New-onset diabetes mellitus after renal transplantation

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Background and Aim. Diabetes mellitus is a very common metabolic disease with a rising incidence. It is both a leading cause of chronic renal disease and one of the most serious comorbidities in renal transplant recipients. New-onset diabetes after renal transplantation (NODAT) is associated with poor graft function, higher rates of cardiovascular complications and a poor prognosis. The aim of this paper is to review current knowledge of NODAT including risk factors, diagnosis and management.
Methods. A MEDLINE search was performed to retrieve both original and review articles addressing the epidemiology, risk factors, screening and management of NODAT. We also focused on microRNAs as potential biomarkers of NODAT.
Results and Conclusion. Understanding the risk factors (both modifiable-e.g. obesity, viruses, and unmodifiable-e.g. age, genetics) may help reduce the incidence and impact of NODAT using pre- and post-transplant management. This can lead to better long-term graft function and general transplant success.

Key words: diabetes mellitus, renal transplantation, NODAT, microRNA

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INTRODUCTION

Kidney transplantation is the treatment of choice for end-stage renal disease, as it allows maximal preservation of kidney function and improves the patients' quality of life. With the improved survival of patients and grafts, more attention is being paid to non-immunological complications of transplantation with significant impact on morbidity and mortality. Among other complications, new-onset diabetes mellitus after transplantation (NODAT) has become more prominent recently. The clinical significance of NODAT is reasonable as it leads to shorter survival of recipients, especially from cardiovascular and infectious complications, as well as of grafts. The purpose of this review is to summarize findings about NODAT, its pathogenesis, diagnosis, prevention and treatment. One part will be devoted on microRNAs (miRNAs), small non-coding RNA molecules playing a role in the pathogenesis of diabetic nephropathy (DN) and probably also in NODAT.

ETIOLOGY AND PATHOGENESIS

New-onset of diabetes mellitus (DM) occurs in approximately one third of renal transplant recipients, with the rate ranging between 7 and 46% (ref.[1-7]). The prevalence depends on the definition of DM, study design, immunosuppressives and time from transplantation.

Although the etiology of NODAT is still not understood, insulin resistance and insulin deficiency have been identified as key metabolic abnormalities that may develop through a variety of biochemical parameters[8]. Both traditional type 2 DM risk factors and risk factors unique to transplant recipients are associated with NODAT (ref.[1,7]). Since NODAT is a very serious complication in patients after renal transplantation, identification of the risk factors may help prevent the condition. The risk factors can be divided into two groups, modifiable and non-modifiable. The non-modifiable risk factors are age, ethnic and genetic background, family history of type 2 DM, polycystic kidney disease and previous impaired glucose tolerance. The modifiable risk factors are obesity, viral infection, immunosuppressive drugs, human leukocyte antigen mismatch, donor gender and underlying renal disease. All these will be described below.

RISK FACTORS

Non-modifiable risk factors
Age
People older than 40-45 years of age are at higher risk for developing NODAT (ref.[3,11]). Recipients older than 45 years are 2.9 times more likely to become diabetic post-transplant than younger recipients[7]. Age increases the risk for developing of NODAT by 1.5 fold for every 10-years increase in age[9].

Race
African American and Hispanic populations are at higher risk for NODAT than Caucasians[1,7]. 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[10]. This finding is consistent with

the fact that the incidence of type 2 DM is significantly higher in African Americans then in Caucasians, in the general American population[11-12].

Family history

Like type 2 DM, a positive family history of diabetes is considered a risk factor for NODAT. People with a history of DM among first-degree relatives should be identified to prevent the development of NODAT. A family history of diabetes increases the risk for NODAT up to seven times[11].

Genetic backround

HLA mismatching has been associated with an increased risk of NODAT, although HLA phenotype cannot be considered a reliable risk factor for NODAT (ref.[3]). 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 (ref.[13-14]), while another study showed no significant relationship between TCF7L2 genotypes and the development of NODAT (ref.[15]). 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 (ref.[16-17]). A plausible mechanism for the association needs to be explained.

Modifiable risk factors
Obesity

Obese patients (BMI over 30kg/m^2) have a relative risk for NODAT of 1.73 (95% CI 1.57-1.90, $P < 0.0001$) (ref.[1]) and obesity, along with age, is one of the strongest risk factors. The NODAT risk increases linearly for every 1 kg above 45 kg[18]. Adipose tissue produces leptin, tumor necrosis factor alpha (TNFα), interleukins and adiponectin[19]. Activation of the TNFα system is associated with insulin resistance through the generation of defects in the phosphorylation of the receptor and decrease in expression in insulin-sensitive glucose transporters. Induction of interleukin 6 synthesis is associated with alteration in glucose tolerance and is possibly a predictor of type 2 DM. For every 1 µg/mL decrease in adiponectin, the risk of developing NODAT is increased by 13% (ref.[19]).

