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# ORGAN GRAFTING OUTCOMES INVOLVING ELEVATED RENAL BIOMARKERS IN END-OF-LIFE DONORS

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SUMMARY – As demand for kidney transplants grows while the availability of donor organs remains relatively stable, transplant programs have begun exploring alternative methods to expand the donor pool. One such approach involves accepting organs from expanded criteria donors (ECD), which were once viewed with caution due to assumptions about increased risks, such as delayed graft function, higher rejection rates, and poor preservation outcomes. Traditionally, these kidneys were considered inferior to those from standard criteria donors (SCD), leading to their underutilization.

Modern transplant programs are now focusing efforts on minimizing the disparity in post-transplant outcomes between recipients of ECD and SCD kidneys. Achieving this involves several strategic adjustments, including minimizing cold ischemia time, implementing tailored immunosuppression protocols, selecting recipients more carefully, and utilizing dual kidney transplants to increase functional nephron mass. Histological assessments have also become an important tool in determining the viability of marginal grafts.
Of particular interest is the use of kidneys from donors who experienced acute renal failure (ARF) or had significantly elevated terminal creatinine levels. Although research in this area remains limited, early findings suggest that such grafts—if managed appropriately during retrieval, implantation, and post-operative care—can offer promising outcomes. Defining what constitutes a marginal donor, particularly in cases involving ARF, is critical in guiding clinical decisions.

Key words: *Kidney transplantation; Donor selection; Treatment outcome*

## Introduction

Kidney transplantation is the treatment of choice for all patients with end-stage renal disease (ESRD), without contraindications for immunosuppressive treatment, while it offers better quality of life and better survival when compared with dialysis[1,2]. The increasing number of potential renal transplant recipients on waiting lists is not followed by appropriate rise in the number of deceased donors. This discrepancy challenges transplantation centers to consider other opportunites for making more organs available for transplantation. In order to expand donor pool, many centers have started to use kidneys from older and expanded criteria donors (ECD).

Until 2002, transplant centers used intuition to discriminate organs that were supposed to have less than optimal function[3]. Based on the 'clinical feeling' of transplantation teams, most of the kidneys supposed to have poor graft outcome were discarded. Thus, donors at advanced age, impaired hemodynamics and prolonged ischemia time, as well as donors

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with elevated serum creatinine level prior to transplantation were refused.

In 2002, Port *et al*. defined ECD as a deceased donor aged 60 years or older, or donor aged 50 to 59, with minimum 2 factors: history of hypertension, serum creatinine level greater than 1.5 mg/dL (132.6 mmol/L) and cerebrovascular cause of death. The risk of graft failure in these transplantations was much higher than for grafts from standard criteria donors (SCD). Using Cox regression models, Port *et al*. demonstrated a 70% higher risk of graft failure compared to ideal kidneys (relative risk greater than 1.7). According to their study, grafts from older donors with diabetes, hypertension or renal impairment have a higher risk of failure but are good enough to be transplanted[4]. However, based on the ECD graft definition, the first assumption is an increased risk of a less favorable outcome compared to SCD graft. In this way, refusals of ECD kidneys are frequent and cold ischemia time is prolonged, leading to organ discarding[5]. Massie *et al*. report that many transplant centers express their villingness to accept ECD transplants, but finally refuse organs when they are offered, thus creating delays that result in organ discarding[6].

As there is no unique definition of appropriate kidney graft, transplantation centers differ according to the criteria for refusal or acceptance of grafts considered to be marginal. The most common reason for refusal is hemodynamically unstable donor and high terminal serum creatinine. Nevertheless, the use of ECD has led to an increased number of transplanted patients with better survival compared to patients on dialysis[2]. A new target of modern kidney transplantation is to reduce the difference between the outcomes of recipients who received allograft from marginal donors and recipients transplanted from optimal donors.

In this review, we discuss the issue of ECD and define the strategies to improve the outcome of kidneys obtained from these donors.

## Donor with Acute Kidney Injury

Acute kidney injury (AKI) represents rapid deterioration of kidney function that occurs in approximately 5% of all hospitalized patients. It is one of the most common complications in intensive care units (ICU) affecting 36% of these patients[7]. In more than 50% of AKI in ICU, the cause of kidney injury is septic shock or sepsis.

The causes of AKI in hospitalized patients without previous kidney disease can be prerenal, renal and postrenal. In 60%-70% of cases, the cause is prerenal, including dehydration, hypoperfusion, ischemia due to blood loss, sepsis, surgery, severe burn and injury, liver or heart failure. Renal damage is the most complicated cause of AKI, which affects filtering function or blood supply within the kidney or kidney tissue responsible for salt and water balance. Infections cause glomerulonephritis. A common cause of acute interstitial nephritis are nephrotoxic agents, including drug abuse such as heroin and cocaine, crush injuries leading to myoglobinuria, and drugs frequently used in ICU at inappropriate doses such as antibiotics, anti-inflammatory drugs, and diuretics. Acute interstitial nephritis is usually reversible if kidney damage is not severe. Acute tubular necrosis is usually the result of other causes of renal damage accounting for 90% of primary renal AKI cases. Postrenal failure is a rare cause of acute kidney failure in ICU[8,9].

