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Pathogenesis and Preventive Strategies of Chronic Dysfunction of Renal Allograft

Wenqian Huo, Keqin Zhang, Chengguo Ge, Gang Wu, Fengshuo Jin, Gang Yuan and Qiansheng Li
Department of Urology, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, China

1. Introduction

Novel immunosuppressants have decreased the incidence rate of acute rejection significantly, but fail to prevent chronic allograft dysfunction (CAD). Around 40% patients develop CAD gradually in several months or several years after renal transplantation. They present with progressive deterioration of long-term allograft function and allograft failure, and end up with resuming dialysis. It has also been demonstrated that CAD may increase the cardiovascular mortality after renal transplantation. Therefore, it is crucial for promoting long-term allograft survival to investigate the pathogenesis and preventive and therapeutic strategies of CAD. CAD, formerly termed chronic rejection (CR), is also known as late graft loss (LGI) or chronic allograft nephropathy (CAN), since it involves both immune factors (transplantation antigen dependent) and non-immune factors (transplantation antigen independent).

CAD refers to progressive functional impairment of allograft, with pathologic changes including tubular atrophy, interstitial fibrosis, progressive glomerulosclerosis, and arterial fibrous intimal thickening and arteriole hyalinosis. These pathologic changes include immune and non-immune injury to allograft. Chronic rejection is usually associated with acute rejection or subclinical rejection, HLA mismatch, panel reactive antibodies (PRA), and donor specific antibodies (DSA). In contrast, non-immune allograft injury is usually associated with calcineurin inhibitors (CNI), preexisting delayed graft function (DGF), hypertension, hyperlipidemia, proteinuria, viral infection, chronic obstruction and chronic pyelonephritis. In addition, CAD includes recurrent kidney disease, de novo nephritis, posttransplantation lymphoproliferative diseases (PTLD). Many of the above-mentioned factors that lead to CAD usually exist simultaneously; thus, the pathologic manifestations of CAD are complex and not specific, making the treatment of CAD difficult. In short, there are many factors influencing the incidence and development of CAD, and the pathogenesis of CAD remains largely unclear. Microcirculation injury mediated by donor specific antibodies is thought to be the major cause for long-term allograft dysfunction.

2. Risk factors for CAD

2.1 Transplantation antigen dependent risk factors

Epidemiologic study indicated that patients with acute rejection are more likely to develop chronic rejection than those without. The frequency, histologic type and time of onset of acute rejection are closely associated with allograft dysfunction. In particular, frequent and delayed (more than one year) acute rejection is likely to result in allograft dysfunction. Gulanikar et al. reported that the risk for CAD was 9% in patients developing acute rejection once after renal transplantation, was 38% in those developing acute rejection twice, and was 50% in those developing acute rejection thrice, and that early-stage acute vascular rejection was more harmful than acute interstitial rejection. Van et al. reported that the the 5-year kidney survival rates were 34%, 71%, and 74% in patients developing acute vascular rejection, acute interstitial rejection, and without acute rejection in the 3 months after transplantation. It was reported that acute rejection may increase the expression of platelet-derived growth factor (PDGF) and its receptor on arterial smooth muscle cells. PDGF is one of the main stimulators for interstitial cell proliferation in CAD. Hence, PDGF may play a role in acute rejection and CAD.

1. HLA match

Major Histocompability Complex (MHC) mismatch is a crucial risk factor for CAD. The long-term allograft survival rate is the highest for cadaveric renal transplantation with perfect MHC match, and CAD does not occur following homogenic transplantation. Among HLA-A, B, and DR, group A is not so important as groups B and D. Mismatch of both loci of group B is likely to lead to acute rejection and subsequent chronic rejection. In the presence of mismatch of one locus of group B and one locus of group DR, 82% of type I helper T cells proliferate; in the absence of mismatch, only 6% proliferate. Meanwhile, in the presence of mismatch, the release of allogenic antigen peptide increases by 10 folds. The long-term allograft survival rates differ significantly with different number of mismatching MHC sites, suggesting the importance of transplantation antigen dependent factors in the development of CAD.

2. Antibodies

The main mechanism for CAD is believed to relate to allograft stimulated production of anti-donor specific circulating antibodies. As currently available immunosuppressants mainly suppress T cells, antibodies might be a main factor for chronic rejection. In chronic allograft rejection, there are many antibody-secreting plasma cells in the kidney, and these antibodies are against mesenterial cells, focal adhesion plaques, molecules synthesized and secreted by activated mesenterial cells or basement membrane antigen. Interfering recombination activation gene 2(RAG-2) will lead to T and B cell defect, and immunoglobin transmembrane domain-encoding gene defect will preclude the production of mature B cells and antibodies. In both cases, allograft atherosclerosis will not occur. In addition, macrophage dysfunction and defect of MHC class II antigen mitigate atherosclerosis, and defects of MHC class I antigen, CD8 positive cells and NK cells exacerbate atherosclerosis.

Hypersensitivity to panel reactive antibodies (PRA) correlates highly to acute rejection. PRA or the reaction rate of donor lymphocytes to recipient serum is frequently used to predict the risk for acute rejection. Preoperative PRA being more than 10% correlates significantly to the three-year allograft survival rate. Anti-lymphocyte antibody was detected in 28.2% patients with chronic rejection, and of them, 57% were found to have anti-HLA antibody. In vitro study confirmed that monoclonal antibody against type I HLA molecule induced the

expression of fibroblast growth factors receptor on endothelial cells and smooth muscle cells. Allogenic antibodies exhibit the same effect, and they promote glomerulosclerosis and fibrosis. Antibodies against occult epitopes may cause chronic damage, and elevated levels of antibodies against molecules contributing to tissue injury will lead to excessive fibrosis during tissue repair.

3. TGF-β1 pathway

It was demonstrated that molecules recognized by antibodies following transplantation, biglycans and modified molecules also bind to TGF-β1. TGF-β1 is the main cytokine regulating CAD fibrosis. Sharma et al. reported that TGF-β1 mRNA expression correlates significantly to kidney allograft interstitial fibrosis and CAD. Angiotensin II receptor antagonists were shown to reduce plasma TGF-β1 level by 50%, suggesting the potential of angiotensin II receptor antagonists to prevent CAD. Meanwhile, urine TGF-β1 secretion is obviously higher in CAD patients than in patients with stable renal function.

2.2 Transplantation antigen independent risk factors

Non-immune factors and multiple risk factors jointly lead to chronic rejection-like changes of allograft. Rats survived for long term following homogenic renal transplantation. In case of renal function damage, macrophage infiltration and cytokine upregulation were observed in the allograft, just like chronic rejection changes following allogenic renal transplantation. After an allograft with functional impairment was transplanted back into the donor, early-stage renal damage may restore normal, but late-stage damage will continue to deteriorate, demonstrating that early-stage chronic rejection depends on allogenic antigens and is reversible, while late-stage injury does not depend on allogenic antigens and is irreversible.

1. Early-stage ischemia /reperfusion injury

Renal allografts will undergo a series of ischemic events during organ harvesting, preservation, and transplantation. The longer the ischemia time, the more serious the reperfusion related injury. During 2- 5 d of ischemia/reperfusion injury, the expression of leukocyte and endothelial cell adhesion molecules, endothelin, MHC class II molecules, interferin γ and TNF-α is upregulated in kidney tissue, which is complicated by increased oxyradical production and T cells and macrophages in the allograft. Connolly et al. reported that prolonged cold ischemia affected the short-term and long-term survival of cadaveric renal allograft adversely, and that the benefit of HLA match for allograft survival was offset by prolonged cold ischemia. Ischemia /reperfusion injury damages the kidney through the following mechanisms: ① microcirculation disturbance, early-stage renal function loss or delayed renal function, tubular necrosis, TGF-p increase, interstitial fibrosis; ② oxyradical caused acute vascular endothelial cell injury and arterial sclerosis; ③ activation of T lymphocytes, causing subclinical immune reaction, arteritis, nephron reduction, monocyte/macrophage infiltration and interstitial fibrosis.

