REVIEW

Prevention and management of new-onset diabetes mellitus in kidney transplantation

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ABSTRACT

New-onset diabetes mellitus after transplantation (NODAT) is one of the complications that is increasingly occurring among kidney transplanted patients. It is associated with the risk of cardiovascular disease, graft failure and mortality. The risk of NODAT development increases with time from transplantation. Therefore, early detection and prompt action are essential in reducing the risk of NODAT and its complications. This paper aims to review the screening parameters, prevention and management strategies for NODAT in both pre- and post-transplantation conditions. The pre-transplant patient should be screened for diabetes and cardiometabolic risk factors. Blood glucose evaluation for the pre-transplantation period is important for early detection of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are highly associated with the incidence of NODAT. Post-kidney transplant patients should have periodical blood glucose monitoring with more frequent assessment in the initial phase. As early hyperglycaemia development is a strong predictor for NODAT, prompt intervention is needed. When NODAT develops, monitoring and control of blood glucose profile, lipid profile, microalbuminuria, diabetic complications and comorbid conditions is recommended. Immunosuppressive regimen modification may be considered as suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline to reverse or to improve the diabetes after weighing the risk of rejection and other potential adverse effects. Strategies for modifying immunosuppressive agents include dose reduction, discontinuation, and selection of calcineurin inhibitor (CNI), anti-metabolite agents, mammalian target of rapamycin inhibitors (mTORi), belatacept and corticosteroids. Lifestyle modification and a conventional anti-diabetic approach, as in the type 2 diabetes mellitus guidelines, are also recommended in NODAT management.

KEYWORDS

New-onset diabetes mellitus, NODAT, post-kidney transplantation, prevention and management

INTRODUCTION

End-stage renal disease (ESRD) is a rising public health problem worldwide with a poor outcome and high cost. As reported by the United States Renal Data System (USRDS), the prevalence of ESRD in the United States has increased from 475,291 patients (1599 per million population) in 2005 to 593,086 patients (1752 per million population) in 2010.[1,2] In Australia, the prevalence of ESRD has also risen from 15,175 patients (746 per million population) in 2005 to 18,243 patients (843 per million population) in 2009.[2] ESRD patients require renal replacement therapy which consists of either dialysis or renal transplantation. Renal transplantation prolongs life, reduces morbidity, improves quality of life, enables social and medical rehabilitation and reduces the costs associated with the medical care of patients with ESRD.[3] Furthermore, the establishment of transplantation has been made possible by the introduction of immunosuppressant therapy.[4] In 2010, 16,843 kidney transplants were performed in patients aged 20 and older in the United States and 935 kidney transplants were performed among patients aged 19 and younger.[1]

Previous evidence demonstrates that post-transplant diabetes mellitus (PTDM),[5] now known as NODAT,[6] is an increasingly common complication of kidney transplantation. NODAT increases the risk of graft-related complications such as graft rejection, reduces graft function, graft loss and infection and subsequently reduces the survival of transplant recipients.[7,8] It is also a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients.[9] NODAT develops

as a consequence of both impaired insulin production and increased insulin resistance. These complications consequently increase medical costs.[8,10]

Definition

PTDM is the term that was commonly used in the past to describe this disorder.[5] Clinically, PTDM was defined as the need for treatment with glucose-lowering agents post-transplantation for more than 30 days consecutively.[5] However, the definition of PTDM underestimated the prevalence of this disorder, particularly for patients with asymptomatic hyperglycaemia. Therefore, in 2003, the World Health Organisation (WHO) and American Diabetes Association (ADA) refined the term to NODAT.[6] NODAT is diagnosed by using three criteria. These criteria include symptoms of diabetes plus casual plasma glucose (PG) concentrations ≥200 mg/dl (11.1 mol/l) or fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l) or two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline[11] added haemoglobin A_{1C} (HbA_{1C}) as part of the screening criteria for NODAT.

