Renal Transplantation from Expanded Criteria Donors

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1. Introduction

The 21st century has come as an era of chronic diseases including chronic kidney diseases. Treatment at the end stage of kidney failure involves replacing the lost functions of kidneys by dialysis or by a kidney transplant. The end stage renal disease (ESRD) population is increasing worldwide. The National Kidney Foundation says that “rates of chronic kidney disease (CKD) in the United States have increased by more than 20% over the past decade, causing dramatic loss of life and sky-rocketing health care costs, according to the 2008 annual report by the US Renal Data System” (National Kidney Foundation, 2009).

Kidney transplantation was proven unquestionably the preferred therapy for most patients with ESRD. Survival, cardiovascular stability and quality of life were found superior in allograft recipients compared to similar patients who remained on dialysis (Wolfe et al, 1999; Nathan et al, 2003).

There was a large gap between the number of patients waiting for a transplant and the number receiving a transplant. This gap has widened over the decade, according to 2009 OPTN/SRTR Annual report. The waiting list for a donor kidney has grown from slightly more than 40,000 people in 1998 to about 110,466 in 2011, as per UNOS (United Network for Organ Sharing) database. Sometimes the wait is two or three years, but often it stretches to five or 10 years or longer. Some die while waiting. During the past few years, there has been renewed interest in the use of expanded criteria donors (ECD) for kidney transplantation to increase the numbers of deceased donor kidneys available. More kidney transplants would result in shorter waiting times and limit the morbidity and mortality associated with long-term dialysis therapy.

Performing renal transplant with a perfectly healthy kidney to all the patients with ESRD is an ideal scenario. But growing waiting lists and shortage of kidneys makes it necessary to make some compromises. Use of so-called, marginal or borderline donors can increase donor pool by almost 20 to 25%.

Terms- expanded criteria donor or marginal donor simply means accepting suboptimal quality grafts, either from a living donor or a cadaver donor with some acceptable medical risks. Scientific Registry of Transplant Recipients (SRTR)/Organ Procurement and Transplantation Network (OPTN) data showed 41% discard rate for ECD kidneys. Common reasons for
discard of these donor kidneys were older donors, glomerulosclerosis on biopsy and poor renal perfusion (Sunga et al, 2008). Current utilization is 15% of all transplanted kidneys.

2. Marginal versus expanded criteria donor

Some authors believe that the term ‘expanded’ be used instead of “marginal” because the term ‘marginal’ may be considered pejorative by the patients who receive them, as well as by the programs that transplant them (Kauffman, 1997).

3. Standard donor versus expanded criteria donors

Graft and patient survival after ECD kidney transplantation are inferior to survival rates with SCD kidney transplantation. The differences are initially insignificant, but increase over time. The half-lives of deceased-donor kidneys (ECD or SCD) are shorter than the half-life of a living-donor kidney (Metzger, 2003). Many large retrospective database analysis compared outcomes of standard-criteria donor (SCD) kidney transplants with ECD kidney transplants. Overall, mortality in the perioperative period was greater in ECD kidney recipients (Merion et al, 2005; Remuzzi et al, 2006). Kidneys transplanted from expanded criteria donors have a higher rate of delayed graft function, more acute rejection episodes, and decreased long-term graft function. Several factors, including prolonged cold ischemia time (CIT), increased immunogenicity, impaired ability to repair tissue, and impaired function with decreased nephron mass may contribute to this (De Fijter et al, 2001). Despite these inferior results, these transplants had definitely survival advantage over patients still receiving dialysis (Ojo et al, 2001; Merion et al, 2005). It was also observed that, despite an increased mortality risk during the initial post-transplant period, the long-term mortality risk was > 50% lower for patients who were 60 to 74 years of age at the time of waiting list registration compared with those who remained on dialysis (Wolfe et al, 1999).

4. Optimised allocation

The strategy proposed by Bryce Kiberd et al was to retrieve all kidneys; but visibly scarred kidneys should be discarded. He also proposed performing biopsy in some deceased donors kidneys > age 65, > age 55 and donor Creatinine clearance<60 - 70 ml/min, discarding advanced arteriolar sclerosis or interstitial fibrosis. Allocating these grafts to Older (>59) or diabetic, avoid the sensitized, minimize cold ischemic time and avoid large weight or age mismatches (Bryce Kiberd, 2011). Schnitzler and colleagues used a Markov model to determine the best timing for an individual patient to accept an offer of an ECD kidney, based on registry data from the United States Renal Data System (USRDS) and expected quality-adjusted life years (Schnitzer et al, 2003). Common practice in the United States as well as Europe is to place older donor kidneys in older patients (Voiculescu et al, 2002; Smits et al, 2002; Kasiske et al, 2002; Lee et al, 1999).