2. Cytomegalovirus

CMV infection of allograft endothelial cells will lead to chronic rejection quickly. CMV may enhance MHC expression, which leads to the production of anti-endothelial cell antibody and endothelial cell damage. In clinical practice, if acute rejection is refractory to immunosuppressants, and if there are a number of memory CD8+T cells in peripheral blood and evidence of asymptomatic CMV infection, anti-CMV treatment is usually effective to improve renal function. The mechanism is as follows: the immediate early gene of CMV encodes homologous protein, which cross-reacts to HLA-DR-β chain, thus enhancing the recipient's immune reaction to donor antigens. CMV encodes a glycoprotein, which is

homologous to the heavy chain of MHC class I antigen and can react to the light chain of MHC class I antigen. Active CMV infection, along with VCAM-1 expression enhancement and leukocyte adhesion and infiltration on capillary endothelial cells will influence allograft function for long term. In addition, in CMV infection, inflammatory cytokines aggavate endothelial cell damage and vascular pathologic changes.

3. Drug toxicity

Cyclosporin (CsA) and Tacrolimus (FK-506) are both CNI-type immunosuppressants. When they relieve early-stage acute rejection significantly, CNI induced long-term kidney toxicity may be an important cause for accelerating CAD progress. As a result, the long-term survival of allograft may decrease. Chronic nephrotoxicity of CNI is characterized by interstitial fibrosis, hyalinization of small artery and tubular vacuolar degeneration in the kidney. The causes of nephrotoxicity include kidney vasospasm, release of endothelin–β, and excessive expression of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF). It has been demonstrated recently that allograft function may be protected and allograft survival be prolonged by early reduction or withdrawal of CNIs and administration of Sirolimus (SRL) following renal transplantation, without the risk of increasing acute rejection (AR). In addition, the combination of nephrotoxicity-free immunosuppressants, e.g., SRL and Mycophenolate mofetil helps to delay the incidence of CAD.

4. Nephron reduction

Nephron reduction due to various causes leads to glomerular hyperfiltration, early-stage compensated glomerular hypertrophy and increased exudation, kidney dysmetabolism, and allograft failure. Nephron reduction may be associated with the following factors: ① donor/recipient mismatch of body size, or inappropriate ratio of kidney weight /body weight. For instance, an allograft from a donor weighing 50kg is transplanted into a recipients weighing more than 90kg, which means nephron reduction and may result in renal functional impairment; ② the donor is too young (less than three years) or too old (more than 60 years). If the donor is too young, the nephron is immature and cannot tolerate the perfusion pressure for adult kidneys. If the donor is too old, there may be vascular sclerosis and nephron reduction in the kidney; ③ sex difference. The three-year survival rate of allografts from female donors is 5% lower than from male donors.

5. Hyperlipidemia

Food rich in cholesterol and hyperlipidemia synergize in kidney injury, and they change macrophage function, and lead to secretion of vasoactive substances and cell proliferation, thus aggravating kidney damage. Controlled intake of protein can temporarily stabilize allograft function in patients with chronic rejection. Cholesterol-rich apoprotein B and triglyceride are independent risk factors for chronic rejection, and they induce arterial sclerosis and enhance oxidization. Oxidized low-density lipoprotein may lead to proliferation and migration of smooth muscle cells and aggravate vasculopathy.

6. Other risk factors

The following factors are shown to associate with chronic rejection: ① blood pressure elevation is associated with allograft failure. However, which occurs first is still unclear; ② smoking may promote allograft vasculopathy and CAD. Little investigational work has been done in this regard; ③ epidemiologic survey has revealed that continuous proteinuria occurs in approximately 20% of patients following transplantation, and two thirds of these patients suffer from CAD. Chronic allograft damage resulting from proteinuria is an important risk factor for CAD, possibly because of persistent protein loss, failure of epithelial cell repair, and epithelial atrophy and secondary tissue fibrosis.

3. Pathologic classification of CAD

Allograft fibrosis and sclerosis are main pathologic changes in CAD, which can be observed in any anatomical structures of allograft. There may also be progressive proliferation and focal sclerosis of glomerular matrix, and intimal thickening of small artery and capillary in the kidney due to fibrosis and hyaline substance aggregation. Peritubular capillaries may develop multilayered basal lamina, and there may be thickening of glomerular capillary walls with reduplication of basement membrane and mesangial interposition. Gradual accumulation of interstitial matrix leads to interstitial fibrosis (IF), collagen scars, interstitial capillary loss and tubular atrophy (TA).

Allograft fibrosis is the final common pathway of multi-factorial injury. Therefore, chronic rejection alone cannot explain the pathogenesis of fibrosis. Chronic allograft nephropathy (CAN) was used to describe chronic allograft fibrosis. Nevertheless, CAN is not an etiologic diagnosis. Thus, in 2005, the Banff consensus conference recommended adopting need-based diagnosis and abandoning the concept of 'CAN'. According to the Banff 2005 meeting report, possible causes of IF/TA include drug toxicity (especially calcineurin inhibitor toxicity), bacterial or viral infection, hypertension, obstruction, recurrent and de novo glomerular and tubulointerstitial diseases, as well as chronic rejection. Pathologic changes vary depending on different etiologic factors, and they should be discriminated.

Macroscopic examination reveals no obvious allograft changes at the early-stage of CAD, but obvious shrinkage, thickening and adhesion of renal capsule, with scars of various sizes on the uneven, pale surface of kidney at the late-stage of CAD. Small scarring kidney is hard and has a thin cortex. Histopathologic changes include glomerular, interstitial, tubular and vascular changes.

1. Transplant glomerulopathy

Transplant glomerulopathy is mainly characterized by glomerular basement membrane thickening, glomerular mesenterial lysis, and accumulation of mesenterial matrix, mesenterial sclerosis, and glomerulosclerosis. However, it usually does not present with obvious proliferative reaction or dense substance deposition. In this way, it can be differentiated from membranoproliferative glomerulonephritis (Figure 1). Immune injury is generally thought to be the main cause for transplant glomerulopathy, because it correlates obviously to endothelial cell C4d deposition.

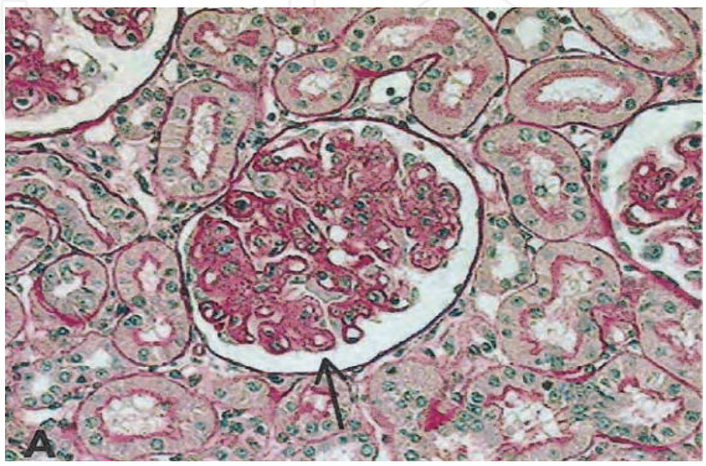

Fig. 1.