Incidence of NODAT

The reported incidence of NODAT mostly ranged from 2-50%.[5,7,10,12-17] The wide variation in the incidence rate is due to differences in diagnostic criteria, observation periods, presence of risk factors and immunosuppressant therapy used in the studies. Data from USRDS showed that adult kidney transplant patients have a higher incidence of NODAT, 41% at 36 months as compared with 13% among paediatric patients.[1]

Risk factors of NODAT

Multiple risk factors have been identified in the development of NODAT. These include older age (≥40-45 years),[18-24] ethnicity,[7,21-25] family history of diabetes,[20,22,23] hepatitis C infection,[21-24] increasing human leukocyte antigen (HLA) mismatches,[7,16] obesity (body mass index, BMI ≥30kg/m²),[20-24] donor source,[26] acute rejection,[21,27] genetic factors[24,28,29] as well as the type of immunosuppressive agents used to prevent and/or treat rejection.[24,30-32] Some studies also suggested that cytomegalovirus infection,[15,22,23] autosomal dominant polycystic kidney disease,[23,27,33] number of metabolic syndrome components[13,21] and peritoneal dialysis[19,34] are risk factors of NODAT development. Further evidence is needed to evaluate the association between these risk factors and NODAT.

Evidence supports a strong link between immunosuppression regimens and the development of NODAT. Immunosuppression therapy has customarily constituted triple therapy with: (1) a calcineurin inhibitor (CNI) (cyclosporine (CsA) or tacrolimus (Tac)); (2) an anti-metabolite agent (azathioprine (AZA) or mycophenolate mofetil (MMF)); and (3) a corticosteroid. Corticosteroids and CNI have both been clearly documented as contributory to the onset of NODAT, whereas AZA and MMF do not seem to influence glucose control. The development of diabetes in transplant recipients receiving prednisolone has been reported to be as high as 46%.[35] Although both CsA and Tac have been associated with an increased risk for diabetes after transplantation, clinical studies indicate that the risk for developing diabetes was found to be up to five times higher with Tac at one year after kidney transplantation compared with CsA.[7,36-39] Sirolimus (Sir), a mammalian target of rapamycin inhibitors (mTORi), has been associated with higher incidence of NODAT especially when used in combination with CNI.[25] Whereas, the use of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody in induction therapy, was linked to the development of NODAT in a single centre, retrospective study.[32]

METHOD

A literature search was performed to identify published studies on prevention and management of NODAT in kidney transplant patients. The search strategy involved using Boolean connectors of the following terms: kidney transplantation, new-onset diabetes mellitus, post-transplantation, diabetes mellitus after transplantation, screening, management, prevention, and risk factors. The search was limited to full-text articles published in English between 1980 and 2013. The electronic databases searched included Scopus, ISI Web of Knowledge, PubMed, Science Direct, Springer Link, Proquest, Ebsco Host and Google Scholar. After excluding all irrelevant articles and duplicated citations, a total of 36 articles were included in the present review.

PREVENTION AND MANAGEMENT

Pre-transplantation screening and management

Before transplantation, all candidates are suggested to undergo a baseline evaluation including complete medical and family history, addressing both risk factors for diabetes[6,7,40] and other cardiometabolic risk factors such as hypertension, dyslipidaemia and smoking.[6,40] Periodical screening of FPG and/or OGTT are also recommended in evaluating the glucose metabolism status.[40,41] This screening helps to detect impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are highly associated with NODAT incidence. IFG is defined as FPG

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≥110 mg/dl (6.1 mmol/l) and <126 mg/dl (7 mmol/l). While assessing further with OGTT, IGT is defined as OGTT ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l).[40,42] However, optimal timing of pre-transplant screening has not been established.[40,43] HbA_{1C} is not recommended as part of the screening strategy owing to low sensitivity in ESRD patients.[40,41]

Patients at risk of NODAT should be counselled on the importance of lifestyle modification including weight control, diet, exercise and smoking cessation.[6,22,40] Overweight patients should achieve a weight reduction of at least 7% of the initial body weight.[43] Dietician referral may be needed to enhance the intervention. A low saturated fat and cholesterol and high complex carbohydrate and fibre diet is encouraged, especially in diabetic dyslipidaemia patients.[22] Physical activity of at least 150 minutes a week is recommended as a prevention strategy for NODAT.[22] Treatment of hepatitis C with interferon and sustained virological response prior to transplantation may reduce the risk of NODAT.[11,44] Studies have shown a lower incidence of NODAT in hepatitis C treated patients.[45,46] Other cardiometabolic risk factors such as dyslipidaemia and hypertension should be addressed accordingly.[43] After pre-transplant assessment, prospective tailoring of immunosuppressants may minimise the risk of NODAT.[6,15,40] *Figure 1* summarises the pre-transplant screening and management recommended by guidelines[6,11,40] and studies.[7,15,22,23,41-48]

