Delayed Graft Function

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1. Introduction

Delayed graft function (DGF) is a common complication of renal transplantation. According to a clinical data analysis of 34,647 cases of cadaveric renal transplantation documented by the Renal Transplantation Registry of the United Network Sharing (UNOS), graft function did not recover instantly after transplantation and for ever in some cases; the 1-year rate of graft loss was up to 20% in cases with poor renal function recovery; the long-term loss rate of graft was higher in cases with poor renal function recovery than those with instant graft function. The half-life time of graft is 7 years in cases with delayed graft function, and is 12 years in cases with instant graft function. Based on our 30 years of experience in renal transplantation and the literature, we reviewed the diagnosis and management of DGF.

2. Diagnostic criteria

Currently, graft function recovery is defined as follows.

1. Instant graft function (IGF): postoperative urine output >7000ml, serum creatinine recovery to normal in 3-7 days.
2. Slow graft function (SGF): postoperative urine output is normal, but serum creatinine decreases slowly, and not to normal in one week. Nevertheless, dialysis is not needed.
3. Delayed graft function (DGF): DGF can be diagnosed according to the three aspects below.
   i. Need for postoperative dialysis: Need for dialysis in the first week after transplant once hyperacute rejection, vascular and urinary tract complications and hyperkalemia are ruled out.
   ii. Urine output and serum creatinine: ① Rise in serum Cr at 6-8 h post-operatively or <300 ml of urine despite adequate volume and diuretics. ② Urine output <1 L in 24 h and <25% fall in serum creatinine from baseline in first 24 h post-transplant. ③ Urine output <75 mL/h in first 48 h or failure of serum Cr to decrease by 10% in the first 48 h. ④ Serum creatinine increases or remains unchanged or decreases <10%/day during 3 consecutive days postoperatively. ⑤ Serum creatinine >2.5 mg/dL on Day 7 or need for post-transplant hemodialysis. ⑥ Time required for the kidney to reach CrCl>10 mL/min greater than 1 week. ⑦ Failure of creatinine to decline in the first 48 h in the absence of rejection.
iii. **Urine enzymes and biopsy**: ① Urine IL-18 in first 24 h > 500 pg/mg. ② Urine NGAL on Day 0 > 1000 ng/mg and IL-18 on Day 0 > 500 pg/mg. ③ Pre-transplant soluble IL-6R of 35 000 pg/mL. ④ Pathologic findings that support acute renal tubular necrosis.

4. **No more graft function (NGF)**: Postoperative failure of graft function that requires dialysis.

5. **Hyper delayed graft function (HDGF)**: In rare cases, the anuria stage persists longer than one month, even several months after renal transplantation, followed by gradual renal function recovery, a phenomenon we called HDGF. In 2000, we performed a second renal transplantation in a female patient. In this patient, the anuria stage lasted 109 days postoperatively, and urine output increased gradually, with serum creatinine decrease to normal on day 155 postoperatively. Ten years of follow-up indicated the graft function to be normal.

### 3. Risk factors for DGF

DGF is a complex pathologic process usually involved donor- and recipient-related factors. Donor-related factors include age, cause of death, and transplantation and cold ischemia time of graft. Recipient-related factors include rejection, anti-HLA antibody level, and times of renal transplantation, cytomegalovirus infection, obesity, body size difference with the donor, pre-transplant dialysis type, and ethnicity.

