Kidney Transplantation in Iran

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Abstract
Kidney transplantation in patients with end stage renal disease is preferred to dialysis because transplantation provides a better quality of life and improved survival. However, the gap between the supply and demand for a renal allograft is widening and the waiting time is increasing. Iranian protocol, a controlled transplant program supported by the government for living unrelated donors, was initiated for solving the problem of organ shortage. Although this system might experience challenges, clearly it has advantages over other organ procurement systems primarily that thousands in need do not die while waiting for a compatible donor.

In the present review I discuss the history of renal transplantation in Iran, "Iranian model" protocol, the situation of Iran’s kidney transplantation from either living or deceased donors compared with the Middle East countries, and our experiences of unrelated renal transplantation.


Keywords ● Iran ● Kidney transplantation ● living donor

Introduction
Renal transplantation has been advocated as the treatment of choice for end stage renal disease (ESRD), however organ shortage remains the main problem in this regard. Deceased donor organ donation is inadequate; hence, the number of patients on the waiting lists is steadily growing. The supply of kidneys does not meet the demand. Consequently, the waiting time for a deceased kidney continues to increase. To deal with the widening gap between the supply and demand of organs for renal transplantation, attempts to expand the organ donor pool have received increased attention. Because many patients with ESRD do not have living genetically related donors, living unrelated donor transplantation is considered. It seems that organ acquisition for renal transplantation has moved down a slippery slope from deceased donors to living unrelated but emotionally related donors. Successful kidney transplantation improves both patients' survival and quality of life. It relieves the burden of dialysis for patients suffering from ESRD. In addition, kidney transplantation is associated with markedly decreasing the cost of healthcare for the society and government.

The first successful kidney transplantation from a live donor to his identical twin was performed 54 years ago by Drs. Murray and Merrill. In accordance with their idea of a voluntary donor for a specific recipient, the concept of "living-unrelated" or "emotionally related" donor emerged. Unrelated renal transplantation was first done in the early 1960s when dialysis therapy was not routinely available. The advantage of living unrelated over deceased kidney donor transplantation is...
maintained over the long term. In a series from the Washington University School of Medicine, the 5-year graft survival rate of living unrelated donor transplantations was 85.9% compared with 70.7% in the deceased group.\(^5\)

In developed countries the number of patients on renal transplant waiting list is progressively increasing. The gap between the supply and demand for a renal allograft is widening and the waiting time is increasing. Each year thousands of patients die while waiting for a renal transplant. In developing countries 500,000 patients with ESRD die each year because of no access to dialysis and renal transplant facilities. In addition, several hundred thousand patients continue dialysis therapy while awaiting renal transplantation.\(^7\)

The present review presents the history of renal transplantation in Iran and explains the “Iranian model” protocol and the current situation for kidney transplantation conducted in Iran compared with other Middle Eastern countries. It also describes the experiences of unrelated renal transplantation in Iran.

### History of renal transplantation in Iran and other Middle Eastern countries

Organ transplantation in the Middle East region began as early as 1967 with a kidney transplantation done in Shiraz, south of Iran.\(^8\) Between 1967 and 1979, of the 500 kidneys transplanted for Iranians, 112 were performed in Iran.\(^9\) More than 5088 renal transplantations were performed in 2003 in the region with Iran leading with 1640. In 2003, the cumulative number of renal transplant patients was nearly 60,000. By the end of 2003, approximately 16,000 kidney transplantations were performed in Iran (24 renal transplantations per million populations).\(^10\) The annual number of kidney transplantations increased from fewer than 100 in 1986 to 1926 in 2008. For living kidney transplantation, the rate increased from 100 in 1986 to 1545 in 2008, and the proportion of deceased donors increased from less than 1% by the end of 2000 to almost 16% and 20% of kidney transplantations in 2007, and 2008, respectively.

