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Renal transplantation practice in Iran and the middle east: report from Iran and a review of the literature

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Summary

Transplantation is the best treatment of end-stage renal disease (ESRD). Life expectancy, the quality of life and reduced medical expenses are greater with kidney transplantation than with maintenance dialysis. However, organ shortage remains the central problem in kidney transplantation. To tackle this problem, we, in Iran, have initiated a living unrelated donor (LURD) program using emotionally related persons, friends and well-motivated volunteers as organ donors, which resulted in eliminating the waiting list. The Iranian transplant program is the most active in the Middle East region in providing equitable, quick, and intermediary-free access to affordable kidney transplantation for everyone regardless of gender and economic circumstances. The results of transplants from living unrelated donors have been very encouraging. This article deals with the kidney transplantation practice in Iran and other Middle Eastern countries, and describes Iran's kidney transplantation experience with cadaveric, living related and living unrelated donors. In conclusion, kidney transplantation experience in the Middle East region is an active practice. Most countries have uplifting trends and effective programs are establishing inside countries. However, the practice should be further promoted and organized towards allograft procurement from deceased donors and in this way passing and enacting proper legislations must be more seriously taken into consideration.

Key words

renal transplantation • kidney • Iran model • middle east • ESRD

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BACKGROUND

There is virtual unanimity that the optimal treatment for most patients with end-stage renal disease is renal transplantation [1]. Life expectancy, the quality of life and reduced medical expenses are greater with kidney transplantation than with maintenance dialysis; however, several factors serve as impediments towards expansion of the experience. Lack of expertise and trained surgeons, legislative obstacles, disregarding the relevance of establishing a feasible and effective renal transplantation program inside the countries by the health care authorities, cultural and religious barriers, existence of serious ethical problems as well as some hypocritical debates about ethical concerns surrounding kidney transplantation methods, have made it difficult to promote renal transplantation practice throughout the world.

The first successful kidney transplantation was carried out by Murray and Merrill in 1954 between living identical twin brothers [2]. In the Middle East, transplantation practice was started during the 60th by a kidney transplant in Shiraz, Iran [3]. However; it did not reach to a popular practice since the second half of 80th, when appropriate legislations were enacted in most countries in the region; and as the time goes on, the practice becomes more popular. At present, kidney transplantation is active in most countries in the region including Saudi Arabia, Lebanon, Kuwait, Jordan, Syria, Libya, Egypt, Sudan, Qatar, Oman, Turkey and Iran and more limitedly in Yemen, Algeria, Tunisia, UAE, and Bahrain; and the practice has found its place as the preferred method of renal replacement therapy throughout the region. However, the method of performing the experience is highly affected by religious, cultural, and legal factors in different countries. Egypt has no legislation for organ procurement from cadavers; hence, from over 3000 renal transplant procedures performed in this country, there were just 4 kidney transplantations from deceased donors; [4] Algeria and Tunisia, although have limited experience, all their allografts come from living sources [5]. Saudi Arabia as well as Turkey, uses both allografts from deceased and living related (LR) donors, but has no program for organ achievement from living unrelated donors (LURD).

In a global perspective, deceased donor organ donation is inadequate for addressing the current need for allograft; [6] hence, the number of pa-

tients on the waiting lists is progressively growing. Although use of organs procuring from living related donors is increasing worldwide, the available gap between demand and supply increases even at a higher speed. One way proposed to meet the growing demand for kidneys is by increasing living unrelated donor (LURD) renal transplantations. The use of emotionally related donors, the most obvious pioneering approach to expand the LD pool, renders extending donor eligibility to include individuals who are not genetically related to the recipient.

Although, organ transplantation in Iran benefits allograft procurement from cadavers, living related donors and living unrelated donors; however, the practice in this country is most often known by its government regulated and compensated organ acquisition from living unrelated donors. This article deals with the situation of Iran's kidney transplantation among Middle Eastern countries and describes the advantages of Iranian model of experience with non-related renal transplantation.