1. **Donor-related factors** Due to an organ shortage, organs from donors of advanced age or organs with other confounding diseases are also used as sources for organ transplantation. The quality of renal graft is crucial. Renal graft function is closely associated with the donor’s age, cause of death and primary disease. Renal graft of poor quality may not survive for long because of immune or non-immune damage to the graft.

   i. **Brain death** Animal study has demonstrated that changes in physiology, hemodynamics, endocrinology, and histomorphology as well as early inflammation damage peripheral organs following brain death. Cytokine storm after brain death may upregulate HLA expression in the graft and make the graft susceptible to attack by preexisting anti-HLA antibody. Rejection occurred earlier in renal grafts from rats after brain death than in the control group. The survival rate of renal grafts from non-kinship living donors is much higher than that of cadaveric renal grafts. Brain death influences the quality of donor organ, increasing the incidence of DGF.

   ii. **Senile donors** It has been clinically shown that senility of donors is a major risk factor for DGF, and it influences the long-term survival of grafts. The UN data demonstrate that senility of donor increases the incidence of DGF significantly. For instance, the incidence of DGF is 15% if the donors’ age is 20 years, and is up to 40% if the donor’s age is over 65 years. The cause for such difference may lie in the fact that the number of functioning nephrons decreases in healthy individuals with aging. In addition, renal grafts may be injured by ultrafiltration following transplantation.

   iii. **Cause of death** The cause of death is another major risk factor influencing the long-term survival of graft. According to the UNOS data, the incidence of DGF was 18%
if the donors died of traffic accident, was 30% if the donors died of cerebrovascular accident, and was 45% in 400 non-heart-beating donors (NHBDs) (possibly related to long periods of warm ischemia).

iv. Ischemia-reperfusion injury Cessation of blood flow leads to anaerobic metabolism and adenosine triphosphate depletion in the organ. The incidence of DGF is 12% if the period of cold ischemia of renal graft is less than 12h, and is up to 45% if the period of cold ischemia exceeds 48h. In addition, the incidence of DGF is less than 10% if the donor is young and the cold ischemia time is less than 12h, and is more than 20% if the donor is senile and the cold ischemia time is short. Given the cold ischemia time of 36-48h, the incidence of DGF is up to 50% if the donor is senile and, and is only 30% if the donor is young. Animal study has shown that the donor’s age and cold ischemia time exert additive effect on chronic graft rejection.

2. Recipient-related factors
The incidence of DGF is relatively high given suboptimal HLA matching, high sensitization status and a second transplantation. The severity of immune injury depends mainly on the severity of early post-transplantation rejection. High sensitization status increases the risk of immune injury. DGF may mask rejection, but rejection may aggravate preexisting injury. It has been demonstrated that the incidence of DGF increases significantly in the presence of early graft rejection and DGF is a predictor for aggravation of rejection. Cytomegalovirus infection, obesity, type of pre-transplant dialysis, and ethnicity are all factors influencing the incidence of DGF. For instance, black recipients are more likely to develop DGF than other people. However, the mechanisms involved remain largely unknown.

3. Other factors
i. Organ preservation: Continuous pulsatile perfusion or pulsatile perfusion plus simple cold preservation of grafts from NHBDs helps decrease the incidence of DGF and improve the long-term survival rate of graft. In NHBDs, comparison of bilateral kidneys subjected to pulsatile perfusion and simple cold preservation, respectively, showed that the incidence of DGF was 10% for grafts subjected to pulsatile perfusion, and was 30% for grafts subjected to simple cold preservation. Valero, et al analyzed in situ perfusion (ISP), total body cooling (TBC), and normothermic recirculation (NR) for grafts from NHBDs, and found that the incidence of DGF was significantly lower in grafts subjected to NR than in those subjected to ISP and TBC. The viability of grafts from NHBDs can be assessed by perfusion parameters, and be improved through infusing drugs. In 2009, Cyril Moers reported that Lifeport Transporter can significantly decrease the incidence and duration of DGF following renal transplantation, while significantly increasing the 1-years survival rate of graft. In addition, Lifeport Transporter provides useful information for professionals to make wise clinical decisions, and helps them choose renal grafts. Hence, Lifeport Transporter is an effective, economical device for renal graft preservation.