2. Interstitial fibrosis

Interstitial fibrosis is not specific to CAD, but is the final outcome of various kidney diseases. Various immune, hemodynamic and metabolic factors may lead to interstitial fibrosis. Tubular cell atrophy, diffuse interstitial infiltration of monocytes and lymphocytes, laminin and fibronectin expression increase, and gradual interstitial fibrosis may be observed (Figure 2). A number of proinflammatory and fibrogenic cytokines expressed in renal allografts may accelerate renal fibrosis, including tumor necrosis factor-α, transforming growth factor-β, platelet-derived growth factor, interferon-γ, and basic fibroblast growth factor. These factors are usually deemed early-stage markers for fibrosis.

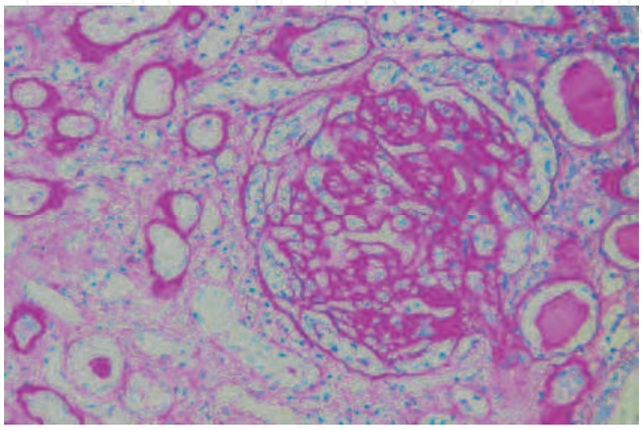

Fig. 2.

3. Tubular atrophy

Tubular atrophy (TA) is also a non-specific manifestation of various chronic kidney injuries. Ischemia/reperfusion injury, drug nephrotoxicity and immune injury may lead to TA. Generally, tubulitis is characteristics of acute cell-mediated rejection; however, whether tubulitis is the sole cause for tubular atrophy is uncertain. Tubular basement membrane loss due to acute rejection may cause late-stage tubular atrophy. At 2-3 weeks following transplantation, persistent peritubular granulomatous reaction, infiltration of tubular basement membrane by multinucleated giant cells, and partial or complete tubular atrophy can be observed (Figure 3). Therefore, immune injury may be an important factor for TA.

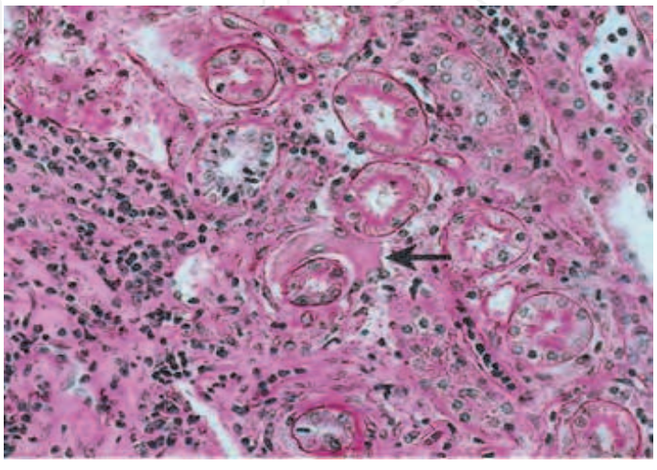

Fig. 3.

4. Transplant vasculopathy

Transplant Atherosclerosis

Transplant atherosclerosis may result from donor factors, non-immune injury (e.g., CNI nephrotoxicity) and chronic rejection. However, there are T cells or macrophages that infiltrate the affected vascular intima, which usually means vascular endothelitis (Figure 4). The incidence rate of systemic atherosclerosis increases in patients with chronic rejection, while renal failure per se does not influence the incidence of atherosclerosis greatly. Moreover, graft atherosclerosis occurs mostly in young, hypersensitive recipients or those with late-stage acute rejection. This suggests that transplant atherosclerosis is closely associated with immune injury. The specification of diagnostic criteria for chronic rejection and other entities by the Banff 2005 conference was an important achievement, and the positive staining for C4d in peritubular capillaries is thought to correlate to AMR (antibody mediated rejection).

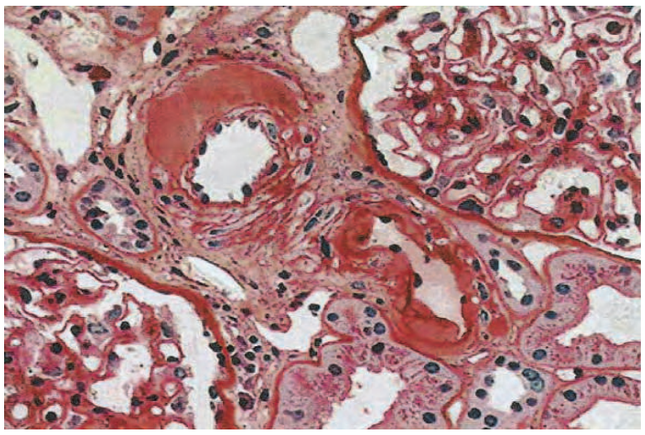

Fig. 4.

Arteriolar hyalinosis

Arteriolar hyalinosis is a characteristic feature of hypertensive nephrosclerosis, diabetic nephropathy, and chronic calcineurin renal toxicity. Hyaline change in the media of the arteriole, which may represent a consequence of myocyte necrosis, is a characteristic feature of cyclosporine-associated arteriolopathy (Figure 5). In many circumstances, such pathologic changes are not direct evidence of diagnosis, and diagnosis should be made with reference to previous pathologic findings obtained by biopsy.

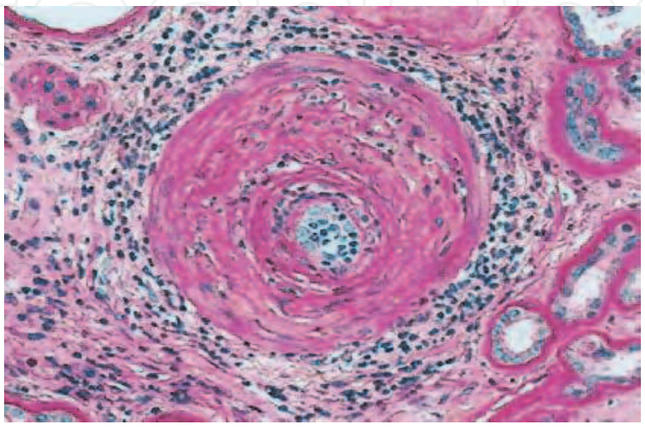

Fig. 5.

In summary, allograft fibrosis and sclerosis are caused by multiple factors, and they are the final manifestations of various acute and chronic kidney injuries. Interstitial fibrosis and tubular atrophy are non-specific. Therefore, a range of diagnostic criteria of CAD should be further investigated, and these diagnostic criteria can and should define specific lesions, thus enabling identification of pathogenic processes that affect the allograft, such as drug toxicity, bacterial or viral infection, hypertension, obstruction, recurrent or de novo renal diseases, and acute and chronic cell and/or antibody-mediated rejection.