In ICU patients with AKI who are considered as potential kidney donors, we are searching for correctable causes of AKI in order to optimize kidney function and prepare them for potential grafting. Interpretation of kidney injury is a problem when evaluating potential donors. In some patients admitted to ICU, AKI is nothing but acutization of chronic renal failure. Some patients admitted with a good kidney function experience rapid deterioration of kidney function due to numerous reasons. As mentioned above, common reasons of renal failure in ICU are prerenal and renal. Radiocontrast induced kidney injury is usually a reversible form of AKI, defined as an increase of serum creatinine level by more than 25% or its absolute increase of 0.5 mg/dL early after radiographic examination using radiocontrast agent. A common question is how to quantify damage in donors to discriminate the potential grafts with good outcome. A problem is that most studies investigating outcome of kidney transplantation from donors with high terminal creatinine are based on the last serum creatinine level rather than its change during intensive care management.

Serum creatinine is a widely used parameter for calculating glomerular filtration rate (GFR) in everyday practice, but its sensitivity and specificity in

predicting AKI are unknown. As a sole parameter, serum creatinine is a poor predictor of kidney damage because of rapidly changing levels in critically ill patients with AKI and its dependence on muscle mass. In recent studies, there is a question of predicting the reversibility of kidney damage, and impact of AKI on long-term graft survival, graft function and rejection. Some studies show that high serum creatinine solely cannot be a measure to discard kidney for transplantation. Reduction of serum creatinine level in donors is not a sign of insult recovery, although high serum creatinine level does not represent irreversible injury[10].

The risk, injury, failure, loss and end-stage renal disease (RIFLE) criteria are internationally accepted classification for kidney damage in AKI in hospitalized patients. In 2010, Rodrigo *et al.* first reported the use of RIFLE criteria to evaluate AKI in deceased donors. The idea of the study was to standardize and quantify renal injury in donors and the possible influence on graft outcome. Risk was defined as creatinine increase x1.5, injury as x2 and failure as the last creatinine increase x3 with respect to its value on admission day. The authors of the study conclude that RIFLE criteria are feasible in the diagnosis of AKI in kidney donors, but further studies including a larger number of patients are needed to confirm this hypothesis[11]. However, this classification cannot be used as isolated criteria for discarding donated kidney.

In 2006, Kumar *et al.* reported three-year results of successful kidney transplantation from deceased donor with AKI, but the authors did not use RIFLE criteria to classify AKI. This study reported comparable three-year kidney function between the kidneys transplanted from selected deceased donors with acute renal failure without previous positive medical history, chronic histologic lesions, and kidneys from SCD[12].

## Quality of Kidney Grafts – Objective Measures and Donor Selection

In 2006, Remuzzi *et al.* assesed outcome of renal transplantation from older donors. It was well known from clinical practice that long-term survival of renal grafts obtained from elderly donors is inferior to survival of grafts from younger donors. However, Remuzzi *et al.* wanted to prove that selection of older kidneys according to histologic characteristics before transplantation could influence graft outcome. An international group of pathologists presented a scoring system for kidneys from donors older than 60, based on biopsy findings. The intention was assessment of kidneys with enough viable nephrons, available for transplantation by thorough analysis of the tubuli, vessels, glomeruli and internal changes. Scores ranged from 0 (absence of lesions) to a maximum of 12 (marked changes in renal parenchyma). Kidneys with scores 3 or lower were supposed to be used as a single transplants. Kidneys with scores 4, 5 or 6 could be used as dual transplants (only if the total number of viable nephrons in two kidneys approached the number in one ideal kidney). Discarded were kidneys with score 7 or higher. The graft survival rate of histologically evaluated marginal kidneys did not differ from kidneys of donors under 60, but it was better than in recipients whose grafts from donors older than 60 were not evaluated histologically. Remuzzi *et al.* conclude that histologic criteria have a critical role in the evaluation of marginal donors, as they are improving graft outcomes and in this way might expand the pool of donors. Nowadays, many transplantation centers have implemented preimplantation kidney biopsy as a routine procedure in order to identify usable grafts[13].

All kidney grafts, either from old or young, marginal or standard criteria donor could be harmed with some events just before donation or previously, even before the donor was admitted to ICU (chronic lesions). Some potential donors may have high serum creatinine at the time of admission to ICU, as they have chronic renal insufficiency. Serum creatinine level could rise a few days before donation because of several reasons related to stay or treatment in ICU. Understandably, only grafts with acute, correctable renal dysfunction are considered for transplantation. Biopsy is necessary to distinguish between cases of high admission serum creatinine due to chronic renal disease and high creatinine due to some acute injury[3]. Specific evaluation and allocation is necessary for marginal grafts with possible chronic lesions before considering them for transplantation.

In 2001, a concensus meeting of the American Society of Transplantation and American Society of Transplant Surgeons was held in Crystal City, Virginia. The goal of the meeting was development of guidelines for improving recovery and transplantation of organs from deceased donor. The Kidney Work Group dis-

cussed how to increase the use of older donor kidneys, decrease cold ischemia time and delay graft function. In this way, patient outcome could be improved, as it could decrease hospital stay and costs[14].

