Cardiovascular complications in renal transplantation

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Introduction

Cardiovascular disease (CVD) is the leading cause of death following renal transplantation. Its frequency varies as a consequence of such factors as age and the prevalence of CVD in the general population. However, its prevalence is around five times higher than in the general population according to an ERA–EDTA Registry analysis [1]. There are four main categories of CVD, namely, coronary artery disease, cerebrovascular and peripheral vascular disease and left ventricular hypertrophy (LVH) of which numerically the first and last are the most important. With regard to mechanisms, atheroma is the main cause of the vascular disease but other factors also contribute such as vascular calcification. The vascular disease is not a consequence of renal transplantation but rather of the patient’s renal failure although it may be aggravated by post-transplant events. The LVH also precedes, rather than follows, the transplant and there is a tendency to amelioration rather than worsening post-transplant [2].

Our growing understanding of the mechanisms of CVD together with the fact that most patients have been under medical supervision for a considerable length of time prior to the transplant, should give rise to the potential for useful preventative measures. This potential has so far been realized for a number of reasons some of which will be referred to later. With regard to the post-transplant treatment of CVD a similar comment applies namely that we often fail to use the available measures. The single most important reason for this unrealized potential is that our attention tends to be focused too much on the renal allograft to the detriment of trying to resolve accompanying co-morbid disease affecting the patient.

Ischaemic heart disease

While cerebrovascular and peripheral vascular disease are important causes of morbidity and mortality, they are overshadowed in scale by ischaemic heart disease (IHD). Atheroma is the main, but not sole, cause of IHD, and in turn is due to a number of factors. Some of these cannot be influenced, in particular older age, male gender, and certain primary renal diseases of which the best example is diabetes mellitus. Of greater importance are the factors which are preventable or reversible. Of these, smoking is the most important. An analysis of 434 transplant patients in our centre showed smokers to have a more than two times increased risk of cardiovascular death when compared with non-smokers with a hazard ratio of 2.2, and P value of <0.001 [3]. Other studies have produced similar figures. The next factor in the likely order of importance is hyperlipidaemia. The typical pattern of hyperlipidaemia found in the general population with IHD has been found as well in some but not all of the studies in renal transplant recipients. Lipid lowering therapy, especially statins, have been shown to improve the lipid profile in renal allograft recipients but proof from prospective studies of a beneficial effect on cardiovascular mortality is not yet available [4]. Until that information is available I would suggest that statins be given to renal transplant patients at high risk of death from IHD but not routinely to all patients.

Hyperhomocysteinaemia has been shown to be an independent cardiovascular risk factor in renal transplant recipients [5]. Although homocysteine blood levels have been reported to fall after renal transplantation, they remain well above those of healthy controls and trials are in progress to determine whether folic acid supplements with the aim of lowering homocysteine levels should be routinely recommended to renal transplant recipients.

Hyperglycaemia is common even in non-diabetic renal transplant patients, the causes including renal dysfunction, steroids, and calcineurin inhibitors. Although the blood glucose can be lowered effectively, mild elevation, while still constituting a risk factor, is frequently ignored. Also, hyperglycaemia is often linked with obesity. While this may also be a cardiovascular risk factor, clear evidence is lacking. Another factor, which in some patients is linked to obesity, is lack of exercise. These two, singly or in combination, probably are important in increasing cardiovascular risk but objective data are very limited. While calorie
restriction and/or exercise training programmes could have a highly effective role in reducing post-transplant CVD, few centres have as yet exploited the potential of this aspect of management.

Increasing attention is being directed to the vascular endothelium which plays a pivotal role in controlling blood vessel tone and linked to this, in preventing the development of atheroma. The mechanism is principally through the production and release of vasoreactive compounds such as nitric oxide [6]. A number of agents, including ACE inhibitors, statins, anti-oxidants, folate and l-arginine, may modulate endothelial function but the exploitation of this approach in preventing atheroma is in its infancy. Another interesting piece in the jigsaw that constitutes the mechanism of atheroma is the role of inflammation. C-reactive protein (CRP) has been used as a marker for inflammation and has been shown to correlate with the presence of early atheroma in pre-dialysis patients [7]. It is likely that the atheroma developing at this earlier stage in the patient’s illness will then progress under the influence of the other factors discussed above to either pre- or post-transplant. The study by Stenvinkel et al. [7] also showed that malnutrition frequently co-exists with the evidence of inflammation and of atheroma as judged by the presence of carotid artery plaques. It has been suggested that oxidation of Lp(a), which is linked to atheroma, is linked also to inflammatory markers. The linkage of these various factors increases the likelihood that anti-oxidants such as vitamin E could have a role in the prevention or amelioration of atheroma [7].