Because of political sanctions and limitations posed on Iran during the Iraq-Iran war, dialysis equipments and dialysate ran out. At the same time Iranian hospitals were primarily obliged to serve the massive civilian and military casualties. So many patients requiring renal replacement therapy died. In 1984, two renal transplant teams were organized and a living related donor transplant program was set up. In 1987, the first spousal transplant was done by a wife donating kidney to her husband.\(^11\) The demand for kidney transplantation was rapidly growing, however, in view of the lack of a permissive law, deceased donation remained insignificant. On the other hand, the number of patients having appropriate or motivated relatives for donation was low. Despite the positive official “Fatwa” (the religious permission release by Grand Ayatollahs who are Shia Muslim leaders), the Iranian parliament passed no act regarding deceased donor transplantation. In 1990, therefore, a controlled living unrelated donor renal transplantation program was launched and the Iranian government agreed to provide funds as “rewarded donation” or “altruistic gift” to the unrelated kidney donors. As a result, the number of renal transplantations gradually increased to almost 21,700 from 1984 up to the end of 2006.\(^12\) In 1999 the waiting list for kidney transplantation fell to almost zero, an achievement based on the development of transplantation with living unrelated donors.\(^13\)

All Middle Eastern countries but Egypt have passed laws that allow deceased donor transplantation and regulate live donations. Iran, Turkey, Saudi Arabia, Kuwait, Tunisia, Jordan, and Lebanon have current active deceased donor programs and perform liver, heart, pancreas, and lung transplants. Although deceased donor programs have been active for more than 10 years, live-related and unrelated transplants account for nearly 85% of the total transplants.\(^10\) In 2000, Iranian parliament made organ retrieval possible from deceased donors by passing a law that approves cessation of brain function as death instead of only heart-lung criteria.\(^14\) Once this legislative initiative was made to respond to cultural and religious concerns regarding donation after death, the number of kidneys from deceased donors increased significantly. Less than one percent of kidney transplants came from deceased donors before passing the law. At the present time deceased donor renal transplantations account for more than 16% of the annual transplantations in Iran (approximately 311 cases in 2007).

At present, Iran has the largest reported experience of living unrelated donor transplants. By the end of 2007, approximately 23,600 kidney transplantations were performed in Iran (94% of the transplant experience has been via live-donor transplantation). The only two transplant centers in 1984 in Iran have progressed to 25 in 2006.\(^12\) Furthermore, the annual number of kidney transplantation was
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steadily increased from fewer than 100 in 1986 to 1011 in 2007 reaching the whole activity to 27.3 renal transplants per million populations (pmp) per year. For living kidney transplantation, the rate increased from 2.7 pmp in 1986 to 22.8 pmp in 2007, and the proportion of kidneys transplanted from deceased donors increased from less than 1% by the end of 2000 to 16.3% in 2007.

How the Iranian Model of Kidney Transplantation Works

Presently, Iran has one of the most successful transplantation programs in the Middle East. Although organ procurement in Iran benefits from allografts received from deceased and living related donors, the practice in the country is most often known by its government regulated and compensated organ acquisition from living unrelated donors. The transplant program, now known as the "Iran Model", has certain special characteristics (table 1). This model is supported by the government. Costs for transplantation and immunosuppressive therapy are also either totally or heavily supported by governmental agencies.

Table 1: Characteristics of “Iran Model” for living unrelated donor renal transplantation

- No coercion
- Donors to be true volunteers (altruistic or emotionally related donors)
- Donors age >18 years
- Donors given rewarded gifts supported by the government
- Donors given one year of free health insurance
- No commercialism
- No matchmaker or broker
- No financial benefit for transplant team
- No foreign recipients for Iranian donors
- No foreign donors for Iranian recipients
- Foreigner recipients and donors must be of the same nationality
- No waiting list
- Rich and poor patients are equally transplanted
- Written consent will be obtained from the donor
- Written consent will be obtained from donors’ parents and/or spouse