4. Injury mechanism for CAD

4.1 Humoral immunity-mediated injury

Antibodies can contribute to transplant rejection through the classical pathways, such as activation of complements and ADCC. After antibody binding to transplantation antigens, complements are activated, followed by activation of the complement-coagulation system, which directly leads to destruction of target cells, vasodilatation, and thrombosis, resulting in allograft rejection. Athough such injury is typical for hyperacute rejection, vascular intimal thickening and presence of complements, immunoglobin and anti-endothelial cell antibody in the necrotic vascular wall have been observed in allografts with chronic rejection. There is another pathway through which T lymphocytes recognize transplantation antigens, i.e., the indirect pathway. In this indirect pathway, TCR on CD4+ T cells can recognize donor's MHC molecule allogenic antigen peptide treated and presented by APCs, also called type II helper T cell (CD4+Th2) reaction. CD4+ T cell activation by the indirect pathway reveals the priming of the rejection effector mechanism, which includes delayed hypersensitivity, cell-mediated toxicty and production of allogenic antibodies. This mechanism exacerbates acute rejection, and plays a major role in CAD. IL-4 and IL-10 produced by Th2 cells are involved in humoral immunity. Activation of helper T cell surface antigen specific TCR triggers intracellular reaction to synthesize specific new antibodies, and this plays an important role in chronic rejection. Early-stage ischemia /reperfusion injury can also activate immunity and upregulate proinflammatory mediators to produce antibodies in the recipients. For instance, in ischemic tissues, vascular endothelial cell phenotype is activated, triggering new antigen expression and leading to immune complex deposition.

4.2 Cellular immunity-mediated injury

In transplant rejection, antigen presenting cells, e.g., dendritic cells, monocytes, and macrophages are crucial for triggering immune response through: ① acquiring, processing and presentating antigens to TH/TDTH and B cells, thus activating first messengers; ② secreting second messengers, e.g., IL-1, thus leading to TH cell activation and release of IL-2, IL-4, IL-5, IL-6 and IFN-γ. Under the action of these cytokines, TDTH, Tc, and B cells that have recognized transplantation antigens begin to proliferate and differentiate into effector Tc, TDTH and antibody secreting cells, leading to transplant rejection. Tc cells directly kill target cells, and TDTH cells contribute to rejection through inducing delayed hypersensitive inflammation. At early-stage acute rejection following renal transplantation, CD4+T cells directly recognize MHC class II antigens in the allograft, and CD8+T cells directly recognize MHC class I antigens in the allograft, producing strong cell- and cytokine-mediated reactions and clinical manifestations of acute rejection. In chronic rejection, weak reactions occur through CD4+Th2 (indirect presentation as mentioned above). Donor MHC may peel

from the parenchymal cells of allograft, enter blood circulation, and be phagocytized and processed by recipient's APCs, and be presented by recipient's MHC, or be taken up and processed in situ by macrophages. The recipient's APCs interalize exogenous proteins derived from the allograft, and process and present polypeptides to T cells, thus providing essential signals for lymphocyte activation. This is the classical pathway for antigen processing and presentation by the immune system. In animals immunized with donor's MHC class II antigens, allograft rejection is accelerated significantly, including serious vascular and cellular rejection, which demonstrates the role of the allogenic recognition based indirect pathway in transplant rejection. Nevertheless, immunosuppressants prevent acute rejection and induce CD4+Th2 reaction, leading to development of chronic rejection.

The intimal plaques of allograft artery in chronic rejection comprise mainly macrophages. Macrophages upregulate the expression of fibrosis factors, interleukin-1(IL-1), IL-6, TNF-a and membrane cofactor protein -1(MCP-1) and growth factors, particularly, fibroblast growth factors (bFGF) and transforming growth factors around glomeruli and vessels, thus promoting vascular wall hypertrophy, glomerulosclerosis and kidney fibrosis. Platelet derived growth factors (PDGF), intracellular adhesion molecule (ICAM) and vascular adhesion molecule -1(VCAM-1) are also present on glomerular capillary endothelial cells and other structures. Upregulation of lymphocytes function associated antigen -1(LFA-1) and very late appearing antigen -4(VLA-4), as well as infiltrating cells and cytokines in the allograft promote the waterfall effect of adhesion molecules.

In triggering immune reactions, multiple cytokines such as TNF and IFN-γ promote lymphocytes to mature and helper T cells Th1 to synthesize IL-2, IFN-γ and IL-12. Anti-inflammatory cytokines, e.g., TGF-β, lead Th2 cytokines IL-4 and IL-10 to mature, and suppress immune reactions against allogenic antigens. During rejection, all these cytokines are present in the allograft. However, in case of immune tolerance, Th1 cytokines reduce, and Th2 cytokines increase. CD4+Th2 cytokines, particularly, IL-4, IL-10 and TGF-β, suppress the synthesis of matrix metalloproteinases (MMPs) on smooth muscle and macrophages. MMPs regulate cellular matrix deposition and degradation. Hence, MMPs suppression causes vascular endothelial cell matrix to accumulate, gradually resulting in arterial sclerosis.

Although CD4+Th2 reactions dominate in chronic rejection, other cells, including endothelial cells, CD8+ T cells, NK cells and macrophages, are required to maintain chronic rejection. For instance, CD8+T cells can activate allogenic class I antigens crosslinking on endothelial cells to produce IL-4, IL-10 and TGF-β. Crosslinking of allogenic antibodies to class I antigen molecules on endothelial cell surface will lead to activation and synthesis of TGF-β, PDGF and FGF.

4.3 Allograft structural component reactivity

Various structural components of allograft exhibit different reactivity at early-stage and late-stage following transplantation. In chronic rejection, vascular obstruction results from repeated activation, injury, proliferation and repair of endothelial cells and deposition of extracellular matrix proteins. Vascular wall injury is caused by homogeneous immune reactions because early-stage antigens or proinflammatory factors (e.g., leukotriene, oxyradicals) upregulate complements and adhesion molecules. Allograft arteriosclerosis is associated with autoimmune reactions induced by heat shock protein produced by activated

endothelial cells. Changes in the phenotype of activated endothelial cells cause cell denudation and exposure of subendothelial collagen to platelets and plasma proteins, which promotes focal coagulation and thrombosis. Ischemic tissues produce various coagulants, and injured or activated endothelial cells release cytokines, chemical inducers, mediators, thromboxanes, leukotriene and growth factors, including PDGF, platelet-activating factor, NOSi and elastin. Chemical inducers and adhesion molecules promote circulating leukocytes to migrate to the site of injury, and then to vascular wall and perivascular space. Inflammatory reactions caused by cytokines and growth factors result in vascular smooth muscle proliferation and migration, tissue deformation, and vascular involvement. In chronic rejection, there are focal or diffuse glomerular changes, and macrophage infiltration may accelerate early-stage glomerular injury to develop into glomerulosclerosis. Glomerulosclerosis and vascular luminal narrowing lead to gradual renal functional impairment and systemic hypertension. As a result, remnant nephrons are subject to glomerular hyperfiltration and fibrosis, and finally lose function. Non-specific interstitial fibrosis and tubular atrophy stem from organ injury. Therefore, in the presence of early-stage injury following organ transplantation, despite persistent administration of immunosuppressants, renal function may be impaired gradually over several months to several years, and these changes correlate to the reactivity of various structural components of allograft.