Post-transplantation screening

According to the 2009 KDIGO guideline,[11] it is recommended to screen all non-diabetic kidney transplanted patients for NODAT with FPG, OGTT and/or HbA_{1C} 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.[11] The diagnosis of NODAT is based on the criterion set by the WHO and ADA.[6] Blood glucose monitoring is essential as studies have demonstrated that occurrence of hyperglycaemia during the initial period of post-renal transplantation[49,50] and IFG or IGT[6,51] are strong predictors for the development of NODAT. However, there are other opinions with regards to NODAT screening. A Norwegian study recommended a combination of OGTT at three months post-transplantation when the FPG is between 95 and 124 mg/dl (5.3-6.9 mmol/l) and/or when HbA_{1C} is ≥5.8%.[52] Rodringo *et al.*[53] recommended the use of the score of Chakkera *et al.*[54] at pre-transplantation to predict NODAT while the San Antonio Diabetes Prediction Model or Framingham Offspring Study-Diabetes Mellitus algorithm are recommended from the first year onwards post-transplantation. A summary of the screening and management strategies recommended by various guidelines[6,11,40] and studies[12,15,21-24,42-44,47,48,52,55-59] is given in *figure 2*.

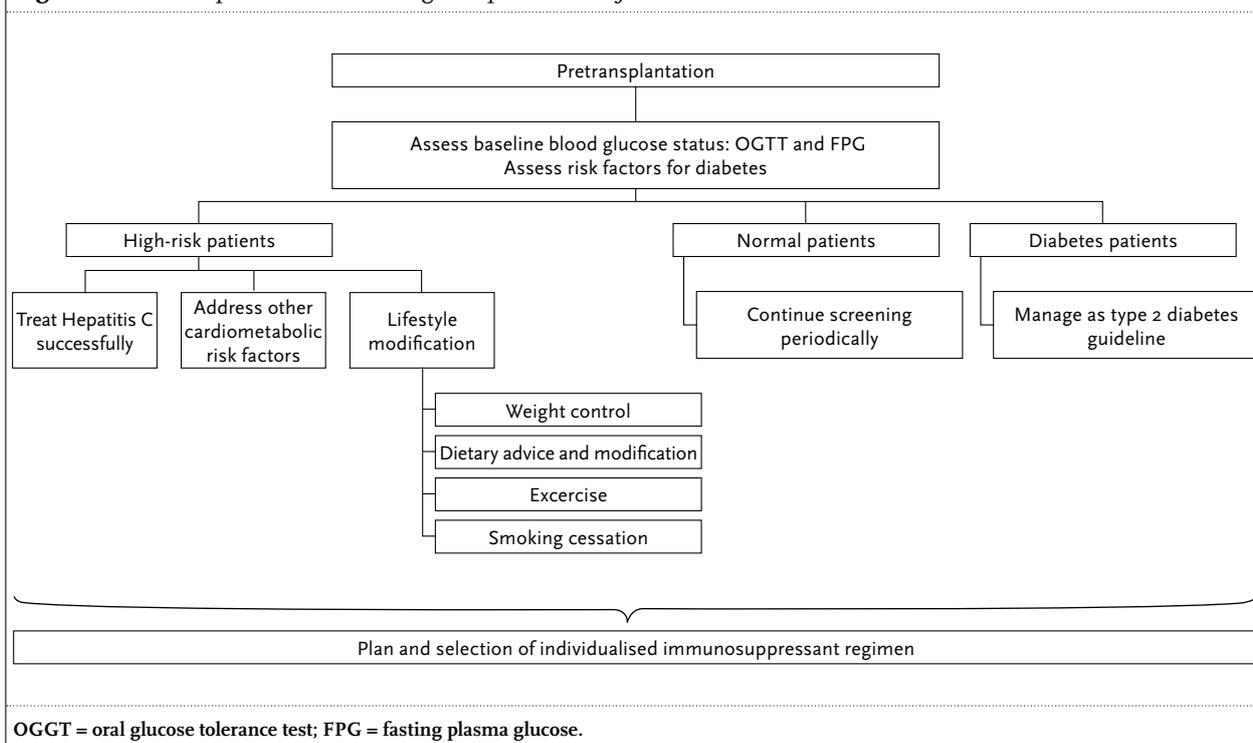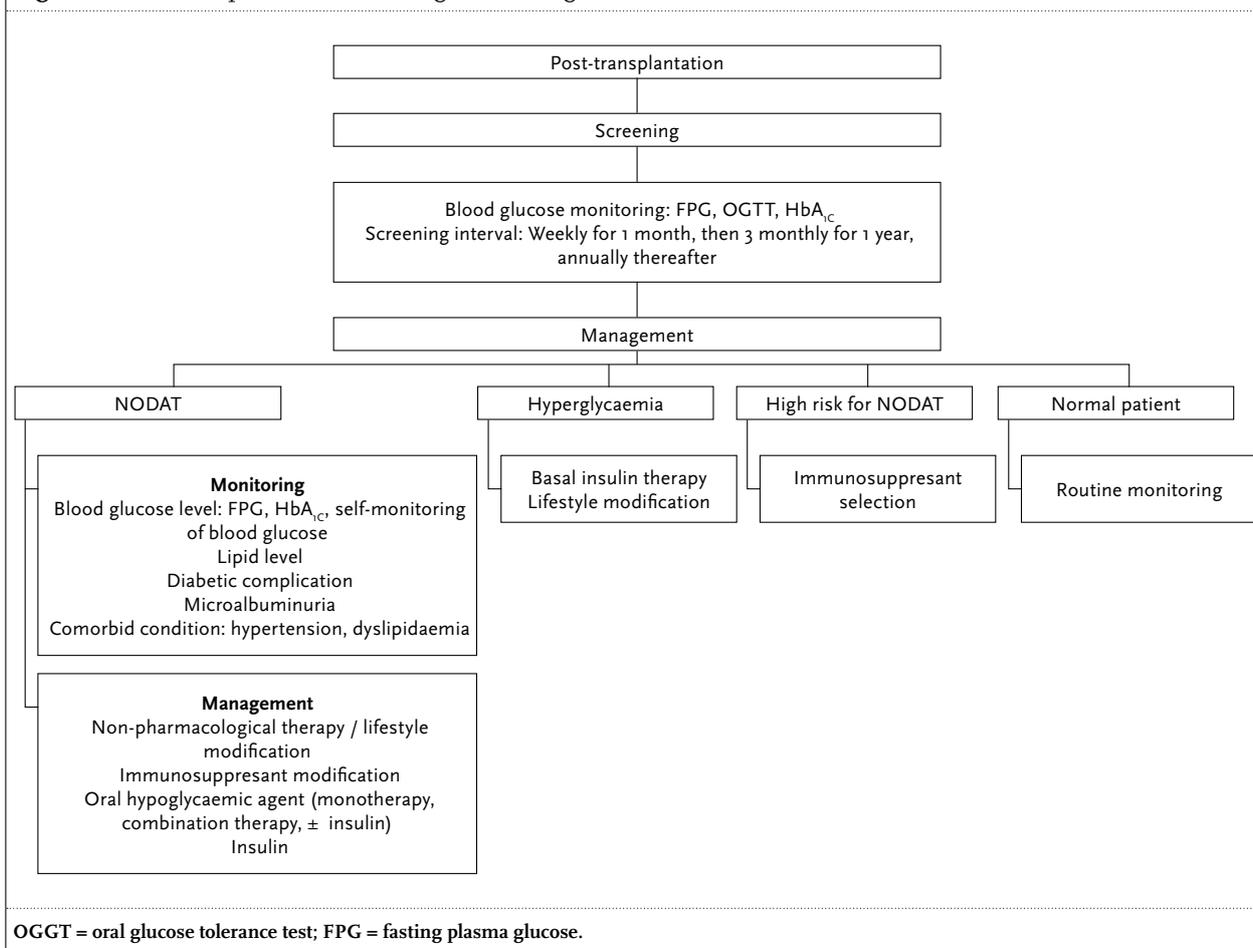**Figure 1.** *Pre-transplantation screening and prevention of NODAT*

OGGT = oral glucose tolerance test; FPG = fasting plasma glucose.