Proteinuria

Proteinuria developing within 3-6 months after transplantation is a strong risk factor for NODAT (ref.[20]). Low-grade (<1 g/day) and very low-grade (<0.3 g/day) proteinuria are independent risk factors for NODAT. There is a dose-dependent relationship across urinary albumin excretion categories (increasing risk from normoalbuminuria to albuminuria) with NODAT (ref.[20]).

Perioperative hyperglycemia

Perioperative hyperglycemia is also associated with NODAT[21-23]. Hyperglycemia is caused by stress reaction to surgery (catecholamines), corticosteroids and restoration of renal function. Hyperglycemia reduces expression of interleukin-1-beta-converting enzyme- inhibitory protein which leads to apoptosis of the pancreatic beta cells. In their study, Chakkera et al. showed that among 377 patients who developed hyperglycemia during their transplantation hospitalization, 29% (ref.[21]) developed NODAT within the first year after transplantation. NODAT developed in just 4% (ref.[21]) patients without inpatient hyperglycemia. Post-transplant inpatient hyperglycemia was defined as any bedside capillary blood glucose over 11.1 mmol/L.

Infection

Viral infections have been described as risk factors for NODAT. Transplanted patients are primarily more prone to infections than the general population. The main relevant viruses are chronic hepatitis C virus (HCV) and cytomegalovirus (CMV) infections correlate with NODAT.

Hepatitis C

A higher prevalence of type 2 DM has been reported with HCV infection in the general population[24]. The infection is a significant comorbid condition in kidney transplant recipients and is associated with increased risk for both graft failure and mortality[3]. A 2005 meta-analysis of 10 studies of 2,502 patients found that anti-HCV-positive patients were nearly four times likely to have NODAT compared with uninfected individuals[25]. Hepatitis C virus elicits an apoptosis-like death of pancreatic beta-cells through an endoplasmic reticulum stress-involved, caspase 3-dependent pathway[26]. 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[10].

Cytomegalovirus

Cytomegalovirus infection has been associated with DM 1. Kidney recipients who have symptomatic or asymptomatic CMV disease are at higher risk for developing NODAT. A study by Hjelmesaeth et al. reported that the incidence of NODAT was 6% in a control group and 26% (ref.[24]) in a group with asymptomatic CMV infection defined by monitoring CMV pp65 protein in blood. A 2014 meta-analysis with 1,389 kidney transplant patients showed that CMV infection is a risk factor for increasing incidence of NODAT. Prophylaxis against CMV infection after kidney transplantation is strongly recommended[27]. 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[27].

Glucocorticoids

Glucocorticoids are well known for leading to hyperglycemia by increasing glucose resistance, reducing insulin secretion and inducing beta cells apoptosis; they have

Table 1. Risk factors associated with NODAT.

Risk factor	Length of study	Type of study	Number of patients	RR/OR	Ref.
Age over 45 years	1982-1999	Observational study	2,078	RR=2.90	7
Race - African American	1996-2003	Observational study	11,659	RR=1.68	1
Race - Hispanic	1996-2003	Observational study	11,659	RR=1.35	1
Obesity (>30kg/m^2)	1996-2003	Observational study	11,659	RR=1.73	1
Proteinuria (>1g/day)	1985-2006	Observational study	828	RR=2.04	20
Perioperative hyperglycemia	1999-2008	Observational study	377	RR=4.01	21
Polycystic kidney disease (AD)	1985-2000	Cohort study	270	RR=2.87	16
Hepatitis C infection	1980-2004	Systematic review	2,502	OR=3.97	25
CMV infection	1990-2014	Meta-analysis	1,389	OR=1.94	27
Steroids	2004-2009	Meta-analysis	25,837	OR=1.42	32
Tacrolimus versus cyclosporine	2004-2009	Meta-analysis	25,837	OR=1.25	32
Sirolimus	1995-2006	Observational study	20,124	RR=1.36	39

RR (relative risk), OR (odds ratio)

been shown to reduce the expression of glucose transporter 2 and glucokinase[28]. The effect of glucocorticoids is dose-dependent.

Although postoperative withdrawal of corticosteroids remains a matter of controversy in clinical studies on renal transplantations, it is recognized that postoperative short-term pulsed therapy and low-dose maintenance therapy are not only safe but also reduce the risk of NODAT (ref.[29]). Also single-center studies have demonstrated that oral prednisolone dose reduction to 5 mg daily significantly improves glucose tolerance during the first year after transplantation[30] while a 0.01 mg/kg/day increase in prednisolone dose is associated with a 5% (ref.[31]) risk of developing NODAT. A large retrospective study from years 2004-2006 with more than 25,000 transplant recipients demonstrated that steroid-free immunosuppression was associated with a significant reduction in the likelihood of developing NODAT compared to steroid-containing regimens. The cumulative incidence rates of NODAT within three years post-transplant were 12.3% and 17.7% (ref.[32]) in steroid-free and steroid-containing regimens, respectively.

