

Kidney donation: State of the Art

Living Donor Kidney Transplantation: How Far Should We Go?

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ABSTRACT

Purpose: To describe the work that the Başkent University Faculty of Medicine has done to increase kidney donors' number in Turkey and also to discuss the major effects that donor-organ shortage is currently having worldwide.

Materials and Methods: From 1975 through 2003, our transplantation team at Hacettepe University Hospital and later at the Başkent University Transplantation Center (BUTC) performed 1451 kidney transplantations. Cadaver donation and patient and graft survival rates for various groupings of transplantation types were compared.

Results: Of all the renal transplantations completed in Turkey from 1975 to January 2004, 20% were performed by our team in our center. For the years 1990 through 2003, the 1-, 3-, and 5-year patient survival rates in the first-degree-living-related kidney transplantation group were 96%, 93%, and 91%, respectively, and the corresponding graft survival rates were 93%, 84%, and 81%. In the second-degree living-related group, the 1-, 3-, and 5-year patient survival rates were 94%, 90%, and 87%, respectively, and the corresponding graft survival rates were 93%, 86%, and 84%. For living-unrelated transplantations, the 1-, 3- and 5-year patient survival rates were 93%, 90%, and 83%, respectively, and the corresponding graft survival rates were 83%, 78%, and 76%. In the cadaver-kidney transplantation group, the 1-, 3- and 5-year patient survival rates were 85%, 78%, and 70%, respectively, and the corresponding graft survival rates were 82%, 64%, and 53%. During this same period, the 1-, 3-, and 5-year graft survival rates for our cadaver donors and living donors older than 55 years of age were 80%, 52%, 46% and 88%, 69%, 61%, respectively.

Conclusion: Vigorous efforts by our group at Başkent University and by other transplant surgeons across the nation have increased the numbers of transplantations performed each year. As well, since the NCC was established in 2001, the number of cadaver-kidney transplantations has more than doubled. The initial results with this new nationwide organ-sharing system are promising, and there is every indication that this approach will continue to raise the number of transplant operations performed across Turkey each year.

KEY WORDS: kidney transplantation, living donor, cadaver, Turkey

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Introduction

For several years after the first successful transplantation of a kidney from one twin to another in 1954, living-related donors were the most frequent source of kidneys for renal transplantation. Over the past few decades, the concept of brain death has been introduced, immunosuppressive therapy has improved, and exciting progress has been made with many transplant-related clinical, biological, and immunological problems. As a result of these advancements, cadaveric organ transplantation has become the predominant mode of treatment for end-stage renal disease (ESRD).

Greater success with kidney transplantation has led to increased numbers of patients on waiting lists and a growing demand for donor organs. However, the shortage of cadaver organs remains a crippling problem that educational changes, legislative efforts, and international cooperation have not yet solved. At the March 2002 National Conference on the Waiting List for Kidney Transplantation, it was reported that, from 1990 to mid-2002, the kidney transplant waiting list in the United States had expanded from approximately 15,000 to 55,000 patients, while the number of cadaveric kidneys transplanted annually had remained stable at approximately 9,000.⁽¹⁾ As a result, the median waiting time between listing and renal transplantation in the United States has been extended from 19 months (as of a decade ago) to more than 3 years for patients listed in 1999.⁽²⁾ It is projected that, by the year 2010, the waiting list for kidney transplants in that country will comprise 100,000 patients and the average waiting time will be nearly 10 years.⁽³⁾ Currently, more than 40,000 patients are registered on waiting lists in Western Europe, and the list grows by several hundred patients each month. The scenario is similar throughout the world. The consequences of this are serious: lower quality of life, poorer rehabilitation, increased numbers of deaths, and higher costs of renal replacement therapy for patients awaiting kidneys compared to costs for transplant recipients.⁽⁴⁾ In Turkey, solid-organ transplantation began in 1969 with two heart transplantations that, unfortunately, were unsuccessful. By the early 1970s, our team had initiated experimental studies on kidney and liver transplantation.⁽⁵⁾ This team performed the country's first living-related kidney transplantation (LRKT) in November 3, 1975.⁽⁶⁾ Today, the supply of cadaver

kidneys in Turkey lags far behind the demand, and the number of potential transplant recipients has dramatically increased with the rising incidence of ESRD. These factors have spurred the expansion of LRKT in our country, and our current kidney transplantation program is still largely dependent on first- and second-degree relatives and spouses. This article describes the work that the Başkent University Faculty of Medicine has done to increase kidney-donor numbers in Turkey. It also discusses the major effects that donor-organ shortage is currently having worldwide.

