

Review

Chronic Renal Allograft Dysfunction: Risk Factors, Immunology and Prevention

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Abstract

Introduction: Kidney transplantation is the treatment of choice for patients with end-stage renal disease. Despite great progress in surgical aspects and immunosuppression therapy, long-term graft survival has not been consistent. Chronic allograft dysfunction (CAD) remains a major cause of late grafts failure.

Review: CAD is a generic term of all causes of chronic renal allograft dysfunction associated with fibrosis. It is clinically characterized by a gradual worsening of renal function in the presence of arterial hypertension and low-grade proteinuria. Histological changes of CAD usually precede functional deterioration and include interstitial fibrosis/tubular atrophy accompanied by vascular changes and glomerulosclerosis. Both immunological and non immunological factors can be responsible for CAD. Immunological causes include chronic active antibody-mediated and T cell-mediated rejection. Non immunological factors include brain death in the donor, increasing donor age, ischemia-reperfusion injury, calcineurin inhibitor nephrotoxicity, hypertension, diabetes mellitus, hyperlipidemia, chronic obstruction and chronic viral infections. Even if the contributing factors to CAD can be identified, not all of them can be interrupted prior to and after grafting. Preventive strategies include improvements in medical and surgical strategies to reduce ischemia-reperfusion injury, strategies to minimize acute rejection and strategies aiming for HLA-matched transplants. Additional measures include tight control of blood pressure, proteinuria, lipids and glucose. Antivirus treatment, appropriate diet, weight control, no smoking and good compliance are also suggested in certain settings.

Conclusion: Evidence-based treatment strategies for CAD are lacking, but several prevention and management strategies are recommended in clinical practice.

Keywords: Calcineurin Inhibitor Toxicity; Chronic Rejection; Ischemia-Reperfusion; Transplantation

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Introduction

In the past few years there has been a tremendous improvement in short-term renal allograft survival but no corresponding improvement in the long-term results [1]. The latest statistics from the scientific registry of transplant recipients (SRTR) for 2008 demonstrate graft survival in kidney transplant patients at the first year that approach or exceed 90% [2]. These advances are attributed to progress in surgical and preservation techniques, better use of immunosuppressants and improved tissue typing. Unfortunately, the overall gain in long-term kidney graft survival rate has not been consistent [3].

Chronic allograft dysfunction (CAD) is the leading cause of chronic allograft failure among kidney transplant recipients [4] and has a major economic impact. In the USA, approximately 4700 patients with failed transplants restarted dialysis in 2002, representing about 5% of the total number of patients starting dialysis [5].

Definition and clinical diagnosis

Chronic allograft dysfunction (CAD), previously named chronic allograft nephropathy (CAN), is a multifactorial process associated with progressive fibrosis and tubular atrophy [4]. Through Banff meetings, the definition of chronic allograft nephropathy was eliminated as it was considered as a generic term of all causes of chronic renal allograft dysfunction with fibrosis that inhibited the accurate diagnosis of causative pathologies and the appropriate therapy [6]. In 2003, Banff classification provided a description of morphological changes corresponding to different causes of chronic allograft injury [6]. These histological changes are generally associated with variably reduced renal transplant function, although histological changes usually precede functional deterioration with hyperfiltration in the remaining nephrons [7]. Chronic allograft dysfunction is clinically

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characterized by a gradual worsening of renal function in the presence of arterial hypertension and low-grade proteinuria [8]. Proteinuria usually ranges from 0.4 to 2 g/day but nephrotic proteinuria can be observed in the presence of transplant glomerulopathy [9]. In the ALERT trial of 2102 long-term kidney transplant recipients, renal dysfunction and proteinuria were the two strongest, independent risk factors for future graft loss [10].

Pathology

The most commonly reported pathological changes in progressive graft failure is chronic interstitial fibrosis and tubular atrophy, which is accompanied by vascular changes and glomerulosclerosis [11]. Both immunological and non-immunological factors may cause chronic allograft injury. Underlying pathophysiology can be detected histologically by typical glomerular and vascular lesions in order to assign a presumed etiology in 60% of chronic allograft biopsies [12]. With the recognition of the entity of chronic antibody-mediated rejection and based on new pathologic knowledge, the traditional CAN has been divided into three parts: (1) chronic active antibody-mediated rejection; (2) chronic active T cell-mediated rejection; (3) interstitial fibrosis and tubular atrophy with no evidence of any specific etiology [6]. The diagnosis of chronic rejection is usually reserved for cases in which there is evidence for a significant role of a host immune rejection of the graft, such as the presence of transplant glomerulopathy and graft atherosclerosis [13]. The presence of C4d deposits in the peritubular capillaries also indicates the presence of humoral rejection [14].