Calcineurin inhibitors

Both cyclosporine and tacrolimus are strongly associated with NODAT development. Calcineurin inhibitors (CNIs) induce NODAT by decreasing insulin secretion and due to direct toxic effects on pancreatic beta cells. In their meta-analysis, Sharif et al. found that CNI-sparing strategies are associated with less delayed graft function, improved graft function and less NODAT (ref.[33]). Tacrolimus has usually been observed to be more diabetogenic[6]. A meta-analysis published in 2004 found that insulin-treated DM occurred in 9.8% of renal transplant recipients on tacrolimus versus 2.7% (ref.[6]) of those on cyclosporine-based regimen. The DIRECT study showed that the incidence of NODAT at 6 months after transplantation was significantly lower in cyclosporine-treated patients than tacrolimus-treated patients[34]. It is not clear whether the effect of CNIs on glucose metabolism is dose-dependent. Gourishankar et al.[9] found no relationship between cyclosporine and tacrolimus trough blood levels at any time points (1 month, 6 month, 1 year, 5 year) and NODAT. In contrast, Maes et al. showed that the number of tacrolimus trough levels over 15ng/mL during the first month after transplantation determined the development of NODAT (ref.[35]). Voclosporin is a novel calcineurin inhibitor being developed for organ transplantation. The PROMISE study showed that the incidence rates of NODAT for voclosporin were 1.6%, 5.7% and 17.7% (low, medium and high concentration, respectively) as compared with 16.4% (ref.[36]) in tacrolimus.

Sirolimus

Sirolimus is a diabetogenic agent. Calcineurin inhibitors to sirolimus conversion therapy and tacrolimus withdrawal in a regimen consisting of tacrolimus and sirolimus were associated with a 30% increased incidence of impaired glucose tolerance[37-38]. Johnston et al. demonstrated that patients treated with sirolimus in combination with CNIs (cyclosporine or tacrolimus) had the highest incidence of NODAT (ref.[39]).

Other immunosuppressive agents, azathioprine and mycophenolate mofetil (MMF) are not diabetogenic. The combinations of tacrolimus+MMF or cyclosporine+MMF are associated with lower rates of NODAT compared to tacrolimus+azathioprine[40]. The combination of either calcineurin inhibitor with sirolimus may be particularly diabetogenic, compared with the combination of a CNI with MMF (ref.[32]).

Table 1. summarizes the relevance of risk factors expressed as relative risk (RR) or odds ratio (OR).

DIAGNOSIS

NODAT usually occurs early after kidney transplantation. The estimated incidence rates in the United States are 9.1% at 3 months, 16% at 12 months, and 24% at 36 months (ref.[1]).

In 2003, the International Consensus Guidelines on NODAT were published. They recommended that the diagnosis of NODAT should be based on the 2003 American Diabetes Association criteria for type 2 DM (ref.[3,4]). Diabetes mellitus is diagnosed by any of the following criteria:

1. Symptoms of DM (polyuria, polydipsia, unexplained weight loss) and random plasma glucose over 11.1 mmol/L.

2. Fasting plasma glucose over 7 mmol/L (8 h of fasting).

3. Using oral glucose tolerance test with 2-hour plasma glucose over 11.1 mmol/L (this test should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water).

FUTURE PERSPECTIVE OF NODAT

Special attention is paid to microRNAs that have attracted a high level of interest lately. miRNAs are endogenously produced short noncording RNAs of 19-23 nucleotides that play an important role in modulating gene expression affecting almost every key cellular function[41]. They can bind to the 3` untranslated region of miRNA of protein-coding genes to down-regulate their expression[42]. miRNAs are potential sensitive biomarkers for human diseases (cancer, cardiovascular disease, autoimmune diaseases, etc.) and tissue injury. They are stable and easy to quantify in a non-invasive manner in plasma and urine[43]. A number of studies have aimed to clarify the repertoire of miRNAs in the development and progression of DN but there is no study on miRNAs and NODAT. miR-155 and miR-146a were found to be increased more than 5-fold in samples from DN patients compared to controls, and miR-155 expression was closely correlated with serum creatinine levels. During the induction and progression of the diasease in type 1 and type 2 DN rat models, miR-155 and miR-146a were demonstraded to increase gradually[44]. Also, miR-126 can be used as a biomarker for pre-diabetes and DM. It is significantly lower in patients with impaired fasting glucose, impaired glucose tolerance or with DM than in healthy controls[45]. Another study showed that deregulation of miR-29 was involved in the pathogenesis of DN and insulin resistance and may thus be implicated in diabetic vascular complication. Patients with albuminuria showed significantly higher levels of urinary miR-29a than those with normal albuminuria[46].