Materials and Methods

From 1975 through 2003, our transplantation team at Hacettepe University Hospital and later at the Başkent University Transplantation Center (BUTC) performed 1451 kidney transplantations. Of these, 1106 (76%) involved living donors and 345 (24%) involved cadaver organs. The total number of kidney transplantations carried out in Turkey during the same period was 6082, with 4572 (75%) of these transplants coming from living donors and 1510 (25%) coming from cadavers. The Başkent University team has also performed re-transplantations of kidneys in 55 cases.⁽⁷⁾ Two of these patients received three renal transplants, and the other 53 received two grafts.

In Turkey, any individual related or married to the recipient who is free of chronic disease and willing to donate a kidney is informed about the risks, benefits, and procedures involved in living-donor transplantation. Care is taken to ensure the person feels no obligation to donate. Multiple ureters, multiple veins, multiple arteries, renal cysts, and ectopic kidneys are not considered contraindications, though we prefer to harvest kidneys that have a single long arterial pedicle. Briefly, our surgical technique for arterial and ureteral anastomosis involves a combination of the parachute technique and the four-quadrant running suture technique, and we prefer to anastomose the renal artery to the external iliac artery. We have also adopted the Lich-Gregoir technique as part of our standard procedure, and this involves placement of a temporary stent that is removed before ureteral re-implantation is completed.^(8,9,10) Recently, in efforts to improve patient compliance with surgery and to reduce postoperative discomfort, we have changed our protocol for recipients from general anesthesia to epidural anesthesia, and have introduced com-

bined spinal-epidural anesthesia for donors.⁽¹¹⁾

For LRKT, we use standard triple-drug immunosuppression. Our initial regimen was 1 mg/kg prednisolone, 5 mg/kg cyclosporine A, and 2 mg/kg azathioprine daily in the postoperative period. In 1999, we modified our protocol by replacing azathioprine with mycophenolate mofetil (MMF) and, in selected cases (steroid resistant acute rejection and cyclosporine toxicity), replacing cyclosporine with tacrolimus. Azathioprine (or MMF) and prednisolone are started 3 days prior to the surgery. Prednisolone is tapered to the maintenance dose of 10 mg/day at two months post-transplantation, and is tapered further to 5 mg/day if the patient develops problems such as diabetes, aseptic necrosis, or obesity. Cyclosporine or tacrolimus doses are adjusted according to serum levels, and doses of azathioprine (or MMF) are altered according to leukocyte count and results of liver function testing.

Episodes of acute rejection are treated with intravenous bolus doses of methylprednisolone (250-500 mg/day) for three consecutive days, and steroid-resistant cases are treated with monoclonal antibody (OKT3) and plasmapheresis.

The severe shortage of kidney donors in Turkey has forced us to expand our list of criteria for donor eligibility. In 1985, we began to use organs from cadaveric and living donors older than 55 years of age⁽¹¹⁾ After 1985, our group also started to perform cadaver-kidney transplantations with cold ischemia times longer than 100 hours,⁽¹²⁾ and in 1987 we began to carry out ABO-incompatible kidney transplantations.⁽¹³⁾ In addition, in May 1992 we harvested multiple organs (segmental liver and kidney) from one living donor, and performed simultaneous liver and kidney transplantation with these grafts.⁽¹⁴⁾ Currently, we also perform kidney transplantations between living-related donors and recipients

with one or two HLA matches if there is no other donor candidate with a better match.

In order to reduce problems with cadaver-donor identification/management and maximize cadaver donor numbers, in January 2001 the Ministry of Health gathered all transplantation centers in Turkey under an umbrella organization called the National Coordination Center (NCC). For this report, we calculated and compared the cadaver donation rates prior to and after the NCC was established. We also compared patient and graft survival rates for various groupings of transplantation types (i.e. first-degree living-related, second-degree living-related, unrelated, ABO-incompatible, and others). All statistical analysis was done using the log-rank test and the software program SPSS for Windows.

