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REVIEW

New-onset diabetes mellitus after solid organ transplantation

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Summary

New-onset diabetes mellitus is a common complication of solid organ transplantation and is likely to become even more common with the current epidemic of obesity in some countries. It has become clear that both new-onset diabetes and prediabetic states (impaired fasting glucose and impaired glucose tolerance) negatively influence graft and patient survival after transplantation. This observation forms the basis for recommending meticulous screening for glucose intolerance before and after transplantation. Although a number of clinical factors including age, weight, ethnicity, family history, and infection with hepatitis C are closely associated with the new-onset diabetes mellitus, immunosuppression with corticosteroids, calcineurin inhibitors and possibly sirolimus plays a dominant role in its pathogenesis. Management of new-onset diabetes after transplantation generally conforms to the guidelines for treatment of type 2 diabetes mellitus in the general population. However, further studies are needed to determine the optimal immunosuppressive regimens for patients with this disorder.

Definitions and prevalence

Diabetes mellitus was first described as a complication of kidney transplantation over 40 years ago [1]. Since that time, it has become clear that new-onset diabetes mellitus promotes cardiovascular disease, graft failure and death in both kidney and other solid organ transplant recipients. However, until recently, the cardiovascular risk associated with prediabetic states, characterized either by impaired fasting glucose (IFG) or impaired glucose intolerance (IGT), has been underappreciated. The term 'new-onset diabetes mellitus after transplantation' (NODAT) has recently replaced the older term 'post-transplant diabetes mellitus' (PTDM) to differentiate new-onset diabetes mellitus from diabetes that existed prior to transplantation. Even more recently, Bloom and colleagues have introduced the term 'transplant-associated hyperglycemia' (TAH) to encompass the entire spectrum of diabetic and prediabetic states encountered after organ transplantation [2,3]. Collectively, these disorders of glucose regulation represent some of the most common complications encountered after solid organ transplantation. This review will focus on new-onset of diabetes mellitus after kidney transplantation with separate consideration of the incidence and natural history of NODAT in extra-renal transplantation.

Historically, the reported incidence of NODAT in kidney transplant recipients varied widely based on different definitions of the disorder in older studies. Nineteen of these older reports were summarized nicely in a meta-analysis that indicated an incidence of NODAT ranging from 2% to 50% in the first post-transplant year [4]. Varying definitions probably also account for the fact that some [5,6], but not all [4] reviews indicate that the incidence of NODAT has increased during the past three decades. It seems likely that the current epidemic of obesity in some countries will ultimately result in a higher incidence of diabetes mellitus in organ transplant recipients.

Some of the largest recent epidemiologic studies of NODAT in kidney transplant recipients each used Medicare claims to define the incidence. Kasiske *et al.* studied 11659 Medicare beneficiaries who received first kidney

transplants between 1996 and 2000 and reported a cumulative incidence of NODAT of 9%, 16%, and 24% at 3, 12, and 36 months, respectively [6]. When reviewing such data, it is important to keep in mind that a significant percentage of patients with NODAT might have developed diabetes mellitus even if they had remained on dialysis. Thus, the incidence of NODAT attributable to factors related to transplantation *per se* is the incremental difference between the baseline rate among wait-listed patients and the observed rate after transplantation. Woodward *et al.* studied Medicare beneficiaries transplanted between 1994 and 1998 and estimated the true incremental incidence of NODAT to be 8–10% during the first post-transplant year [7]. Although such studies have provided a wealth of information about NODAT in kidney recipients, it is likely that use of Medicare claims grossly underestimated the incidence of diabetic and prediabetic states.

In the past decade, most experts have embraced the strict definitions of diabetes mellitus and prediabetic states defined by the American Diabetes Association (ADA) [8] (see Table 1) in an effort to more rigorously define the prevalence and natural history of these disorders in the post-transplant setting. In a single-center study of 490 kidney recipients, Cosio used ADA criteria and described a 13% prevalence of NODAT and a 33% incidence of either IFG or IGT at 1 year post-transplant [9]. Nam *et al.* used World Health Organization criteria (similar, but not identical to the ADA criteria) for defining diabetes mellitus based on serial oral glucose tolerance tests in living-donor kidney recipients and reported either IFG or IGT in 46% of the patients at 1 year [10].

