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# Determinants of Long-Term Graft and Patient Survival after Transplantation of Kidney and Liver

*Harald Schrem, Stefan Schütze, Thomas Becker, Rainer Lück, Björn Nashan, and Jürgen Klempnauer*

Chronic graft dysfunction leads to reduced allograft survival and is associated with reduced life expectancy after liver and kidney transplantation. Chronic rejection of the allograft, recurrence of the underlying disease in the graft, ischemia/reperfusion injury of the graft, cytomegalovirus (CMV) infection, CMV disease after transplantation, and factors associated with the organ donor have an impact on the development of chronic graft dysfunction and patient survival following kidney and liver grafting. Common side effects of immunosuppressive therapy after transplantation include acknowledged risk factors for deteriorating allograft function, as well as an elevated risk for the development of malignancies and opportunistic infections, whereas lack of compliance to immunosuppression usually leads to graft loss. With improved overall results after kidney and liver transplantation, the comorbidity of the allograft recipient becomes an increasingly important factor for the long-term prognosis after transplantation. Living-related and living-unrelated kidney donations are associated with improved graft and patient survival after renal transplantation. In this article, the authors review the current knowledge about the factors that have been implicated in the pathogenesis of chronic graft dysfunction, as well as allograft and patient survival.

## Introduction

The development of new immunosuppressive agents has led to substantial improvements in the field of solid organ transplantation. Additionally, the refinements in perioperative care, surgical technique, and patient selection, along with improved understanding of the underlying diseases, have improved results after transplantation. Chronic graft dysfunction still represents the major obstacle to long-term allograft survival. Since the precise mechanisms leading to chronic rejection are still unclear, chronic allograft dysfunction and chronic rejection are frequently used as synonyms.<sup>1</sup> Today, it is generally agreed upon that immunologic and nonimmunologic factors contribute to the gradual deterioration of graft function, including HLA-mismatching, ischemia/reperfusion injury, organ quality and function before transplantation,

and conditions associated with the brain death of the donor.<sup>1-4</sup> Chronic rejection regularly leads to the histological lesion characterized by vascular and interstitial fibrosis.<sup>5</sup> Chronic rejection has been associated with accelerated cell senescence in the graft, which is thought to be the consequence of nonimmune and immune interactions.<sup>3</sup> Other hypotheses on the pathogenesis of chronic rejection include the immunolymphatic theory, the cytokine excess theory, and the loss of supporting architecture theory.<sup>6</sup>

After liver and kidney transplantations, the recurrence of the underlying disease in the graft accounts for many cases of chronic allograft dysfunction.<sup>7,8</sup> Although graft loss after liver transplantation due to acute or chronic rejection has emerged as a rarity,<sup>2,8</sup> it still accounts for 25% to 30% of all isolated graft losses within 10 years after kidney transplantation.<sup>9</sup>

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Whereas renal allograft failure leads to a long-term decrease in life expectancy, liver allograft failure is an immediately life-threatening condition with a short-term need for hepatic retransplantation.

Factors independent of allograft function that influence long-term survival after solid organ transplantation include the increased incidence of malignancies and opportunistic infections after transplantation due to immunosuppression. We exclude these factors in this review. Here, we discuss our current understanding of the determinants for long-term graft and associated patient survival after kidney and liver transplantation.

### Chronic Rejection after Liver Transplantation

After liver transplantation, chronic rejection is characterized histologically by the presence of biliary epithelial atrophy or pyknosis, involving the majority of small ducts leading to progressive ductopenia, a decreased number of hepatic arteries, and a lipid-rich vasculopathy with foam cells that may be difficult to diagnose in early phases.<sup>10,11</sup> The incidence of chronic rejection after liver transplantation is declining. Currently, most transplantation centers report rates between 4% and 8%, whereas in earlier series rates between 15% and 20% were frequently reported.<sup>11,12</sup> This decline is probably a result of improved immunosuppressive therapy. Acknowledged risk factors for chronic rejection after liver transplantation include selected indications (retransplantation for chronic rejection, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis), as well as cytomegalovirus infection and low levels of immune suppression.<sup>11,12</sup> In contrast to the kidney, the liver can be perceived as an immunologically privileged organ since the liver displays a relative resistance to antibody-mediated injury, low frequency of chronic rejection, relatively easy reversibility of acute rejection, and even possible reversibility of chronic rejection.<sup>2</sup>

