

# Factors Influencing Long-term Outcomes following Renal Transplantation: A Review

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## ABSTRACT

Despite continuing advances in immunosuppressive and supportive therapies, the success of renal transplantation is impacted by factors present in the donor and recipient pre- and post-transplantation. The pre-transplant factors influencing the long-term graft function in the donor include source, age, sex, and HLA mismatches; and in the recipient include age, duration of dialysis and sensitisation. After transplantation, a number of events may lead to progressive deterioration of renal function and graft loss, which include delayed graft function, acute rejection, viral infections, recurrent disease, drug nephrotoxicity, non-compliance and chronic allograft nephropathy. Modulation of individual factor is mandatory to preserve satisfactory renal function in long-term. In this review, each factor is discussed in the context of current transplant practice and an up to date review of literature is presented.

**Key words:** Calcineurin inhibitors, Chronic allograft nephropathy, Long-term outcomes, Renal transplantation.

## INTRODUCTION

Renal transplantation (RT) is the treatment of choice for most patients with end-stage renal failure as this improves quality of life, survival and is cost-effective.<sup>1</sup> The number of patients added to the waiting list each year for RT is increasing globally, whereas the number of RTs performed annually has remained relatively constant, which has resulted from the increasing demand of organs outstripping the supply.<sup>2</sup> Despite significant advances in immunosuppressive and supportive therapies, several factors still compromise the long-term success of renal transplantation.<sup>3</sup> Some of these factors are present at the time of transplantation in both donor and recipient, while others, in the form of complications, develop after RT. In this review, the main factors and events which

influence the long-term graft function and the current practice to resolve these problems are discussed.

## 1. PRETRANSPLANTATION FACTORS

### DONOR FACTORS

**Source:** The source or donor strongly affects the long-term graft survival as the outcome following live donor (LD) RT is superior to that from cadaveric donors (CD). This has been confirmed by Hariharan et al. on analysis of 93,934 RTs performed in the United States between 1988 and 1996, where the one-year survival and half-life for grafts from LD and CD were 93.9 and 87.7 percent; and 21.6 and 13.8 years, respectively.<sup>4</sup> The findings can not be attributed to better HLA matching as graft half-life of transplants between spouses, who

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are HLA-mismatched, is more than one-third better than CD grafts.<sup>5</sup> The difference in outcome is due to several reasons. In CDs, the brain-stem death is associated with a cytokine storm leading to profound ischaemia and endothelial damage of peripheral organs. The ischaemia-reperfusion injury following cold-storage is less severe with LD kidney and so is the up regulation of cytokines and chemokines which favour over expression of HLA antigens by the endothelial and tubular epithelial cells, which increases the risk of acute and chronic rejection.<sup>6</sup>

**Age:** The poorer results of kidneys from elderly donors are mainly caused by the age-dependent progressive reduction of glomerular filtration rate and renal reserve, which is related to senescence.<sup>7</sup> To overcome this problem, dual transplantation, that is, transplanting both kidneys from borderline donors to single recipients has been performed, but the results from various centres are not consistent.<sup>8</sup> However, the current trend is to transplant kidney from elderly donors to an age matched recipients and this leads to best utilisation of the available kidneys.<sup>9</sup>

**Sex:** Women tend to have smaller kidneys with 17% fewer nephrons than male kidneys thereby affecting functional renal mass. The number of glomeruli per kidney as well as the mean glomerular volume closely correlates with kidney weight. The long-term survival of a graft from a female donor to a male recipient is significantly lower than other sex combinations.<sup>10</sup>

