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Review Article

New Onset of Diabetes Mellitus After Renal Transplantation

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ABSTRACT

Objective: Diabetes after transplantation is associated with poor graft function as well as increased risks of infection and death after renal transplantation. The term "new-onset diabetes mellitus" (NODM) is used exclusively for the development of diabetes after transplantation. Significance: This paper reported the incidence of NODAT that greatly depends on the length of follow-up, diagnostic criteria, and immunosuppression regimen. The true incremental incidence of diabetes occurs mainly during the first 6 months post transplantation, when patients are treated with high doses of immunosuppression. Conclusion: New-onset diabetes after transplantation is an important comorbidity in renal transplant recipients. The condition is common, and likely to be caused by a number of pre- and post-transplant-related factors, including pre- and post-transplant therapy, and patient-related risk factors for metabolic problems. The onset of hyperglycaemia after renal transplant appears to lead to increased risks, and these need careful management.

INTRODUCTION

The term NODAT was first used in 2003 and should be primarily and cautiously referred only to patients with no pre-transplant diagnosis of diabetes mellitus, on a stable maintenance immunosuppressive regimen, and no ongoing acute infection[1]. Diabetes after transplantation is associated with poor graft function as well as increased risks of infection and death after renal transplantation. The term "new-onset diabetes mellitus" (NODM) is used exclusively for the development of diabetes after transplantation[2]. Multiple risk factors have been identified in the development of NODAT. These include older age (≥40-45 years), ethnicity, family history of diabetes, hepatitis C infection, increasing human leukocyte antigen (HLA) mismatches, obesity (body mass index, BMI ≥30kg/m2), donor source, acute rejection, genetic factors as well as the type of immunosuppressive agents used to prevent and/or treat rejection[3]. The NODAT has been related to several risk factors, and the used

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immunosuppressive medications such as calcineurin inhibitors (e.g., cyclosporine and tacrolimus) and corticosteroids play an important role on its pathogenesis. Renal transplantation has gradually become commonplace since the first successful attempt in the 1950s, and is the preferred mode of renal replacement therapy for many patients with end-stage renal disease. The development of new onset diabetes after transplantation (NODAT) is a serious complication of kidney transplantation that is associated with cardiovascular morbidity and mortality and may be associated with an increased risk of chronic transplant dysfunction. Diabetes is highly prevalent in kidney transplant recipients (KTRs). Pre-existing diabetes has been shown to be associated with three-fold increased risk of cardiovascular disease. Further, a haemoglobin A1c (HbA1c) level of 7% at 1 year post–kidney transplant has been shown to be associated with an increased risk of subsequent cardiovascular events, even in the setting of non obstructive coronary disease. New-onset diabetes after transplantation (NODAT) is a serious and frequent metabolic complication after renal transplantation[4]. The reported incidence of NODAT greatly depends on the length of follow-up, diagnostic criteria, and immunosuppression regimen. The true incremental incidence of diabetes occurs mainly during the first 6 months post transplantation, when patients are treated with high doses of immunosuppression.

Risk factors for NODAT is of two types

Table 1

Non modifiable risk factors	Modifiable risk factors
Older age	Over weight
Race	Obesity
Genetic background	HCV infection
Family history of diabetes	CMV infection
Metabolic syndrome	Immunosuppressive drugs
Cadaveric kidney dysfunction	Steroids
	Pulses
	Calcinurin inhibitor

1.1. Non modifiable risk factors:

Old age

older age is a strong independent risk factor of NODAT. There is a 90% increase of relative risk (RR) in renal transplant patients aged 45–59 and a 160% increase in patients ≥60 (versus 18–44 years as a reference)[4.] Recipients older than 45 years are 2.9 times more likely to become diabetic post-transplant than younger recipients. Age increases the risk for developing of NODAT by 1.5 fold for every 10-years increase in age.[5] incidence of NODAT increased by 29% with every increase of 10 years in age[6].