5. Types of marginal donors

5.1 Living marginal donor

Living-related kidney donation is a way out of the current dilemma of insufficient supply of renal allografts. The risk to the donor is minimal, but not zero. Apart from these perioperative risks, are there potential long-term risks with respect to renal function, proteinuria.
and hypertension. Potential risks must be excluded by careful work-up of the donor (Duraj et al, 1995; Natarajan et al, 1992; Foster et al, 1991). There is enough evidence to suggest that, standard living donors do not face risks for ESRD any higher than those of age-matched peers (Fehrman-Ekholm et al, 2001). But this doesn’t hold true for marginal living donors. In fact, emphasis should be given to ascertain the risk of developing CKD as well as ESRD in these donors.

Marginal Donors - Inclusion

- Elderly donors
- GFR – 60 to 70 ml/ min
- Mild Hypertension
- Donor with Stone Disease
- Donors with Renal cysts
- Donors with BMI>30
- Other issues like tuberculosis, DM, proteinuria, hematuria, malignancy, family history of ESRD and CMV Infections

5.1.1 Aged kidney donors

Glomerulosclerosis increases with age. There is decrease in GFR of approx 1 ml/min per 1.73 m² per year after age 40. There is a documented acute decrease in GFR of approximately 30% after unilateral nephrectomy; however, the impact of unilateral nephrectomy on this rate of decline in GFR is unknown.

Twenty per cent glomerulosclerosis is usually considered the upper limit for accepting kidneys from a donor. There is higher incidence of delayed graft function with such kidneys. Further, there may be associated increased rate of acute rejection. Advancing age is associated with higher incidence of hypertension (Moreso et al, 1999). The influence of donor age on the outcome of living donor kidney transplantation is not very clear. Gill et al in their observational cohort study of 23,754 kidney transplantations performed in recipients 60 years and older, found that old living donor transplants were associated with inferior 3-year graft survival rates, but similar 3-year patient survival rates compared with young living donor transplants. Elderly deceased criteria donor transplantations were associated with a greater risk of graft loss. He proposed old living donors an important option for elderly transplantation (Gill et al, 2008). There are other few studies in the literature that found encouraging results with elderly living donor transplants (Kumar et al, 2000; De La Vega, 2004). Graft survival, patient survival, degree of hypertension and renal function were similar in elderly and young living donor transplant groups. Contrary to these encouraging results, others noted poor patient and graft survival in elderly donor transplants (Toma et al, 2001; Prommool et al, 2000). Long term outcome of this group is not known.

5.1.2 Hypertensive donors

There are no precise guidelines regarding donation from patients with arterial hypertension. It is now accepted that systolic blood pressure greater than 140 mmHg is a much more
important cardiovascular risk factor than raised diastolic blood pressure. In fact, there is little evidence that well-controlled hypertension may lead to kidney damage in an otherwise healthy subject. According to a Consensus Conference held in Amsterdam (Delmonico, 2005), there is no reason to reject as a kidney donor a subject more than 50 years of age who has a normal blood pressure on therapy with a GFR > 80 ml/min and proteinuria < 300 mg per day (Delmonico et al., 2005). Ambulatory blood pressure monitoring has been proposed as a more sensitive method than office blood pressure measurements in identifying hypertension in living donors (Ozdemir et al., 2000).

### 5.1.3 Diabetic donors

Diabetics are generally excluded because of the increased risk of postoperative complications in the short term and because of the potential risk of developing diabetic nephropathy in the long term (Delmonico et al., 2005; Kasiske et al., 1995). Diabetic nephropathy occurs in familial clusters and heredity helps to determine susceptibility to diabetic nephropathy (Sequist et al., 1989). It was clearly stated in Consensus Conference held in Amsterdam, that individuals with a history of diabetes or fasting blood glucose of ≥ 126mg/dl (7.0mmol/L) on at least two occasions (or 2-h glucose with OGTT ≥ 200mg/dl (11.1mmol/L)) should not donate (Delmonico et al., 2005).

