IV.2.3 Non-alloimmune factors

Guidelines

A. Whereas immunological mechanisms dominate in the initiation and propagation of the injury that leads to chronic allograft dysfunction and nephropathy, there is circumstantial evidence that non-immunological factors, such as advanced donor age, hyperfiltration, overweight, delayed graft function, heavy proteinuria, smoking, arterial hypertension, hypercholesterolaemia and hypertriglyceridaemia, play a role as aggravating or progression factors. It is recommended to prevent or, if possible, treat all these factors. ([Evidence level B])

B. As arterial hypertension is very frequent among renal transplant patients and associated with increased graft (and patient) loss, it is recommended to aim at a blood pressure less than 130/85 mmHg in renal transplant patients and <125/75 mmHg in recipients with proteinuria $\geq 1$ g day. ([Evidence level A])

Commentary on Guidelines IV.2.3: Non-alloimmune factors

Advanced donor age

The UNOS database shows that kidneys from old donors (\(>60\) years) more often have delayed graft function, and recipients of such kidneys more often require post-operative dialysis and treatment for acute rejection episodes compared with recipients who received a kidney from a young donor. Also, the discharge serum creatinine concentration of recipients who received an old donor kidney is often greater than that of patients who received a kidney from a young donor [1,2]. Moreover, there is a 25% improved 5-year graft survival and a corresponding longer half-life of young donor kidneys compared with old donor kidneys [1]. Finally, a recent UNOS analysis identified donor age as the factor that determines 30–50% of the variability in long-term graft outcome [3].

Similar adverse outcomes of old donor kidneys have been reported in other studies [4]. Moreso et al. observed increased loss of old donor kidneys if such grafts had undergone delayed graft function or acute rejection episodes [5]. In a time-dependent analysis of risk factors, a study from Edmonton found that after 5 years, donor age alone was associated with increased graft loss [6]. In a study from Leiden, an increased prevalence of acute interstitial rejection episodes was found in the first 3 months post-transplant, with an increased rate of graft loss between years 1 and 5 in grafts that had been exposed to an acute rejection episode [7]. These data are consistent with the hypothesis that kidneys from old donors are more immunogenic than kidneys from young donors and that the increased rate of graft loss results from an inability of old donor kidneys to mount an adequate tissue restoration response after an interstitial rejection episode.

Hyperfiltration/overweight

Hyperfiltration and glomerular hypertension occur in remnant kidneys in rats, and it has been proposed that these changes account for the progressive nature of renal failure once a critical amount of renal mass has been lost. It is not certain whether such changes occur in man. It has been argued that focal glomerulosclerosis, the histopathological hallmark of glomerular hyperfiltration and hypertension, is not a prominent feature of human chronic allograft nephropathy [8]. However, several clinical observations suggest that an imbalance between recipient metabolic demands and graft renal mass explains, in part, chronic allograft nephropathy. The 3-year graft survival rates of transplants that come from female, black, very young or old donors (\(\geq 60\) years) are lower compared with grafts from donors who are supposedly endowed with a larger nephron mass [9]. Unfortunately, studies that have examined more directly the relationship between nephron mass, recipient metabolic needs and long-term outcome have been inconsistent, in part because of difficulties in measuring nephron mass. Although there is consensus that recipient overweight and obesity are associated with shortened graft survival [10–12], it is not clear whether this results from glomerular hyperfiltration and hypertension, inadequacies of immunosuppressive medication or some other as yet unidentified mechanism.

Glomerular hyperfiltration seems to occur, but it is unknown whether this is associated with glomerular hypertension [13,14]. These observations, together with experimental evidence [15–18], strongly suggest that glomerular hyperfiltration plays a modulating role in chronic allograft nephropathy, perhaps in the subgroup of patients with transplant glomerulopathy [19].

