Role of anaemia in cardiovascular mortality and morbidity in transplant patients

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Abstract
Cardiovascular complications are a major cause of morbidity and the leading cause of mortality in renal transplant recipients. Multiple cardiovascular risk factors are often present before transplantation. Prior ischaemic heart disease, cerebrovascular disease and peripheral vascular disease predict post-transplantation mortality, as do older age, diabetes mellitus, smoking and length of time on dialysis. After transplantation, immunosuppressive agents and/or graft dysfunction may increase cardiovascular risk by causing hypertension, hyperlipidaemia and diabetes mellitus or glucose intolerance. Graft dysfunction may also contribute to cardiovascular risk by causing anaemia or hyperhomocysteinaemia. To assess the relative importance of potential cardiovascular risk factors in renal transplant recipients, a retrospective analysis has been performed on data from 911 patients at the Ospedale Maggiore, Milan, Italy. Preliminary findings confirm that cardiovascular complications are the leading cause of death in renal transplant recipients, accounting for 32% of all deaths. Other major factors predicting post-transplantation cardiovascular events include pre-transplant cardiovascular events, age, smoking, diabetes mellitus (often acquired after transplantation) and hypertension. Careful selection and adequate preparation of patients in addition to appropriate treatment of cardiovascular risk factors are needed before transplantation to reduce the risk of post-transplantation cardiovascular events. After transplantation, appropriate treatment of diabetes, hypertension and hyperlipidaemia, as well as avoidance of smoking, obesity and physical inactivity may reduce the risk of cardiovascular complications further.

Keywords: anaemia; cardiovascular diseases; diabetes; hyperlipidaemia; hypertension; renal transplantation

Introduction
Cardiovascular disease is a major problem in patients with renal failure, a problem that does not end with transplantation. Although renal transplant patients are less likely to die of cardiovascular causes than those on dialysis, they still show cardiovascular morbidity and mortality far in excess of the general population. Indeed, cardiovascular disease remains the leading cause of death in renal transplant recipients.

For example, the US Renal Data System [1] reported in 1999 that cardiovascular causes (cardiac arrest, acute myocardial infarction, other cardiac disease and cerebrovascular disease) accounted for 16–36% of deaths among transplant recipients, depending on age. The risk of death from cardiovascular complications was 3.8 per 1000 patient-years for renal transplant recipients aged 20–44 years, rising to 10.4 per 1000 patient-years for patients aged 45–64 years. Diabetic renal transplant recipients had a substantially greater risk of dying from cardiovascular causes than non-diabetic patients.

Both pre- and post-transplantation factors account for the continuing high levels of cardiovascular disease in renal transplant recipients.

Pre-transplantation risk factors
In many cases, multiple cardiovascular risk factors are already present before transplantation in patients with renal failure. A retrospective analysis in the USA found that age, male sex and cigarette smoking before transplantation increased the risk of cardiovascular complications after transplantation [2]. The presence of ischaemic heart disease, cerebrovascular disease or peripheral vascular disease before transplantation also predicted a higher post-transplantation cardiovascular
risk. A more recent multivariate analysis found that age, diabetes mellitus, smoking and time on dialysis were strongly associated with the risk of death after transplantation [3].

**Post-transplantation risk factors**

After transplantation, additional influences come into play, especially immunosuppressive drug treatment, graft function and lifestyle factors. Different immunosuppressive drugs differ in their potential to act as cardiovascular risk factors. Corticosteroids and cyclosporin are known to increase the risk of diabetes mellitus, hyperlipidaemia and hypertension [4]. Tacrolimus appears to be more diabetogenic [5] than cyclosporin, but carries a lower risk of hyperlipidaemia and hypertension [6]. Rapamycin is not associated with diabetes mellitus or hypertension, but increases the risk of hyperlipidaemia [7]. Currently, there is no evidence to show that mycophenolate mofetil and azathioprine have an effect on those risk factors.

Lifestyle factors are important contributors to cardiovascular risk in post-transplantation patients (as they are in pre-transplantation patients and the general population). The most important modifiable risk factors are smoking, diet, obesity and lack of physical activity. Every effort should be made to help post-transplantation patients change their lifestyle to reduce their cardiovascular risk.

Graft dysfunction is another potentially important contributor to cardiovascular risk. A poorly functioning graft may be associated with hypertension, hyperlipidaemia, diabetes mellitus or glucose intolerance, all of which contribute to cardiovascular risk. Graft dysfunction may also be associated with hyperhomocystinaemia, which is an independent risk factor for cardiovascular disease in the general population [8].

A nested case-control study of 42 renal transplant recipients found that their mean serum homocysteine concentrations were significantly higher than those of the 35 control subjects [9].

