplants were performed in India each year. According to Professor Chugh [16], almost all of these were

done in private back street clinics with incomplete donor and recipient evaluation and resulted in a high incidence of surgical complications and transmission of HIV and hepatitis infections. The kidneys were sold by middle-men to wealthy patients who came not only from India but also from overseas. This type of commercial renal transplantation has also been reported from countries of Middle East, South Asia, and South America. When commercial transplantation was banned in India it moved to some other countries such as Iraq. At present Iraq has become an international kidney trafficking market and the news media report on large scale, uncontrolled commercial renal transplantation in this country [17]. In China, kidneys from executed prisoners have been used on a large scale for renal transplantation of patients from China and foreign countries. Organ procurements have been done under uncertain conditions, often without obtaining appropriate consent from the prisoner or his family [18].

In response to the commercial transplants, the transplants from executed prisoners and the sporadic news media reports of an organ 'Mafia', the World Transplantation Society and the World Health Organization have condemned paid LURD transplantation. The LURD renal transplantation programme in Iran involves paid kidney donation, but the transplant teams and the Iranian Society of Organ Transplantation strictly enforce ethical rules. The programme is very different from LURD transplantation carried out elsewhere.

In a cultural sense, the LURD renal transplantation in Iran might be compared with breast-feeding of unrelated infants by wet nurses, which was a common practice until several decades ago. Before the introduction of condensed and dehydrated milk, some women would breast-feed unrelated infants whose mothers had died or who had no breast milk. Wet nursing was a paid donation and was usually from lower to higher socioeconomic classes. Nevertheless not only was the practice ethically accepted, but in the Islamic religion wet nursing was so encouraged and admired that unrelated infants breast-fed by one woman were considered as siblings. When the transplant teams and the national transplantation societies ensure the ethics of LURD transplantation, this approach can be used effectively in developing countries as a supplement to their limited scale cadaveric renal transplantation.

One argument against paid LURD renal transplantation is that wealthy patients will be transplanted and this will be denied to poor patients. In Iran's LURD renal transplantation programme, all donors receive a defined governmental award and most donors also receive a rewarding gift from the recipient. The amount of the gift or payment for a LURD kidney has been controlled within a range by DATPA so that poor patients are able to afford transplantation. We conducted previously a study on 500 renal transplant recipients and their LURDs to see which socioeconomic classes benefitted most from LURDs [19]. In this study 6.0% of LURDs were illiterate, 24.4% had elementary school, 63.3% high school, and 6.2% university training. Corresponding levels in their 500 recipients were 18.0%, 20.0%, 50.8%, and 11.2%, respectively. All 500 LURD and their recipients were also grouped according to whether they were poor, middle class, or rich. The results showed that 84.0% of LURDs were poor and 16.0% were middle class. Of the 500 LURD transplant recipients, 50.4% were poor, 36.2% from the middle socioeconomic class, and 13.4% were rich. So more than 50% of LURD kidneys were transplanted to patients from the poor socioeconomic class.

Another argument against paid LURD renal transplantation is that it will have an adverse effect on the development of a cadaveric organ transplantation programme especially in developing countries and that it may also reduce LRD grafting. LURD renal transplantion in Iran might have some negative effect on the development

of cadaveric organ transplantation. However, with the strong cultural barriers that exist in Iran, it would have required too many years to perform over 8000 cadaveric renal transplants that we have already performed with the LURDs programme. The number of LRD renal transplants have been two to three per million per year in the country before and after adoption of the LURD renal transplant programme. The superior results of LRD compared with LURD renal transplantation and the minimal risk to the donor have always been clearly explained to transplant candidates and their families. In spite of this approach, the number of LRD renal transplants remained unchanged but the number of LURD renal transplants steadily increased since 1988. In one study we found that 81% of our LURD renal transplant recipients had a potential LRD [20]. The LRD was not used in these cases for cultural reasons, because the LRD was reluctant to donate in some cases because of the availability of LURD renal transplantation. With a well-controlled LURD renal transplantation programme in place, it may be more ethical to perform a paid renal transplant from a volunteer LURD than from a LRD or spouse under family pressure or with some coercion. It is noteworthy that we have seen rewarded gifting or paid kidney donation in LRD renal transplant as well.

I admit that the best practice of renal transplantation can only be accomplished by an effective cadaveric renal transplant programme; but in its absence and when inadequate numbers of LRD transplants are available, the adoption of a controlled LURD renal transplant programme remains the only alternative. Otherwise many patients will have to stay on dialysis forever, without being given the chance to receive a renal transplant. Finally, in presence of a controlled LURD renal transplant programme, which is closely observed by national societies and transplant teams, the development of uncontrolled, commercial and illegal LURD renal transplantation will be prevented.

Editor's Note

Please see also Editorial comment by A. A. Al-Khader, pp. 213–215.

Notes

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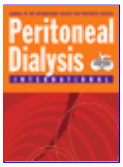

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