Delayed graft function

There is controversy regarding the impact of delayed graft function on long-term outcome. In the UNOS registry, delayed graft function, defined as the need
for dialysis in the first week after transplantation, had a significant and independent impact on the graft half-life. This effect was distinct from cold ischaemia time, acute rejection episodes, old donor age and serum creatinine [20,21]. Others also found a detrimental effect of delayed graft function on long-term outcome [22,23]. However, using the time required to reach a renal clearance of >10 ml/min, other investigators found that only delayed graft function lasting for more than 6 days had a deleterious effect on graft survival, whereas delayed graft function of shorter duration had no effect [24]. In another single-centre study, delayed graft function was defined by stringent functional criteria and was found to be one of the risk factors for acute rejection episodes and suboptimal function at 1 year, but it was not associated independently with an increased rate of graft loss [25]. Risk factors for delayed graft function include pre-transplantation low blood pressure in recipients, a female kidney to a male recipient, donor age of >50 years, cold ischaemia time of >28 h and peak panel-reactive antibodies of >50% [25]. Pre-transplant dialysis modalities also play a role in the occurrence of delayed graft function (see Part 1, pp. 59–60 and 69–70). Delayed graft function is a predictor of tubulointerstitial damage, fibrosis and widening of the tubulointerstitial space 3–4 months post-transplant [26,27].

It is recommended to take all pre- and peri-transplant measures to avoid or reduce delayed graft function in order to achieve optimal long-term function.

Heavy proteinuria

Proteinuria correlates with chronic allograft nephropathy [28–30] and it affects the slope of decline of renal function with time [31]. The pathogenetic role of heavy proteinuria (>1 g/24 h) in the progression of non-transplant renal diseases has been well documented [32], and treatment modalities that lower the protein excretion rate have a favourable effect on the rate of progression of the disease [33]. In renal transplant patients, there is evidence that ACE inhibitors or angiotensin II receptor blockers decrease the urinary protein excretion loss and preserve the GFR [34,35]. Although lowering of the intraglomerular hydrostatic pressure in general may lower the urinary protein excretion rate, ACE inhibitors or angiotensin II receptor blockers may have a maximal anti-proteinuric effect. Concerns regarding the use of this class of drugs in renal transplant patients have been expressed. It is mandatory, therefore, to monitor renal function and serum electrolytes during the first weeks of treatment [36].

Smoking

Cigarette smoking increases the risk of cancer, cardiovascular and lung diseases. It also exerts an adverse effect on renal function [37]. Smoking causes intense sympathetic excitation, increases the concentration of circulating catecholamines and increases the blood pressure and pulse rate. In the kidney, this results in a decrease in GFR and filtration fraction [38]. Compared with non-smokers, chronic smokers have a normal glomerular filtration rate but a significant reduction in renal plasma filtration rate [39], resulting in an increase in the filtration fraction.

Strong biostatistical evidence links smoking to accelerated progression of renal failure in various forms of renal diseases [38]. In renal transplant patients, smoking is also associated with an increased graft failure rate [30,40] and atherosclerotic vessel wall disease [41]. In the Leiden experience, smoking at the time of transplantation was associated with a 55% greater risk of graft failure (relative risk 1.55; 95% confidence interval 1.00–2.39; P = 0.05) [30].

In a study from Minneapolis, it was shown that smoking more than 25 pack-years (one pack-year is one pack/day/year) at transplantation was associated with a 30% higher risk of graft failure and a higher mortality rate. Having quit smoking more than 5 years before transplantation reduced the relative risk by 34%. Most of the adverse effects of smoking on graft survival in this study seemed to be due to its effects on mortality, as smoking had no effect on the number of patients returning to dialysis [40]. However, it was found that cigarette smoking at the time of transplantation increases the risk of late graft loss [30]. Similarly, a retrospective study by Opelz suggests that smoking adversely affects late graft function, even if corrections are made for cardiovascular deaths [38]. It is recommended to give up smoking (see also Guideline IV.5.6).

Arterial hypertension

In patients with chronic renal disease, the importance of blood pressure control on the renal function prognosis has been documented extensively [42]. This relationship is causal, since lowering of the blood pressure using anti-hypertensive medication reduces the rate of functional decline [43]. There is no doubt that blood pressure control is of prime importance, but the question has been raised whether one class of anti-hypertensive drugs provides better protection of the kidney than another. ACE inhibitors are likely to confer tissue protection, especially under proteinuric conditions [32]. In renal transplant patients, an increased diastolic [44] or systolic blood pressure has also been associated with an increased risk of graft failure.

