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New insight in the immune mechanisms in hyperuricemia after renal transplantation: a narrative review

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Abstract. – OBJECTIVE: Due to underlying allograft rejection and renal ischemia reperfusion injury (IRI) inducing renal injury, hyperuricemia (HUA) is one of the common complications after renal transplantation and may be a major contributor to reduced renal function. Currently, there are no uniform mechanisms of HUA after renal transplantation. This review aimed to figure out the immune mechanisms of HUA after renal transplantation and the molecular mechanisms of HUA-induced renal injury to provide new insights into renal function protection and prolonged survival time of grafts.

MATERIALS AND METHODS: The search terms included 'Hyperuricemia', 'Renal transplantation', 'Urea acid', 'Gout' 'Graft Rejection', 'Graft Survival'. Databases including PubMed, Cochrane Library, Embase, Clinicaltrials.gov and China National Knowledge Infrastructure (CNKI) were searched for studies including mechanisms of hyperuricemia after renal transplantation from the beginning of databases to March 2022.

RESULTS: Our study reviews the immune mechanisms of HUA after renal transplantation. HUA induces renal injury mainly by renal inflammation, oxidative stress, and endothelial dysfunction. IRI contributes to increased inflammation in renal grafts, mediates the recruitment of various inflammatory cell types.

CONCLUSIONS: Due to underlying allograft rejection and IRI, renal transplant recipients are especially prone to HUA. HUA further reduces renal function and even graft loss. Treg targeting could be a novel therapeutic approach in renal transplantation.

Key Words:

Hyperuricemia, Renal transplantation, Immune mechanisms, Graft rejection, Graft survivals.

Introduction

Renal transplantation is the best treatment approach for end-stage renal disease and can highly improve the prognosis of patients[1]. Although immunosuppressive regimens are routinely applied pre- and post-transplantation, allograft rejection and renal ischemia-reperfusion injury (IRI) can inevitably occur in patients treated with renal transplantation. Consequently, the graft is injured and functionally imparied[2-4]. The kidney plays a predominant role in the excretion of uric acid (UA). In humans, approximately 70% of daily produced UA is excreted by the kidneys[5]. Hyperuricemia (HUA) is one of the common complications after renal transplantation[6], and the incidence of HUA in renal transplant recipients reportedly ranges from 25% to 84%[7]. HUA is classically defined as a serum UA (SUA) level > 7.0 mg/dL in men and 6.0 mg/dL in women[8,9]. In the general population, 85-90% of HUA cases are in the asymptomatic stage and thus show no clinical feature[10]. Symptomatic HUA patients develop gout or kidney stones[11,12], and HUA is also recognized as an independent risk factor for kidney injury[13]. In renal transplant recipients, high SUA levels have been reported[14] to be related to graft failure. A study[15] has reported that high SUA levels can accelerate deterioration of kidney function and aggravate cardiovascular disease (CVD) progression. High SUA levels can lead to a long-term decline in estimated glomerular filtration rate and deterioration of graft function in renal transplant recipients[14]. Additionally, HUA has been found to be related to increased renal-graft loss, CVD risk, and mor-

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tality[16] and can thus highly diminish the quality of life and dramatically increase the economic burden on renal transplant recipients. Therefore, it is necessary to study the mechanisms underlying HUA after renal transplantation.

This review aimed at investigating the immune mechanisms involved in HUA after renal transplantation and deciphering the molecular mechanisms underlying HUA-induced renal injury, thereby providing new insights into customized prevention and treatment of HUA in renal transplant recipients.

Why are Renal Transplant Recipients Prone to Hyperuricemia?

Allograft Rejection

T-Cells-Mediated Rejection (TCMR)