Impact on allograft and patient outcomes

A number of reports indicate that the development of NODAT adversely affects the survival and function of renal allografts. Using NODAT as a time-dependent covariate in a Cox regression analysis, Kasiske *et al.* showed that new-onset diabetes was associated with an increased risk of graft failure (relative risk 1.63, $P < 0.0001$) and death-censored graft failure (relative risk 1.87, $P < 0.0001$) [6]. Similarly, Roth *et al.* reported that, when compared with nondiabetic controls, kidney transplant recipients with NODAT exhibited a significant decrease in graft survival at 4 years (54% vs. 82%, $P < 0.05$) [11]. In a large single-center experience, Revanur *et al.* concluded that the long-term graft survival of patients with NODAT was comparable to that of patients with pre-existing diabetes mellitus and statistically inferior to that of nondiabetic patients [12]. Patients with NODAT have been shown to have significantly impaired renal function, based on serum creatinine concentrations, compared with nondiabetic controls at 5 years [13].

It is now also widely recognized that NODAT confers a higher likelihood of death after kidney transplantation when compared with that observed in patients without diabetes [6,12,14]. By the end of the first post-transplant year, the effect on patient mortality approaches that observed in patients with pre-existing diabetes mellitus [12]. Excess mortality may be attributable, in part, to a higher incidence of infectious diseases [6,15] but is primarily related to a higher incidence of cardiovascular disease [16,17]. One registry analysis actually showed that the risk of myocardial infarction in the first 3 years after transplantation was more strongly related to NODAT than to pre-existing diabetes mellitus [16]. The study of Cosio *et al.* demonstrated that even the prediabetic state characterized by IFG, 1 year after transplantation, is associated with a higher risk of cardiovascular events than that observed in patients with a normal fasting blood glucose (see Fig. 1). These observations form the basis for protocols that meticulously screen not only for overt diabetes, but for earlier prediabetic states (see below).

Table 1. American Diabetes Association Criteria for diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance.

Blood glucose concentration	Terminology
FPG (mg/dl)	
<100	Normal
100–125	IFG
>126	Diabetes mellitus
2-h glucose after 75 gm oral glucose load	
<140	Normal
140–199	IGT
>200	Diabetes mellitus

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

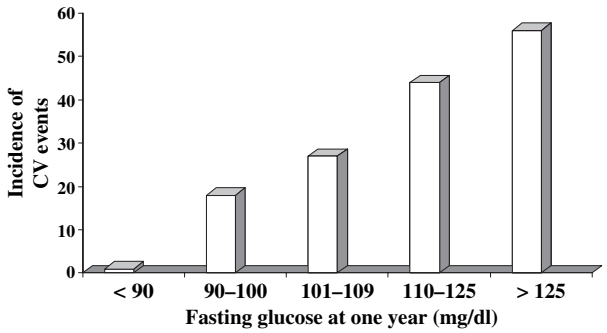

Figure 1 Cumulative 5-year incidence of cardiovascular (CV) events based on fasting plasma glucose levels measured 1 year after kidney transplantation. Adapted from reference [8].

NODAT almost certainly increases the economic burden of kidney transplantation, not only because of the cost of therapy to control hyperglycemia, but also because of the association between diabetes mellitus and cardiovascular complications. Woodward *et al.* estimated that Medicare paid an extra $21500 per new-onset diabetic patient by 2 years post-transplant [7].

New-onset diabetes mellitus after extra-renal transplantation

Assessing the incidence of NODAT after extra-renal transplantation also has been hampered by variable definitions. With that caveat in mind, Montori *et al.* reported a 12-month cumulative incidence of 13% and 11.9% among heart- and liver transplant recipients, respectively [4]. In a subsequent systematic review of the literature, Heisel *et al.* reported that the incidence of NODAT ranged from 7% to 26% in heart transplant recipients and from 0 to 32% in liver transplant recipients after follow-up of 5 to 11 years [18]. Data from the registry of the International Society for Heart and Lung Transplantation (ISHLT) indicates that the prevalence of diabetes mellitus is 24.3% and 33.5% at 1 and 5 years, respectively, after lung transplantation and 15.4% and 20% at comparable time intervals after heart-lung transplantation [19]. However, after excluding patients with pre-existing diabetes mellitus in a population of lung transplant recipients with relatively low rates of cystic fibrosis, Silverborn *et al.* reported lower rates of 6 and 7% at 1 and 5 years, respectively [20]. Among pancreas transplant recipients with functioning allografts (defined by intact perfusion and detectable serum levels of C-peptide), the incidence of NODAT has been reported at 19% at 39 months post-transplant [21], although the diagnosis of NODAT can be particularly difficult in pancreas transplant recipients who also can become hyperglycemic based on allograft rejection or recurrence of autoimmunity.