4.4 Recurrent and de novo allograft disease

Recurrent glomerulonephritis posttransplantation refers to glomerulonephritis of allograft following renal transplantation, which is pathologically identical to glomerulonephritis of autologous kidney. De novo glomerulonephritis posttransplantation refers to glomerulonephritis of allograft following renal transplantation, which is pathologically different from glomerulonephritis of autologous kidney or the pathology of allograft prior to transplantation. The key to diagnose recurrent and de novo glomerulonephritis lies in the availability of biopsy findings of the autologous kidney and allograft prior to transplantation. In effect, glomerulonephritis is virtually recurrent in all cases. The incidence of recurrent nephropathy of allograft correlates obviously to the histologic type of kidney before transplantation and the time following transplantation. Some glomerular diseases are likely to recur, e.g., mesenterial capillary nephritis, and IgA nephropathy, with the incidence rate of 50-90%. However, these recurrent diseases are unnecessarily influence allograft function seriously. Generally, renal function impairment progresses slowly, with long stable periods. Tables 1-2 list common recurrent and de novo allograft diseases. Currently, most investigations focus on the incidence rate, risk factors and clinical manifestations of recurrent allograft nephritis. Clinically, large doses of immunosuppressants are administered to prevent allograft rejection, but allografts may develop recurrent nephritis, demonstrating that currently available immunosuppressants cannot suppress the incidence of preexisting glomerular diseases. Novel immunosuppressants e.g., MMF and Rapamycin, can suppress cell proliferation in vitro, but their efficacy for recurrent glomerular disease has not been established. Therefore, further investigating the treatment of recurrent and de novo nephritis will deepen the understanding of the pathophysiology of autologous glomerulonephritis and immune pathogenesis of allograft rejection.

Pathologic classification	Recurrent rate (%)	Allograft loss rate (%)
FSGS	20~40	25
IgA nephropathy	50	5~10
Membranous nephropathy	20	5~10
MPGN-I	25	5~10
MPGN-II	90	20
HUS	10~50	10~50
HSPN	30~80	10
Wegener's granuloma	5~20	5~20
Anti-GBM disease	<10	<1
Lupus nephritis	5~10	<5

FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative nephritis, HUS: hemolytic uremic syndrome, HSPN: anaphylactoid purpura nephritis

Table 1. Recurrent rate and allograft loss rate of allograft nephritis

Pathologic classification Incidence rate (%)
Etiologies
Allograft nephropathy 5 Rejection? T cell mediated endothelial cell injury? viral infection?
De novo membranous nephropathy 2 Rejection related? de novo antigens produced after allograft injury form immune complexes in situ
De novo HUS 1~3 Calcium channel blockers, allograft ischemia, transplant rejection
De novo MPGN ? 2 HCV, cryoglobulin? deposition of HCV antigens in glomeruli
Alport syndrome
Anti-GBM disease Rare IgG product related to type IV collagen α chain

Table 2. Common de novo allograft diseases

4.5 Posttransplantation lymphoproliferative disease

PTLD is one of the serious complications after organ and marrow transplantation, which presents with lymphocyte proliferation disorder and formation of lymphoma. The probability of PTLD in renal transplantation patients is 20 times that in normal populations. Nevertheless, the incidence rate of PTLD is relatively low (1 %-10%) in renal transplantation patients. PTLD usually affects lymph nodes, the allograft, small intestine and central nervous system, and it occurs mostly in the 2 years following transplantation. PTLD localized to the allograft usually occurs earlier than that outside the allograft. PTLD occurs earlier in patients positive for EB virus than in those negative for EB virus. PTLD mostly stems from B lymphocytes (approximately 87%), and sometimes from T lymphocytes (12%). PTLD stemming from B lymphocytes is mostly complicated by EB virus positivity, while only 38% of PTLD stemming from T lymphocytes is complicated by EB virus positivity. Although PTLD may originate from the donor's cells or the recipient's cells, it mainly originates from the donor's cells. PTLD originating from the donor's cells has a better prognosis than that originating from the recipient's cells. PTLD has varied clinical manifestations, which relate mainly to the affected site and severity of pathologic changes. Common clinical manifestations include ardent fever, neutrocytopenia, anemia, anorexia, diarrhea, and stomachache. Imaging examinations are not specific for the diagnosis of

PTLD. A definite diagnosis depends on pathologic examination. When PTLD is localized to the allograft, with diffuse infiltration, but without obvious masses, it resembles allograft rejection with gradual function loss.

5. Diagnosis of CAD

5.1 Clinical manifestations

Chronic allograft rejection mostly occurs at 2 months to several years following transplantation, with clinical manifestations such as progressive impairment of allograft function, proteinuria and /or anuria, slow increase in blood creatinine (clinically termed "climbing creatinine"), hypertension, progressive anemia and allograft shrinkage.

5.2 Imaging examinations

1. Color Doppler ultrasonography

Since the allograft is shallow, ultrasonic imaging of the allograft will not be influenced substantially by organs and muscle tissue. In addition, due to great acoustic impedance difference between the kidney and surrounding tissues, allograft structures, kidney vessels, ureters and adjacent tissues are shown distinctly. Ultrasonography is able to reveal the allograft size, kidney structures, and various complications of renal transplantation. With the use of color Doppler flow imaging (CDFI) and color Doppler energy (CDE) techniques, blood flow and blood supply to the allograft, and vascular complications following transplantation can be shown clearly. In addition, under ultrasonic guide, biopsy, puncturation and drainage, and visualization are accurate, simple, safe, and non-radioactive, and unlikely to cause complications. Hence, ultrasonography is the preferred imaging modality for allograft. Under ultrasonography, CAD exhibits the following manifestations: the allograft size increases first and then decreases gradually, with a long diameter usually less than 9cm; the kidney parenchyma has enhanced and thickened echoes; the cortex becomes thinner, with indistinct borderline between the kidney parenchyma and renal sinus; at late-stage, the kidney structure is deranged. CDFI frequency spectrum indicates reduced vessels. At late-stage in serious cases, in absence of blood flow in interlobar and arcuate arteries, acute rejection cannot be excluded by ultrasonography. The renal vascular systolic peak flow rate decreases, and the end-diastolic flow rate also decreases. The renal vascular resistance differs significantly between various orders of vessels, particularly between the renal artery and arculate artery. However, the renal vascular resistance is lower than that in hyperacute rejection, accelerated rejection, and acute rejection, but higher than normal. Interstitial vascular resistance is thought to be small; hence, it may be insensitive to Doppler ultrasonography. In contrast, vascular resistance is obvious; hence, it may be sensitive to Doppler ultrasonography. If the RI is normal or less than0.7, CAD cannot be ruled out by ultrasonography. CDE indicates decreased renal vascular perfusion, particularly, in the cortex.

2. Radionuclide imaging

In CAD, the allograft is diminished, and its perfusion and excretion, particularly, uptake, are impaired. Isotope nephrogram indicates perfusion reduction.

3. Digital subtraction angiography (DSA)

In CAD, kidney arteries reduce, and they are thin and bead-like. The kidney parenchyma presents with nonuniform density and patchy changes.

4. CT and MRI

CT and MRI are atraumatic, and have high resolution for soft tissues; hence, they are complementary to other imaging methods for allograft.

5.3 Pathologic study

Currently, biopsy is the most direct, reliable tool for rejection diagnosis. In clinical practice, biopsy findings should be considered in combination with various clinical manifestations and other immunologic, biochemical and imaging findings. Percutaneous thick needle aspiration biopsy or fine needle aspiration biopsy (FNAB) are frequently adopted. If they fail to establish a diagnosis, open biopsy may be considered.