In order not to discard kidneys from ECD, but improve their allocation and graft survival, Nyberg *et al.* developed a scoring system for these kidneys. Deceased donor score (DDS) includes scores for donor's age, hypertension, creatinine clearance, HLA mismatch and cause of death. If the score is higher than 20, 6-year graft survival is lower than 70%; if DDS score is lower than 20, 6-year graft survival is higher than 80%[15].

## Dual Kidney Transplantation

Transplantation of dual ECD kidneys represents one of the possible ways to reduce number of discarded kidneys and increase nephron mass of "marginal" kidneys. It may be a good approach in expanding the donor pool. Still, there are no determined criteria for single or dual transplantation in a recipient of ECD kidney.

One of the first reports of dual kidney transplantations from older donors showed that these recipients had decreased incidence of delayed graft function, better graft function and survival than recipients of single kidney from similar age donors[16]. Some studies praise strategy of dual kidney transplantation in expanding the donor pool, but found a high incidence of primary nonfunction[17,18].

In 2003, Bunnapradist *et al.* showed similar outcome of 403 dual transplantations (mean donor age 60.8 years) with 11033 single kidney transplantations when recipients of single kidney were grafted with donors aged over 55 years[19].

In 1999, Remuzzi *et al.* compared graft survival of single and dual kidney transplants from ECD (donor age >60, history of diabetes or hypertension, urine protein excretion up to 3 g/24 h) based on clinical or preimplantation histologic evaluation. This study showed that graft evaluated histologically before implantation had similar outcome in dual transplant recipients as single grafted recipients from younger donors. These results strongly suggest that histologic criteria should be considered as an important part on choosing between single and dual kidney transplantation from marginal donor[20].

## Recipient Selection and Immunosuppression

It is important to mention that long-term graft and patient survival after transplantation has improved in the last years, as a result of factors like good patient care, enhanced organ preservation and surgical techniques, effective antimicrobial prophylaxis and availability of potent immunosuppression regimens[21]. One possible additive factor may be proper selection of recipients for certain graft.

Elderly patients make up an increasing percent of the waitlist, as well as of donated and recovered kidneys. The use of older donors for kidney transplantation may create obstacles to long-term survival, as older kidneys are associated with inferior outcomes. However, the major risk for dialysis patients is to stay on dialysis, thus elderly patients should be individually evaluated for renal transplantation. 'Physiologic' age is much more important than 'chronologic' age in this group of patients[22].

Stratta *et al.* studied 90 recipients of adult donor kidneys transplanted from 2001 to 2003 (37 from ECDs and 53 from SCDs). Recipient selection for marginal kidney was based on their estimated need for nephron mass by using the criteria of age >40 years, low body mass index (<25 kg/m$^2$), and low immunologic risk (first transplantation, 0% PRA, HLA matching). They conclude that ECD kidneys should be used for carefully selected patients, with the use of 'nephron sparing strategy'. It means that long-cold ischemia time should be avoided, as well as nephrotoxic immunosuppressive protocols[23]. Severe donor-recipient size mismatching should be avoided.

The Eurotransplant Senior Program (ESP) allocates kidneys from older donors to recipients older than 65 years. This program has significantly increased the number of transplantations performed in elderly patients. Croatia has introduced its own 'senior' program in 2005, based on ESP but with HLA matching, which improved outcomes compared to Eurotransplant results[24]. Currently, elderly patients wait for less than 6 months to receive transplant in Croatia.

While kidneys from ECD are supposed to have already suffered injury, any further damage should be avoided. Stratta *et al.* have presented the management protocol for ECD kidneys. It is based on the number of nephron sparing maneuvers by minimizing cold

ischemia time, pulsatile perfusion preservation, immunosuppression with depletion antibodies to minimize preservation injury and risk of rejection, delayed calcineurin administration and lower tacrolimus levels to maintain balance between effectiveness and toxicity[23].

Nephrotoxic immunosuppressive protocols should be avoided, which means delayed introduction of calcineurin inhibitors under the umbrella of antibodies (either monoclonal in patients with low immune risk, or polyclonal in patients with high immune risk). Based on our experience, these protocols are safe and are not associated with increased incidence of acute rejections. Mammalian target of rapamycin inhibitors (mTOR) seems promising in this setting. Three preliminary reports suggest that calcineurin inhibitor-free protocols with costimulation blockade in recipients from ECD decrease the incidence of delayed graft function, but further studies have to confirm this. Thus, novel immunosuppressive drugs may contribute to less nephrotoxic protocols[25]. However, current protocols recommend their use after at least one month of transplantation to avoid problems with wound healing.

## Conclusion

Kidney donor pool has evolved over the last few years mainly due to the utilization of ECD. However, recipients of kidneys from ECD have by definition inferior graft and worse overall survival. Potential recipient has to be well informed about the risks of transplanting grafts from ECD. Such grafts are not for 'expanded recipient criteria', but for recipients with low risks and demands. To find the best donor-recipient match, specific allocation policies are required. A challenge is to minimize transplantation outcome differences between grafts from SCD and ECD.

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