IRAN MODEL OF KIDNEY TRANSPLANTATION

Iran's renal transplantation program, also now known as the "Iran Model", supported by the government for LURD transplantation, has several important characteristics (Table 1). Patients with ESRD are confirmed officially by nephrologists, as suffering from end-stage renal disease (ESRD) after appropriate examination and tests. Members of the transplantation team have no role in identifying potential donors. If a patient is suitable for a transplant, the nephrologist refers him/her to the patient kidney foundation society. The foundation, a charity was formed in 1978 by ESRD patients, acts as a liaison agency between potential donors and recipients. The altruistic volunteers have to register with the charity, and undergo evaluation in the foundation's clinics. Advertising of living donation is officially banned. Donors are all 18–35 years old; permission from the parents or the spouse to register is mandatory. 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). The potential donors should be in complete health and consents are obtained prior to introduction to the potential recipients. The foundation receives no financial incentives for finding a living unrelated donor or for referring the recipient and the donor to a trans-

Table 1. Characteristics considered in "Iran Model" for living unrelated donor renal transplantation.

• No coercion
• Donors to be true volunteers (altruistic or emotionally related donors)
• Donors age >18 y & <35 y
• Donors given rewarded gifts supported by the government
• Donors given one year of free health insurance
• No commercialism
• No middle-man
• 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 from the donor
• Written consent from donor's parents and/or spouse

plant center. There is no role for a middle-man or agency in this model. The donor and recipient are introduced together at the patient kidney foundation society and agree upon the center to be referred to. All kidney transplant centers are university hospitals and are licensed by the government.

Unfortunately, more than 50% of the recipients in our country are poor [7] and would have died without this program. To prevent transplant tourism, the donor and recipient must be the same nationality. Foreigners can also receive a transplant in Iran; but even they should be from the same nationality, and authorization for such transplantation should be obtained from the ESRD Office of the Ministry of Health. The government imports and greatly subsidizes these essential immunosuppressive drugs (Neoral, CellCept, azathioprine, and prednisone) and makes those available to all transplant recipients in a much reduced price.

Iran's deceased kidney donation system is similar to that of many other countries. It is centralized under the Ministry of Health and removal of organs requires either a donor card signed by the deceased or family consent. Organ procure-

ment organizations and brain death identification units identify potential donors and procure organs, ensuring transparency in the process of matching donors and recipients. In university hospitals, each case of brain death is determined by five physicians, one of them being a specialist in forensic medicine appointed by the Ministry of Health. The deceased donation program is "purely altruistic" with no money given to the families, except funeral expenses in a few cases.

KIDNEY TRANSPLANTATION IN IRAN

The prevalence and incidence of ESRD in Iran is now 357 and 59.9 pmp, respectively; 48.5% have a functioning renal graft, 48.3% are on hemodialysis and 3.2 percent are under peritoneal dialysis therapy [8]. We previously have shown that the prevalence of chronic renal failure (CRF) in Iran was much more than reported data by others [9]. One major problem is, as CRF usually has no prominent symptom(s) until ESRD develops, the majority of patients do not get referred to physicians; hence, they remain unrecognized in the early stages and consequently are not recorded in any registries of the organizations responsible for public health care in different countries.

By the end of 2006, a total of 21728 renal transplants were performed in Iran (LR: 15.2%, LURD: 79.6%, cadaver: 5.2%). We went from having two transplant centers in 1988 to having 25 in 2006. Figure 1 shows the annual number of renal transplants that were performed in Iran from 1988 to 2006. Renal transplant activity in Iran has reached 26.5 renal transplants per million per year of that more than 75% come from living-unrelated donors.

History of kidney transplantation in Iran

By the end of 2006, approximately 21,728 kidney transplantations were done in Iran; all of which were performed inside the country [10]. Furthermore, the annual number of kidney transplantation was steadily increased from fewer than 100 in 1986 to 1693 in 2006 reaching the whole activity to 26.5 renal transplant per million per year. For living kidney transplantation, the rate increased from 2.7 pmp in 1986 to 24 pmp in 2006, and the proportion of kidneys transplanted from deceased donors increased from less than 1% by the end of year 2000 to almost 13% of kidney transplantations in 2006.