### Chronic Rejection after Kidney Transplantation

Chronic rejection is the most common cause for long-term graft loss after renal transplantation.<sup>13</sup> It is characterized histologically by prominent changes within the glomeruli, or the so-called transplant glomerulopathy. This is recognized in allograft biopsies by increased mesangial expansion, ac-

centuation of the normal glomerular lobularity, and a segmental increase in mesangial cellularity. In other cases, the essential change is a marked atherosclerotic narrowing of renal vascular tree, and the term *chronic vascular rejection* seems more appropriate. Depositions of mucopolysaccharides and hyaluronic acid may cause myxoid degeneration in the vessel wall. Foamy macrophages can be seen infiltrating the intima and the media of the affected arteries. Progressive vascular narrowing leads to patchy interstitial fibrosis and tubular atrophy. Ischemia of the glomerular capillary bed leads to shrinkage and collapse of the capillary tufts. Glomerular and vascular changes can be seen concomitantly.<sup>14</sup>

In the pathogenesis of chronic rejection following kidney transplantation, factors such as hyperlipidemia, hypertension, infection, nephrotoxicity, delayed graft function, diabetes mellitus, inadequate immunosuppression, and reduced nephron dose have been implicated in addition to factors associated with HLA-mismatching.<sup>15</sup>

In a multivariate, risk factor analysis using data from 862 patients from a single center, early and late acute rejection episodes, proteinuria, and elevated serum triglycerides were significant factors for the development of chronic allograft failure after renal transplantation.<sup>13</sup> Hyperlipidemia, nephrotoxicity, hypertension, and decreased glucose tolerance are well-recognized side effects of current immunosuppressive regimens with potential detrimental effects on kidney allograft function.<sup>9</sup>

Acute allograft rejection occurs in 30% to 40% of patients after renal transplantation, leading to acute allograft dysfunction. Although in the majority of patients these episodes are reversible, acute rejection remains a major risk factor for the development of chronic rejection. Prior episodes of acute allograft rejection are associated with decreased allograft survival.<sup>16,17</sup> In a study on 31,600 first cadaveric renal transplants from 217 U.S. centers using the U.S. Renal Data System, it could be demonstrated that the late occurrence of acute allograft rejection after the 1st year portends a worse prognosis for allograft survival. Acute rejection episodes more than 1 year after renal transplantation, in combination with previous acute rejection episodes, also lead to decreased allograft survival in this study.<sup>16</sup> Late episodes of acute rejection more

than 1 year after transplantation either indicate a lack or disruption of immune tolerance to the graft or may be the consequence of noncompliance to the immunosuppressive regime.

### Recurrence of the Underlying Disease after Liver Transplantation

Chronic hepatic dysfunction and acute liver failure due to viral hepatitis represent the most frequent indications for liver transplantation.<sup>8,18</sup> Liver grafting is the only available lifesaving intervention for most of these patients. Reinfection of the graft is still a central problem. In hepatitis B, reinfection frequently leads to cirrhosis, with subsequent dysfunction of the graft. Prophylaxis of HBV reinfection with polyclonal human antibodies against HbsAg alone, or in combination with the nucleoside analogue lamivudine, is effective but costly. Reinfection in hepatitis C is a regular event in all patients and has a far better prognosis than HBV reinfection of the graft. Effective prophylaxis of HCV reinfection has still not been established and requires further studies. After HCV reinfection, the prognosis of allograft survival is negatively affected. If slowly deteriorating graft function occurs after HCV reinfection, early retransplantation is indicated.<sup>18,19</sup>

Since chronic viral hepatitis is a well-acknowledged risk factor for the development of hepatocellular carcinoma (HCC), it is not surprising that those patients with viral hepatitis and HCC proven in the histology of the explanted native liver display a significantly reduced 10-year actuarial survival rate as compared with those with viral hepatitis without HCC.<sup>18</sup>

Tumor recurrence is the major limitation of long-term survival after liver transplantation for HCC or fibrolamellar carcinoma (FLC). In our series, as published by Schlitt et al.<sup>20</sup> in 69 patients who underwent potentially curative liver transplantation for HCC or FLC, 39 patients developed tumor recurrences in a total of 67 locations after a minimum follow-up of 33 months. Most frequent sites for recurrences included liver (62%), lung (56%), and bone (18%).