Race

African American and Hispanic patients have higher risk for development of NODAT because of their genetic polymorphisms which allow for more common disease prevalence compared to Caucasians[5]. The fact that the incidence of type 2 DM is significantly higher in African Americans then in Caucasians, in the general American population[5] The RR of NODAT is increased by 32–68% in black patients and by 35% in Hispanic patients in comparison with white patients [4].

Genetic background

HLA mismatching has been associated with an increased risk of NODAT, although HLA phenotype cannot be considered a reliable risk factor for NODAT. However, the results of published reports are contradictory. Some studies suggest an association between variants of the transcription factor 7-like 2 (TCF7L2) gene and

NODAT, while another study showed no significant relationship between TCF7L2 genotypes and the development of NODAT. Moreover, research into the candidate genes is limited by its expense and inconvenience. Autosomal dominant or recessive polycystic kidney disease is also linked to NODAT. A plausible mechanism for the association needs to be explained [5]

Family history of diabetes

A positive family history of diabetes in first- or second-degree relatives is an unmodifiable risk factor and is related to a high risk of NODAT in adults and children[6]

1.2.Modifiable Risk Factors:

Over weight (Obesity)

Overweight or obese patients have a higher risk of developing NODAT, with an RR of 1.4 for patients with a BMI between 25 and 30 kg/m2 and an RR of 1.7–1.8 for patients with a BMI .30 kg/m2 [7] a body mass index (BMI) ≥30 kg/m2 can be connected to the occurrence of NODAT [6]

HCV infection

A higher prevalence of type 2 DM has been reported with HCV infection in the general population. The infection is a significant comorbid condition in kidney transplant recipients and is associated with increased risk for both graft failure and mortality[5]. Interferon has been the drug of choice for treating HCV infection in the non-transplant population for several decades. Its use in HCV-infected transplant patients has been largely avoided due to its propensity to elicit acute rejection of the allograft. Novel drugs (protease and nucleotide analog inhibitors) have been released to the market for treatment of HCV infection but they lack approval for use in transplant patients[5].

CMV infection

With regard to cytomegalovirus (CMV), a group showed that both ganciclovir treated and asymptomatic CMV infection episodes are independent risk factors of NODAT[4].(8) Cytomegalovirus infection has been associated with DM 1. Kidney recipients who have symptomatic or asymptomatic CMV disease are at higher risk for developing NODA Several mechanisms have been suggested to explain the impact of CMV on diminishing insulin secretion, such as beta cell damage directly by CMV and apoptosis or by infiltrative leukocytes or by induction of pro-inflammatory cytokines[5].

Immunosuppressive drugs

Immunosuppressive drugs, including glucocorticoids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors, all play important roles in the development of PTDM, and are more vital than traditional risk factors[8]. Although antiproliferative agents, mycophenolate mofetil, mycophenolic acid and azathioprine, do not seem to influence NODAT rates, sirolimus is associated with an increased risk of NODAT approaching that seen with tacrolimus**.** the anti-CD52 induction agent Alemtuzumab has been associated with a reduced NODAT risk through unknown mechanisms, when compared to cyclosporine based regimens[7] the incidence rate of NODAT is 30% and 18% of adult patients who receive cyclosporine A (CsA) and tacrolimus (FK506), respectively, in the first year after transplantation[6].

1.2.1. Steroids

Glucocorticoids

Glucocorticoids induce NODAT predominantly via increasing insulin resistance, however impairment of beta-cell function has also been demonstrated. Although glucocorticoids seem more diabetogenic than other immunosuppressive agents, avoiding or withdrawing steroid early to reduce NODAT carries the potential risk of AR and an increased incidence of chronic renal allograft pathology[7].

Calcinurin inhibitor

Calcineurin is critical to beta-cell growth and function. CNIs contribute to NODAT through a dose related and partially reversible islet cell toxicity with impairment of insulin gene expression and secretion[7] When CNIs are used in combination with prednisone, mycophenolate mofetil and basiliximab (interleukin-2 receptor antibody) therapy, the risk for the combined endpoint of impaired glucose metabolism or NODAT is in the order of 33% with tacrolimus and 26% with cyclosporine at 6 months [7]. Calcineurin inhibitors (CNIs) include cyclosporine and tacrolimus, which inhibit calcineurin. Calcineurin is essential for the survival, replication, and function of b cells. Currently, it is believed that calcineurin inhibitors lead to an increase in plasma glucose mainly in the following ways: damage to pancreatic b cells; and affecting of insulin secretion[8].