Results

Of all the renal transplantations completed in Turkey from 1975 to January 2004, 20% were performed by our team in our center. Figure 1 lists the yearly distribution of living- and cadaver-donor renal transplantations carried out by our team from 1975 through 2003. Figure 2 summarizes similar data compiled from 29 other transplantation centers in Turkey from 1990 through 2003.

For the years 1990 through 2003, the 1-, 3-, and 5-year patient survival rates in the first-degree-living-related kidney transplantation group were 96%, 93%, and 91%, respectively, and the corresponding graft survival rates were 93%, 84%, and 81%. In the second-degree living-related group, the 1-, 3-, and 5-year patient survival rates were 94%, 90%, and 87%, respectively, and the corresponding graft survival rates were 93%, 86%, and 84%. For living-unrelated transplantations, the 1-, 3- and 5-year patient survival rates were 93%, 90%, and 83%, respectively, and the correspon-

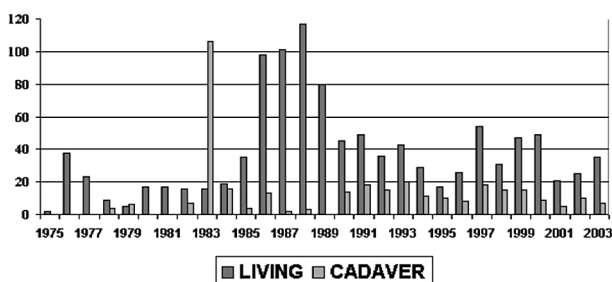


FIG. 1. The distributions of living- and cadaver-donor renal transplantations performed at the BUTC from 1975 through 2003

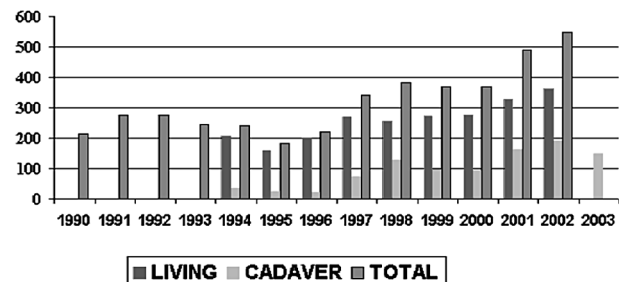


FIG. 2. The distributions of living- and cadaver-donor renal transplantations performed at 29 other transplantation centers in Turkey from 1990 through 2003. Cadaver and living donor numbers are not available before 1994.

ding graft survival rates were 83%, 78%, and 76%. In the cadaver-kidney transplantation group, the 1-, 3- and 5-year patient survival rates were 85%, 78%, and 70%, respectively, and the corresponding graft survival rates were 82%, 64%, and 53%. The 1-, 3-, and 5-year patient and graft survival rates for first-degree, second-degree, unrelated, and cadaver-donor kidney transplantations are presented in Figures 3 and 4.

During this same period, the 1-, 3-, and 5-year graft survival rates for our cadaver donors and living donors older than 55 years of age were 80%, 52%, 46% and 88%, 69%, 61%, respectively. These rates were slightly lower than those for the transplantations done with grafts from younger donors, but we found that patient survival rates were similar in the older and younger donor age groups. The graft survival rates for transplants from our donors older than 55 years are presented in Figure 5.

The respective 1-, 3-, and 5-year graft survival rates for the ABO-incompatible transplantations performed during this time were 66.7%, 52.4%, and 47.6%. These rates were slightly lower than the corresponding figures for the ABO-compatible transplantations.

