Chapter 1

Prevention of renal function loss after non-renal solid organ transplantation: How can nephrologists help to keep the kidneys out of the line of fire?

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After solid organ transplantation, be it renal or non-renal, renal function loss is common\textsuperscript{1,2,3,4}. In renal transplantation, chronic renal function deterioration as an important cause of long term graft loss is well recognized\textsuperscript{1}. In this population, studies aimed at elucidating its mechanisms and improving long-term renal allograft prognosis are performed. Whereas in recipients after non-renal solid organ transplantation progressive renal function loss is an important problem as well, the knowledge on renal morbidity in these populations is relatively limited and scattered. Improvements in non-renal solid organ transplantation have led to improved patient and graft survival. The burden of renal morbidity in these populations grows with the increasing number of recipients, and with the increasing number surviving long enough to develop clinically significant renal problems. Therefore, it becomes mandatory to develop renoprotective strategies in these high-risk groups. As failing kidneys after non-renal organ transplantation share many features, such as vascular obliteration with ischemic glomerular collapse and sclerosis, tubular atrophy, and interstitial fibrosis\textsuperscript{5} with chronic renal transplant failure, insights derived from renal transplantation may be useful in this respect\textsuperscript{1}. However, subtle differences have been found at the matrix protein level between kidneys after renal as compared to non-renal transplantation, pointing to some differences in pathogenic mechanisms\textsuperscript{6}. Clearly, insights derived from renal transplantation need to be combined with knowledge on specific risk factors for each particular population in non-renal transplant recipients. The other way round, insights from renal function loss in non-renal transplant recipients may increase our understanding of non-immunological factors in chronic renal transplant failure.

Renal function loss in non-renal as compared to renal transplant recipients

Chronic renal function loss occurs in many patients after initially successful renal transplantation. Multiple risk factors, both related and unrelated to the allograft status of the grafted kidney, have been identified, suggesting a complex and multifactorial pathogenesis\textsuperscript{4}. After renal transplantation, renal function initially improves and later on stabilises in most recipients. Acute deteriorations caused by preservation trauma or acute rejection are clearly related to the allograft status of the kidney. Slowly progressive renal function loss first occurs after months or even years. Although immunological factors are clearly involved, as acute rejection episodes are the strongest predictor for subsequent chronic renal transplant failure\textsuperscript{1}, non-immunological factors such as blood pressure\textsuperscript{7} or cyclosporin toxicity play an important role. In contrast, in heart or lung transplant recipients renal function loss is most prominent the first 6 months after transplantation with stabilisation or slow progression thereafter\textsuperscript{2,5}. So, despite clear differences in the early post-transplant course and the allograft status of the transplanted kidney, long-term renal function loss may be comparable, both clinically and histologically, with involvement of non-immunological factors in both renal
and other solid organ recipients. Identifying the importance and role of these factors in the different transplant recipient populations is the necessary first step for the development of preventive measures.

**Diversity in renal function loss after non-renal solid organ transplantation**

Cyclosporin A and tacrolimus are important causes of both acute and chronic renal function loss after non-renal solid organ transplantation. Despite that all receive cyclosporin A or tacrolimus, the severity and course of renal dysfunction displays great diversity between and within different populations of non-renal transplant recipients. As compared to heart- or lung recipients with 5-10% end-stage renal failure within 5-7 years after transplantation, liver transplant recipients are clearly less at risk. Also, within the groups of heart or lung transplant recipients the individual course of post-transplant renal function ranges from rapid deterioration to long-term stability. This diversity in renal prognosis suggests differences in exposure and susceptibility to nephrotoxic insults, which are related both to the type of organ transplant and individual patient factors.

Differences in immunosuppressive dosing regimens may contribute to differences in renal damage. High cyclosporin levels and exposure early post-transplant, common after heart and lung transplantation and combined with increased susceptibility caused by perioperative instability and the use of extra-corporeal circulation, may be a factor. A recent analysis of factors predicting loss of renal function 1 month after lung transplantation in 83 patients in our centre identified items such as duration of the operation, hypotensive episodes (mean arterial pressure (MAP) <70 mmHg), use of aminoglycoside antibiotics and early post-operative diuresis as important determinants.