For renal transplant recipients, the immune system is the primary barrier to long-term graft survival. TCMR is the most frequent cause of graft rejection and, mainly occurs within a year after transplantation, but dramatically declines over time[17]. In graft rejection, antigen-presenting cells (APCs) can display donor or recipient human leukocyte antigen (HLA) molecules[18]. In the TCMR of grafts, APCs display graft-derived foreign peptides to T cells; T cell receptors can bind thousands of HLA-peptide complexes[19.] As extensively reported, T cells usually destroy target cells *via* two mechanisms – one driven by cytotoxic cluster of differentiation (CD) 8+ cells, and the other by cytotoxic CD4+ cells – both contributing to the activation of pathways that ultimately kill foreign cells[19]. Notably, regulatory T-cells (Tregs) play a central role in the induction of transplant tolerance[20]. Tregs have been shown to suppress effector T-cell (Teff) responses *via* inhibition of their development and proliferation as well as inducing apoptosis in mouse model[20,21]. Joffre et al[22] have shown that adequately pre-stimulated Tregs can prevent acute and chronic allografts rejection in skin and cardiac transplantation. Preclinical studies[23] have reported that Tregs can delay or prevent graft rejection after solid organ transplantation. Depletion of Tregs causes a significantly diminished allograft survival[24]. One of the reasonable mechanisms of suppression of Teff by Tregs is that Tregs secrete anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-β, and inhibit the generation of memory T-cells[25].

Immunosuppressive agents can effectively prevent acute graft rejection in renal transplantation, but have different effects on Tregs[25]. The recommended immunosuppressive protocol after renal transplantation is a triple-immunosuppression regimen, consisting of calcineurin inhibitors (CNIs), anti-proliferative agents, and corticosteroids, with the anti-proliferative agents specifically referring to azathioprine or mycophenolate[26]. The two CNIs widely used in clinical practice, cyclosporin A and tacrolimus, suppress graft rejection by inhibiting T-cell lymphoproliferative responses to donor antigen presentation[27]. It has been reported[28] that CNIs decrease Treg frequencies in peripheral blood lymphocytes. CNIs prevent interleukin-2 (IL-2) production by inhibiting activation of "nuclear factor of activated T-cells" (NFAT)[25]. As Tregs highly rely on IL-2 signaling for survival but do not produce it[28], CNIs potentially affect the development and function of Tregs and significantly reduce the Treg frequencies[29]. Korczak-Kowalska et al[30] found that the percentage of Tregs in renal allograft recipients treated with rapamycin is significantly higher than the patients treated with CsA. Rapamycin and derivatives, sirolimus and everolimus, favor Treg survival and function due to continued production of IL-2 and inhibit mammalian target of rapamycin (mTOR)[31]. Mycophenolate mofetil (MMF) and its active metabolite, mycophenolic acid (MPA), are widely used in transplantation. These anti-lymphocyte agents can decrease *de novo* synthesis of guanosine nucleotide by selectively inhibiting inosine monophosphate dehydrogenase. Since this enzyme is primarily expressed by T- and B-cells, MMF and MPA inhibit B- and T-cell proliferation[32,33], but do not affect the function of Tregs[34]. Corticosteroids can preserve suppressive activity and survival of Tregs by magnifying the IL-2-dependent expansion and restricting Teff cells[35]. Thus, immunosuppressive agents with positive effects on Tregs should be taken with priority in renal transplantation to preserve graft function.

Antibody-Mediated Rejeection (ABMR)