**HLA mismatches:** Human leucocyte antigen (HLA) molecules of the grafts are the principal targets of the immune response in transplantation. The clinical benefits of HLA matching on the graft survival are being appreciated in large registries even in the recent era of effective immunosuppressive regimens. HLA matched grafts have an estimated half-life of 12.4 years as compared with 8.6 years for HLA mismatched graft.<sup>11</sup> In addition to HLA matching, cross-reactive group (CREG) matching is being increasingly emphasised as CREG matching is associated with a reduced frequency of late acute rejection episodes and improved graft function at 2 years.<sup>12</sup> In the United Network of Organ Sharing (UNOS) database the risk of chronic rejection was 62% higher in CREG-mismatched recipients compared with those receiving a HLA- and CREG-matched kidney.<sup>13</sup>

## RECIPIENT FACTORS

**Age:** Young age is associated with relatively high state of immune responsiveness to alloantigens and increased

risk of acute rejection and this is compounded by non-compliance.<sup>14</sup> This calls for more intense immunosuppression and vigilance. As the age advances, there is increased risk of death from cardiovascular diseases, malignancies and infectious complications related to over-immunosuppression. Death with a functioning graft is more common in elderly recipients, hence the importance of adequate screening prior to and a less aggressive immunosuppressive regimen following transplantation.<sup>15</sup>

**Duration of dialysis treatment:** The outcome of RT is adversely affected by the duration of dialysis pre-transplantation the evidence is in favour of pre-emptive transplantation.<sup>16</sup> Analysis from United States Renal Data System (USRDS) has shown transplantation of a kidney from a living donor without previous long-term dialysis was associated with a 52 percent reduction in the risk of allograft failure during the first year after transplantation ( $P=0.002$ ), an 82 percent reduction during the second year ( $P=0.001$ ), and an 86 percent reduction during subsequent years ( $P=0.001$ ), as compared with transplantation after dialysis.<sup>17</sup> Using a paired donor kidney analysis, Meire-Kriesche *et al.* have demonstrated worse outcome with longer time on dialysis which was true for both CD and LD RTs. The time on dialysis remains the strongest modifiable factor influencing transplant outcome.<sup>18</sup>

**Sensitisation (Anti-HLA antibodies):** Patients with anti-HLA antibodies elicited by pregnancies, blood transfusions, or failed transplants, despite negative cross-match at the time of transplantation, are at increased risk of acute and chronic rejections leading to graft loss.<sup>19</sup> Antibodies to both HLA class I and class II antigens are detrimental and presence of donor-specific antibodies in particular, before or after transplantation, is associated with rejection and graft loss. However, transplant glomerulopathy may occur in the absence of demonstrable CD4 staining in the peritubular capillaries.<sup>20</sup>

## 2. POSTTRANSPLANTATION FACTORS

### SPECIFIC FACTORS AFFECTING GRAFT DYSFUNCTION

**Delayed graft function:** Delayed graft function (DGF) is a common complication after cadaveric renal transplantation, and may affect graft function.<sup>21</sup> Logistic regression analysis ( $N = 8950$ ) of the data from the ongoing international, prospective; observational study, the Neoral-MOST (Multinational Observational Study in renal Transplantation), showed higher donor age, longer cold ischaemia time, male recipients, Caucasian

recipients, high recipients body mass index, and panel reactive antibodies were all associated with a higher risk for DGF.<sup>22</sup> Institution of less nephrotoxic immunosuppressive regimen and supportive therapy is mandatory.

**Acute rejection:** There has been a significant reduction in the incidence of acute rejection since the introduction of tacrolimus and mycophenolate mofetil, which according to recent report from USA had reduced from 43.5% in 1991 to 15.55% in 2000.<sup>23</sup> The impact of acute rejection on long-term outcome depends on its time of occurrence (early or late), number (one or more), reversibility with steroid treatment (complete or partial), and the histological grade according to Banff criteria and on development of humoral antibodies. Sijpkens demonstrated that 10 year graft survival was 86% for patients who developed acute rejection by third post-transplant month and 45% for those who had rejection after three months. The humoral rejection is diagnosed by detecting CD in the peritubular capillaries and/or presence of circulating donor specific antibodies and is treated with escalation of immunosuppression in addition to plasmapheresis, rituximab<sup>24</sup> and intravenous immunoglobulin therapy.<sup>25-27</sup>