One remaining phenomenon which should be mentioned in the context of vascular damage is calcification. This is common even in young dialysis patients and worsens with increasing time on dialysis. It presumably contributes to vascular insufficiency but its importance vis-à-vis atheroma in this respect has not been fully worked out. Also, the factors causing the calcification require further study although hyperphosphataemia is certainly an important one.

Finally, the presence of advanced coronary artery disease may require the use of a revascularization procedure, either by a surgical approach or angioplasty and stenting. In this context it is important that pre-transplant assessment includes investigation for coronary artery disease and it is preferable that should a revascularization procedure be required, that this be carried out before rather than after the transplant.

Cerebrovascular and peripheral vascular disease

These complications make an important contribution to the morbidity and mortality which comes under the heading of cardiovascular disease. The comments which apply to the mechanisms of coronary artery disease apply also to these complications.

LVH

LVH begins early in the course of chronic renal failure and worsens with time. It is present in around 70% of patients at the time of starting dialysis and is even commoner at the time of transplantation. The main causes of LVH pre-transplant are anaemia, fluid overload, an arterio-venous fistula if it has a high flow rate, and hypertension. Post-transplant the first three of these factors either cease to be relevant or become less important while hypertension will often persist and may worsen. Thus, the degree of post-transplant hypertension is the main determinant of the subsequent course of the LVH.

While LVH tends to be portrayed as the predominant abnormality of cardiac structure and function in uraemia, it is often accompanied by two other phenomena, left ventricular dilatation and systolic dysfunction. The first of these is predominantly a consequence of anaemia and/or fluid overload during the pre-transplant phase although other factors such as myocardial ischaemic and long-standing LVH being the dominant ones.

Post-transplant, there is often improvement in all three types of cardiac abnormality. The most marked benefit has been observed with regard to systolic dysfunction but some improvement has also been observed in the degree of left ventricular dilation and LVH [2]. However, this improvement may not be mirrored by improved life expectancy as was observed in a recent study [8]. It was also found in this study that echocardiography at the time of transplantation provided a useful prognostic marker with respect to subsequent cardiac death. In particular, left ventricular dilation and systolic dysfunction were adverse prognostic features.

Blood pressure

Hypertension is considered to be one of the major contributory factors to the high cardiovascular mortality that is seen in the transplant recipient although direct evidence for this is limited. Also, blood pressure control in this group of patients is often unsatisfactory. A recent study in Glasgow showed that 32% of 634 patients had suboptimal control [9]. While the diastolic level was thought for a long time to be the most important component of the blood pressure, it is now clear that this is not the case. A recent interview of the available evidence suggested that an increased pulse pressure is a more important predictor of cardiovascular mortality [10]. The increased pulse pressure is associated with an increase in stiffness of the arterial wall and this in turn is due to arteriosclerosis which is usually accompanied by but is not synonymous with atheroma. Although the importance of pulse pressure and arterial wall stiffness have been observed in patients with renal failure and with essential
hypertension, their significance can almost certainly be translated to the renal transplant recipient.

In addition to the suboptimal blood pressure control which is commonly seen in renal transplant recipients, one needs to be aware of the mode of action of the different groups of drugs in the light of the need to reduce pulse pressure as well as diastolic pressure. This aim can probably best be achieved by such means as a low sodium intake, exercise, and ACE inhibitors. Calcium antagonists have been shown to be less effective than ACE inhibitors in reducing pulse pressure and beta blockers may increase vessel stiffness [11]. However in practice, the degree of hypertension present often makes it necessary to use two or three drugs in combination.

Conclusions

A reduction in cardiovascular mortality is crucial to the aim of improving the prognosis of the transplant recipient and lessening the incidence of death with a functioning graft. This review has outlined the measures which can be applied to the two main problems, namely atheroma and left ventricular dysfunction. The importance of early intervention, i.e. not only before the transplant but, if possible, before the stage of advanced renal failure cannot be overemphasized. There are now available sufficient effective methods to bring about a considerable reduction in cardiovascular death if they are applied appropriately and in particular at an early enough stage. Finally, one needs to be conscious of the fact that pulse pressure is a more important prognostic factor than diastolic pressure and apply antihypertensive measures accordingly.

References