We also analyzed graft survival in relation to numbers of HLA mismatches. Comparison of the findings showed that zero-mismatch cases had significantly higher graft survival rates than cases with one, two, three, four or five mismatch-

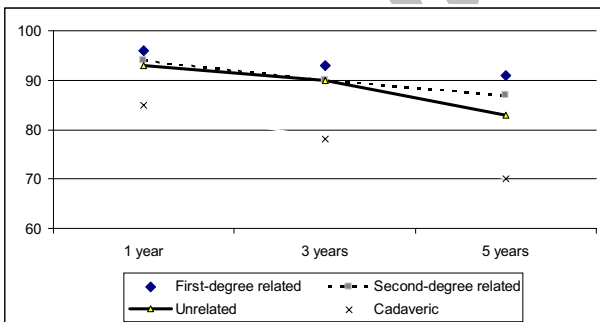


FIG. 3. Patient survival rates for kidney transplantations carried out at the BUTC from 1990 through 2003

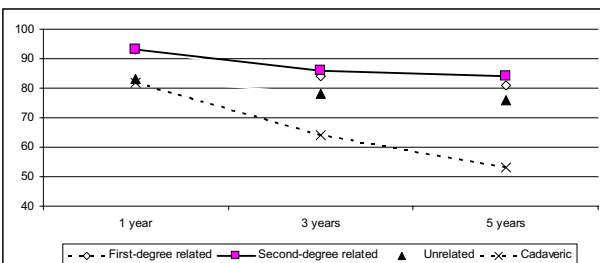


FIG. 4. Graft survival rates for kidney transplantations carried out at the BUTC from 1990 through 2003

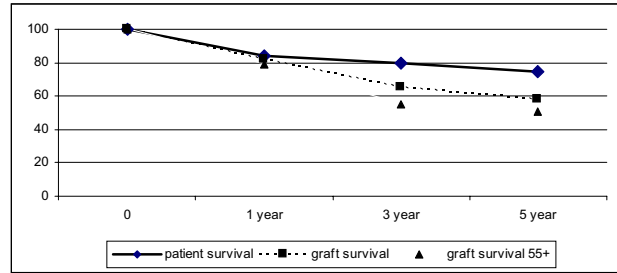


FIG. 5. Overall graft and patient survival rates, and graft survival rates in donors over 55 years of age for kidney transplantations carried out at the BUTC from 1990 through 2003

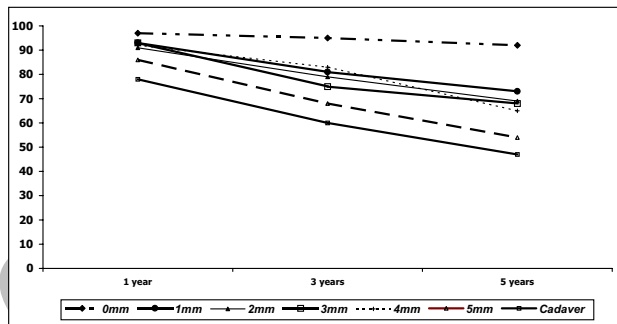


FIG. 6. Comparison of findings with grafts grouped according to HLA matching showed that cases with zero mismatches (mm) had the best graft survival rates. The 5-year graft survival rate was poorest in the cases with five mismatches, but there were no statistically significant differences among the groups with one, two, three, four or five mismatches.

es; however, there were no significant differences among the rates for the latter five groups (fig. 6).

It has been three years since the NCC was established. Although the current levels of organ donation and procurement in Turkey still do not meet the need, rates have risen during this period. In the first year after the NCC was formed, the number of cadaver-kidney transplantations increased from 92 to 162. This figure rose to 189 in the second year, and the total number was 177 in the third year. Table 1 shows the numbers of different types of cadaver-organ transplantations performed in our country from 2001 through 2003.

TABLE 1. Cadaver-organ transplantation activities in Turkey before and in the years since the National Coordination Center (NCC) was established

	Heart	Valve	Liver	Kidney	Cornea
Before NCC (Jan 2001)	63	70	212	989	6259
2001	27	25	68	162	1267
2002	20	15	82	189	1538
2003	23	24	87	177	1060
Total	133	134	449	1517	10124