### 5.1.4 Patients with nephrolithiasis

It seems reasonable to accept as donors only those subjects without stones at the time of evaluation and with normal values within a 24-hour urine collection of calcium, urate, and oxalate. According to a Consensus Conference, patients with stones caused by inherited disorders, inflammatory bowel disease, or systemic disease are at high risk of recurrence and should not be considered for donation (Delmonico et al., 2005). In the series a cohort of 710 renal transplant recipients from Mayo Clinic, evaluation was done for the risk transplant graft renal calculus formation over duration of 4 years. 44 donor kidneys had calculi, majority being <2mm. Stable stone size was seen in four patients, increase in stone size averaging 2.9 millimeters in four patients. No loss of the transplanted kidneys occurred due to stone obstruction in the patients studied (Ho et al., 2005). Whether or not kidney stone formers should donate a kidney is controversial. The American Society of Transplantation (AST) position paper proposes guidelines that a kidney stone former may donate a kidney if: only one stone has ever formed; stones have been multiple, but none have formed for >10 years and none are seen on radiograph; and the donor is screened for metabolic abnormalities and is offered life-long follow-up that includes periodic risk reassessment, medical treatment, and hydration (Michelle et al., 2006).

### 5.1.5 Obese donors

There is little information on the long-term follow-up of obese donors. Of some concern, in patients submitted to unilateral nephrectomy for various reasons, those with a BMI > 30 had a significantly higher risk of developing proteinuria or renal dysfunction in the long term than did those with a BMI < 30 (Praga et al., 2000). The Consensus Conference held in Amsterdam discouraged donation from persons with a BMI higher than 35 (Delmonico et al., 2005). Dyslipidemia are associated with decreased kidney function in the general population.
and have faster rates of progression in patients who have chronic kidney disease. However, isolated dyslipidemia is not a contraindication for donation.

5.1.6 Other issues

- Adult relatives of patients with polycystic kidney disease can be accepted for donation if they have a normal CT or renal ultrasound scan.
- Donors with malignancy - a history of malignancy is in general a contraindication to living kidney donation, other than carcinoma in situ of the uterine cervix or treated low grade, non-melanotic skin carcinoma.
- Donors with transmissible infections - HIV positive status remains a contraindication for donation. Cytomegalovirus (CMV) and Ebstein-barr virus (EBV) status is measured at some transplant centers and they delay transplant till PCR for CMV becomes negative. Most of the adults are EBV and CMV-positive; most of the children are negative. The risk of post-transplantation lymphoproliferative disorder (PTLD) is the concern in CMV and EBV-negative individuals receiving positive donors. However, the risk is not as high to prohibit renal transplantation (Delmonico et al, 2005). Renal transplantation should be considered using HCV-seropositive grafts for qualified patients with chronic kidney disease (CKD) stage 5 and HCV infection since good information indicates that the transplantation of kidneys from HCV-infected donors results in improved survival compared to wait-listed and dialysis-dependent candidates (Fabrizi et al, 2009). Hepatitis C Virus (HCV) positive donor may be considered for donation to a HCV positive recipient only if the donor PCR is negative, certain genotypes (Genotype 4) are treated and eradicated of the donor and there is no evidence of chronic hepatitis or cirrhosis on liver biopsy. However, there is no data on live kidney transplantation from HCV positive donors. Hepatitis B Virus (HBV) positive status currently is not accepted for donation. However, there are some isolated reports of transplantation by groups in New Zealand (Delmonico et al, 2005). Donors treated for pulmonary TB require a more specific and extensive examination of the urinary tract and the kidneys prior to donation.

5.1.7 Ethical issues

Ethical issues in accepting marginal criteria donors are very complex. The living kidney donation means giving life to a patient on dialysis but at the same time avoiding risks to the donor. An important problem with marginal donors is that these marginal living donors may themselves add up the pool of chronic kidney disease patients in the long run.

At American Transplant Congress 2003, in cases of marginal donor transplantation, a prior sample consent by both donor and recipient was proposed stating expect increase in delayed graft function, expected decrease in graft survival, expected decrease in waiting time, expected increase in survival compared to waiting and benefit of transplant prior to increased morbidity.

It is truly anticipated that the transplantation of ECD and DCD kidneys would result in higher costs. More frequent need for hemodialysis, more hospital readmissions due to poor or late onset graft function and more opportunistic infections in recipients of ECD and DCD kidneys results in higher cost for their initial medical care.
5.2 Marginal cadaveric donor

The Organ Procurement and Transplantation Network instituted a formalized definition of marginal kidneys in 2002 with the advent of the Expanded Criteria Donor (ECD) (Metzger et al, 2003). These deceased donor kidneys were demonstrated to convey a 70% or greater risk for graft loss for transplant recipients relative to an ideal donation and were characterized by a donor age older than 60 yr or older than 50 yr and accompanied by two additional risk factors, including a history of hypertension, elevated terminal donor Creatinine, and cerebrovascular cause of death.