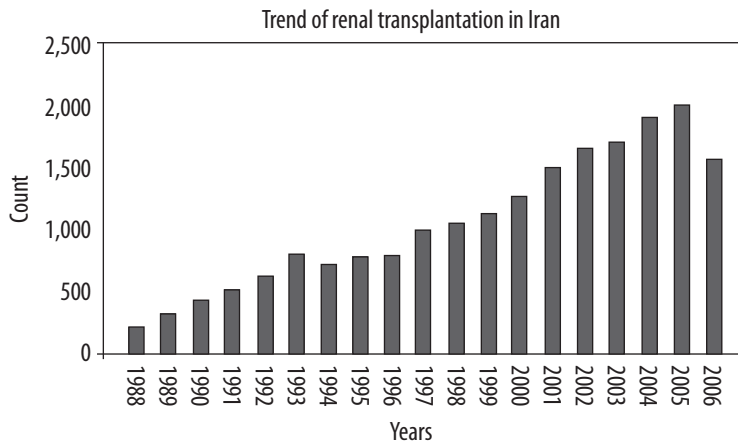


Figure 1. Trend of renal transplantation in Iran.

Due to Western sanctions and limitations on Iran during the Iran-Iraq war, dialysis equipment and dialysate ran out and massive civilian and military casualties saturated the hospitals, and as a consequence, many patients died while requiring renal replacement therapy. After the war and in 1984, two renal transplant teams were organized and they set up a living related donor (LRD) transplant program, with full government scrutiny and a strict and clear protocol that will be delineated below. In the early period of transplantation of kidneys from living donors in Iran, all donors and recipients were genetically related. In 1987, the first spousal transplant was carried out by a wife donating to her husband [11]. Demand for kidney allograft was rapidly growing, but in view of the lack of permissive laws, organ procurement from deceased donors remained insignificant. On the other hand, the number of patients having suitable or motivated relatives for donation was low. Despite the positive official fatwa, the Iranian parliament passed no law regarding deceased transplantation. In 1990, therefore, a controlled living unrelated donor renal transplantation program was launched and the government agreed to pay some money as “rewarded donation” or “altruistic gift” to the unrelated kidney donors. As a result, the number of renal transplants gradually increased to almost 21700 from 1984 up to the end of 2006. [8] In 1999, the national renal transplant waiting list dropped to zero [7], an achievement that was based on the development of transplantation with living unrelated donors. From a historical and sociological perspective, it is noteworthy that all this was happening at a time the country was not too long getting free of a devastating war in which groups of people were volunteering en masse to sacrifice their lives for their beliefs and freedom. This attitude of sacrifice car-

ried over to the willingness to donate an organ, altruistically, in order to save the life of a fellow human being.

Iranian practice and outcome

In 2007, we reported our experience with 3028 patients who received living kidney donor transplants with more than 15 years of follow-up [12]. 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). The majority of patients received a kidney from LURDs (80%). In our previous report on the outcome of 2822 kidney transplantation published in 2003 [13], the results of LURD renal transplantations were as good as those who underwent living related transplantations. A study by Simforoosh et al. demonstrated that patient and graft survival in 2155 Iranian LURD renal recipients after 15 years of follow-up are promising (76.4% and 53.2%, respectively) [14]. The results were also comparable with the USRDS reports in which long-term graft survival of LD kidneys was encouraging [15].

A prospective national study in 2002, reported the short-term results of all living donor renal transplants carried out in the country; [16] the overall one- and three-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 [17–20].

Laparoscopic donor nephrectomy

Laparoscopic techniques to procure the kidney from the living donors have recently been carried out in Iran at Labbafi-Nejad hospital. Laparoscopic nephrectomy was proposed as an alternative to the standard open approach to minimize short-term risks to donors, decrease in the hospital stay and convalescence period with time away from the job as well as perioperative pain because of the small incision alongside its cosmetic advantages. Since June 2000, laparoscopic nephrectomy has been performed in 309 cases with no significant impact on graft survival and an obvious positive outcome for the donor. Simforoosh has reported the results of the first prospective randomized study of laparoscopic versus open living nephrectomy confirming both techniques as equally safe and successful [21].

Gender and age

Living unrelated donors are significantly younger than living related donors in Iran [13]. The patients who received grafts from donors under 30 years of age had significantly better patient and graft survival compared to recipients whose donors were 30 years and older. Thus, evidence suggests 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 [22].