Discussion

In Turkey, the leading cause of chronic renal failure is chronic glomerulonephritis. In the year 2000, the cadaver donation rate in our country was 0.9 per million people, the lowest rate in Europe. According to year 2002 data from the registry of the Turkish Nephrology Association, the prevalence and incidence of ESRD are 395 per million and 70 per million, respectively. This registry listed a total of 25,397 ESRD patients in Turkey as of 2002, with 7086 new cases diagnosed in that year alone.⁽¹⁵⁾ However, of the 6060 patients who were placed on renal transplant center waiting lists in 2002, only 550 (9%) received a graft kidney that year. In our country, many people with ESRD remain unaware of the possibility of renal transplantation, and the number of patients who receive transplants is far less than the number who could benefit from transplantation. There is a great need to inform this group that kidney transplantation is the most efficient mode of renal replacement therapy. Also, aside from the general problems of organ supply and demand, there is a specific issue with pediatric transplantation in Turkey. Although pediatric ESRD patients are given priority over adults, very few of these children are registered on transplant waiting lists by their parents. As of 1999, only 118 pediatric ESRD patients in Turkey had undergone renal transplantation. Forty-two (36%) of these children were transplanted at BUTC.⁽¹⁵⁾

Why Living Donation?

The worldwide medical literature on various aspects of living donation indicates that postoperative mortality in living kidney donation is approximately 1 in 3,000 cases.⁽¹⁶⁾ Long-term follow-up investigations of donors have shown that the risks of progressive renal failure, hypertension, and proteinuria are not increased by nephrectomy per se, and that these problems occur occasionally due to other causes.⁽¹⁷⁾ Overall, the findings suggest that unilateral nephrectomy is not harmful in healthy individuals. In addition, there are other valid reasons to expand living donation: 1) the demand for cadaveric donor kidneys far exceeds the supply; 2) the quality of kidneys from living donors is better due to shorter ischemia time, lack of effects from the agonal phase, and lack of effects from cytokine release after brain death; 3) better results with kidney transplants from living donors compared to grafts from cadaver donors in the cyclosporine

era (and this also appears to hold for grafts from unrelated living donors despite HLA incompatibility); and 4) pre-emptive transplantation with an organ from a living donor not only avoids the risks, cost, and inconvenience of dialysis, but is also associated with better graft survival than transplantation after a period of dialysis (particularly within the live-donor cohort).

At our center, only first-degree (father, mother, sibling, offspring) and second-degree (aunt, uncle, cousin, nephew, grandmother, grandfather) relatives are considered "related" donors. The only "unrelated" donors we accept in our program are those legally married to the recipient. Interestingly, although unrelated donor-recipient pairings invariably have poorer HLA matches than is typical of living-related pairings, we have found that graft and patient survival rates are comparable. The current percentages of living donors are near 12% in Europe, 35% in the United States, 50% in Latin America, 90% in Asia, and 75% in Turkey.

Expanding the Organ Pool in Turkey

As noted above, in order to increase the numbers of organs available for transplantation at our center we raised the acceptable donor age range for both cadaver and living-related donors. Also, in the 1980s we began to use cadaver grafts with longer ischemia times. This strategy added a new dimension to the field, and reports of renal transplantations involving cold ischemia times of 48-72 hours started to appear in the worldwide literature.⁽¹²⁾

In 1987, we also broke barriers related to major histocompatibility complex and blood type compatibility, transplanting ABO-incompatible kidneys after donor-specific skin grafting. Initially, we performed both splenectomy and plasmapheresis in these cases; however, we later adopted a strategy of using plasmapheresis until the recipient's anti-A immunoglobulin IgG/IgM or anti-B IgG/IgM titers dropped to 1:16 or lower.⁽¹⁴⁾ We also adopted the policy of accepting donor-recipient pairs with few HLA matching if a more suitable donor was unavailable. The safety and value of organ sharing in a donor-recipient pair with zero HLA mismatches are undisputed, and policies of accepting higher numbers of HLA mismatches when selecting recipients for available organs are much criticized. However, awarding points for donor-recipient matching at the HLA A locus has already been eliminated from the algo-

rithm for waiting list allocation (UNOS policy 3.5.11.2), and it is also proposed that B locus mismatching should be eliminated from the UNOS sharing algorithm.⁽¹⁸⁾ In the future, as more potent and selective immunosuppressive drugs and methods become available, tissue typing may be totally eliminated from the donor-recipient selection protocol.

