Accelerated arterial disease in renal transplant recipients

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Introduction

Along with infectious complications, cardiovascular disease is the predominant cause of morbidity and mortality in renal transplant recipients [1,2]. The reasons for this association of arterial disease with renal transplantation are complex and have not been fully elucidated, which makes prevention difficult.

To progress in this field, it is essential to make a clear distinction between the arterial disease affecting the graft itself and the discrete involvement of host arteries, the mechanisms and consequences of these two pathologies being probably different.

Arterial disease of the graft

A specific type of arterial disease has been recognized consistently in all solid organs used in human transplantation (heart, lung, liver, pancreas or kidney) [3]. This so called allovasculopathy often plays an important role in chronic rejection. It is characterized mainly by a diffuse thickening of the arterial intima, leading to small vessel obstruction. The most salient and constant features of intimal allovasculopathy are massive sclerosis, infiltration by lymphocytes and monocytes, profuse formation of foamy cells (whose cytoplasm is studded with lipid vacuoles) and extracellular lipid deposits. The media is also affected, although to a lesser extent. In cardiac grafts, the epicardial segment of the coronary arteries exhibits diffuse atherosclerotic lesions which progress rapidly. Similar lesions are also present in the renal artery of kidney grafts [4], which are responsible for stenoses that may require percutaneous angioplasty or surgery.

The determinants of graft arterial disease have been studied mostly in cardiac transplantation where it is the predominant cause of late graft failure. The first culprit is an immuno-inflammatory reaction. As a still controversial addendum, immunosuppression might enhance this reaction through opportunistic infections by agents with an arterial tropism, such as cytomegalovirus [5].

Other mechanisms may be involved: graft anoxia, haemostatic disorders or lipid metabolism, arterial trauma during transplant surgery (clamping and suturing of renal artery) or pre-existing atherosclerotic patches in graft arteries (especially in coronary arteries).

Most attempts at preventing graft arterial disease have failed. One notable exception has been the protective efficacy of pravastatin (an inhibitor of hydroxymethylglutaryl coenzyme A reductase) against coronary disease after cardiac transplantation, through a decrease in plasma cholesterol and/or in the cytotoxicity of natural killer cells [6]. Nonetheless, it would be premature to extend this relative success to the prevention of allovasculopathy involving arteries other than the coronaries.

An essential feature of graft arterial disease is that it only affects graft arteries and spares the host arteries.

Diffuse arterial disease of renal transplant recipients

The incidence of cardiovascular diseases (coronary heart disease, lower limb arterial disease, strokes) is about four times greater in renal transplant recipients than in the general population [1].

One explanation could be that an allograft of any solid organ may induce arterial disease in general, and atherosclerosis in particular. The link would be either direct, through the immune reaction triggered by the graft, or indirect through the immunosuppressive treatments necessitated by transplantation. However, such a view is not tenable because the association with host arterial disease has been established only in renal transplantation and does not exist in cardiac transplantation.

Therefore, there must be another explanation: the disease that initially called for renal transplantation was the real cause of systemic arterial disease; chronic renal failure, although cured by grafting, leads to irreversible arterial damage which continues to progress on its own after transplantation. This is strongly supported by Kasiske’s retrospective study [1] involving 403 renal transplant recipients over 10 years (mean follow-up 46 months after transplantation). Pre-existing arterial disease was the most influential predict-
Arterial disease in chronic renal failure remains the key issue

Graft arterial disease is not specific to renal transplantation. It is shared by all solid organs that are eligible for transplantation and depends on mechanisms that have not been entirely clarified. In contrast, systemic arterial disease of the host is specific to renal transplantation and it is broadly similar to arterial disease in chronic renal failure. We submit the following concluding remarks.

Arterial disease in chronic renal failure depends on complex and intricate mechanisms. Beyond the sustained loss of full clearing function which is only partially compensated for by the dialysis techniques available, the cause of renal failure has to be taken into account: diabetes mellitus and hypertension are two major determinants of chronic renal failure, which by themselves strongly promote the development of obstructive arterial disease; plasma lipid abnormalities resulting from the nephrotic syndrome act concurrently [9].

Arterial disease in chronic renal failure cannot be viewed as a mere aggravation of atherosclerosis. The arterial lesions are generally more diffuse and distal than usual atherosclerosis (strictly defined as a focal disease of large- and medium-size arteries, with plaques associating sclerosis and atheromatous lipid deposits). This difference is especially obvious in lower limb arteries, with a predominant involvement of the distal run-off. In addition to classical atherosclerosis, arteriosclerosis (defined as purely obstructive sclerosis with frequent calcification, involving the whole arterial tree) appears to be a key component of arterial disease in chronic renal failure [10]. Arteriosclerosis may result from distinct mechanisms, such as increased glycation of arterial and plasma proteins, initiated by the chronic loss of renal function [11].

Dialysis by itself appears to promote the development of arterial disease [7]. The risk factors involved here, such as the dose of haemodialysis [7] or associated lipid disorders [9], should be carefully identified to develop effective prevention. Alternatively, renal transplantation may have to be performed as early as possible following the onset of chronic renal failure. Nonetheless, the arterial pros and cons of such an aggressive strategy should first be thoroughly assessed and discussed.

References