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Figure 2. *Post-transplantation screening and management*

Post-transplantation

Screening

Blood glucose monitoring: FPG, OGTT, HbA$_{1C}$
Screening interval: Weekly for 1 month, then 3 monthly for 1 year, annually thereafter

Management

NODAT | Hyperglycaemia | High risk for NODAT | Normal patient

Monitoring
Blood glucose level: FPG, HbA$_{1C}$, self-monitoring of blood glucose
Lipid level
Diabetic complication
Microalbuminuria
Comorbid condition: hypertension, dyslipidaemia

Management
Non-pharmacological therapy / lifestyle modification
Immunosuppresant modification
Oral hypoglycaemic agent (monotherapy, combination therapy, ± insulin)
Insulin

Basal insulin therapy
Lifestyle modification

Immunosuppresant selection

Routine monitoring

OGGT = oral glucose tolerance test; FPG = fasting plasma glucose.

NODAT

When NODAT develops, patients should be routinely monitored for FPG and HbA$_{1C}$. HbA$_{1C}$ should be monitored three monthly[6] with a target of 7-7.5%.[11] Targeting HbA$_{1C}$ ≤6.0% should be avoided especially if hypoglycaemic reactions are common.[11] Careful interpretation of the HbA$_{1C}$ test result is needed in patients with anaemia or kidney impairment.[6] Self-monitoring of blood glucose is encouraged, particularly for patients on non-pharmacological therapy and receiving oral hypoglycaemic agents or insulin.[6] The suggested target of fasting blood glucose in the morning is 90-130 mg/dl (5.0-7.2 mmol/l) and the target before bedtime is 110-150 mg/dl (6.1-8.3 mmol/l).[40]

Annual screening of the lipid profile is advocated in NODAT patients, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides[6] due to frequent changes in glycaemic control in these patients and the effect of this on the lipoprotein level. Besides, NODAT patients need to be screened for diabetic complications annually, such as retinopathy and neuropathy.[6] Consideration may also be given to screening for the presence of microalbuminuria, although the validity of such screening has not been verified.[6] Lifestyle modification including dietary, exercise, weight control and smoking cessation is emphasised as initial non-pharmacological therapy to improve glycaemic control in NODAT and early post-transplant hyperglycaemic patients.[22,48,60]

Immunosuppressive regimen
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.[11] The changes suggested by KDIGO[11] 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.
However, a combination of CNI and mTORi therapy[21,22,30,31] and switching from Tac to Sir is not recommended because

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it can worsen insulin resistance.[61] Tapering the dose of Tac[48] and Sir[30] to a lower range is not recommended due to the rejection risk, particularly in high immunological risk.

Steroid-sparing strategies have been shown to reduce NODAT incidence requiring any treatment. Although these strategies were associated with an increase in acute rejection, there was no increment in the mortality due to graft loss.[59,62] These strategies may be safe, provided antibody induction treatment is prescribed a few days post-kidney transplantation or after 3-6 months if such induction is not applied.[59] Prednisolone withdrawal is generally not recommended due to the risk of acute rejection, despite marginal effects on glucose control. Thus, a low maintenance dose of prednisolone 5 mg/day is advocated.[51,63] Careful selection of patients with low immunological risk is advisable if prednisolone withdrawal is to be considered.[63,64] In a 12-month study a regimen based on belatacept, a selective T-cell costimulation blocker, was associated with better cardiovascular and metabolic risk profiles, with lower blood pressure and serum lipids, and less incidence of NODAT as compared with CsA.[65] Currently, an on-going randomised study is being conducted to assess whether belatacept is an appropriate alternative immunosuppressive agent against Tac for NODAT patients.[66]

Ghisdal *et al.*[15] suggested an algorithm for the management of immunosuppressant regimens aiming to reduce the risk of NODAT and improve established NODAT. The first choice of immunosuppressant depends on the patient's immunological risk. High immunological risk is defined as those patients with a third or fourth transplantation, second transplantation if the first was lost in less than two years, presence of anti-HLA antibodies or high panel-reactive antibodies and five to six HLA mismatches. These patients are recommended to undertake regimens consisting of Tac, corticosteroid and mycophenolic acid (MPA). Whereas regimens of either CsA or belatacept plus corticosteroids and MPA are suggested for those with low immunological risk but high NODAT risk. When NODAT develops, the level of Tac and MPA should be monitored to ensure better glucose control. With Tac regimens a trough level of 6-8 ng/ml should be achieved in low immunological-risk patients and 8-10 ng/ml in high immunological-risk patients, while the area under the curve (AUC) of MPA should be 30-60 mg h/l.[67] For patients with CsA regimens, the strategy of tapering off the steroid while maintaining MPA at the optimal AUC level can be considered. When diabetes is no longer controllable (HbA$_{1C}$ >7% and/or insulin requirement), switching from Tac to CsA in high immunological-risk patients is advised, whereas a switch from CsA to belatacept may be considered when the immunological risk is low. Tac offered a better