Once potential kidney recipients are identified, they are evaluated by transplant nephrologists. If no biologically related living donor is available or willing to donate, the recipient is referred to the Society for Supporting Dialysis and Transplantation Patients, which has numerous branches across the country. The society, a charity founded in 1978 by volunteers with ESRD, acts as a liaison between potential donors and recipients. Neither the transplant centers nor transplant physicians are involved in identifying potential donors. The society connects potential recipients and donors, and organizes tests to ensure compatibility. The charity registers the altruistic volunteers, mainly unrelated donors and introduces them to transplant candidates. The permission from the parents or the spouse to register is necessary. The potential donors should be in good health, of 18 to 40 years old, and provide consents before meeting the potential recipients. The charity also makes sure that the potential recipient realizes that the transplantation could be cancelled at any time (e.g. because of the donor’s decision to withdraw from the program). Advertising of living donation is officially banned. The society receives no remuneration for matching living unrelated donors with recipients or for referring them to transplant centers. There is no place for a broker or matchmaker agency in this model. The donor and recipient are introduced together at the society and agree upon the center to be referred to. The surgical team is not involved in this interaction. The donation and medical process are performed by very well known specialists in specific centers, mostly university-based hospitals and are licensed by the government. The expenses are fully paid by the government through the insurance system. The donor also receives full medical attention and a bonus of about US$1200 from governmental funds for the period of absence from work. In 1997, governmental rewarding donation was legislated, and now, the living unrelated donor receives an award plus limited health insurance coverage, which currently extends to one year after the donation and covers only conditions deemed related to the surgery.12 Neither transplantation teams nor hospitals are involved in the financial rewards for donation, however, many generous people and charity foundations also participate financially in this respect. Consequently, patients’ economic status does not affect their chance of receiving a renal graft. Unfortunately, more than 50% of the recipients are poor,13 and would have died without this program. As with dialysis, the administration assumes the cost of treatment, including the kidney procurement, transplant surgery, immunosuppressive medications, and postoperative care of the donor and recipient.

It is important to note that non-Iranian citizens are not eligible to participate in our organ procurement system as either donors or recipients. These people can only receive a transplant in Iran when both the foreign donor and recipient hold the same citizenship, and obtain authorization for such transplantation from the ESRD Office of the Ministry of Health. On the other hand, the Iranian model of kidney
transplantation has provided good support for kidney transplantation in refugees. Interestingly, our experience shows that there is no noticeable difference in the patient and graft survival rates between Iranians and refugees.15

Unlike the rest of the world, we have found ways to solve our organ shortage. Although our system is not without problems, it clearly has advantages over other organ procurement systems primarily that thousands in need do not die while waiting for a compatible donor.

Risk of Surgery to an Otherwise Healthy Individual

The risks of general anesthesia and surgery are an important concern, regardless of the relationship between the living donor and recipient and should be discussed with any potential donor. Fortunately, the incidence of mortality associated with kidney donation has been relatively low, 0.03-0.1% according to surveys and single center reviews.16 According to this estimate, three deaths in 10,000 donations can be expected. Surgical complications have been reported more frequently (8-48%), and some have been serious. However, nowadays the risks of complications associated with these surgeries may also be even lower.16

Deceased Kidney Donor Transplantation

Iran's organ sharing system is similar to that of many other countries. The system is centralized under the Ministry of Health. Removal of organs requires either a donor card signed by the deceased or family consent. Iran Transplant Organ Procurement (Iran-TOP) was established in 2000 in Tehran. Organ procurement organizations and brain death identification units recognize potential donors and procure organs, ensuring transparency in the process of matching donors and recipients. Brain death must be diagnosed and certified by five physicians, namely a neurologist, a neurosurgeon, an internist, an anesthesiologist, and a specialist in forensic medicine appointed by the Ministry of Health. Members of the team who diagnose and establish brain death must not be part of the transplantation team. The deceased donor program is "purely altruistic" according to the Transplantation and Special Disease Centre. And the families of deceased donors receive no payment for the kidneys, except funeral expenses in a few cases.17

Transplantation Activities in Iran

The prevalence and incidence of patients with ESRD in the year 2006 were 357 pmp and 66 pmp, respectively. Of the patients 48.5% have received kidney transplantation, 48.5% were on hemodialysis, and 3% were on peritoneal dialysis.12 We have shown that the prevalence of chronic renal failure in Iran was much more than the reported data.8 However, as chronic renal failure usually has no prominent symptoms until ESRD develops, most patients are not referred to physicians. Thus, they remain unrecognized in early stages and consequently are not recorded in any charts of the organizations responsible for public health care in different countries.