1. Fine needle aspiration biopsy (FNAB)

This method is safe, fast, highly sensitive and specific, and allows continuous observation. Under the guide by ultrasonography or palpation, a 0.7-0.8mm needle with core is inserted into the cortex of the shallower kidney pole, and 10-15tB kidney parenchyma is aspirated and mixed with 5ml heparinized RPMl 1640. The cells are harvested by centrifugation and smeared onto slides. May-Grunlvcald-Giemsa or Wright staining is performed, and cells are counted under an immersion objective. Meanwhile, blood is sampled from the fingers and cells are counted as described above. In typical specimens, there are at least 7 kidney parenchymal cells (endothelial cells, basophilic small tubular epithelial cells, large transparent tubular epithelial cells, large granular tubular epithelial cells or glomerular mesenterial cells) out of 100 inflammatory cells, or there is at least 0.25 parenchymal cell per high power field. The number of a kind of inflammatory cells in the peripheral blood is subtracted from the number of the same kind of inflammatory cells in the allograft to obtain the increament (I). The negative values are discarded. Then, the I values that represent various types of inflammatory cells multiply with a correction coefficient that reflects the contribution of the inflammatory cell type to obtain the corrected I (CI). The CI for each type of inflammatory cells is cumulated to get the total CI (TCI), which represents the extent of inflammatory reactions. Meanwhile, kidney parenchymal cells are graded according to their morphology: 0, morphologically normal; 1, swelling; 2, swelling and vacuolar degeneration; 3, swelling, vacuolization and presence of inclusion materials; 4, necrosis. FNAB specimens can also be investigated by immunocytochemical staining, e.g., peroxide-anti-peroxydase (PAP) staining, indirect immunofluorescence staining, double immunofluorescence staining, immunogold or immunosilver staining, and biotin-avidin immunostaining. FNAB is accurate for diagnosing acute cell-mediated rejection, but is useless for diagnosing CAD and vascular rejection.

2. Percutaneous thick needle aspiration biopsy

This method is the most determinant and reliable tool for differentiating allograft rejection, cyclosporin A toxicity or acute tubular necrosis. In China, the most frequently used needles are Menghini, Franklin-Vim-Silverman, Tru-Cut and Jamshidi types, which are all fit for allograft puncturation. Specimens can be aspirated from the outer edge of the midpoint of the upper and lower kidney poles or the upper kidney pole. For shallow allografts, the needle can be inserted under the guide of palpation. However, in obese patients, ultrasonography or fluoroscopy (with or without intravenous pyelography) may be adopted to guide needle insertion. In case that all these methods failed, CT guide may be considered. The complications are mainly hematuria, perirenal hematoma, arteriovenous fistula, lymphatic fistula and infection.

3. Pathologic diagnosis
   a. The allograft is slightly enlarged or normal at early-stage, and is diminished obviously at late stage. At late stage, the allograft is light and pale, with uneven surface and scars; hence, it is called "small scarring kidney". The renal capsule is obviously thickened and adhered, and cortex atrophy can be observed on the cross-section. Renal function deteriorates progressively, which is proportional to the degree of interstitial fibrosis and glomerulotubular atrophy.
   b. Histologic changes include intimal proliferation dominated proliferating vasculitis, capillary basement membrane thickening and mesenterial matrix increase. There are several pathologic types.

1. Occlusive vasculitis Small artery and arteriole are affected seriously, and interlobar and arcuate arteries may also be affected. In small interlobar artery, afferent glomerular artery and larger artery, smooth muscle and fibroblast proliferation and fibrosis of intima, intima thickening, and luminal narrowing and even obstruction can be observed. Proliferating cells are mostly intimal fibroblasts, and smooth muscle cells originate from the intima. Both cell types produce collagen fibers ultimately. In some cases, subendothelial smooth muscle cells proliferate obviously around the lumen axis, and take on a cyclic, onion-like shape, forming so-called "second tunica media". Serious arterial lesions may influence blood supply to the kidney, lead to multiple infarction, ischemic renal parenchymal atrophy, and renal interstitial sclerosis.

2. Renal interstitial sclerosis Diffuse or focal renal interstitial fibrous proliferation is the major change, which involves the cortex to the medulla. Renal interstitial matrix proliferates, with rare cells and infiltration by lymphocytes and monocytes. Tubular changes are varied, including basement membrane thickening and tubular epithelial cell regeneration. Regenerated tubular epithelial cells are large and may have multiple nuclei. Occasionally, there are single or groups of necrotic epithelial cells. Some tubules are dilated in compensation, resembling mesenchyme. Rejection glomerulonephritis or recurrent glomerulonephritis may be observed. Some patients present with obvious proliferative glomerulonephritis, with obvious increase of glomerular matrix or crescent formation.

   c. Immunofluorescence assay: IgG, IgM and C3 deposit on the glomerular capillary wall and interstitial vascular wall. In particular, in occlusive vasculitis, infiltrating inflammatory cells contain strong fluorescence-emitting IgM.
   d. Electron microscopy: The space between endothelial cells and basement membrane is widened obviously in capillary loop and electron dense substance deposits in a linear or granular manner, with obvious basement membrane thickening. There is a lot of linear and granular electron dense substance deposition along the tubular basement membrane. Mesenterial matrix and surrounding basement membrane are thickened obviously, and are curved. Collagen increases in small artery wall, and smooth muscle cells and fibroblasts proliferate. Lipid droplets increase and myofilaments decrease in the cytoplasm of smooth muscle cells, which may become fibroblasts or foam cells.
   e. Oligonucleotide microarray hybridization assay: B cell chemokine (CXCL13) and mast cells may be determined as predictors for CAD.

4. Differential diagnosis

CAD presents with glomerulosclerosis, recurrent or rejection related glomerulonephritis. Recurrent glomerulonephritis refers recurrence of preexisting nephritis in the allograft, which can be recognized through examining the recipient's original kidney specimens.

Rejection related glomerulonephritis and focal glomerulonephritis can be differentiated by vasculopathy. In serious rejection-related glomerulonephritis, glomerular capillary basement membrane is thickened obviously, which should be differentiated from membranous glomerulonephritis through PAS or PASM staining. In rejection-related glomerulonephritis, there are no spike-like deposits on the epithelial surface of basement membrane, but bilayer basement membrane. In CAD, vascular sclerosis of the allograft should be differentiated from atherosclerosis. Vascular sclerosis is characterized by typical concentric proliferation of smooth muscle and breach of internal elastic layer, but no cholesterol crystals. In contrast, atherosclerosis is characterized by deranged intimal fibers and obvious cholesterol crystals. In CAD, interstitial sclerosis is obvious sometimes, which should be differentiated from chronic interstitial nephritis. In CAD, there are renal interstitial sclerosis, rare nuclei, spare fibers, and few inflammatory cells; hence, the tissue resembles mesenchyme. In chronic interstitial nephritis, fibers are usually dense in scar tissues, with abundant nuclei and a certain number of inflammatory cells.