**Viral infections:** Over-immunosuppression leads to myriads of infectious complications post-transplantation. Of these, BK polyoma virus and cytomegalovirus (CMV) can lead to graft dysfunction and loss, if not diagnosed and treated early.<sup>28</sup> BK virus, which remains latent in the urinary tract, can reactivate in patients treated with tacrolimus and mycophenolate mofetil (MMF) and present with progressive graft dysfunction.<sup>29</sup> Diagnosis is established by detection of viral DNA by polymerase chain reaction and histological demonstration of cytopathic changes and inclusion bodies. Reduction of immunosuppression or replacement of tacrolimus and MMF with leflunomide, may rescue the kidney.<sup>30</sup> CMV infection is associated with acute rejection and chronic allograft dysfunction, which had led to significant development of strategies in prophylactic and pre-emptive therapy.<sup>31-33</sup>

**Calcineurin inhibitors (CNI) nephrotoxicity:** Chronic calcineurin inhibitors (tacrolimus and ciclosporin) nephrotoxicity is dose-dependent and manifests histologically with progressive glomerular sclerosis, arteriolopathy, interstitial fibrosis and tubular atrophy leading to progressive decline in renal function.<sup>34</sup> CNI reducing or sparing strategies have shown to be the way forward in reducing premature graft loss.<sup>35,36</sup>

**Recurrence of primary disease:** Recurrence of primary

disease has remained an unresolved problem and leading to significant renal allograft loss. Immunoglobulin-A nephritis, membranous nephropathy and lupus nephritis do not affect 10 year graft survival even if they have recurred in the graft.<sup>37</sup> On the other hand, recurrence of focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, Henoch-Schonlein purpura and haemolytic uraemic syndrome will lead to graft loss, although sporadic cases of response to plasmapheresis and immunoadsorption have been reported.<sup>38,39</sup>

**De novo glomerulonephritis** may develop in the transplanted kidneys. Membranous nephropathy related to hepatitis-B and membranoproliferative glomerulonephritis related to hepatitis-c virus carriers are most frequent forms. However, de novo idiopathic membranous nephropathy, acute glomerulonephritis, minimal change nephropathy and collapsing focal glomerulosclerosis have been described.<sup>40</sup>

**De novo thrombotic microangiopathy:** *De novo* thrombotic microangiopathy may occur in patients on ciclosporin, tacrolimus, sirolimus and monoclonal antibodies (OKT3) presenting with features of haemolytic uraemic syndrome of graft dysfunction. Renal biopsy is indispensable for diagnosis. Withdrawal of offending agent and plasmapheresis have been successful in several studies.<sup>41</sup>

## NON-SPECIFIC FACTORS AFFECTING GRAFT DYSFUNCTION

**De novo diabetes:** Up to 25% of RT recipient develop de novo diabetes related to immunosuppressive therapy, particularly due to steroids and tacrolimus, thereby increasing risk of cardiac, cerebrovascular and peripheral vascular disease.<sup>42</sup> Steroid and CNI sparing regimens reduces this risk.

**Arterial hypertension:** Post-transplant hypertension, resulting from immunosuppressive agents, has significant influence on the long-term graft and patient survival, hence the importance of adequate control of blood pressure.<sup>43, 44</sup>

**Nephrotoxic agents:** The inappropriate use of nephrotoxic agent such as aminoglycosides, fluoroquinolones, non-steroidal anti-inflammatory drugs, sulphonamides and contrast media causes dose-dependent toxicity and progressive graft dysfunction. Adequate hydration and infusion of N-acetylcysteine prior to injection of radiological contrast media has shown to reduce nephrotoxicity.<sup>45</sup>

**Non-compliance:** Non-compliance to immunosuppressants

in RT recipients is a major factor affecting graft survival, but it is difficult to detect accurately in clinical practice.