Figure 1 shows the annual number of renal
transplants that were performed in Iran from 2000 to 2008. The annual rate of kidney transplantation is between 1800 and 1900 with 75%, 12%, and 13% from living unrelated, living related, and deceased donors, respectively. Brain death organ donors are 1.8 pmp, no heart-beating tissue donors are 26 pmp, and living donors are 23 pmp.\textsuperscript{12}

In 2007, Iran's Minister of Health has announced at the Eastern Mediterranean Region Organization (EMRO) preparatory meeting that the country ranks fourth in the world in kidney transplantation.\textsuperscript{16}

Finally, after legislation in 2000 a virtual network has been developed by the Management Center for Transplantation and Special Diseases, affiliated to the Ministry of Health, and the number of Organ Procurement Units and Brain Death Identification Units in Iran increased and reached 13 and 18 respectively. There are now 25 kidney and 2 liver transplantation centers nationwide, which facilitate procurement of organs all over the country.\textsuperscript{12}

**Results of Living Donor Kidney Transplantation**

A prospective national study in 2002 reported the short-term results of all living donor renal transplants carried out in the country.\textsuperscript{19} The overall 1 and 3-year patient survival rates were 94.23% and 92.90%, respectively. One- and three-year graft survival rates were also 90.80% and 85.93%, respectively. A marked center effect with respect to graft survival has been observed among different transplantation units. Unfortunately, there is no national study to report long-term results in Iran, and most centers report their own data as single center experiences with excellent results of living donor transplantation reported by several authors.\textsuperscript{20-23}

We have extensive experience in transplantation of kidneys from living donors in two major centers, Labbafi Nejad and Baqiyatallah hospitals. From 1984, we have performed approximately 5600 renal transplantations. In order to minimize donor morbidity, laparoscopic surgery has been used to remove the donor kidney at Labbafi Nejad and Baqiyatallah hospitals. Although this approach is technically demanding, it was proposed as an alternative to the standard open approach to reduce recovery time with time away from the job and consequently the impact of the surgery on the donor. A study by Simforoosh and co-workers reported the results of the first prospective randomized study of laparoscopic versus open living nephrectomy confirming that both techniques are equally safe and successful.\textsuperscript{24} The results of our transplants from living unrelated donors have been very encouraging. In 2005, we reported the outcome of 3028 patients who received living kidney donor transplants with more than 15 years follow-up.\textsuperscript{25} Recipients were generally young (mean age 36 years) and most donors were less than 35 years old at the time of transplantation (mean age 28 years). Most of the patients received a kidney from living unrelated donors (80%). Interestingly, living unrelated donors were significantly younger than living related donors (\textit{P}<0.05). The patients who received grafts from donors under 30 years of age had significantly better patient and graft survival compared with the recipients whose donors were 30 years and older (\textit{P}=0.01 and \textit{P}=0.02, respectively). Thus, our findings show a superior patient and graft survival outcome for those receiving kidneys from younger donors. Old kidneys have relatively decreased numbers of functioning nephrons and survive less when transplanted.\textsuperscript{26}

Patients' survival after renal transplantation varied according to the recipients' age. Older patients who underwent renal transplantation had a higher mortality rate than younger patients (\textit{P}<0.05). Rejection occurred less commonly in older recipients compared with younger patients (\textit{P}<0.05).

In our transplantation centers, immunosuppressive therapy is usually modified in the elderly recipient because of the increased risk of infection and death. We, however, suggest that transplantation should be offered as renal replacement therapy to elderly patients with ESRD, in the absence of contraindications. We did not find significant differences between patient and graft survival rates with respect to donors' gender.