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent classic indications for liver transplantation with excellent

long-term results.<sup>21</sup> The existence and incidence of recurrences of PBC, PSC, or autoimmune hepatitis after liver transplantation remain a matter of significant controversy.<sup>21,22</sup>

### Recurrence of the Underlying Disease after Kidney Transplantation

Recurrence of the underlying disease in renal transplants is a rare but serious complication leading to a marked deterioration of long-term survival. With the exception of Alport syndrome, polycystic kidney disease, chronic pyelonephritis, and chronic interstitial nephritis, virtually all diseases affecting the native kidney have the potential to recur in the renal transplant. In the majority of patients, recurrence of the underlying disease has only minimal clinical impact. Membranoproliferative glomerulonephritis type II, IgA nephropathy, and focal and segmental glomerulosclerosis more frequently recur in the graft (for review, see ref. 23). In a study on 5000 patients after renal transplantation using the Renal Allograft Disease Registry, Hariharan et al.<sup>7</sup> found a 3.4% recurrence rate of the underlying disease. In these patients, the 5-year actuarial survival rate declined from 67.6% to 39.8%. The highest risk of graft loss is found in patients with recurrent or de novo focal segmental glomerulosclerosis and hemolytic uremic syndrome.

### Cytomegalovirus Disease after Kidney Transplantation

Cytomegalovirus (CMV) is the most frequent single cause of infectious complications after kidney transplantation. This is because CMV, like other herpes viruses, results in a latent infection that may reactivate under immunosuppression. Almost all CMV seropositive recipients reactivate their latent virus after kidney transplantation. However, the clinical manifestations of this infection vary widely, and fewer than 20% of patients actually develop symptoms related to CMV infection.<sup>24</sup> CMV infection without clinical disease, as well as CMV disease, represent prognostic factors for patient and graft survival.<sup>25</sup> Besides its histopathological impact on the kidney allograft, a CMV infection also exerts an indirect effect on long-term graft survival by impairing the ability to adequately treat acute rejection due to the presence of the virus.<sup>26</sup>

#### PYKNOSIS:

A contraction of nuclear contents in the cell to a deep staining irregular mass. It represents a sign of cell death in histology specimens.

Various rat transplantation models have been established that prove an accelerated and enhanced immune response after CMV infection, leading to an increased influx of CD4+ cells and macrophages early after infection with CMV and an increase in glomerular sclerosis and intima proliferation<sup>27</sup> and the development of chronic allograft rejection.<sup>28</sup>

In our population of 1959 patients after kidney transplantation, 411 (21%) developed CMV infection and 220 (11%) had CMV disease, which was severe in 41 (2%). An important factor for infection was baseline immunosuppression, indicating that triple therapy with the proliferation inhibitors azathioprine and mycophenolate mofetil (MMF) leads to a significantly higher infection rate in comparison with dual, cyclosporine-based immunosuppression. The cumulative dose of steroids correlated strongly with an increased number of CMV infections and disease, as did the addition of ALG/ATG or OKT3 for the treatment of either steroid-resistant rejection or induction therapy.<sup>29</sup>

### **Cytomegalovirus (CMV) Disease after Liver Transplantation**

Previously, several reports were published that described CMV disease as a risk factor for graft loss and death after orthotopic liver transplantation.<sup>30</sup> Furthermore, an association between CMV infection and chronic rejection after liver transplantation was reported.<sup>31</sup>

### **Living-Related Donation in Kidney Transplantation**

Living-related donor kidney transplants have a higher overall graft survival than cadaver donor transplants, which is in part attributable to obtaining kidneys under optimal conditions from healthy donors. Cadaveric renal transplants, on the other hand, may have experienced injury as a result of inflammatory events associated with the release of cytokines around the time of brain death.<sup>32</sup> Additionally, cadaveric renal transplants regularly experience a significantly longer time of cold ischemia.<sup>33</sup> Five-year patient survival rates are considerably better after transplantation of a kidney from a living related donor (94%) than after cadaveric kidney transplantation (76%).<sup>34</sup> Significantly higher graft survival rates can be expected after transplantation

of kidneys from living related and from living unrelated donors.<sup>35</sup> On the other hand, longer waiting time on dialysis is known to be a risk factor for death-censored graft survival and patient death with functioning graft.<sup>36</sup>

From these studies, one can conclude that living related and living unrelated renal transplantation could become a reasonable tool to decrease the lack of organs and to improve long-term survival of kidney transplant recipients. Clearly, ethical issues and the potential risk to the living donor must be kept in mind. Long-term follow-up investigations of living donors demonstrated that the risk of progressive renal failure, hypertension, and proteinuria was not increased by nephrectomy per se, but other causes were responsible for that in occasional patients.<sup>33</sup>