Reports of cyclosporine A (CsA) and tacrolimus (Tac) nephrotoxicity are increasingly common late after transplantation [15]. CsA-induced arteriopathy is characterized by vacuolisation and necrosis of smooth muscle and endothelial cells with hyaline deposits, considered to be the most characteristic marker of CNIs nephrotoxicity [16].

Non-immune chronic graft injury can be also induced by chronic obstruction of the ureter and chronic viral infections [6]. Chronic obstruction is characterized by marked tubular dilation and large Tamm-Horsfall protein casts with extravasation into the interstitium, and/or lymphatic channels. Chronic polyomavirus infection can lead to interstitial fibrosis and tubular atrophy with chronic inflammation and viral intranuclear inclusions [6].

Risk factors

Immune-mediated factors

Acute rejection has been recognized as one of the most important risk factors for chronic rejection [17].

Numerous studies indicated that acute rejection, the time of occurrence, and the number of episodes were all associated with an increased risk of graft loss, but less is known regarding the severity of rejection [18]. Factors contributing to ongoing alloimmune responses include breakdown in immunosuppression as a result of patient non compliance, therapeutic decisions to minimize exposure to complications of immunosuppressive drugs or increased HLA mismatches [18]. The deleterious long-term impact of cytotoxic anti-HLA antibodies that develop after transplantation is another factor supporting immunological involvement in chronic rejection [19].

Non-immune factors

The main non-immunologic factors include brain death in the donor, ischemia-reperfusion injury, calcineurin inhibitor toxicity, hypertension, diabetes mellitus (post-transplant or pre-existing), hyperlipidemia and Cytomegalovirus (CMV) infection [20].

Donor age

Increasing donor age has been linked with an increased risk of CAD [21]. A donor age over 60 years or over 50 years but with vascular comorbidity reduced graft survival [11]. It is now hypothesized that the development of chronic allograft injury may be related to replicative senescence. The senescence hypothesis is based upon cellular exhaustion leading to endothelial and epithelial dysfunction and atrophy and thus persistence of profibrotic stimuli [22].

Donor source

The results observed with living-unrelated donors are better than with cadaveric HLA-matched donors [23]. Donor brain death is an independent factor for graft failure [24] and is associated with an increased risk of acute vascular rejection [25]. Brain death is often associated with severe hypotension, an increase in catecholamines, electrolytes abnormalities and intracranial hypertension that can favor the overproduction of cytokines and growth factors leading to overexpression of alloantigens on tubular and endothelial cells [26].

Delayed graft function and ischemia-reperfusion injury

Delayed graft function is one of the most important independent risk factors for the development of CAD [27]. Ischemia-reperfusion injury can be responsible for delayed graft function and can be associated with late graft dysfunction particularly when it is combined with acute rejection [28]. Tissue ischemia and reperfusion represent a complex interplay between biochemical, cellular, vascular endothelial and tissue-specific factors [29]. Ischemia-reperfusion injury has been shown to

cause endothelial injury with consequent upregulation of adhesion molecules and infiltration of leucocytes and thus create a proinflammatory and profibrotic state within the graft [27].

Donor organ quality and comorbidity

Most donors die from cerebrovascular events, which are frequently caused by underlying hypertension, diabetes and/or atherosclerosis that may also involve the kidney [30]. Donor diabetes mellitus, even lasting more than 10 years, is not necessary an overwhelming risk factor for graft and patient survival [31]. On the other hand, hypertension is a significant independent risk factor for graft survival, especially if it lasts for more than 10 years [32].

Calcineurin inhibitors (CNI) nephrotoxicity

Reports of cyclosporine A and tacrolimus nephrotoxicity are increasingly common late after transplantation [33]. Both cyclosporine and tacrolimus can cause renal and systemic vasoconstriction, through increased release of endothelin-1, activation of the renin-angiotension system, increased production of thromboxane A₂, and decreased production of vasodilators such as nitric oxide and prostacyclin [34]. At renal biopsy, calcineurin inhibitor nephrotoxicity is mainly expressed as progressive arteriolar hyalinosis and downstream glomerulosclerosis [11].

Cytomegalovirus (CMV) infection

CMV-seronegative recipients of seronegative grafts have a 10% higher graft survival rate than those receiving seropositive grafts [18]. CMV disease is frequent after transplantation and determines changes in immune cell function favoring acute rejection [35]. Chronic rejection is also accelerated by CMV infection which is associated with upregulation of TGF β and platelet derived growth factor (PDGF) in endothelial cells and connective tissue growth factor within fibroblasts [36].