Several studies suggest that NODAT negatively influences graft and patient outcomes after extra-renal transplantation. John *et al.* compared 46 liver transplant recipients with NODAT (defined crudely as the need for insulin or an oral hypoglycemic agent 12 months post-transplant) to 92 nondiabetic controls. The rates of cardiovascular or neurologic events, infectious diseases, and acute rejection were higher in patients with NODAT although no difference in patient survival was detectable after 5 years [22]. In contrast, Baid *et al.* noted that NODAT was an independent risk factor for mortality after liver transplantation, especially in patients with hepatitis C [23]. Data from the ISHLT registry indicate that, in lung transplant recipients, 5-year mortality rates are 24% higher in patients with diabetes mellitus than in those without pre-existing diabetes mellitus or NODAT [19]. Valentine *et al.* have reported that heart transplant recipients with TAH have decreased actuarial survival rates and increased coronary intimal thickness as assessed by intracoronary ultrasound [24].

Pathogenesis and risk factors

Hyperglycemia after kidney transplantation results from some combination of increased insulin clearance, insulin resistance, and decreased insulin production (see Fig. 2). In the general population, the metabolic syndrome, characterized by obesity, hyperlipidemia, hypertension, and/or

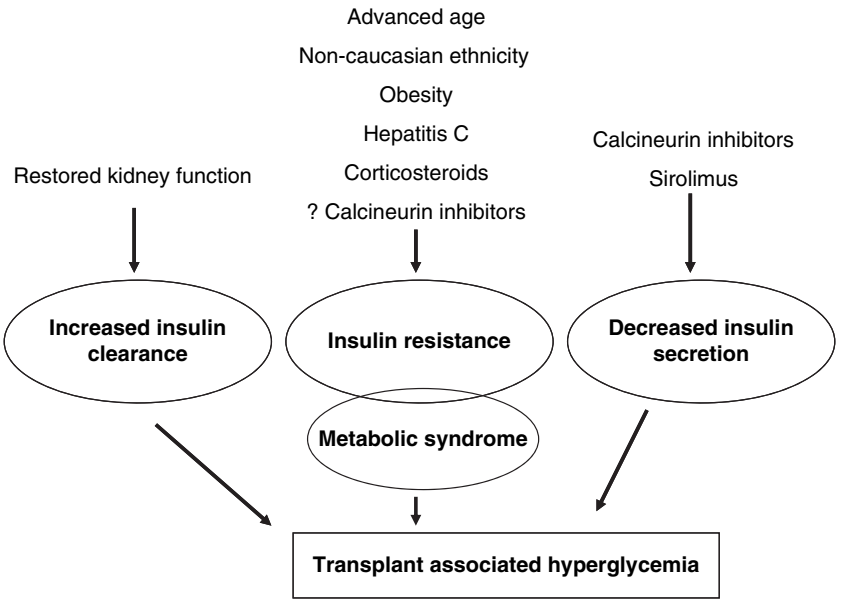

Figure 2 Pathogenic mechanisms leading to transplant associated hyperglycemia in kidney transplant recipients.

Table 2. Components of the metabolic syndrome (defined by the presence of three or more of the listed criteria).