Shortening the ischemia time: Topical ischemia/reperfusion injury is the pathogenetic basis for DGF, and the severity of DGF depends on the duration of ischemia. The incidence of DGF is lower in China than in other countries. This is because the warm ischemia time (WIT) of cadaveric renal graft is usually maintained between 10 and 15min in the transplantation centers in China. The warm ischemia time should also be shortened during
nephrectomy in living donors. It helps reduce the incidence of DGF to shorten the time for graft trimming and possible second warm ischemia of graft. The cold ischemia time (CIT) directly influences the incidence of DGF and graft survival. It was demonstrated that the risk of DGF increased by 23% every 6h.

Kidney preservatives: They are used to minimize topical ischemic injury. They comprise special components to relieve cellular swelling, maintain calcium homeostasis, reduce the production of oxyradicals and provide energy-rich substances. The UW preservative is superior to Euro-Collins solution in reducing the incidence of DGF. The research on preservatives is now focusing on additives to the standard formulas, e.g., Trimetazidine.

ii. Recipient management: Many patients have inadequate blood volume preoperatively, and the use of crystalline or colloid solutions under central venous pressure monitoring can reduce the incidence of DGF. The kidney is one of the organs that need plentiful blood supply, and the volume of blood supplied to the kidneys accounts for approximately 1/4 of cardiac output. The kidney is sensitive to ischemia, and the ischemia time is correlated to the severity of reperfusion-related injury. Appropriate blood pressure is a prerequisite for adequate graft perfusion. In particular, the blood pressure in the recipient prior to reperfusion determines the recovery of metabolism of graft after a series of ischemic events. A proper blood pressure ensures oxygenated blood perfusion and benefits graft functional recovery. The incidence of DGF is lower in patients receiving peritoneal dialysis prior to transplantation than those receiving hemodialysis. This may relate to decreased blood volume in patients receiving hemodialysis upon the procedure of transplantation. Therefore, sufficient fluid extension is beneficial for patients. Effective blood pressure must be maintained intra- and post-operatively, and blood pressure should better be kept 10-20mmHg (1mmHg=0.133kPa) above the basic blood pressure upon reperfusion and in the first three days postoperatively, thus ensuring effective graft perfusion. Stable blood pressure but poor graft vessel tension and anuria during operation may relate to arteriospasm that results from traction of the renal artery. Polyuria may be induce by postoperative administration of dopamine to dilate the renal artery and elevate systolic pressure.

iii. Vasodilators: During reperfusion, direct infusion of calcium channel blockers into the renal artery improves early renal function due to direct vasodilation and relief of lipid peroxide. A randomized trial has demonstrated that diltiazem treatment of the donor or treatment of the recipient with other calcium channel blockers benefits early graft function. Atrial natriuretic peptide (ANP), a peptide hormone increasing glomerular filtration rate and urine output, improves renal function and histopathologic changes in animals with acute ischemic renal failure. After infusion of ANP increases serum creatinine clearance quickly and reduces the need for dialysis. In addition, ANP antagonizes vasoconstrictors following topical ischemic injury and promotes renal function recovery. Furosemide suppresses prostaglandin lyases and increases prostaglandin E, thus dilating renal vessels, decreasing renal vascular resistance, and increasing blood flow to the kidney, particularly to the tissues under renal cortex. Therefore, furosemide can relieve ischemic renal injury, promote renal function recovery, and decrease the incidence of DGF.

iv. HLA mismatching: Based on our data, HLA is no a risk factor for DGF, possibly because we controlled the number of HLA mismatches strictly. In addition, HLA matching directly influences the incidence of AR, and AR is one risk factor for
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DGF. We also found that early urinary fistula and ureteral obstruction are not risk factors for DGF.