In our previous experience with 2822 kidney transplantation published in 2003,\textsuperscript{27} the results of living unrelated donor renal transplantations were as good as those who underwent living related transplantations (15-year overall patient and graft survival rates were 76.2% and 54.8%, respectively). A study by Simforoosh and colleagues demonstrated that patient and graft survival rate in 2155 living unrelated donor renal recipients after 15 years of follow-up were promising (76.4% and 53.2%, respectively).\textsuperscript{23} The results were also comparable with the United States Renal Data System reports in which long-term graft survival of living donor kidneys was encouraging.\textsuperscript{28}

Most unrelated donors in Iran have been male,\textsuperscript{29} and men were also more likely to be a donor (86% vs. 14%) in Baqiyatallah medical center.\textsuperscript{30} However, a number of studies from
different countries have reported the existence of a profound gender imbalance among kidney recipients and living donors. Men are in the majority among kidney recipients but women constitute the predominant source for living kidney donations, both in industrialized and non-industrialized countries. In Iran, women are 30% less likely to receive kidney transplants than men.

On the other hand, women in the United States are 30% less likely to receive kidney transplants than men. In Iran, women were more likely to receive a kidney than to donate it. At Hasheminejad and Baqiyatallah medical centers women were at least 4 and 2.5 times, respectively, more likely to receive an unrelated renal allograft than to be a donor. On the other hand, women in the United States are 30% less likely to receive kidney transplants than men.

The prevalence of hepatitis C virus (HCV) infection among kidney recipients in our study was 4.8%, whereas, in a large study performed on 838 patients with chronic renal failure undergoing hemodialysis in Tehran, anti-HCV antibody was detected in the sera of 13.2% of patients. This marked difference indicates that HCV-infected patients with chronic renal failure probably should not be recommended to undergo renal transplantation. We observed that HCV infection had no impact on patient and graft survival in short and medium-term follow-up periods (less than 10 years). We, however, found lower graft survival with no effect on patient survival among HCV Ab-positive recipients in long-term (15 years) follow-up.

Infection with Mycobacterium tuberculosis after kidney transplantation is one of serious complications in developing countries, which leads to patients' morbidity and mortality. We found that the prevalence of this infection in our centers was not high (1.4%). Furthermore a nationwide study showed that among patients who had received a kidney transplant in 15 university-affiliated hospitals from different geographic areas in Iran between 1984 and 2003, 120 (1%) patients developed tuberculosis. Post-transplant malignancy is an important long-term complication. Skin cancer, especially squamous cell carcinoma is the most common malignancy after renal transplantation. Incidence of post-transplant malignancy in our experience was 1.6%, a figure which is less than reports from western countries. Skin cancer, predominantly Kaposi's sarcoma, was the most common neoplasm after transplantation followed by lymphoproliferative disorders.

Another aspect of particular relevance to Muslim recipients is fasting in the holy month of Ramadan. The month of Ramadan, Muslims around the world wake up before dawn to eat the “Sahar” meal (the pre dawn meal) and break their fast (“Iftar”) after sunset. Fasting during Ramadan is a religious duty for all healthy adult Muslims, but not mandatory for patients. We, however, prospectively studied 19 kidney transplant recipients who voluntarily chose to fast during the month of Ramadan and compared the results with 20 matched recipients who were not on fasting for three consecutive years. The results did not show any adverse effect of fasting in these recipients with stable allograft renal function after one year of transplantation. However, we recommend that recipients must consult with their healthcare specialists including physicians to adjust the time and dosage of their medications including immunosuppressive agents, diuretics, and anti hypertensive drugs, as well as diet and precautions to be taken during the month. We also recommend that patients drink sufficient water between Iftar and sleep to avoid dehydration and renal hypoperfusion during the fasting time. In all cases of fasting creatinine levels should be closely monitored, especially before, during, and after Ramadan.

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