A recent multivariate analysis [10] examined the association between atherosclerotic events and homocysteine concentrations in 207 stable renal transplant recipients. Of these patients, 70% were hyperhomocysteinaemic (total homocysteine >15 μmol/l). For each increase of 1 μmol/l in total homocysteine, there was a 6% increase in the risk of developing cardiovascular complications. Age and creatinine concentration were also independent risk factors for cardiovascular events; an increase of serum creatinine of 50 μmol/l increased the risk by 34%. Despite these intriguing findings, homocysteine levels may not be a true risk factor for cardiovascular disease in renal transplant recipients, but simply a benign consequence of renal dysfunction [11].

Graft dysfunction may also result in anaemia, which can contribute to cardiovascular risk in renal transplant recipients. Generally, haemoglobin levels increase after transplantation, but anaemia can persist in patients with a suboptimal functioning graft due to previous rejections, chronic transplant nephropathy or donor-related factors. Anaemia may therefore occur even in the presence of a functioning transplant.

In patients on dialysis, anaemia is linked to the development of left ventricular hypertrophy, and is believed to be a major contributor to cardiovascular risk [12,13]. The same may be true in post-transplant patients. In pre-transplant patients, observational studies and clinical trials indicate that early treatment of anaemia of renal failure with recombinant human erythropoietin (r-HuEPO, epoetin) improves left ventricular structure and function, increases cardiac output and improves quality of life [14,15]. Therefore, the cardiovascular effects of treating anaemia in post-transplant patients also require evaluation.

**Cardiovascular morbidity and mortality in renal transplant patients: an observational study**

Further data clearly are needed on cardiovascular outcomes after renal transplantation, so that the principal modifiable risk factors can be identified and addressed. With this in mind, a retrospective analysis has been performed on a large series of renal transplant patients treated at the Ospedale Maggiore, Milan, Italy. The objectives of the study were to document long-term outcomes in renal transplantation patients, to assess cardiovascular morbidity and mortality and to evaluate the evolution of cardiovascular morbidity after renal transplantation. A brief overview of the methodology and preliminary findings is given here, and the study will be published in full at a later date.

**Subjects and methods**

The study analysed data from 911 patients who received renal transplants at the Ospedale Maggiore, Milan, Italy between 1983 and 1999. Recipients of both living (n = 156) and cadaveric transplants (n = 775) were included. Patients were required to be at least 15 years of age, with a renal allograft functioning for at least 1 year. Patients who received combined organ transplants (i.e. pancreas and kidney or liver and kidney) were excluded.

**Demographic data**

The mean age of patients who received a cadaveric renal transplant was 40 years, compared with 32 years in patients who received kidneys from living donors. Around two-thirds (62%) of the patients were men. The mean duration of dialysis before transplantation was 40 months for both men and women. The most common cause of renal failure was chronic glomerulonephritis (44.1%). A further 10.1% had polycystic kidney disease, 8.9% urological disease, 7.5% congenital kidney disease, 4.5% systemic disease and 0.8% diabetic renal disease. Undetermined and other causes accounted for the remaining patients.
Mortality

The study confirms that chances of survival after transplantation are improving. The 5-year patient survival was 97% for patients transplanted between 1994 and 1999, 95% for those transplanted between 1988 and 1993, and 88% for those transplanted between 1983 and 1987.

In the first two time periods examined (between 1983 and 1993), the risk of death following transplantation was markedly greater in patients >50 years of age. However, among patients transplanted between 1994 and 1999 at age >50 years, the 7-year mortality rate was considerably lower, only a little higher than among younger patients (Figure 1).

Any type of pre-transplantation cardiovascular event, particularly cerebrovascular and peripheral vascular events, increased the risk of death after transplantation. The main cause of death was cardiovascular disease (32%), followed by cancer (27.8%), infections (18.1%) and liver disease (12.5%).

Patients with diabetes ($n=60$) died earlier after transplantation than non-diabetic patients ($n=660$) and their overall survival rate was lower. As with the overall population, patients with diabetes transplanted between 1994 and 1999 had a better probability of survival than those transplanted between 1983 or 1987 or between 1988 and 1993 (Figure 2).

Graft survival

Graft survival was better in patients transplanted between 1994 and 1999 than in patients transplanted in the periods 1983–1987 or 1988–1993. Patients >50 years of age transplanted before 1994 were more likely to suffer graft failure than younger patients. However, among the 1994–1999 transplant cohort, graft failure rates were similar in older and younger patients (Figure 3).

Mean serum creatinine levels in patients without graft failure remained at 1.5–2 mg/dl throughout the study. As would be expected, patients who had two or more acute rejections either within or after the first 3 months after transplantation had higher levels of plasma creatinine than patients with no rejections or patients with one rejection. Mean serum creatinine did not vary with the age of the patient.

Cardiovascular data

Before transplantation, 11.1% of patients had experienced cardiac events, 5.0% peripheral vascular events and 1.9% cerebrovascular events. After transplantation, the frequency of cardiovascular events did not change to any great extent. Of these cardiovascular events, ~3.4% were myocardial infarctions, 1.9% angina pectoris, 5.2% arrhythmias (mainly atrial fibrillation), 0.5% congestive heart failure, 4.5% peripheral vascular disease, 1.1% stroke and 0.4% transient ischaemic attack. The majority of patients had only one cardiovascular event. Fewer than 4% of patients had a second event, and fewer than 1% had a third event. The risk of having an event increased with age (Table 1).