Although advances in immunosuppressants and protocols have significantly decreased the incidence of acute rejection, the outcome of renal grafts is still markedly influenced by the development of humoral rejection[3]. ABMR, also known as B-cell-mediated rejection, is a severe post-transplantation complication that causes graft dysfunction and loss[36]. ABMR accounts for 20-30% of all acute rejection episodes after renal transplantation and is significantly related to poor allograft survival[37]. ABMR is usually mediated by antibodies that are directed against allogeneic HLAs by the complement system[38]. Antibodies that specifically recognize donor antigens are often called donor-specific antibodies (DSAs). Donor-specific HLA antibodies, particularly the anti- class II antibodies, are sub-grouped into C4d-positive and C4d-negative populations[39]. DSAs trigger ABMR mainly through three mechanisms, namely antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and direct endothelial injury[17], and allograft cells are consequently destroyed by the activation of the complement system or cytotoxic cells[36]. In acute ABMR, the activation of the complement system causes tissue injury and thrombosis; activated complement can also recruit neutrophils, macrophages, and inflammatory factors, which damage the graft tissues further[36]. Interestingly, one of the complement split proteins, C4d, which is often produced during complement activation, can covalently bind to the basement membrane or endothelial collagen, and C4d deposition in capillaries has been reported to be the most reliable marker of ABMR[38]. A study has shown that HLA-DSA-negative ABMR has a dramatically better outcome than HLA-DSA-positive ABMR, in which C4d deposition is observed relatively more frequently[40]. ABMR is characterized by the thickening of the glomerular basement membrane, proliferation of the arterial intima, and mononuclear-cell infiltration and lamination of the peri-tubular capillary basement membrane[38]. Thus, ABMR diagnosis is often based on the histopathological features in the renal graft biopsy (glomerulitis, thrombotic microangiopathy, arterial-transmural lesions, etc.) and the presence of DSAs, with or without C4d expression[41]. In chronic ABMR, complement-independent mechanisms, especially those associated with the expression of genes in C4d-negative cells and natural killer (NK) cell, have been reported[17] to play significant roles. Sablik et al[42] have found that the major renal-infiltrating immune cells in allograft biopsies from ABMR cases are M2-type macrophages and CD8+ T-cells in both the glomeruli and tubulointerstitial compartment and that the increased number of CD3+FoxP3+ (Treg) cells is significantly related to poor renal allograft survival. Most current protocols of immunosuppressive therapies for rejection mainly focus on acute ABMR and are relatively less effective in chronic ABMR[17]. In addition, the vast majority of ABMR episodes are diagnosed after the transplantation when pre-transplantation DSA titres are increased or *de novo* DSAs are produced; the production of *de novo* DSAs is usually caused by substantial HLA mismatches between the host and donor, increased non-adherence over time, immunosuppressive regimen minimization, and other relevant factors[37]. The above factors may explain why renal graft injury still occurs in renal transplant recipients despite the long-term traditional immunosuppressant regimens.

Innate Immune Responses Underlying Rejection

Over the past two decades, increasing evidence has indicated that innate immune responses can significantly promote graft rejection and activate adaptive alloimmunity[43]. The innate immune system is the first line of defense against pathogens and responds to sterile injury[44]; it also plays a significant role in immunological events during renal transplantation. The primary constituents of the innate immunity include cellular components [macrophages, neutrophils, NK cells, dendritic cells (DCs), and innate lymphoid cells] and molecular components, including members of the complement system and other inflammatory factors[3]. Molecules carrying stereotypical motifs and mainly produced during infection (pathogen-associated molecular patterns), or injury (damage-associated molecular patterns, DAMPs), can activate innate immune cells, which directly exert pro-inflammatory and anti-inflammatory effects[45]. Toll-like receptors (TLRs), as pattern recognition receptors (PRRs), mainly trigger intracellular signal transduction cascades that activate nuclear factor (NF)-κB and up-regulate cytokines, adhesion molecules, and co-stimulatory factors, all of which are pivotal to immune activation and development of an adaptive immune response[43]. NK cells generally mediate immediate effector functions under pathological conditions by producing pro-inflammatory cytokines and exerting cytotoxic activity[46]. Various cell subsets are activated and recruited upon the immunological response activated by allografts, and NK cells can dramatically lead to TCMR and ABMR, both of which cause renal allograft dysfunction and loss[47]. NK cells are usually categorized into two subsets depending on the expression level of CD56 – low-density ($CD56^{dim}$) and high density ($CD56^{bright}$) subsets – which differ in their phenotypic and functional properties[48]. Kildey et al[46] have found that renal graft biopsies from patients with TCMR present with an increased absolute number of CD56^{bright} NK cells, whereas patients with ABMR show up-regulation of both CD56^{bright} and CD56^{dim} NK cells. CD56^{bright} NK cells play a significant role in TCMR by secreting pro-inflammatory factors, such as IFN-γ, which can up-regulate HLA alloantigens (MHC I and II) and enhance the recruitment of alloreactive T-cells to graft cells, thus increasing the susceptibility of the graft cells to cytotoxic killing[47]. However, renal graft biopsies from ABMR cases have shown that only CD56^{dim} NK cells express high levels of cytotoxic effectors (granulysin, granzyme A, and perforin) and CD69, as an activated phenotype marker[46]. NK cells are involved in the complement-independent rejection mechanisms after transplantation, such as ADCC. These mechanisms can be induced by CD16, which is expressed by CD56^{dim} NK cells[49-51]. Yazdani et al[49] have compared the density of NK cells between samples from ABMR cases, samples from TCMR cases, and samples from without rejection cases; they found that the number of infiltrating NK cells is strongly associated with the presence of DSAs, C4d deposition in peri-tubular capillaries, and microcirculation inflammation in renal transplant recipients[49]. Therefore, biopsies of renal grafts from ABMR cases are typically characterized by enrichment of transcripts associated with NK-cell activation; NK cell infiltration can distinguish ABMR and TCMR and even predict graft failure after renal transplantation[49]. A review by Rajalingam[50] proposed a mechanistic concept indicating a predominant role of "killer cell immunoglobulin-like receptor"– HLA interactions in assisting NK cells in Fc-receptor-mediated ADCC effector function, which is involved in ABMR of renal transplantation and could directly guide a new therapeutic target for ABMR. In addition, innate immune cells in the late post-transplantation period can form an inflammatory microenvironment either in response to chronic ABMR or independently from ABMR, thereby exacerbating the chronic allograft damage[52]. Thus, innate immune responses, particularly NK cells, are significantly associated with long-term survival of renal grafts, and thus these responses may be targeted for novel therapeutic strategies against graft rejection.