When treating a patient with multiple organ failure, in order to maximize the use of a living donor who has given consent we prefer to harvest multiple organs (e.g. one kidney and a segment of liver). To date, we have completed two such transplantations.

Governmental policies related to cadaver donation have also been important in terms of the organ pool. In Turkey, the initial law on organ/tissue harvesting, storage, grafting and transplantation (Turkish Law 2238) was enacted on June 3, 1979, much earlier than similar legislation in many other countries. According to this law buying and selling of organs and tissues for a momentary sum or other gain is forbidden, and all advertisement in connection with the harvesting and donation of organs and tissues is forbidden. Harvesting organs and tissues from person under age of 18 or who are not of sound mind is forbidden. On January 2, 1982, new articles were added to Law 2238 that make it possible to harvest organs when a person dies due to accident or natural causes and there are no next of kin.⁽¹³⁾

According to a recent study in the United States, problems with donor identification and/or management (42%), and family or coroner refusals (26%) account for most cases in which brain-dead donors' organs are not used.⁽¹⁹⁾ To minimize these problems and maximize the use of available donor organs nationwide, in early 2001 Turkish Parliament founded a new national organ-sharing organization (the above-mentioned NCC) under the auspices of the Turkish Ministry of Health. Under this system, the country is divided into six regions, each with its own regional coordination center (RCC).⁽²⁰⁾ Every transplant center has a transplant team comprising a transplant coordinator, clinicians (nephrologists, gastroenterologist, and pathologist), and surgeons. The transplant coordinator works in a role that is completely separate from the clinical departments and other members of the transplantation team. This person's primary responsibilities are to promote organ donation and procurement; to organize interviews with donor families; to main-

tain contact with national and international organ-sharing organizations on a 24-hour on-call basis; and to train all personnel involved in the transplantation process.

Since 2001, the number of transplantation procedures performed per year throughout Turkey has risen by more than 30%, and the proportion of cadaver-donor organs has increased significantly, from 21% to 50%. This rise likely reflects increased collaboration among transplantation centers, as well as a change in Turkish people's attitudes toward organ donation. The latter has been achieved through the dedicated efforts of staff at transplantation centers and the Ministry of Health and through persuasive speeches by officials in the Department of Religious Affairs, who have explained that organ donation is not forbidden in Islamic belief. As Table 1 shows, the numbers of all forms of solid-organ transplantation in Turkey have risen since the NCC was founded.

The World Situation

There is much ethical debate about certain aspects of transplantation, but alternatives to directed donation (donors who are biologically or emotionally connected to the recipient) are growing. Today, the options include non-directed donation (e.g., permitting a volunteer to donate a kidney to an anonymous recipient), donor-recipient pair exchanges (a donor who is better matched to another recipient is switched and donates to that other recipient), and list-paired donation (an HLA-mismatched directed donor is paired with a stranger on the cadaver waiting list, which means that the intended recipient moves to the top of the list).

A report from the Organ Procurement and Transplantation Network (OPTN) stated that, for the first time, in 2001 the number of living donors in the United States (6371; preliminary data from the OPTN as of February 8, 2002) surpassed the number of cadaveric donors (6070; preliminary data as of the same date). Between 1990 and 2000, the total number of living-donor kidney transplants in the United States more than doubled, from 2095 to 5304. While this increase for living donors biologically related to kidney recipients was impressive (more than twofold), the number of living-unrelated donors increased nearly 15-fold, from 87 to 1243. In contrast, the increase in cadaver-donor kidney transplants was only 10.5%, and this was largely attributed to acceptance of more donors through

expanded criteria.⁽²¹⁾

Today, very few countries are able to reduce the numbers of patients on transplantation waiting lists. However, Iran has completely eliminated its renal transplant waiting list by implementing a new model called "controlled living-unrelated transplantation." As of the end of the year 2000, a total of 10,957 renal transplantations (involving 2,468 living-related donors and 8,404 living-unrelated donors) had been performed in Iran.⁽²²⁾ Living-unrelated transplantation is currently gaining popularity in many parts of the world, and some experts are presenting this as a viable solution for organ insufficiency. Still, it is of major concern that unrelated transplantation (that in which the donor is not a relative or spouse) is not strictly controlled in countries where it is practiced.