Immunology of chronic allograft injury

Chronic allograft injury is an active procedure that is closely related to immunoreactivity [37]. The pathogenesis of chronic allograft injury appears to be a complex network of immunological, metabolic, and hemodynamic changes in renal allograft [38]. There is evidence to show that CD4 + and CD8 + T cells play roles in recipients with chronic allograft injury [37]. In the initial phases of the transplantation procedure, during ischemia-reperfusion injury, CD4 + T cells may be key mediators of the resultant subacute inflammatory response [39]. CD4 + T cells produce a variety of cytokines that result not only in the amplification of the immune response in

other cells but also act in an autocrine fashion as well. Infiltrating inflammatory cells (macrophages, natural killer cells, neutrophils) also promote the process of CAN by secreting a variety of cytokines and growth factors for local damage [39]. Allogeneic differences between donor and host lead to a persistence of graft-infiltrating cells, including T cells, B cells, and macrophages, accompanied by a proliferative response, mediated by chemokines, cytokines, and growth factors [41].

Humoral immunity plays also a role in CAN, the humoral responses can be directed against HLA or non-HLA antigens of the graft [37]. Renal transplant recipients with anti-HLA antibodies were 5 to 6 times more likely to develop chronic rejection and lose their grafts [42]. Peritubular capillary deposition of C4d reflects complement activation via the classical pathway and represents a trace of the remaining alloantibodies [43]. C4d is a suitable marker of acute humoral rejection [44], but it is also documented in late renal allograft biopsies with chronic rejection [43]. The endothelial cells are the first target of alloreaction [37]. Apoptosis of endothelium leads to a series of events that culminate, including mononuclear leucocyte recruitment, vascular smooth muscle cell proliferation, neointima formation, and abnormal vascular remodeling [45]. Emerging evidence suggests that epithelial-to-mesenchymal transition (EMT) is an important event in chronic allograft tubular atrophy/interstitial fibrosis [46]. During the EMT process, the tubular epithelial cells lose the epithelial cell characteristics, gradually acquire mesenchymal cell characteristics and finally transdifferentiate towards fibroblasts, resulting in interstitial fibrosis [37].

Preventive measures

Even if the contributing factors to CAD can be identified, not all of them can be interrupted prior to and after grafting [37]. Improvements in medical and surgical strategies reduced the incidence of delayed graft function which is a key factor for CAD [47]. Most programs strive to minimize acute rejection rates based on the understanding that both clinical and subclinical rejections are major factors for the development of interstitial fibrosis and tubular atrophy [48]. Allocation strategies primarily aim for HLA-matched transplants that have an established superior long-term outcome compared with HLA-mismatched grafts [49].

Additional preventive measures include the pre-transplant identification of sensitized patients and pre-treatment of sensitized recipients, because of the strong association between pre-sensitization and development of CAN or humoral-driven chronic rejection [14]. Various modalities have been used for pre-treatment of sensitized

patients, including either plasmapheresis combined with intravenous immunoglobulins or rituximab [50]. After transplantation, a sufficient level of immunosuppression is definitely required to prevent the onset of acute rejection [37].

Some investigators reported that, in the long term, practically all cyclosporine A-treated transplant patients showed histologic signs of nephrotoxicity, but in spite of this the 10-year kidney graft survival was 95% [15]. Three main protocols have been investigated to prevent toxicity of calcineurin-inhibitors (CNI): CNI minimization, CNI withdrawal and complete avoidance [51]. Reduction and possible withdrawal of CNI with either the addition or continuation of mycophenolate mofetil slowed the rate of loss of renal function in patients with CAN [52]. A CNI-free immunosuppression based on sirolimus, mycophenolate mofetil and steroids appeared to be effective but the available studies have only a short follow-up [53].

Besides optimal immunosuppression, prevention of premature graft failure requires a multifactorial approach aiming at early and tight control of blood pressure, proteinuria, lipids, glucose and weight [54]. Significant reduction in proteinuria has been reported as a beneficial effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists in clinical transplantation [37]. The treatment of hyperlipidemia and hypertension is also warranted to prevent both progressive graft dysfunction and cardiovascular disease [55]. Antivirus treatment, diet, weight control, no smoking and good compliance are also suggested in certain settings [37].

Conclusion

CAD remains one of the major causes of chronic graft loss. The etiology of CAD includes both immune and non-immune causes. To date, evidence-based treatment strategies for CAD are lacking, but several prevention and management strategies are recommended in clinical practice.

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