Renal IRI

Renal IRI, a common and unavoidable event after renal transplantation, refers to the immediate graft injury; it occurs when the donor kidney experiences warm ischemia and cold ischemia. Renal IRI usually causes acute kidney injury, significantly increases the risk of delayed graft function, and can even lead to graft loss[4,53]. Early IRI induces later graft loss *via* chronic hypoxia, reduced kidney mass, graft vascular injury, and subsequent fibrosis[54]. IRI contributes to increased inflammation in renal grafts, especially by activating DCs and macrophages and mediating the recruitment of various inflammatory cell types[55]. The restoration of blood flow to the ischemic tissue contributes to synergistic activation of the innate and acquired immune responses, which trigger tissue inflammation[56]. DCs can rapidly activate NK T-cells and accelerate the innate immune response during IRI. CD11c+ DCs are usually resident in the renal parenchyma and produce tumor necrosis factor-α, which is a crucial factor for the neutrophil infiltration post-IRI, tubular epithelial cell apoptosis, and glomerular endothelial injury[57]. Additionally, infiltrating macrophages secrete pro-fibrotic cytokines, such as transforming growth factor-β, which triggers myofibroblast transformation of the tubular epithelium *via* epithelial-to-mesenchymal transition; macrophages, myofibroblast and tubular epithelium cells can result in extracellular matrix deposition, collagen formation, and ultimately renal fibrosis[58,59]. Ischemic insult can also trigger an acute inflammatory reaction through PRRs, which are typically expressed on both tubular epithelial cells and infiltrating immune cells[4]. Among the PRRs, TLRs and their synergistic receptors, nod-like receptors (NLRs), as well as inflammasomes, play significant roles in the inflammatory response to renal IRI[4,60]. In addition, the complement system plays a pivotal role in renal IRI. C3a and C5a release have been widely reported[56] to contribute to renal damage by activating innate immune cells and recruiting them to the injury site, subsequently resulting in reactive oxygen species (ROS) formation, apoptosis, and necrosis. In addition, hypoxia and ischemia induce the anaerobic metabolism and suppress the mitochondrial electron-transport chain, thereby decreasing ATP production and cellular retention of calcium, sodium ions, and hydrogen. Consequently, graft cells swell and also decline in enzymatic activity[61]. Recent studies[62] have reported that Tregs suppress innate immunity and play protective roles in the renal IRI. Studies[63] have demonstrated that Tregs can protect kidneys from IRI due to their immune-suppressive properties. Gandolfo et al[64] have demonstrated that Tregs are infiltrated during tissue repair in the IRI, likely through negative modulation of pro-inflammatory cytokines produced by other T-cells. Kinsey et al[65] suggested that a probable mechanism of Treg-mediated kidney protection is mainly by IL-10 production, and further inhibits innate immune response to kidney injury.

Taken together, an imperceptible graft rejection response and IRI after renal transplantation can cause complex systemic changes in the immune state, which reduce renal graft function and contribute to reduced UA excretion. The significant role of Tregs in renal allograft acceptance indicates that Tregs as therapeutic agents in conferring transplant tolerance is very promising[21]. The use of Tregs in renal transplantation is aimed at reducing or eliminating the complications of immunosuppressive drugs, as well as maintaining tissue repair and managing acute rejection[66]. Thus, Treg targeting could be a novel therapeutic approach in renal transplantation. In the following section, we will discuss the mechanisms underlying HUA-induced renal inflammation.