Along with the impressive results that have been made in living-donor transplantation, there has also been some distressing news. Debates about providing incentives for organ donors, and reports on the sale of human organs for transplantation as means of motivating living donation are two examples. News items about organ removal after executions, uncontrolled commercial renal transplantation, and the black market for organs show the ugly face of transplantation.^(23,24,25)

In general, experience with living-unrelated donation indicates that this practice leads to commercialism. Paid unrelated living donors may be found in places such as India, Iraq, and even the United States. Sale of organs has been banned universally, but some countries, such as Israel, are now deliberating about lifting this ban. The argument in favor of this is based on humanitarian considerations for people who are dying due to lack of transplantable organs, or due to the lack of funds to pay for transplantation surgery. However, societies with large low-income populations will be unable to avoid commercialism of organ trading. We agree with the statement made by Drs. Hasan Rizvi and Anwar Naqvi: "Being an optimist, one has great faith in the goodness of human nature and the human desire to live longer, which may be for even just one month. This flame is difficult to extinguish."⁽²⁶⁾ The will to live is extremely strong; if the spark of living-unrelated kidney donation (excluding that between spouses) is permitted to burn, it will be impossible to prevent the sale of other organs. The less privileged countries of the world will be

transformed to universal donors, with poor masses and oppressed groups as the most widely exploited victims.

There are also health-related arguments to be made against living-unrelated organ donation. Although current data on kidney donation indicate that donor nephrectomy is safe, this procedure is not without risks. As of February 2002, 56 individuals in the United States who had previously been kidney donors were identified as listed for cadaveric kidney transplantation.⁽²¹⁾ A survey of live donors conducted by the American Society of Transplant Physicians in 1995 reported 0.03% mortality and a 0.23% rate of serious complications.⁽²⁷⁾ The same report noted that 15 donors (0.15%) developed advanced renal disease after donation (4 cases of renal insufficiency and 11 cases of ESRD). In another study of 1800 live donors, 7 (0.4%) developed ESRD.⁽¹⁸⁾ The Consensus Statement on the Live Organ Donor concluded that, "The benefits to both donor and recipient must outweigh the risks associated with the donation and transplantation of the living-donor organ."⁽²⁸⁾ Current data from around the world suggest that both short- and long-term follow-up is mandatory for living donors. Considering all the societal and health risks, and the costs connected with living-unrelated donation, we believe that it is not wise to expand living organ donation to include individuals who are not married or blood relatives.

In our opinion, the most logical way to tackle the organ shortage problem is to expand cadaver donation, although living-donation is feasible option for patient with chronic liver and kidney diseases, there are also among of these who needs lung, heart, cornea, pancreas, and skin transplantation. Various nations around the globe have established different systems for donating organs, such as "opt-in" policies (consent is required) and "opt-out" policies (consent is presumed). Four European nations with opt-in policies (Denmark, the Netherlands, the United Kingdom and Germany) have much lower cadaver donation rates than countries with opt-out policies (Austria, Belgium, French, Hungary, Poland, Portugal and Sweden). Changing a country's standard policy on organ donation can result in striking differences in organ donation. The studies done by Eric Johnson and Daniel Goldstein at Columbia University in the United States have shown that donation rates can rise significantly under opt-out conditions.⁽²⁹⁾

Conclusion

Today, Turkish organ donors and recipients are being cared for with the most advanced scientific and medical techniques available in the world. Vigorous efforts by our group at Başkent University and by other transplant surgeons across the nation have increased the numbers of transplantations performed each year. Newly developed, effective immunosuppressive protocols are prolonging graft and patient survival. As well, since the NCC was established in 2001, the number of cadaver-kidney transplantations has more than doubled. The initial results with this new nationwide organ-sharing system are promising, and there is every indication that this approach will continue to raise the number of transplant operations performed across Turkey each year. We suggest that Turkish citizens should consider changing our national policies on organ donation. Opt-out policies can increase the pool of cadaver-organ transplants. In addition to increasing cadaver donation, we feel that living-related donation restricted to first- and second-degree relatives and acceptable non-blood-related donors (such as spouses) is the best path to expanding kidney transplantation worldwide.

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