protection against rejection than CsA despite higher incidence of NODAT.[7] However, long-term data are not available to justify the benefit of diabetes control in Tac conversion therapy.[22,48]

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 choice of drugs should be based on pharmacological properties[24] with benefits weighed against side effects including weight gain and hypoglycaemia,[68] and potential drug-drug interactions with immunosuppressant regimens, which may lead to glomerular filtration impairment, weight gain and/or risk of osteoporosis.[23,47] Besides, with advancement of atherosclerosis, these agents serve to improve rather than worsen the risk of progressive cardiovascular disease. Thus, the recommended first-line oral glucose-lowering agents are mainly insulin secretagogues, including sulfonylurea (glipizide) and meglitinides (repaglinide and nateglinide).[48,58] Meglitinides are recognised to be the safest due to no interaction with the CNI, no renal or liver insufficiency effect and are the first choice drug for elderly transplant patients at low dose.[6] Metformin, an insulin sensitiser, is recommended for use only if the patient's glomerular filtration rate is more than 60 ml/min/1.73m^2.[48,69] Thiazolidinedione usage has yielded variable results. In a study, it was shown to be safe to use up to 37 months post-transplant.[69] However, thiazolidinediones should be used with caution due to various side effects including oedema, weight gain and fracture.[22,23,43] Metformin and pioglitazone are claimed to be useful in treating preexisting diabetes mellitus and NODAT in patients with good allograft function,[69] but not as prevention strategies.[44] Sarno *et al.*[24] suggested that the use of oral glucose-lowering agents should be based on the patient's diabetic risk factors and the probable diabetogenic effects aroused. When combination therapy is required, metformin may be used with glipizide, sitagliptin or insulin, while sitagliptin may be used with insulin.[48] Nonetheless, dose adjustment is needed for sitagliptin in renal insufficient patients. Currently, there is no established safety and efficacy evidence to support the use of incretin-based therapy in the treatment of NODAT.[22,43,48]

Insulin therapy
When glycaemic control fails to achieve FPG <120 mg/dl (6.7 mmol/l), PG <160 mg/dl (8.88 mmol/l) or HbA$_{1C}$ <7%, insulin in combination with oral glucose-lowering agents is often initiated.[70] In order to control late afternoon or early evening glucose level, intermediate-acting neutral protamine Hagedorn (NPH) insulin would be useful. If the approach fails to control the postprandial glucose level,

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short-acting insulin aspart or lispro may be added into the routine treatment. NPH insulin, glargine or detemir insulin may be given in addition at night to control the surge of morning blood glucose.[70]

Chakkera *et al.*[49] showed that hyperglycaemia post-transplantation is significantly associated with the development of NODAT. Thus, intervention for hyperglycaemia is needed in order to prevent NODAT. Experts have suggested that keeping the average PG at <180.2 mg/dl (10 mmol/l) and HbA_{1C} <8%, is safe in the first post-transplantation week.[48] Hecking *et al.*[55] proposed that for post-transplanted patients with evening hyperglycaemia (glucose level >200 mg/dl or 11.10 mmol/l), early basal insulin is effective in reducing both NODAT development and HbA_{1C}. In the randomised study conducted by Hecking *et al.*[55] the basal insulin group was first treated with a morning dose of 6, 8, or 10 IU of NPH insulin when the previous evening blood glucose was >140 mg/dl (7.8 mmol/l), 180 mg/dl (10.0 mmol/l) or 240 mg/dl (13.3 mmol/l). Short-acting insulin will be used to further correct the hyperglycaemia event during postoperative inpatient care, followed by NPH insulin dose increment. The normoglycaemic goal was 110-120 mg/dl (6.1-6.7 mmol/l). The control group received conventional anti-diabetic and anti-hyperglycaemic treatment with short-acting insulin and/or oral glucose-lowering agents when the blood glucose level was ≥180 mg/dl (10.0 mmol/l). As a result, the treatment group had a 37% lower chance of NODAT (odds ratio 0.27; 95% confidence interval, 0.10-0.72) than the control group while HbA_{1C} was on average 0.38% lower in the treatment group than the control group.[55]