v. Type of dialysis: The type of pre-transplant dialysis may influence the incidence of DGF. A review of a number of cases showed that peritoneal dialysis is in favor of immediate recovery of renal function after renal transplantation, which was attributed to fluid load in the recipient. After analysis of multiple variables, e.g., DGF, ARF in patients who underwent preoperative hemodialysis (HD) or peritoneal dialysis (PD) and received the first cadaveric renal transplantation, it was found that there were 33 cases of DGF (27 cases of HD and 6 cases of PD, p=0.03, and there were 14 cases of ARF (14 cases of HD and 0 case of PD, p=0.01). The time for serum creatinine to decrease to 50% of the pre-transplant level correlates positively to the cold ischemia time and body weight increase in the recipient, and correlates negatively to the urine output in the first 24h, fluid load, and central venous pressure. PD is thought to decrease the incidence and severity of DGF after renal transplantation. Joseph, et al investigated acute rejection, DGF, graft survival, and patient survival in 325 patients who underwent preoperative HD and PD and the first cadaveric renal transplantation, and found 56 DGF cases in 183 PD patients and 58 DGF cases in 117 HD patients. The incidence of DGF was significantly higher in HD patients than in PD patients.

4. Mental disorders and interventions in DGF patients

With technical advance in renal transplantation, mental problems in patients with renal failure or undergoing renal transplantation have drawn more and more attention. These problems include personality change, emotional disorders, mental disorders, psychological reaction, and psychosocial dysfunction. Mental problems may directly influence graft function recovery, and even lead to graft nonfunction or serious adverse events, such as non-compliance to treatment or autoamputation (suicide). Therefore, it is crucial to pay close attention to the patient’s mental status before and after renal transplantation and manage mental disorders promptly.

Because of biological factors, e.g., renal failure and rejection, immunosuppressant-associated adverse reactions and psychosocial factors, patients may develop various mental disorders before and after renal transplantation, including anxiety, depression, psychotic symptoms, and psychological rejection. Anxiety/depression disorder is characterized by mental stress, excessive anxiety, worry, depression, self-abasement, self-blame, and decreased interest. Some patients may present with panic attack and social anxiety disorder, and serious patients may have suicidal idea and commit suicide. Psychotic symptoms include delusion, hallucination, lack of self-awareness due to mental and somatic disorders, and detachment of the real world. Patients with psychotic symptoms may suffer from secondary behavioral disorders. These symptoms persist for varying length of time. Psychological rejection occurs mainly after renal transplantation. The patients are unable to accept the grafts mentally, and they cannot cope with the mental stress associated with transplantation. They may refuse to take anti-rejection drugs or ask for removal of the grafts. These mental disorders may cause autonomic nerve dysfunction, immune dysfunction and behavioral disorders, e.g., somatic pain, insomnia, anorexia (or apastia), and non-compliance to treatment or autoamputation (suicide).

Most patients expect much from renal transplantation, and they are likely to develop mental disorders in case of DGF. There are interacting biological and psychosocial factors that underlie mental disorders.
1. Biological factors:
   i. Acute renal failure
   Following renal transplantation, ATN leads to accumulation of toxic substances which damage nerve cells directly or indirectly and influence nerve cell functions. For instance, alteration in intracerebral monamine neurotransmitters may lead to anxiety, depression and psychotic symptoms.
   ii. Immunosuppressants
   Large doses of immunosuppressants may impair the immune system, and interfere with neuroendocrine function and neurotransmitters in the brain. Neuroendocrine and neurotransmitter dysfunction serve the principal biological mechanism for mental disorders in DGF patients.
   iii. Transplantation procedure
   Renal transplantation procedure per se is a traumatic stress, which can also cause mental disorders, particularly in patients with poor physical status. In addition, perioperative administration of medications, e.g., anesthetics, is one of the causes for mental disorders in DGF patients.