Gender distribution in living kidney donors and recipients is also of extreme interest. Most unrelated donors in Iran are males (81% vs. 19%) [13]. In contrast with a previous study [23], there were greater proportion of male living unrelated donors and a smaller proportion of female donors compared to their counterparts in living related group. Moreover, we did not find any significant differences between patient and graft survival rates regarding donors' gender. However, recipients' age at the time of transplantation is a significant intervening factor in renal recipients' survival; older patients who underwent renal transplantation had a higher mortality rate than younger recipients; rejection occurs less commonly in elderly than young recipients. In Iranian centers, immunosuppressive therapy is usually modified for the elderly recipients due to the increased risk of infection and death. Anyhow, we suggest that transplantation should be offered as the preferred method of renal replacement therapy

to the elderly ESRD patients, in the absence of contraindications.

Infection

Infection after transplantation is of the most serious complications leads to patient's morbidity and mortality. Hepatitis B surface antigen (HBsAg) is reported to be found in 3.1% of Iranian renal recipients; presence of HBsAg in the sera of kidney transplant recipients was found to be associated with lower patient survival but no impact on graft survival. Hepatitis C virus (HCV) infection is also prevalent among kidney recipients and its prevalence is 4.8%; whereas in a study performed on 838 patients undergoing maintenance hemodialysis in Tehran, anti-HCV antibody was detected in the sera of 13.2% of patients [24]. HCV infection represented no impact on patient and graft survival in short and medium-term follow-up periods (less than 10 years) [13,25], however, lower graft survival among HCV Ab-positive recipients, without any deleterious effect on patient survival, in long-term (15 years) follow-up was observed [13]. A longer time on hemodialysis in Iranian HCV positive renal recipients was observed [25]. These results confirm hemodialysis as a significant route of HCV infection spreading. This may also can provide an explanation for why patients who have had more than one transplant are more likely to be anti-HCV positive.

Mycobacterium tuberculosis is one of the important organisms particularly in developing countries. In Iran, the reported prevalence of TB among kidney recipients is not high (1–1.4%) [26]. Basiri and colleagues found that among kidney recipients transplanted between 1984 and 2003 in 15 university hospitals from different geographic areas of Iran, only 120 (1%) developed tuberculosis [27].

Malignancy

Post-transplant malignancy is also a very important long-term complication. 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 in Iran, followed by lymphoproliferative disorders [28,29].

KIDNEY TRANSPLANTATION PRACTICE IN THE MIDDLE EAST

Transplantation in the Middle East region began as early as 1967, with a kidney transplant from a

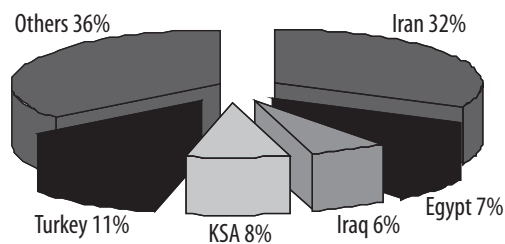


Figure 2. Renal transplantation activity in the Middle Eastern countries in 2003.

deceased donor in Iran [3]. During the seventies, sporadic renal transplants were performed in few of the Middle East region countries including Iran, Turkey, Jordan, Egypt, Lebanon, Kuwait, and Saudi Arabia. The rest of the countries in the region followed in 1980. Currently, kidney transplantation is the preferred therapy for end-stage renal failure in nearly all the Middle East region countries, with Bahrain, United Arab Emirates (UAE), Qatar, and Yemen as exceptions [30]. More than 5088 renal transplants/year 2003 were performed in the region with Iran leading with 1640 (Figures 2,3). In 2003, the cumulative number of renal transplant patients was nearly 60,000; the rate/million for renal transplantation in the Middle East region was a mere 9/million; considering the trend, it is presumable that the cumulative procedures since performed in the region to reach 80,000 [30].

All Middle Eastern countries except Egypt passed laws that allow deceased transplantation and regulate live donations. Although cadaver donation programs have been active for more than 10 years, deceased renal transplants account for nearly 13% of the total transplants [6]. Some countries such as Turkey, Kuwait, and Saudi Arabia have a higher rate of deceased renal transplantation than that of Iran, while some others like Lebanon and Egypt are behind Iran [31]. But, however, when we consider the absolute number of cadaveric kidney transplants, it reveals that Iran more benefits cadaveric renal donations than Turkey; because, although deceased donor kidney transplantation in Iran comprises about 13% of the whole experience compared to 25% in Turkey; however, the practice in Iran is about 3 times larger than that of Turkey, which makes Iran having a higher cadaveric allograft usage per million population. Until April 2000, when the parliament passed the law justifying deceased donor organ procurement after brain-death [32], less than one percent of kidney transplants came from ca-