Accumulation of extracellular matrix proteins such as collagen (fibrosis) and mesangial expansion (hypertrophy) in the kidney mesangium and tubular compartments, along with podocyte dysfunction, are major hallmarks of DN, and contribute to renal failure in DM (ref.[47-49]). Transforming growth factor- β1 (TGF-β1) levels and signaling are enhanced in renal cells during the progression of DN. TGF- β plays a key role in mesangial fibrosis and hypertrophy under diabetic conditions by inducing the expression of extracellular matrix proteins such as collagen and fibronectin[48,50]. miR-216a, miR-217 and key miR-200 family members were increased in mouse kidney glomerular mesangial cells treated with TGF- β and in kidney glomeruli from mouse models of DM (ref.[51-52]). In addition, miR-192, which is highly expressed in kidney, is upregulated in mouse kidney glomerular mesangial cells treated with TGF- β and renal glomeruli from mouse models of type 1 and type 2 DM relative to the corresponding controls[49].

Therapeutic options may be focused on manipulating miRNA activity to attenuate disease progression. Inhibitors of miRNA expression include antagomirs which bind directly to miRNAs[53] or miRNA sponges which contain tandem repeats of miRNA-binding sites[54].

MANAGEMENT OF NODAT

Pre-transplantation management

Making an early diagnosis of NODAT is important because preventive measures can enhance the kidney transplant recipients` chances for a better quality of life and prolong graft survival[55]. All candidates on a waiting list should undergo a baseline evaluation including age, a history of the risk factors (BMI, hypertension, dyslipidemia, smoking) and a family history. At-risk patients should then be counselled on lifestyle changes, diet, exercise and smoking cessation. Overweight patients should achieve a weight reduction of at least 7% (ref.[56]) of initial body weight. Physical activity of at least 150 minutes a week is recommended as a strategy for preventing NODAT (ref.[57]).

Post-transplantation management

The 2009 KDIGO recommendations suggest screening for NODAT with fasting blood glucose, oral glucose tolerance and/or HbA1c tests weekly during the first four weeks after transplantation, then three, six and nine months posttransplant and then yearly. Screening for NODAT should also be performed after starting treatment with glucocorticoids, sirolimus or CNIs (ref.[58]).

Immunosuppressive protocols should be individualized according to the risk of NODAT, but the potential benefit of altering an immunosuppressive regimen must be weighed against the risk of allograft rejection. Glucocorticoid doses should be decreased as soon as possible, but complete withdrawal is recommended only in patients with low immunological risk and no history of acute rejection episodes[3]. Prednisolone dose reduction to 5 mg/day at one year has been associated with a decrease in glucose intolerance ranging from 55% to 34% (ref.[30]).

If lifestyle modifications alone are insufficient to control the hyperglycemia, pharmacotherapy targeting glucose metabolism should be initiated. The choice between insulin and oral hypoglycemic agents depends on the severity, timing and expected duration of hyperglycemia[59]. Since corticosteroids are typically administered in the morning, a combination of intermediate and short-acting insulin administered several times during the day and corresponding to mealtimes may be required[60]. In less urgent cases, oral hypoglycemic medication is recommended. No hypoglycemic agent is contraindicated in kid-

ney transplant recipients and there are no significant drug interactions with immunosuppressive drugs. Metformin as a first line agent in DM patients improves insulin sensitivity. The choice of metformin is dictated by the level of renal function. It is safe in patients with glomerular filtration rate over 50 mL/min per 1.73 m^2. One serious side effect is dyspepsia which can be aggravated by immunosuppressive agents used in kidney transplant recipients. Weight gain is common among solid organ recipients, with average weight gains of 8-14 kg in the first year post-transplantation[61]. A Cochrane review and meta-analysis that included randomized controlled trials of over 12 weeks duration found metformin to be weight neutral in comparison to placebo or diet in the general population[62]. Compared to sulfonylureas, metformin had a weighted mean difference in weight of -2.9 kg (95% CI -4.4 to -1.1) (ref.[62]). Sulfonylureas enhance insulin secretion and their use is also dictated by renal function. Thiazolidinediones are insulin sensitisers, rosiglitazone has been shown to improve glucose tolerance, insulin sensitivity, and even endothelial function[63]. Dipeptyl peptidase-4 inhibitors selectively foster insulin secretion without inducing hypoglycemia, which might be advantageous in kidney transplant recipients with NODAT. Dipeptyl peptidase-4 inhibition (vildagliptin, sitagliptin) in kidney transplant recipients with overt NODAT was found to be safe and efficient, providing a novel treatment alternative for this specific form of diabetes[64-66].

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