Diagnostic Criteria

The use of an oral glucose tolerance test before transplantation has been evaluated as a screening tool to identify people at high risk of developing NODAT. Individuals with fasting glucose values of 6.1–6.9 mmol/l (110–125mg/dl) are defined as having impaired fasting glucose and those with 2-h glucose values of 7.8–11.1 mmol/l (140–199mg/dl) after an oral glucose tolerance test are defined as having impaired glucose tolerance. Both conditions are associated with an increased risk of developing diabetes and cardiovascular disease[9] In renal transplantation, HbA1c should probably not be used < 3 months after transplant, as the test may not be accurate before adequate time is allowed for synthesis and glycation of new haemoglobin in the post-transplant period. One study has suggested that an HbA1c level > 39 mmol/mol (5.7%) at 10 weeks can identify the need for oral glucose tolerance test assessment, with a 91% sensitivity[9] Cognizant of the need for greater uniformity, international consensus guidelines for NODAT were developed in 2003, with approval from the World Health Organization (WHO) and American Diabetes Association (ADA)[7].

1.3. Diagnostic criteria for posttransplant diabetes mellitus and impaired glucose metabolism:

Criteria for new-onset diabetes after transplantation mellitus (Require one of three)

- Symptoms of hyperglycaemia with a random plasma glucose ≥11.1 mmol/L (200 mg/dL) OR
- FBG ≥7.0 mmol/L (126 mg/dL; minimum 8 h fast) OR
- 2 h post-75 g OGTT plasma glucose ≥11.1 mmol/L (200 mg/dL)
- A confirmatory test must be done on another day in the absence of unequivocal hyper-glycemia accompanied by acute metabolic decompensation.
- Criteria for posttransplant impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)

- IFG FBG ≥6.1 (110 mg/dL) and <7.0 mmol/l (126 mg/dl) (assess further with OGTT)
- IGT 2 h post-75 g OGTT plasma glucose ≥7.8 (140 mg/dL) and <11.1 mmol/l (200 mg/dl)
- Recommended diabetes screening intervals after transplantation: weekly for first 4 weeks; months 3, 6 and 12; annually after the first year[7].

Prevention And Screening

Before transplantation, all candidates are suggested to undergo a baseline evaluation including complete medical and family history, addressing both risk factors for diabetes and other cardiometabolic risk factors such as hypertension, dyslipidaemia and smoking. Periodical screening of FPG and/or OGTT are also recommended in evaluating the glucose metabolism status[3].

1.4. Lifestyle Measures

Advice on lifestyle modification is an essential part of T2DM management, and interventions focusing on diet and exercise remain the most effective strategy to prevent progression from impaired glucose metabolism to overt T2DM[7] Adoption of healthy dietary, exercise and weight control strategies has shown a 15% improvement in 2-h postprandial glucose over 6 months versus a 12% deterioration in controls[7]. Renal transplant recipients have successfully undergone laparoscopic gastric bypass surgery both before and after transplantation. However, the role of bariatric surgery in the prevention and treatment of NODAT has not been established and an important consideration is the potential effect on the absorption of immunosuppressive and other drugs[7].

1.5.Oral glucose-lowering agents

When initial glycaemic control with immunosuppressant modification and non-pharmacological therapy fails, oral glucose-lowering agents may be prescribed as the first-line agents, as a traditional standard approach[6]. The goals for management at this juncture include adequate glycemic control, perhaps with complete resolution of hyperglycemia without pharmacotherapy, and minimizing the short- and longterm complications of hyperglycemia[10].