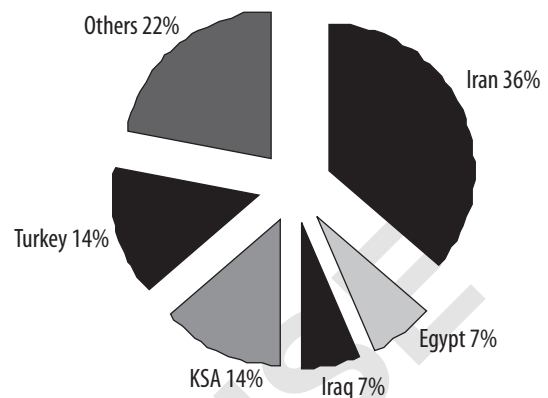


Figure 3. Cumulative renal transplants performed in the Middle Eastern countries since 2006 (for countries without reliable data, the estimated values using previous publish and trends are presented).

davers. Despite the religious permission, especially Imam Khomeini's fatwa, there were only sporadic deceased transplantations before passing the law. At the present time, deceased kidney transplants account for about 13% of the annual transplantation in Iran (approximately 245 cases in 2006) [8].

Saudi Arabia

The first kidney transplantation was performed in 1979. Now, there are 14 active transplant centers throughout the country with "King Faisal Specialist Hospital" as the leading one. Of about 17700 (770 pmp) patients under renal replacement therapy in Saudi Arabia, kidney transplant patients constitute 8172 (46.1%) of the population while Hemodialysis leads with 8761 (49.5%) and peritoneal dialysis also comprises 772 (4.4%) of ESRD therapy [33]. 70% of the allograft come from living related donors whereas cadaveric graft achieving comprises about 30% [34]. Patient survival at 1, 3, and 5 years was 98.4%, 96.7%, and 96.7%, respectively. One and 5 year allograft survival for living related donor transplantation was 96.9%, 92.2% and for cadaveric transplantation 96.2%, 87.2%, respectively [35].

Yemen [36]

Kidney transplantation first introduced in Yemen in May 1998. During this time to June 2006, a total of 31 patients (68% male) received a kidney transplant in this country. All allograft procured from living related donors. Of these, 5 have lost their graft; two had peri-transplant graft failure and 26 continue to have functioning grafts.

A well-established regular program for kidney transplantation was started since the beginning of 2005 at the Urology and Nephrology Center in the Al-Thawra Modern General Hospital, Sana'a, Republic of Yemen. The reported incidence and prevalence of ESRD in Yemen is 64 and 320 pmp, respectively [37].

Turkey [38]

The first kidney transplantation in turkey was performed on November 1975 from a mother to her child; and the first cadaveric renal transplant in 1978. According to 2002 data from the Turkish Nephrology Association Registry, the prevalence of end-stage renal disease in Turkey is 395 pmp. 28 different centers in Turkey perform renal transplantation in the country. Since the introduction to January 2004, a total of 6686 kidney transplants were done in Turkey with living donors as the dominant source of allograft procurement, representing 75.7% of cases. With the approximate annual number of 600 renal transplantations, it is presumable that the cumulative number of patients undergone kidney transplantation to reach about 9,000 (130 pmp).

Qatar [39]

Between 1986 and 2002, a total of 432 kidney transplantations were done on Qatari ESRD patients, of these 70 were transplanted inside the country at Hamad General Hospital. The reported incidence of end-stage renal disease occurrence is 212 and 262 pmp, respectively [37]. diabetic nephropathy is the leading cause of ESRD development in Qatar accounting about 30% of the total. Two year patient and graft survival for patients undergone transplantation at the Qatari center were 85.7% and 82.5%, respectively.

Jordan

Renal transplantation started in Jordan as early as 1972. The incidence of ESRD in Jordan is about 120 pmp [40]. Jordan also serves as a center for transplantation for some other Arab states [30].

Syria [40]

The incidence and prevalence of ESRD in Syria is 100 and 143, respectively. In 2005, a total number of 264 (13 pmp) kidney transplants were done in Syria. Renal transplantation in Syria as in many other developing countries is marked by its exclu-

sive reliance on living donor transplantation. In 2003, required legislations for promotion of kidney achieving from deceased donors were enacted in the country. A large proportion of allograft in Syria comes from living unrelated donors.