6. Prevention and treatment of CAD

CAD treatment

No effective treatments for CAD are available yet. The main therapeutic options include controlling blood pressure, administering immunosuppressants, stosstherapy with Methyllprednisolone (MP), intermittent intravenous infusion of Cyclophosphamide (CTX), and use of antithymocyte globulin (ATG), antilymphocyte globulin (ALG), OKT3 and OKT4 monoclonal antibodies, tripterygium glycosides, Bailing capsule, and Niaoduqing granules. The overall therapeutic effect is not good. Over recent years, many treatments have been reported. However, the overall strategy involves the rational use of immunosuppressants, preventing and treating risk factors, and prolonging the functioning life of remnant nephrons. Below are some treatments that are effective for CAD:

1. Dietary therapy Dietary therapy is one of the fundamental measures to delay renal failure in CAD. It has been established both clinically and experimentally that low protein diet and essential amino acid therapy can delay chronic renal failure in most patients. Dietary therapy is mainly aimed to minimize metabolic waste, while providing nutrients to meet basic physiologic needs. By correcting dysmetabolism of nutrients, dietary therapy can relieve the burden on remnant nephrons, correct hemodynamic disturbances, and delay the progress of kidney disease. The measures include ① low protein diet: It is generally thought that low protein diet should be prescribed for patients with chronic renal failure once the endogenous creatinine clearance rate (Ccr) falls to 55ml/min. Meanwhile, sufficient energy should be supplied. This is because high protein diet will increase kidney blood flow and the glomerular filtration rate drastically. Long-term high protein diet will result in persistent high glomerular filtration and glomerulosclerosis through cumulative effect. ② essential amino acids (EAAs): It has been demonstrated that EAAs can improve the nutritional status of patients with chronic renal failure, and can reduce the adverse effect of proteins and common amino acids on the hemodynamics of kidney, thus effectively delaying renal functional impairment. Generally EAAs should be given at week 2 of low protein diet. ⑨ low phosphorus diet and calcium supplementation: Strict control of dietary phosphorus will prevent hyperphosphatemia and secondary

hyperparathyroidism, and relieve tubular interstitial damage. Calcium supplementation should be considered for patients with hypocalcemia and controlled hyperphosphatemia. ④ Supplementation of vitamins and trace elements: Proper supplementatin of water soluble vitamins and trace elements may benefit CAD patients.

2. Cyclosporin A (CsA) The efficacy for CsA is still controversial. According to a retrospective study following up 435 cases for 14 years in the United States, the median allograft survival rate is 3 years. Compared to Azathioprine, CsA showed non-inferiority in relieving renal functional impairment. The median allograft survival rate was 11.6 years in CsA treated patients, and was 9.7 years in Aza treated patients. In animal models, CsA cannot prevent the emergence of pathologic characteristics of CAD after heart, kidney or aorta transplantation. It was also demonstrated that the use of CsA can increase the early-stage success rate obviously and the long-term survival rate as well. Long-term use of CsA is especially superior to Aza. Nevertheless, CsA may increase angiotensin and TGF-β, which is not desirable for CAD treatment. A few scholars hold that low doses of cyclosporin A (CsA) in combination with other immunosuppressants e.g., Mycophenolate mofetil (MMF), is somewhat effective for CAD.
3. FK506 Ji et al. reported that FK506 may delay the progress of CAD safely and effectively. Wang et al. reported that FK506, in place of CsA, was effective for early-stage CAD, particularly, in cases with Scr less than 400umo/L. After FK506 treatment, the Scr level decreased substantially, and hypertension and renal dysfunction improved obviously. One-year follow-up indicated that the patients' condition was stable. Nevertheless, FK506 treatment is less effective in cases with Scr more than 400umol/L. Hence, it is concluded that FK506, in place of CsA is effective for early-stage CAD. Theruvath et al. reported that the FK506+MMF immunosuppressant regimen can reduce anti-donor HLA antibody in recipients, which is of significance to prevent and treat CAD. A US-based, multi-center study primarily on renal transplantation showed that in comparison with CsA, FK506 can effectively prevent acute or glucocorticosteroids or antibody resistant allograft rejection, with increasing side effects. Among 77 patients with acute rejection, 74% of them healed after the combined use of CsA and FK506. 20 patients had obvious vasculopathy, which was refractory to antibody treatment. However, whether FK506 stabilizes allograft function for long is still unclear.
4. Mycophenolate mofetil (MMF) MMF is superior to azathioprine in the treatment of CAD. It was reported that three large clinical trials were undergoing to investigate the efficacy of MMF plus CsA plus prednisone. The dose of MMF to prevent acute rejection is 2g/d or 3g/d. Compared to the control group or the Aza treatment group, the incidence rate of acute rejection decreased obviously at 6 months postoperatively, as confirmed by biopsy. The dose of 3g/d was more effective than 2g/d. MMF may lead to abdominal discomfort, leukopenia and infection. It is now thought that MMF can reduce the incidence of acute rejection and irreversible CAD. MMF in combination with low doses of cyclosporin A (CsA) and prednisone decreased blood creatinine, cured proteinuria and improved renal function in patients with CAD. MMF was found to ameliorate CAD caused chronic renal dysfunction, particularly, mild to moderate renal dysfunction that develops in the first three years after renal transplantation. Nevertheless, long-term follow-ups should be carried out. With the use of MMF, the dose of CsA and glucocorticosteroids can be decreased to reduce the toxic or side effects

of CsA and glucocorticosteroids. The toxic or side effects of MMF are acceptable. With accumulating experience with the clinical use of MMF, the incidence rate of MMF's adverse reactions may be further decreased. CAD patients may benefit from the replacement of Azathioprine with MMF.

5. Sirolimus Sirolimus is a macrolide antibiotic produced by Streptomyces (an actinomycete). As an immunosuppressant, it resembles FK506 structurally. It is not nephrotoxic, and can reduce chronic CsA toxicity. Sirolimus suppresses vascular proliferation, and fibroblast proliferation in vitro; hence, it may prevent CAD. Sirolimus prevents allogenic CAD also through downregulation of adhesion molecule and growth factor encoding gene expression. Replacing calcineurin inhibitors with Sirolimus may delay the incidence of CAD and relieve its clinical symptoms.
6. Lelfunomide In rodent models of heart transplantation with chronic vascular rejection, Lelfunomide exhibited very significant efficacy, and it can reduce and reverse chronic vasculopathy in the allograft. Unlike other immunosuppressants, Lelfunomide will not induce diabetes. Lelfunomide has not been approved for clinical use, but it may become a new treatment for CAD.
7. Polyunsaturated fatty acids Experimental and clinical studies have demonstrated that fish oil treatment can regulate immune reaction. In rat models of heart transplantation, ω-3 polyunsaturated fatty acid can prolong the survival time of allograft obviously. However, allograft survival prolongation correlated to and the reduction of the ω-3 fatty acid content. It is possible that the ratio of dietary ω-3/ω-6 fatty acids is more important than the level of certain fatty acids. ω-3 polyunsaturated fatty acids may regulate immunity via multiple mechanisms: to suppress the effects of IL-1/TNF, to change DR antigen expression, and to reduce vascular smooth muscle cell proliferation and vascular permeability. Another study demonstrated that ω-3 polyunsaturated fatty acids (e.g., fish oil) in combination with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors can reduce the incidence rate of allograft rejection, and they have no obvious toxic and adverse effects.
8. Hypolipidemic treatment HMG-CoA reductase inhibitors (e.g., Statins) are commonly used hypolipidemic agents. Regardless of the blood lipid level in patients, these drugs exhibit good protective effect. In addition to decreasing cholesterol, these drugs can stimulate vascular endothelial cells to release monoxide nitrogen, restore endothelial cell function, and improve kidney hemodynamics. They can also suppress platelet aggregation and thrombosis. It was reported that Simvastatin can reduce the incidence rate of coronary heart disease in rat models for heart transplantation, possibly through reducing the production of 7FXAz. Statins reduce the incidence rate of CAD indirectly, through protecting allograft vessels. CsA, glucocorticosteroids and rapamycin can lead to blood lipid increase. However, it is still unclear to what extent blood lipid should be increased for long. Large multicenter randomized controlled trials or systematic appraisals should be carried out to address this issue.
9. Control of hypertension It has been demonstrated that 90% of CAD patients present with various degrees of hypertension, and require antihypertensive treatment. Hypertension leads to CAD, possibly through increasing renal vascular shear stress, leading to vascular sclerosis, increasing renal vascular resistance, and finally leading to renal ischemia. CAD treatments include control of hypertension and hyperlipidemia. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers can change

intraglomerular pressure and slow down renal functional impairment. Angiotensin suppression can relieve vascular fibrosis and injury in CAD.