How Does HUA Cause Renal Impairment?

HUA induces renal injury mainly *via* renal inflammation, oxidative stress, and endothelial dysfunction[67]. Elevated SUA levels cause the formation and deposition of monosodium urate (MSU) crystals in the extracellular fluid. These crystals are recognized as DAMPs by PRRs (such as TLRs) and thereby ultimately activate inflammatory responses[68]. Innate phagocytes, such as DCs, neutrophils, and macrophages can recognize MSU crystals[69]. Macrophages are regarded as a key mediator in MSU-crystal-induced renal inflammation, and MSU crystals usually deposited in renal tubules or the interstitium can be recognized and phagocytosed by macrophages[70,71]. These crystals are subsequently engulfed by the lysosomes in macrophages but cannot be degraded by lysosomal enzymes, ultimately causing the activation and oligomerization of the Nod-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome, a multimolecular complex that can activate inflammatory caspase-1 and induce the pyroptosis cell-death pathway[68,72,73]. The NLRP3 inflammasome is mainly dependent on a two-signal initiation system. The first activation signal activates NF-κB signaling pathway *via* TLR4/TLR2 of macrophages recognizing MSU[69,74], induces macrophage activation[75], recruits the intracellular effector protein myeloid differentiation factor 88[76], and synthesizes pro-interleukin (IL)-1β and inflammasome components[77,78]. MSU crystals often serve as the second activation signal, promoting the assembly of the inflammasome and activation of caspase-1, which proteolyses pro-IL-1β to mature IL-1β[79,80]. Thus, *via* NLRP3-inflammasome–dependent caspase-1 activation, MSU crystals can stimulate macrophages to secrete IL-1β[81]. In addition, IL-1β subsequently interacts with the IL-1β receptor to trigger downstream signaling cascades involving pro-inflammatory cytokines and chemokines, further recruiting neutrophils and other inflammatory cells to the site of crystal deposits[72] and causing further tubular injury and albuminuria[82].

The formation and deposition of MSU crystals can lead to kidney stones. A low urine pH (< 5.5), caused by impaired urinary UA excretion, is the most significant factor for MSU crystallization and stone formation[83]. Large stones usually lead to hydronephrosis, which eventually causes the loss of renal-graft function and acute renal failure[84]. Additionally, MSU crystals not only induce inflammation but also stimulate the adaptive immunity[85]. Eleftheriadis et al[85] have found that MSU crystals enhance zeta chain phosphorylation, thereby directly inducing the activation of the T-cell receptor complex and up-regulating the transcription factor c-Myc, which induces T-cells proliferation. Another study has reported that MSU crystals increase the level of phosphorylated Igα, a component of the B-cell receptor (BCR) complex, and up-regulate c-Myc, which induces B-cell proliferation in a BCR dependent manner. Thus, MSU crystals trigger BCR signal transduction and induce B-cell proliferation[86]. Taken together, MSU crystals stimulate both the cellular and humoral immunity and can contribute to poor outcomes in renal transplant recipients with HUA[87,88]. Therefore, renal injury caused by MSU crystals may not be mediated solely through the activation of inflammatory cells but also through a direct effect on B- and T-cells[86]. However, this aspect requires further investigation in the future to prolong renal-graft survival.