Egypt [4]

The issue of renal transplantation in Egypt is overshadowed by a lack of enough legislation for organ procurement from deceased donors; hence, almost all procedures in this country done from living donors. Kidney transplantation in Egypt has been started at 1976. The reported incidence and prevalence of ESRD and patients undergoing renal replacement therapy are about 180 [41], 270 [41] and 129 [42] pmp, respectively. The number of patients undergone kidney transplantation up to 2003 was about 3000, of which just 4 were from deceased donors. 80% of the kidney allografts come from living unrelated donors and living related donors constitute about 20% of the donation pool [34].

Tunisia

Up to 2003, the total number of kidney transplantations performed in this country was 14, all were living transplantations [4]; but through the end of 2003, the number of kidney transplantations performed in this country raised to a number of 543, of which 67% of the allograft came from living donors [30]. Over 80% of the donor pool in Tunisia is living related and the remaining is from deceased donors. Incidence and prevalence of ESRD and the availability of renal replacement therapy in Tunisia are about 110 [4], 430 [41], and 186.5 pmp, [42] respectively.

Kuwait

The Incidence and prevalence of ESRD in Kuwait is reported 72 and 80 pmp, respectively [43,37]. Kuwait has a very active program for kidney transplantation. Since 1979 to 2003, a total number of 1146 renal transplantations were performed in this country; over 75% of the renal allograft was obtained from living donors. Kuwait also has a very high rate of kidney transplantation with 37 per year per million procedures [30].

Lebanon

Lebanon is of the pioneering countries in kidney transplantation in the Middle East and the first procedure in this country has been performed in

1972. Incidence and prevalence of ESRD in this country comprised to 120 and 243 pmp, respectively [37]. between years 1979 and 2003 a total of 740 kidney transplants have been performed in this country of which 86.5% were from living donors [30].

Other countries

Among the Middle Eastern countries, Oman, Bahrain and United Arab Emirates have no real transplant program and only sporadic transplants are being done in these countries. Algeria and Libya have very limited programs for renal transplantations. According to a report by Rashad S. Barsoum in 2003 [4,44], the total number of renal transplants performed in Algeria and Libya was 35 and 248, respectively, of which 100% and 54%, respectively, were from living donors. Moreover, renal replacement therapy in Algeria and Libya is available at rates of 78.5 and 30 pmp, respectively [42]. Oman also established its transplantation program at 1988. Up to the end of 2005, a total number of 111 kidney transplants were performed inside this country; all were from living related donors [45].

CONCLUSIONS

Kidney transplantation is generally considered the best treatment for patients developing end-stage renal disease, both in the quality of life, long-term outcomes and financial burden on the society and patient. In the Middle East, the practice has been well accepted by different nations and has become the first choice of renal replacement therapy except a few numbers of countries; however, there is still a large area to work. Syria and Yemen as well as some other countries had good engagements. Some other countries should move toward establishing effective kidney transplantation programs in their countries; methods of kidney transplantation in most countries also need to be modified and a higher priority should be assigned to the experience by the health care authorities. Usage of heart-beating deceased donors must be encouraged and promoted and the appropriate legislations should be passed. For example, we can offer some types of rewards for cadaveric donations. On the other hand, use of living unrelated donors can be only considered for addressing the gap between allograft supply and demand. Inclusion criteria for living donors can be tightened. Elderly transplantation and retransplantation from living donors can be restricted to organs from deceased

donors. Implementation of a strict follow up program for living donors in all countries in the region is of extreme relevance; the short- and long-term potential complications and the associated risk factors should be seriously assessed. Iran has recently started its organ transplantation with organs from deceased donors; although a good trend exists in cadaveric kidney transplantation in Iran, the program could be far more precisely organized and promoted. Turkey and Saudi Arabia also can promote their experience with cadaveric donations; Egypt also has a potential to promote to pass necessary laws for organ procurement from deceased donors and most other nations have the potential to expand the experience in their countries.

The outlook of kidney transplantation practice in the Middle East region is promising. Countries had encouraging movements towards using advantages of different types of renal transplantation programs. Health authorities as well as professionals of each country should do their best for their nations. Countries can also help each other in the subject. The future seems positive.

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