### **Survival after Liver Transplantation**

An analysis of the biggest single-center series so far, containing 4000 consecutive liver transplants between 1981 and 1998, revealed that the risk of graft failure and death was relatively stable after the 1st year posttransplantation. The overall patient survival for the entire cohort was 59%, whereas the actuarial 18-year survival was 48%. Patient survival was significantly better in children, in female recipients, and in patients transplanted after 1990,<sup>8</sup> possibly due to improved immunosuppression, patient selection, and operative technique. In the Pittsburgh series, age-related causes of graft loss, as well as the recurrence of the underlying disease and malignancies, represented the greatest threats to long-term survival.<sup>8</sup>

### **Impact of Organ Quality on Long-Term Survival in Renal Transplantation**

The criteria used to decide whether to use a given organ are reasonably well established. When relative contraindications exist, the donor is sometimes described as marginal (age over 55 years, non-heart-beating-donor, cold ischemia time > 36 h, hypertension, diabetes). Reports of decreased graft survival in recipients of kidneys from donors with greater or equal to 20% glomerular sclerosis (GS) have led many centers to refuse these donor kidneys. A study by Lu et al.<sup>37</sup> revealed no difference in graft loss compared with kidneys with no GS based on vasculopathy.

Hypertension and diabetes predispose a patient to systemic atherosclerosis with renal involvement. In a study comparing survival rates of affected donors with donor-age-matched controls, transplants from affected donors were at minimally increased risk for primary nonfunction, delayed graft function, and acute rejection, the 3-year survival rate being 71% in affected donors and 75% in controls.<sup>38</sup> The duration of hypertension was an independent risk factor in this study, compared with controls (3-year graft survival rates 75% versus 65%).

The average increase in life expectancy for patients receiving a marginal donor organ, compared with patients wait-listed on dialysis, appears to be about 5 years.<sup>39</sup> Two-year survival rates of marginal donor kidneys using double renal transplants, compared with the outcome using only 1 marginal organ, were significantly higher (96% versus 73%).<sup>40</sup> After renal transplantation, the long-term mortality rate can be expected to be 48% to 82% lower among transplant recipients compared with patients on dialysis awaiting transplantation.<sup>41</sup> Compared with the alternative of continued hemodialysis until an ideal organ becomes available, the aforementioned facts seem to provide a strong argument for also transplanting marginal organs in selected patients.

In a series of 1849 adult, primary kidney transplants, the patient survival rate 5 years posttransplantation was significantly higher in the group of patients with end-stage renal disease where preemptive transplantation before dialysis had to be instituted ( $n = 385$ ), as compared with the group of patients receiving grafts after dialysis was started ( $n = 1464$ ) (cadaver donors 92.6% versus 76.6%,  $P = 0.001$ ; living donors 93.3% versus 89.5%,  $P = 0.02$ ).<sup>42</sup> Therefore, chronic allograft dysfunction after kidney transplantation with subsequent return to hemodialysis might be associated with an increased long-term mortality, compared with patients without chronic allograft dysfunction.

### Death with Graft Function after Kidney Transplantation

A population-based survival analysis of 86,502 adult U.S. patients with end-stage renal disease transplanted between 1988 and 1997 showed that out of 18,482 deaths 38% ( $n = 7,040$ ) were deaths

with graft function accounting for 42.5% of all graft losses.<sup>43</sup> In this study, the predominant reported cause of death with graft function was cardiovascular disease.

### Conclusion

With improved overall results after kidney and liver transplantation, the comorbidity of the allograft recipient becomes an increasingly important factor for the long-term prognosis after transplantation. Today, it is clear that hypertension, hyperlipidemia, and diabetes mellitus need careful medical attention and treatment, because several lines of evidence indicate that these conditions are associated with decreased allograft and patient survival. Thorough surveillance of the immunosuppressive therapy is crucial to avoid adverse effects of overimmunosuppression, including malignancies, opportunistic infections, nephrotoxicity, hypertension, hyperlipidemia, and decreased glucose tolerance, as well as the adverse effects of underimmunosuppression eventually leading to graft loss in most patients. Further improvements in the long-term prognosis after kidney or liver transplantation may be achieved by new immunosuppressive agents with fewer side effects, whereas the successful induction of immunological tolerance toward the allograft remains the ultimate goal in transplantation medicine. Improvements in our understanding of the pathogenetic mechanisms associated with chronic rejection, or the recurrence of the underlying disease in the allograft, may lead to improved prophylactic and therapeutic concepts in the future and, eventually, better long-term results after kidney and liver transplantation. More effective treatment of CMV disease after transplantation, conditioning of the cadaveric organ donor, and the prevention and/or successful treatment of reperfusion injury are the goals of current research.

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