In addition, recent studies have suggested that soluble UA also has pro-inflammatory effects, which can also activate the NLRP3 inflammasome and promote the synthesis of IL-1β[67]. Elevated SUA levels can damage tubular epithelial cells *via* increased oxidative stress, promote epithelial cell apoptosis, and impair epithelial cells' structure and function; mitochondria are the main organelles damaged in this process[89]. Renal mitochondrial dysfunction increases the production of ROS[90]. The NLRP3 inflammasome, activated by HUA, can respond to the DAMPs (including ROS, ATP, and extracellular matrix components) released from the damaged renal tissue[91]. Additionally, soluble UA may activate the NLRP3 inflammasome in a mitochondrial ROS-dependent manner in macrophages, such as altering cell membrane morphology, inducing ROS production and potassium efflux[92]. HUA induces renal inflammation through the NF-kB signaling. NF-kB is a key transcription factor that mediates inflammation by regulating the expression of cytokines and chemokines; its activation is regarded as a hallmark of acute inflammatory processes[93,94]. Renal cells and infiltrating macrophages can up-regulate NF-κB, which is a key factor in mediating sterile kidney damage[94]. Zhou et al[70] have found that tubular expression and secretion of "regulated upon activation normal T-cell expressed and secreted factor" (RANTES) and monocyte chemoattractant protein-1 (MCP-1), which are pro-inflammatory chemokines stimulated by UA *via* the NF-kB signaling, are potent and critical for the infiltration of macrophages. The mitogen-activated protein kinase signaling pathway plays an important role in the up-regulation of MCP-1 by UA; the increased MCP-1can subsequently increase cell proliferation and up-regulate C-reactive protein and other inflammatory factors[95]. Kidney-resident macrophages can initiate and regulate inflammatory responses and thereby promote renal fibrosis in the pathogeneses of renal diseases[96]. Thus, macrophages may serve as therapeutic targets against renal tissue injury and fibrosis.

The endothelium acts as a communication bridge between blood and cells and mediates the processes and functions of surrounding cells *via* complex signaling pathways[97]. Endothelium-derived nitric oxide (NO) plays a pivotal role in regulating the vascular tone and anti-inflammatory effects, inhibiting platelet activation, and preventing the proliferation of smooth muscle cells[98]. Endothelial dysfunction, particularly impaired NO production, is commonly observed in cardiovascular and kidney diseases and is thought to be mediated partly by ROS[99,100]. One of the mechanisms of ROS production is the reaction of xanthine oxidase with xanthine to generate superoxide anion and UA[101]. A study[95] has indicated that 9 mg/dL UA induces endothelial cell apoptosis and increases the levels of ROS, and UA also up-regulates angiotensinogen, angiotensin II receptors, and angiotensin II. Thus, UA-induced endothelial dysfunction may exacerbate renal injury by activating the renin angiotensin aldosterone system, inhibiting neuronal nitric oxide synthase, and stimulating the proliferation of vascular smooth muscle cells[102]. Endothelial NO synthase (eNOS) can be activated by kinase-dependent signaling pathways, which include the PI3K/Akt and calmodulin kinase II, and AMP-activated protein kinase pathways[103]. Thus, enhancing the activity of the eNOS-NO signaling is a promising therapeutic strategy against UA-induced renal injury.

Apart from the above mechanisms, the role of SUA in coronary artery disease has also been extensively investigated. Related studies[97,104] have suggested that SUA is an independent predictor of endothelial dysfunction and contributes to coronary artery lesions. Endothelial dysfunction has been widely reported to play a pivotal role in the development and progression of atherosclerosis, which usually causes serious cardiovascular complications[105]. A growing body of evidence[106] suggests that SUA has a detrimental effect on kidneys, cardiovascular system, and brain. Thus, elevated SUA can also increase the risk of CVD and mortality in renal-transplant recipients; thus, the incidence of CVD is a critical factor in poor graft survival.

Overall, the mechanisms underlying HUA-induced renal injury are complex and not yet completely understood. In-depth investigation of these mechanisms may contribute to improving the treatment of HUA and HUA-induced renal injury.

Conclusions

In summary, due to the underlying allograft rejection and IRI contributing to a decline in renal function, renal-transplant recipients are especially prone to HUA. HUA, in turn, induces injury to the renal graft, mainly through inflammation, oxidative stress, and endothelial dysfunction, all of which further reduces renal function and can even lead to graft loss. The significant role of Tregs in renal allograft acceptance and tissue repair in IRI, suggests that Treg targeting could be a novel therapeutic approach in renal transplantation. The precise mechanisms of Tregs in renal allograft acceptance are definitely complex and not fully understood. Thus, further studies are required to elucidate the specific mechanisms of Tregs in renal allograft acceptance and target them to achieve optimal renal-graft function and prolonged survival of grafts.

Conflict of Interest

The authors declare that there is no conflict of interests in this study.

Authors' Contributions

Xi Zhang and Xiaoyu Zi designed the study and wrote the original draft. Chuan Hao reviewed and edited the manuscript. All authors read and approved the final manuscript.

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