Patients who developed diabetes after transplantation had an increased risk of cardiovascular complications, compared with those who did not. In fact, >50% of patients with diabetes had at least one post-transplantation cardiovascular event, as did only 25% of those with polycystic kidney disease.

Smokers (23.3%) had a higher risk of post-transplantation cardiovascular events than non-smokers (15.1%), with an intermediate risk in ex-smokers (20.4%). There was a particularly high
incidence of peripheral vascular disease in patients who continued to smoke after transplantation (9.3%) when compared with non-smokers (3.2%) and ex-smokers (3.5%).

Statins were used at low doses in ~10% of patients. Throughout the study, mean triglyceride levels were towards the upper limit of normal, at ~200 mg/dl. Mean cholesterol levels were also relatively high at 250 mg/dl, and did not change throughout the study. Body mass index was within the normal range for both men and women. Mean arterial pressure was also relatively normal throughout the study at ~102 mmHg, although many patients were receiving antihypertensive therapy.

The following is an analysis of the most recent measurements. Patients without cardiovascular events tended to have lower mean levels of triglycerides (194.7 mg/dl) than those with cardiac (202.0 mg/dl), peripheral vascular (218.5 mg/dl) or cerebrovascular events (209.9 mg/dl). Little difference was seen for serum cholesterol (247.9 mg/dl in patients without

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### Table 1. Cardiovascular events by age of the transplant recipients

<table>
<thead>
<tr>
<th>Age (years)*</th>
<th>% of patients</th>
<th>None (n = 752)</th>
<th>Cardiac (n = 100)</th>
<th>Peripheral vascular (n = 46)</th>
<th>Cerebrovascular (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–29</td>
<td>95.4%</td>
<td>3.3%</td>
<td>1.3%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>80.4%</td>
<td>13.1%</td>
<td>5.5%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>50–69</td>
<td>72.5%</td>
<td>15.7%</td>
<td>7.9%</td>
<td>4.5%</td>
<td></td>
</tr>
</tbody>
</table>

*Age at transplantation.
events, 246.4 mg/dl in those with cardiac events, 251.0 mg/dl in patients with peripheral vascular disease and 262.3 mg/dl in those with cerebrovascular disease). Body mass index did not appear to predict post-transplantation cardiovascular risk. Mean arterial pressure was higher in patients with post-transplantation peripheral vascular events (120.8 mmHg) than in those without such events (101.8 mmHg for patients without events, 103.6 mmHg for those with cardiac events and 104.7 mmHg for those with cerebral events).

**Anaemia in post-transplant patients**

In this study, anaemia was defined as a haemoglobin <13 g/dl for men and <12 g/dl for women. Anaemia was common in post-transplantation patients, but only a few patients developed severe anaemia. The mean haemoglobin level throughout the follow-up period remained at ~13 g/dl, and was not affected by age. Of the patients without cardiovascular events (n = 755), the proportion of anaemic and non-anaemic patients was 50.1 and 49.9%, respectively. This proportion was also similar among patients who experienced post-transplantation cardiovascular events (n = 105): 45.7% anaemic and 54.3% non-anaemic patients. The prevalence of anaemia among patients who experienced peripheral vascular and cerebrovascular events was relatively low (Figure 4).

**Conclusions**

Preliminary data from this study confirm that cardiovascular complications are the leading cause of death in renal transplant recipients. Many transplant recipients are at risk of cardiovascular disease, because of advanced age, smoking, previous long-term dialysis or diabetes. Careful selection and adequate preparation of the patients are needed before transplantation to reduce the risk of post-transplantation cardiovascular events.

A careful work-up to identify cardiovascular risk factors is needed before admitting a patient to a transplant programme. Echocardiography and coronary angiography should be performed where appropriate. Investigations should be coupled with interventions to modify risk factors wherever possible. Such measures may include correction of hypertension, intensive treatment of diabetes mellitus, smoking cessation and weight reduction. Correction of anaemia is also essential in pre-transplant patients to reduce the risk of left ventricular hypertrophy. After transplantation, reduced corticosteroid therapy, appropriate treatment of hypertension, hyperlipidaemia and diabetes, avoidance of smoking and regular physical activity may also reduce the risk of cardiovascular disease.

There was no clear indication from this relatively small series of patients (including only 105 with cardiovascular events) that mild to moderate anaemia plays an important role in cardiovascular morbidity and mortality after transplantation. Further studies with larger numbers of patients are required to investigate this question. Several such studies are ongoing, including the TRansplant European Survey on Anaemia Management (TRESAM). These larger series of data will help to establish the key causes of cardiovascular morbidity and mortality among renal transplant recipients. Armed with such data, it may then be possible to devise strategies for reducing the burden of
cardiovascular morbidity and mortality in patients scheduled for transplantation.

References