In one study, poor compliance was recorded in 22% patients and in 36% of patients, graft loss was preceded by episodes of non-compliance. Meta-analysis of several studies has shown the odds of graft failure increased seven fold in non-compliant patients.<sup>46</sup>

### 3. IMMUNOSUPPRESSIVE THERAPY

The introduction of ciclosporin in 1980s<sup>47,48</sup>, ciclosporin micro-emulsion (Neoral)<sup>49</sup>, tacrolimus<sup>50,51</sup> and MMF<sup>52,53</sup> in 1990s, sirolimus<sup>54</sup> and anti-interleukin-2 receptor antibodies (basiliximab and daclizumab)<sup>55, 56</sup> recently has been associated with reduced incidence of acute rejection episodes during the first year after RT. In a recent systematic review from Australia, the graft survival with tacrolimus was superior compared with ciclosporin, although individual randomized controlled trials (RCTs) had shown no difference in the past.<sup>57</sup> Monitoring blood ciclosporin level at 2 hours post-dose (C2) significantly reduces the severity and incidence of acute rejection compared with 12 hours post-dose trough (C0) monitoring, without adverse consequences in terms of renal function or tolerability.<sup>58</sup> Induction regimens using polyclonal antibodies (antithymocyte globulin)<sup>59</sup>, monoclonal antibodies (OKT3)<sup>60</sup> and anti-IL2 receptor antibodies in combination with combinations of above-mentioned drugs have been studied in several RCTs<sup>61</sup> and all of them have been effective in reducing acute rejections, albeit with their individual side-effects. CNI sparing<sup>62</sup> and steroid-free regimens<sup>63</sup> have been evaluated. Reduction and possible withdrawal of CNI with either addition or continuation of MMF has slowed the rate of loss of renal function in patients with CAN.<sup>64</sup> Everolimus (Certican)<sup>65</sup>, mycophenolate sodium (Myfortic)<sup>66</sup>, alemtuzumab (Campath 1H)<sup>67, 68</sup>, FTY-720<sup>69</sup> are in various stages of trials showing promising results.<sup>70</sup>

### 4. CHRONIC ALLOGRAFT NEPHROPATHY

Chronic allograft nephropathy (CAN) is the leading

cause of RT failure which presents clinically as progressive and irreversible deterioration of renal function, proteinuria and hypertension, and histologically with concentric arteriosclerosis, glomerulosclerosis, tubular atrophy and interstitial fibrosis.<sup>3</sup> Both immunological (late acute rejection, HLA-mismatches, sensitisation and non-compliance) and non-immunological factors (brain death, delayed graft function, infection, hyperlipidaemia, hypertension, smoking, donor age, donor sex, donor race and CNI toxicity) are implicated in the aetiology of CAN.<sup>71</sup>

There is no established treatment for CAN, mainly because of presence of irreversible damage at the time of diagnosis.<sup>72</sup> Nevertheless, in early phases of disease, change in immunosuppressive agents to less nephrotoxic regimen consisting of MMF or sirolimus may stabilise or even reverse part of renal dysfunction.<sup>73-75</sup> Belatacept, a selective costimulation blocker, is being shown to preserve the glomerular filtration rate and reduce the rate of CAN. Non-immunological interventions to decelerate the progression CAN include control of hypertension<sup>76</sup>, proteinuria<sup>77</sup> and hyperlipidaemia.<sup>78</sup> Significant reduction of proteinuria has been reported following the use of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists in clinical transplantation.<sup>79, 80</sup>

### CONCLUSIONS

Several factors present in the donor and recipients pre-transplantation and events taking place post-transplantation described above influence the long-term outcome following RT. CAN is the leading cause of graft loss following RT and its prevention by modulation of the aetiological factors, early diagnosis and measures to halt the progression of CAN are paramount. A low threshold for biopsy helps to detect sub-clinical rejection and early changes of CAN. Least nephrotoxic and steroid sparing immunosuppressive regimens are the way forward in preservation of renal function in long-term.

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