New-onset diabetes after transplantation—should it be a factor in choosing an immunosuppressant regimen for kidney transplant recipients?

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The capacity to prevent acute rejection has been paramount in the minds of most clinicians in selecting an immunosuppressive strategy for kidney transplant recipients. This was certainly reasonable during the 1970s, 1980s and 1990s, as acute rejection was a common cause of graft loss. As efficacy improved over that period of time, rates of acute rejection fell and 1-year graft survival surpassed 90%. Although rates of graft loss beyond the first year remained unchanged, the reductions in early graft loss produced equal improvements in 5- and 10-year graft survival [1].

Since the 1990s, rates of acute rejection have continued to fall; however, this has not been associated with further improvements in short- or long-term graft survival [2,3]. One reason is that acute rejection is no longer a major contributor to graft loss, causing graft loss in only 4% of recipients in the first 10 years after transplantation in one registry analysis [4]. Another reason is that our immunosuppressive regimens inadequately address the causes of graft loss beyond the first year.

The key causes of graft loss beyond the first year after transplantation are death with a functioning graft and chronic allograft dysfunction [4]. In a bid to improve graft and patient outcomes, our attention should therefore shift more towards the prevention and management of factors that contribute to these two outcomes. Causes of death include cardiovascular events, cancer and infections. Contributors to chronic allograft dysfunction include calcineurin inhibitor toxicity, ongoing chronic rejection, hypertension, and recurrent and de novo diseases such as glomerulonephritis and diabetes [5].

New-onset diabetes after transplantation (NODAT) is common. Registry-based studies undertaken in the USA, using prescription records to indicate the onset of diabetes, reported rates ~20% at 1-year post-transplant [6], significantly higher than had been reported in randomized controlled trials [7], suggesting under-reporting in the trials or a higher rate of diabetes among patients excluded from such trials. The DIRECT trial prospectively examined patients randomized to receive either tacrolimus- or cyclosporine-based immunosuppression and, with the use of oral glucose tolerance testing (OGTT) and WHO criteria, demonstrated an incidence of NODAT of 20% for the entire study population [8]. Consistent with previous data [6], the primary endpoint of NODAT or impaired fasting glucose (26% versus 34%) and the incidence of NODAT requiring treatment (8.9% versus 16.8%) were both significantly more common in the tacrolimus group [8]. Similar findings have been reported in a French, multicentre, observational study where tacrolimus was associated with a higher incidence of NODAT than cyclosporine micro-emulsion by multivariate analysis with an odds ratio of 3.0 [9].

NODAT is caused by the combination of insulin resistance and deficient insulin production [10]. Risk factors for the development of NODAT are numerous [6]. Several risk factors are not modifiable, including age, ethnicity, family history of type-2 diabetes and HCV infection. Key modifiable risk factors include obesity and choice of immunosuppressive regimen, particularly steroid exposure and use of tacrolimus [10].

NODAT places patients at increased risk of the key causes of premature graft failure—death with function and chronic allograft dysfunction [6]. Several studies have documented that NODAT, whether defined by requirement for treatment [11] or by screening with a post-transplant OGTT [12], is an independent predictor of major cardiovascular events after transplantation. The magnitude of risk is similar to that experienced by patients who are diagnosed with diabetes prior to transplant [12]. Although less well documented, NODAT is also a likely contributor to chronic allograft dysfunction [5]. Thus, NODAT is a contributor to the major causes of graft loss today.

The natural history and optimal management of NODAT remain unclear. The best available data suggest that the disorder is not a temporary aberration restricted to the
early post-transplant phase driven by steroid exposure but is a life-long problem for the majority of those diagnosed [13]. Management options, including insulin, oral hypoglycaemic agents, diet and exercise, are all useful for glycaemic control, although randomized controlled trials examining the efficacy of these different approaches in NODAT are lacking. Steroid dose reduction may lead to some improvement in glycaemic control; however, complete withdrawal appears to provide no significant metabolic benefits over low-dose maintenance of 5 mg/day of prednisolone [14] and may incur an increased risk of graft loss [15]. Tacrolimus withdrawal may lead to improved glucose tolerance [16]; however, substitution with rapamycin does not [17]. Switching from tacrolimus to cyclosporine has been reported to lead to resolution of NODAT in a significant minority of patients and better glycaemic control overall in two single-centre studies of kidney [18] and liver [19] transplant recipients. What is likely to be of most benefit, however, is prevention.

Choice of immunosuppressive strategy may be an effective means of preventing the development of NODAT, thereby improving graft survival rates through a reduction in death with function and chronic allograft dysfunction. The two agents most strongly associated with NODAT are steroids and tacrolimus [6,8,9]. Steroids dose dependently increase peripheral insulin resistance [9]. Steroid avoidance and minimization strategies are widely reported; however, published randomized controlled data are sparse and in general demonstrate modest reductions in metabolic complication rates, including NODAT, but higher rates of acute rejection (reviewed in 20). Thus, steroid avoidance or minimization appears to be suitable only for selected cases at low immunological risk. Tacrolimus and cyclosporine both cause insulin resistance; however, tacrolimus is a far more potent inhibitor of insulin production [21]. Consistent with this, a meta-analysis of randomized controlled trials of cyclosporine versus tacrolimus after renal transplantation found a higher incidence of diabetes among those treated with tacrolimus [7], suggesting that the use of cyclosporine rather than tacrolimus may be an effective strategy to prevent NODAT.

The DIRECT study tested this hypothesis directly and found a significantly lower incidence of NODAT and impaired fasting glucose in cyclosporine- versus tacrolimus-treated subjects (26.0% versus 33.6%; \( P = 0.046 \)) [8]. Treated diabetes was also significantly lower in the cyclosporine group (8.9% versus 16.8%; \( P = 0.005 \)). In contrast to previous studies [7], the use of cyclosporine in the DIRECT study was associated with a non-significant increase in the incidence of acute rejection as compared to tacrolimus, possibly due to the use of C2 monitoring [8]. The rate of acute rejection was much lower than has been seen with steroid avoidance [20].

In conclusion, NODAT affects \( \sim 20\% \) of kidney transplant recipients who receive calcineurin-based immunosuppression, with those receiving tacrolimus more frequently affected than those receiving cyclosporine. Patients who develop NODAT incur increased risks of morbidity and mortality. The use of cyclosporine rather than tacrolimus will decrease a patient’s risk of developing NODAT, and whilst the potential long-term benefits of this strategy are yet to be demonstrated, risk of NODAT should be a factor in selecting an immunosuppressive strategy for kidney transplant recipients.

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References


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