1.6. Modifying Immunosuppression

When NODAT develops, modification of the immunosuppressive regimen may be considered to reverse or improve diabetes after weighing the risk of rejection and other potential adverse effects. The changes suggested by KDIGO include:

1. Reducing the dose of Tac, CsA or corticosteroids.

2. Discontinuing Tac, CsA or corticosteroids.

3. Replacing Tac with CsA, MMF or AZA.

4. Replacing CsA with either MMF or AZA[6]

4.3.1.Glucocorticoids

For patients with hyperglycaemia or at high risk of NODAT, rapid tapering, withdrawal and avoidance of prednisolone/prednisone have been associated with improved glucose metabolism; however, this increases the risk of AR and chronic allograft nephropathy[7]. Reduction below 5 mg/dL seems to provide limited metabolic benefit. The half-life of 2–3 h indicates that daily dosing cannot achieve steady-state plasma levels, and kidney transplant recipients exhibiting a shorter half-life for methylprednisolone have shown an increased risk of rejection. Recent evidence has suggested that divided daily dosing of prednisolone may be

safer and more effective than daily dosing and warrants investigation[7].

4.3.2. Calcineurin Inhibitors

For those with NODAT or at high risk for its development, some clinicians advocate preferential use of cyclosporine, but the choice of immunosuppressive agent must consider the risk of graft rejection and overall cardiovascular risk. With tacrolimus posing a greater risk of NODAT and cyclosporine associated with more hypertension, dyslipidemia and renal impairment, long-term outcome studies are required[7]

1.7. Post-Transplantation Screening

According to the 2009 KDIGO guideline, it is recommended to screen all non-diabetic kidney transplanted patients for NODAT with FPG, OGTT and/ or HbA1C testing at least weekly for the first four weeks, followed by every three monthly for one year and annually thereafter. These screening tests are also suggested to be performed on patients after initiation or substantial increases in the dose of CNIs, mTORi or corticosteroids[3].

DISCUSSION

The development of NODM is a well-known complication in renal transplant patients with an incidences of 2% to 50% reported in various studies. Most patients develop NODM within the early postoperative months[2]. Five risk factors were associated with the development of NODAT: older age at transplantation, heavier weight, higher mean pre-transplant random plasma glucose concentration, higher plasma glucose concentration in the first week post-transplant and the use of tacrolimus. Patients who at the time of transplantation are older, heavier and who have pre-transplant random plasma glucose concentrations above 5.5 mmol/L should be considered at a higher risk of developing NODAT and subsequent management should be tailored to reduce the risk[11]. We observed that older age, impaired glucose tolerance at the time of transplantation, and a family history of diabetes were significantly associated with the development of NODM[2]. Fifteen percent of patients over the age of 50 year developed NODAT in the study. The same is true regarding obesity, this known risk factor for diabetes in the general population, was also a risk factor for the development of NODAT in the study[11]. BMI which emerged as a more reliable independent risk factor for NODM than the BMI at the time of transplantation. This parameter may be more suitable for the purposes of prediction and prevention because it may better represent a personal tendency to be overweight given that many patients have lost weight before transplantation. Abnormal glucose metabolism prior to transplantation was strongly predictive of NODM[12]. Following the identification of a high-risk group, the next stage would be to develop strategies to reduce the incidence of NODAT. There are two main areas that should be addressed: firstly, tailoring immunosuppression and secondly, targeting risk factors for the development of diabetes and cardiovascular disease including the avoidance of diabetogenic medication. The combination of corticosteroids and tacrolimus has an additive effect in the development of NODAT and either early withdrawal of corticosteroids or the avoidance of tacrolimus has been shown to be beneficial. Selective use of ciclosporin rather than tacrolimus in the high-risk group may prevent the development of NODAT[11].

CONCLUSION

New-onset diabetes after transplantation is an important comorbidity in renal transplant recipients. The condition is common, and likely to be caused by a number of pre- and post-transplant-related factors, including pre- and post-transplant therapy, and patient-related risk factors for metabolic problems. The onset of hyperglycaemia after renal transplant appears to lead to increased risks, and these need careful management.

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