In a study comparing the calcium channel blocker amlodipine and the angiotensin receptor blocker, losartan, both treatments controlled the blood pressure to a similar degree, but amlodipine increased the GFR through an increase in the estimated glomerular hydrostatic pressure and filtration fraction. In contrast, losartan maintained the GFR and reduced the estimated glomerular hydrostatic pressure and filtration fraction significantly. Amlodipine did not affect
transforming growth factor (TGF)-β1 concentrations, but losartan reduced the plasma TGF-β1 by ~50% and the majority of the patients reached normal levels of TGF-β1. Endothelin-1 concentrations were also significantly higher during amlodipine compared with losartan treatment [45]. Experimental studies also favour the use of ACE inhibitors in chronic allograft rejection [15,17].

It is recommended that all transplant patients have their blood pressure taken at regular intervals. The National Kidney Foundation Task Force on cardiovascular disease recommends that the blood pressure of patients without proteinuria should be ≤130/85 mmHg for renal transplant patients without proteinuria and ≤125/75 mmHg for proteinuric patients [46]. The use of ACE inhibitors or angiotensin II receptor antagonists in renal transplant patients has been reported [34,35]. As in the non-transplant situation, reduction of the proteinuria was associated with preservation of renal function [34].

It is mandatory to monitor renal function and serum electrolytes during the first weeks of treatment with an ACE inhibitor. In the case of severe hypertension or hypertension resistant to drugs, native kidney nephrectomy should be considered.

**Hyperlipidaemia**

Many studies have reported associations between pre- or post-transplant serum cholesterol and chronic allograft nephropathy [47–49], but it has not been possible to dissociate the predictive value of total serum cholesterol from other predictors of chronic allograft nephropathy. In a large study using a multivariate analysis of multiple post-transplant risk factors, it was found that serum triglycerides were most closely associated with chronic allograft dysfunction [28]. A study from Brussels found no impact of hypercholesterolaemia on 10-year graft loss in patients free of acute rejection at 1 year, while it had a significant effect on graft loss in patients who had experienced acute rejection episodes [50]. In a recent study from Rotterdam, it was shown that serum cholesterol is an independent risk factor for patient and graft survival and the overall graft failure rate. However, the effect is non-linear and the risks are largest in young recipients. The risk of cholesterol-associated death-censored graft failure is highest in patients with a low creatinine level [51].

In a study of protocol biopsies, pre-existing donor damage, cold ischaemia times, plasma cyclosporine and acute rejection episodes were associated with chronic tubulo-interstitial damage, whereas the only predictor of renal transplant vascular disease was total serum cholesterol [52]. In a follow-up study, it was confirmed that post-transplant hypercholesterolaemia contributes to the development of transplant vasculopathy in the kidney [27].

A prospective randomized open-label trial in renal transplant patients has shown that pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, lowers total cholesterol, LDL and triglyceride levels. In addition, there is some evidence that this drug may have beneficial effects independent of cholesterol reduction. Pravastatin reduced the incidence of acute kidney graft rejection [53], which could relate to the ability of statins to repress the induction of interferon-γ-induced MHC class II induction [54]. Moreover, lovastatin and simvastatin inhibit the interactions between leucocyte function-associated antigen type 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) by binding to a specific recognition site on LFA-1, independently of HMG-CoA reductase activity [55]. Recently, a multi-centre placebo-controlled study, including simvastatin in one arm, failed to demonstrate any effect of simvastatin on acute renal allograft rejection [56]. In another randomized, double-blind and adequately powered study, it was shown that fluvastatin has no effect on the incidence or severity of acute rejection following renal transplantation [57]. No data are available on the efficacy of these drugs on long-term outcome, although the beneficial effect of lipid-lowering drugs on cardiovascular events have been well established in non-renal patients and heart transplant patients with hypercholesterolaemia [58].

It is recommended to treat hyperlipidaemia as outlined in Guideline IV.5.3. Treatment includes exercise, dietary therapy, modification of the immunosuppressive protocol and lipid-lowering agents, especially HMG-CoA reductase inhibitors [59,60].

**References**

SECTION IV: Long-term management of the transplant recipient


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SECTION IV: Long-term management of the transplant recipient

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