10. Anticoagulant therapy As most patients with chronic renal failure have disturbances of blood coagulation, anticoagulant therapy can delay the progress of kidney disease. It has been demonstrated recently [39] that low molecule weight heparin can effectively improve the functional and morphologic status of CAD; however, the precise mechanism is to be elucidated. In addition, traditional Chinese medicines that can promote blood flow and remove blood stasis, e.g., Danshen and Szechwan Lovage Rhizome, exhibit certain therapeutic effects on CAD. However, these therapies need further experimental investigation and clinical observation.
11. Hyperbaric oxygen treatment Pang et al. demonstrated in animals that hyperbaric oxygen is important to prevent or relieve CAD. It was found that proteinuria was milder and the creatinine clearance rate was higher in the hyperbaric oxygen treatment group than the control group. Renal interstitial fibrosis, glomerulosclerosis, artery intimal thickening and T cell, monocyte/macrophage infiltration were milder in the hyperbaric oxygen treatment group than the control group. Therefore, it is concluded that hyperbaric oxygen is useful for CAD treatment. However, further clinical trials should be carried out in larger sample sizes.
12. Traditional Chinese medicines Glucosidorum Tripterygll Totorum and Bailing capsules are effective for CAD, and they help protect remnant nephrons and improve renal function in CAD. However, their mechanisms of action remain unclear. Further studies should be carried out to determine the pharmacokinetics, optimal medication regimen and dosage of traditional Chinese medicines.
13. Excision of renal allograft When CAD develops to renal failure and uremia, the patient needs dialysis to sustain life. The renal allograft is excised prior to discontinuation of immunosuppressants, so as to avoid the production of antibody in allograft and allow a second renal transplantation.
14. Gene therapy It may be one of the important directions in the management of CAD.

In summary, CAD should be treated comprehensively and individually.

CAD prevention

1. To optimize allograft quality Damage should be avoided during harvesting, preserving and trimming allografts. It has been demonstrated that the older the donor is, the earlier and more serious allograft glomerulosclerosis and renal interstitial fibrosis occur. Therefore, allografts should better be harvested from young donors.
2. Preoperative HLA match CAD is mainly caused by immunologic injury. Preoperative HLA match is critical to reduce CAD. It is currently thought that the UNOS six-antigen matching program is a useful tool to achieve optimal HLA match. Allografts with perfect match on the HI, A-A, B and DR loci should better be chosen.
3. To reduce ischemia /reperfusion injury The cold ischemia time should better be less than 20h. High quality vascular anastomosis and avoidance of vascular restenosis are important to reduce ischemia /reperfusion injury. In cadaveric renal transplantation, the use of 200mg recombinant human-superoxide dismutase (RH-SOD) can suppress radical-induced injury, allograft immunity, and MHCII antigen and adhesion molecule upregulation, thus relieving acute and chronic rejection.
4. To reduce acute rejection The severity, frequency and time of onset of acute rejection correlate closely to CAD, and acute rejection is the major immune factor for CAD.

Immunosuppressants have certain toxicity to allografts. Therefore, acute rejection should be prevented with most effective immunosuppressants at the smallest possible dose.

5. To improve the patient's compliance Poor compliance is found to be an important factor for allograft failure. Hence, the patient's compliance should be improved by minimizing the drug dose, educating the patient about the unwanted outcomes of irregular medication, helping the patient to schedule the medication, and establishing a close relationship with the patient.
6. To closely monitor renal function To monitor renal function closely can help physicians to supervise patients taking immunosuppressants, and to find acute rejection promptly. Both patients and physicians must bear in mind that CAD following transplantation seldom has symptoms and physical signs. Therefore, regular monitoring of blood creatinine is feasible for monitoring long-term CAD.
7. To perform biopsy regularly It has been demonstrated that low-grade tubulitis or critical acute rejection can increase the risk for CAD. If biopsy was performed regularly in the first several months following transplantation and rejection was detected and managed promptly, the creatinine level remained low in the first two years. In contrast, in the control group without receiving regular biopsy, the creatinine level was found high upon biopsy and treatment. Therefore, it is concluded that it is crucial to caution against acute and chronic rejection and prescribe kidney biopsy for more patients.
8. To manage hyperlipidemia Hyperlipidemia can promote arteriosclerosis and damage renal function. Pravastatin decreases lowly oxidized low density lipoprotein-cholesterol and triglyceride, and suppress growth factor expression and vascular smooth muscle proliferation. Therefore, to manage hyperlipidemia proactively may exert certain effect on renal arteriosclerosis.
9. To treat hypertension Cardiovascular complications are the second leading cause for death one year after renal transplantation. Both CsA and FK506 can cause hypertension. If the systolic pressure exceeds 150mmg, autoregulation of afferent glomerular artery fails, and the glomerular artery dilates, which results in the production of angiotensin-2 peptide and TGF-β. TGF-β promotes renin secretion. Various factors may reduce nephrons of the allograft, and remnant nephrons are subject to high perfusion pressure, high filtration and high secretion, thus causing glomerulosclerosis. At the early-stage of CAD, if the systolic pressure is controlled below 140mmHg, and the urine protein at 0.25-1g/d, the renal function may not deteriorate for three years. If the urine protein is kept at 1-3g/d, blood pressure may be controlled with higher doses of drugs or more drugs. If the urine protein exceeds 3g/d, blood pressure must be controlled strictly to prevent renal functional deterioration for long. In addition to antihypertensive action, Carvedil suppresses smooth muscle proliferation.
10. To prevent cytomegalovirus infection The CMV infection rate is 70% -100% in the population. Following cadaveric renal transplantation, 8% patients develops symptomatic CMV disease, and the mortality rate is 20%. When CMV disease leads to interstitial pneumonia which requires machine ventilation, the mortality rate is 90%. In the CMV infection group, the three-year allograft survival rate reduced by 30%. Active CMV replication can be detected by CMV antigen assay, LSAB assay, and monoclonal antibody determination of CMV encoded PP65 antige as early as 1-6 days prior to onset of CMV disease. CMV disease can be prevented and treated with Ganciclovir in the first three postoperative months in patients positive for CMV infection.

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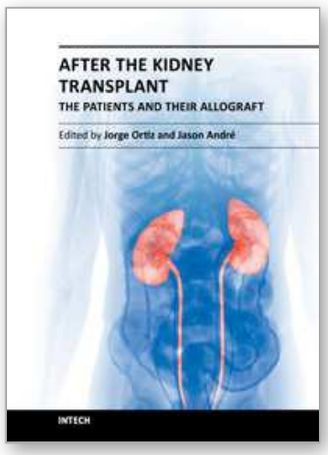

After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

ISBN 978-953-307-807-6
Hard cover, 386 pages
Publisher InTech
Published online 17, August, 2011
Published in print edition August, 2011

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

How to reference

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Wenqian Huo, Keqin Zhang, Chengguo Ge, Gang Wu, Fengshuo Jin, Gang Yuan and Qiansheng Li (2011). Pathogenesis and Preventive Strategies of Chronic Dysfunction of Renal Allograft, After the Kidney Transplant - The Patients and Their Allograft, Prof. Jorge Ortiz (Ed.), ISBN: 978-953-307-807-6, InTech, Available from: http://www.intechopen.com/books/after-the-kidney-transplant-the-patients-and-their-allograft/pathogenesis-and-preventive-strategies-of-chronic-dysfunction-of-renal-allograft

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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