Pre-existing renal status could also explain differences in renal function loss after solid organ transplantation. Atherosclerotic vascular disease, present in heart transplant recipients with ischemic heart disease, may predispose to increased renal susceptibility. Among lung transplant recipients, patients with cystic fibrosis have a particularly poor renal prognosis despite normal pre-transplant renal function, which may be related to prior and current exposure to aminoglycoside antibiotics, diabetes mellitus, or to pre-existent renal tubular function disorders or microcalcinosis. In liver transplantation, pre-transplant renal disease related to the hepatic disease may be present. On the other hand, patients with cardiac failure or pulmonary hypertension with severely impaired renal function pre-transplantation, often show renal function improvement following successful heart or lung transplantation. Likewise, successful liver transplantation cures hepatorenal syndrome.
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Less nephrotoxic immunosuppressives may reduce renal morbidity, but until now cyclosporin A or tacrolimus are indispensable to preserve graft function. In the early post-transplantation phase, the nephrotoxicity of these agents may be aggravated by haemodynamic, operation related instability or concomitant use of other nephrotoxic agents. As induction therapy with newer monoclonal agents and addition of mycophenolate mofetil are available, critical reappraisal of the moment of introduction of cyclosporin or tacrolimus and the targeted levels may reduce this early toxicity. During long-term follow up, careful monitoring of trough cyclosporin or tacrolimus levels, withdrawal of these agents or the use of calcium-entry-blockers\textsuperscript{10} are possible tools. Early diagnosis and adequate therapy of cyclosporin-induced hypertension is likely to be important as in native kidney diseases and renal transplantation hypertension is associated with worse renal prognosis\textsuperscript{7}. Whether these potential preventive measures will result in relevant renoprotection in non-renal transplant recipients remains, however, to be investigated.

Monitoring of renal function after solid organ transplantation

Accurate monitoring is a prerequisite for the prevention of renal function loss. After non-renal solid organ transplantation serum creatinine is the usual parameter for renal function during follow up. Its interpretation, however, is subject to the confounding effects of (changes in) muscle mass and tubular creatinine secretion. Following renal and non-renal organ transplantation body composition may change considerably, with increased (greater muscle mass by improved well-being and exercise capacity) or decreased (muscle mass wasting after operation or infections; corticosteroids) creatinine generation. Measurement of creatinine clearance may circumvent some of these problems, but induces inaccuracies by urine collection errors. Moreover, early after transplantation the extent of nephrotoxic damage may be masked by the favourable effects of improved circulatory status in patients with prior heart failure or cor pulmonale, or by correction of hepatorenal syndrome. Long-term renal function monitoring by more sophisticated methods like iothalamate clearance is laborious, demanding on patient compliance and costly. These disadvantages, however, may be outweighed by its accuracy, which provides the possibility to detect small changes in GFR leading to early identification of high risk individuals or subgroups\textsuperscript{11}. Even with sophisticated renal haemodynamic measurements, however, renal function may inadequately reflect changes in the kidney. In a small follow up study after cardiac transplantation repeated renal biopsies showed clear-cut progression of glomerular and interstitial fibrosis while the glomerular filtration rate had stabilised or even improved\textsuperscript{12}. As after renal transplantation, where serial renal biopsies have been found to be a good
predictor of long-term graft failure\textsuperscript{13}, serial renal biopsies in patients after non-renal solid organ transplantation, albeit invasive, may be relevant for our understanding of the pathophysiology and prediction of possible progression or reversibility.

**Conclusion**

Renal dysfunction after non-renal solid organ transplantation is a problem of growing importance. Nephrologists should play an active role in the care and research in these patients as early as the pre- and peri-transplantation phase, less patients may come to nephrological attention only after end-stage renal failure has become inevitable. Expertise from renal transplantation, by virtue of large patient numbers and better documentation of renal structural damage may be turned into benefit for these populations as well. This may help to keep the kidneys out of the line of fire -and the patients out of the dialysis units-, and improve our understanding of chronic graft dysfunction after renal transplantation as well. Improvements in renal risk assessment, monitoring and prevention of renal failure are clearly needed in patients after non-renal transplantation. It will be worth the effort!
References