2. Psychosocial factors:
   i. Personality
   Positive and optimistic attitude, good cognition assessment system and coping capacity are crucial for mental health of patients undergoing renal transplantation. Personality traits such as anxiety, paranoid idea, and disadvantage-guided thought are the personality basis for mental disorders in DGF patients.
   ii. Stressful events
   In case of accumulation of adverse life events or major adverse life events, DGF patients may suffer from serious mental trauma and mental disorders.
   iii. Psychosocial supportive system
   The psychosocial supportive system for DGF patients involves social security system, family support and other interpersonal support. Social security system includes medical insurance and psychological support (e.g., unemployment). Family support mainly involves husband-wife and parent-child relationships and socioeconomic status of family. Other interpersonal support mainly includes career, friendship and special group relationships.

Proper assessment and effective management of DGF patients with mental disorders directly influence the efficacy of medical interventions and the life quality of patients.

3. Assessment of mental disorders:
   i. The patient is interviewed face-to-face by psychiatrist and psychologist to assess his/her mental status, personality traits and life events. Meanwhile, the need for medical management and the specific interventions, e.g., psychological intervention or medical treatment, are evaluated.
   ii. Mental status scale based measurements: including measurements of mental status, personality traits, life events and life quality.

4. Prevention of mental disorders:
   i. To establish an integrated social security supportive system, including medical insurance system and government funded special social security system.
ii. To set up a team of psychiatrists or psychologists, who monitor the patients’ mental status during the perioperative stage of renal transplantation, and diagnose and treat mental problems promptly.

iii. To educate DGF patients, including introducing renal transplantation related issues and possible mental problems.

5. Treatment of mental disorders:
   i. Psychotherapy
      Individualized psychotherapy, primarily supportive psychotherapy, is considered. Cognitive and behavioral therapy may also be utilized. In addition, volunteers who ever suffered from DGF and now have their renal function recovered normal are invited to communicate with the patients, which is the most effective modality.
   ii. Drug treatment
      In DGF patients with serious mental disorders, antipsychotic drugs, e.g., Olanzapine, may be prescribed. The dose must be increased gradually. In case of serious emotional disorder, e.g., anxiety-depression, particularly, high risk of suicide, antidepressant drugs should be administered immediately. SSRIs and SSNIs drugs may be prescribed. For patients with serious anxiety, benzodiazepines may be used. Electroshock should be considered with caution.

4. Prevention and management of DGF

DGF leads to adverse outcomes, including prolonged hospital stay, need for postoperative hemodialysis, significant increase in medical care costs, decrease in the 1-year survival rate of graft, increase in the rejection incidence, and decrease in the long-term graft survival and the short-term and long-term survival rate of patients. Various medical modalities may decrease the incidence of DGF:

1. To choose young donors and ensure good match of the graft with the recipient.
2. To reduce warm and cold ischemia time.
3. To assess the graft quality and utilize optimal renal grafts.
4. To preserve renal grafts by pulsatile mechanical perfusion.
5. To administer small doses of calcineurin inhibitors (CNIs), biological immunosuppressants and calcium channel blockers. Calcium channel blockers may regulate the immune system and reduce acute rejection. In addition, they prevent the toxic and adverse effects of CNIs and decrease blood pressure.
6. To maintain a proper level of mean arterial pressure in the recipient prior to graft reperfusion.

5. Summary

DGF is an early complication after transplantation caused jointly by immunologic and non-immunologic factors. Various novel immunosuppressants can effectively control or relieve immunologic graft injury, thus improving the short-term and long-term survival rate of grafts. However, the mechanism of pre-transplant injury to the renal graft remains largely unclear. The risk factors for DGF include the warm ischemia time, cold ischemia time, intraoperative and early postoperative hypotension, ATN, nephrotoxicity of CNIs and AR.
Further study should be carried out with large sample sizes to investigate the correlation of
times of transplantation, number of HLA mismatch, early postoperative urinary fistula,
ureteral obstruction, and preoperative blood transfusion with DGF. Renal graft protection
has seldom been investigated. Further efforts should be made to prevent non-immunologic
injury to the renal graft, so as to increase the quality of renal graft and the short-term and
long-term survival rate of renal grafts.

6. References

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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient’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.

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