In a guideline developed by the International Diabetes Federation,[40] insulin is recommended to manage acute hyperglycaemia when the PG level is ≥250 mg/dl (13.9 mmol/l). A continuous infusion of insulin 50 IU/hour is recommended to maintain a morning blood glucose level between 80-110 mg/dl (4.4-6.1 mmol/l). When the condition is stabilised, conventional glycaemic maintenance level will be implemented and conventional type 2 diabetes mellitus therapeutic practice may be adopted. However, when chronic hyperglycaemia occurs, blood glucose targets should be individualised and a conventional diabetes therapy is adjusted accordingly to control the patient's blood glucose level. Thus the precise intervention requirement will be individualised to achieve optimum outcome.[40]

Comorbid conditions

Comorbid conditions, mainly dyslipidaemia and hypertension, should be aggressively treated to reduce the risk of cardiovascular morbidity and mortality.[6,23] The target of LDL-C in the post-kidney transplant patient is ≤100 mg/dl (2.60 mmol/l) or ≤70 mg/dl (1.8 mmol/l) for those with established cardiovascular disease.[11,42] Medical nutritional therapy should be initiated while statins may be considered for patients with LDL-C of 100-129 mg/dl (2.60-3.35 mmol/l). Whereas, patients with LDL-C ≥130 mg/dl (3.38 mmol/l) should receive statins as primary treatment plus a medical nutritional therapy.[6] Pravastatin and fluvastatin[48,56] are the preferred statins, since they are not metabolised by CYP 3A4.[43] Furthermore, exposure to Sir and glucocorticoids is associated with hypertriglyceridaemia. Thus, close monitoring of the degree of hypertriglyceridaemia is warranted and treatment with fibrates may be required. However, if the patient is prescribed a statin, fish oil is an alternative instead of fibrates, which are associated with the risk of rhabdomyolysis.[43]

A 50-90% incidence of hypertension is observed among kidney transplant patients and it is an independent risk factor for cardiovascular disease.[11] The recommended target for blood pressure control by ADA[6] and KDIGO[11] is <130/80 mm/Hg for a type 2 diabetes mellitus patient. However, Jenssen *et al.*[48] suggested that the high blood pressure should be treated with caution in NODAT patients with a proposed target not lower than 140/90 mmHg. This is to prevent the development of orthostatic hypotension due to aggressive treatment, especially in patients with extensive arteriosclerosis and autonomic neuropathy. Generally, there is no specific contraindicated antihypertensive drug in post-kidney transplant patients and any class of it may be used.[11] The initial choice is weighted by the benefits against the presence of post-transplant complications while monitoring closely for any adverse effects and drug-drug interactions.[11] Immunosuppressive agents including corticosteroids and CsA may also lead to blood pressure elevation[11,43] and justification is needed in considering dose adjustment, immunosuppressive agents selection and modification. Aspirin therapy should be given for patients with cardiovascular disease.[48]

CONCLUSION

Currently, the diagnostic criteria for IFG, IGT and NODAT set by the WHO and ADA are widely used. The use of these criteria allows early detection and prompt action to be taken to manage the condition. Apart from using OGTT and FPG, as recommended by WHO and ADA, the KDIGO has suggested HbA_{1C} as an additional screening parameter for NODAT after the kidney transplantation. NODAT and type 2 diabetes mellitus have many similarities in terms of risk factors, screening, monitoring, management and prevention strategies. Early detection and proper intervention should be taken during pre- and post-kidney

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transplantation to reduce the incidence of NODAT and the consequent cardiovascular risk factors. Individualisation of immunosuppressive therapy also plays a role in reducing the risk and ameliorates the NODAT. Selection of immunosuppressive and anti-diabetic regimens should be justified based on the benefits, immunological risk, risk of NODAT and the probability of drug-drug interaction.

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