Despite expected higher rate of graft failure compared to SCD kidneys, multiple studies have subsequently shown that kidney transplantation using ECDs is still associated with a substantial reduction in morbidity and improvement in life expectancy when compared with suitable transplant candidates who remained on maintenance dialysis treatment (UNOS Policy 3.5.1, 2002; Institute of Medicine, 1997; Ojo et al, 2001).

6. Donation after cardiac death (DCD)

Another approach to the organ shortage has been the utilization of donors after cardiac death. The recovery of organs from nonheart beating donors is an important, medically effective and ethically acceptable approach to reducing the gap that exists now and will continue to exist in future between the demand for and available supply of organs for transplantation'. A lot of investigators have reported excellent short-term outcomes using these donors, and 10–15% growth in organ donation as a result of the use of DCD donors was demonstrated. Multiple studies have shown that the overall results of DCD (without ECD characteristics) and SCD kidney transplants are comparable (Institute of Medicine, 1997; Ojo et al, 2001; Stratta et al, 2004). A main issue with NHBD is the significantly higher rate of delayed graft function, compared with that associated with heart-beating donor (Keizer et al, 2005).

7. Role of kidney biopsy

Outcomes of ECD kidney transplantation are improved when a pre-implantation biopsy of the donor kidney is evaluated using the scoring system introduced by Karpinski and colleagues (Karpinski et al, 1999). Using this system, donor renal pathology is scored from 0 to 3 (none to severe disease) in 4 areas: glomerulosclerosis, interstitial fibrosis, tubular atrophy, and vascular disease. A donor vessel score of 3/3 is associated with a 100% incidence of delayed graft function and a significantly worse renal function at one year.

8. Patient management: Immunosuppressive protocols

Optimal management is a challenge in ECD kidney transplant recipients. These transplants are feared with increased rates of acute rejections and delayed graft function. Therefore, adequate level of Immunosuppression is desired. Management for an ECD kidney is based on potential nephron-protecting strategies, including cold ischemia time minimization, pulsatile perfusion preservation, immunosuppression focused on nephrotoxicity minimization, and adequate infection prophylaxis. Although calcineurin inhibitors are excellent drugs, the nephrotoxicity they impart is largely responsible for postponing chronic
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allograft dysfunction and achieve better long-term graft survival. The problem of calcineurin inhibitor-related nephrotoxicity is an even greater concern in older recipients of ECD kidneys. Various strategies of CNI withdrawal, minimization as well as avoidance were utilized by a number of investigators.

- Antibody induction, MMF, steroids.
- MMF monotherapy or MMF plus steroids.
- Antibody induction, sirolimus, MMF, steroids.
- Antibody induction, sirolimus, MMF, steroids.
- Conversion from a calcineurin-inhibitor-based regimen to a sirolimus-based regimen

The potential for CNI-free sirolimus and MMF-based therapy in ECD kidney transplant recipients has not been adequately studied to date. Consequently, extrapolation of the best results obtained with anti-interleukin 2 receptors, MMF, steroids, and moderate exposure to tacrolimus might constitute an advisable strategy (Ekberg et al, 2007).

9. Conclusion

In summary, the use of marginal donors for kidney transplantation increases the numbers of donor kidneys available, results in shorter waiting times, and limits the morbidity and mortality associated with long-term dialysis therapy. These kidneys are known to have worse long-term survival than standard criteria kidneys. Elderly patients with longer waiting times show better survival receiving such kidney than remaining on dialysis therapy. A management protocol for ECD kidney transplantation should be based on potential nephronprotecting strategies like, minimization of cold ischemia time, tailored immunosuppression with early CNI minimization or delayed moderate dose, CNI addition after induction, and adequate infection prophylaxis.

10. References

http://www.cdha.nshealth.ca/multi-organ-transplant-program/documents,
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This book presents a nice international compilation of scholarly papers and chapters which address the latest advances in renal transplant surgery. These works cover a variety of topics; the last advance and success of renal transplant science: biochemistry, immunology, molecular genetics, pharmacology - pharmacogenetics, pediatric transplant and a few rare uropathies that warrant organ replacement.

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