Waist Circumference
Men: >40 inches (102 cm)
Women: >35 inches (88 cm)
Triglycerides: ≥150 mg/dl
Decreased high density lipoproteins
Men: <40 mg/dl
Women: <50 mg/dl
Elevated blood pressure
≥130/85 mm Hg, OR
Treatment with antihypertensive medications
Elevated fasting plasma glucose
≥100 mg/dl, OR
Treatment with antidiabetic medications

IFG (see Table 2) [25] is closely related to the development of overt diabetes mellitus and cardiovascular disease. In the transplant setting, there is almost certainly an interplay between metabolic syndrome and NODAT [26]. Weight gain may be a common link in some patients, although it is clear that NODAT can occur in the absence of weight gain or obesity. When compared with wait-listed dialysis patients, the incremental incidence of diabetes mellitus in kidney transplant recipients is pathogenetically linked most closely to immunosuppressive therapy with corticosteroids, calcineurin inhibitors, and/or sirolimus. However, several other clinical factors, in addition to metabolic syndrome, have been associated with an increased risk of developing NODAT. Consideration of such factors prior to transplantation can be used to predict a patient's risk for developing NODAT, to identify those who may require intensive laboratory monitoring, and possibly to individualize immunosuppression.

Role of immunosuppressive drugs

Corticosteroids

Glucose intolerance is a well-recognized complication of therapy with corticosteroids. These agents induce a state of insulin resistance characterized by decreased binding of insulin to insulin receptors and decreased utilization of glucose [27]. Corticosteroids also increase hepatic gluconeogenesis by enhancing the activity of gluconeogenic enzymes and by increasing the availability of gluconeogenic amino acids [27].

The diabetogenic effects of corticosteroids appear to be dose-related [28]. Conversely, several studies have demonstrated at least short-term improvements in glucose intolerance or even 'cure' of diabetes mellitus with either reduction in corticosteroid doses [29,30] or complete withdrawal of steroid therapy [31–33]. Some patients show a short-term improvement in glucose intolerance after steroid withdrawal, only to exhibit a later relapse of glucose intolerance [32], as might be expected when there is an underlying genetic predisposition to diabetes mellitus. The effects of complete corticosteroid avoidance or early corticosteroid withdrawal on the development of NODAT have been described in the Freedom trial [34], the CARMEN study [35], and the Astellas Corticosteroid Withdrawal Study [36]. In each of these studies, there were no statistically significant differences in the overall incidence of NODAT in steroid-free versus steroid-treated patients. However, in each study, there were trends towards less severe NODAT among steroid-free patients based on a reduced need for insulin therapy.

Calcineurin Inhibitors

Direct evidence of a diabetogenic effect of calcineurin inhibitors has been derived largely from studies of cyclosporine in animals. *In vivo* studies in rats suggest that cyclosporine administration is associated with decreased pancreatic insulin content and decreased beta islet cell volume [37–39]. Garvin *et al.* reported pancreatic islet cell toxicity resulting from cyclosporine in experimental islet cell autotransplantation in dogs [40]. Nielsen *et al.* demonstrated that cyclosporine also impairs the release of insulin from cultured human pancreatic islet cells [41]. However, the observations that cyclosporine-induced glucose intolerance is accompanied by relatively high levels of plasma insulin in rats [42] and of plasma C-peptide in humans [43] suggest that cyclosporine also may induce a state of peripheral insulin resistance.

Data on the mechanism of glucose intolerance mediated by tacrolimus are also contradictory. Animal experiments show decreased insulin secretion related to inhibition of the transcription of mRNA for insulin [44–46]. However, data in humans suggest insulin resistance with hyperinsulinemia [47–49].

Results from a number of clinical trials and multivariate analyses consistently indicate that use of tacrolimus is associated with a greater risk of NODAT than cyclosporine in kidney transplant recipients [6,7,50]. In the analysis of Kasiske *et al.* [6], the incidence of new-onset diabetes mellitus within the first 2 years post-transplant was approximately 70% higher in tacrolimus-treated patients than in those receiving nontacrolimus-based immunosuppression (29.7% vs. 17.9%) (Fig. 3). Most recently, the international multicenter DIRECT trial studied 682 patients randomized to receive either cyclosporine microemulsion or tacrolimus in addition to therapy with basiliximab, mycophenolic acid, and steroids. The incidence of NODAT or IFG was 26% and 33.6% ($P < 0.05$) in the cyclosporine versus tacrolimus groups, respectively [50]. It is noteworthy that these rates of NODAT and IFG are quite comparable to those described in US-based studies even though the DIRECT

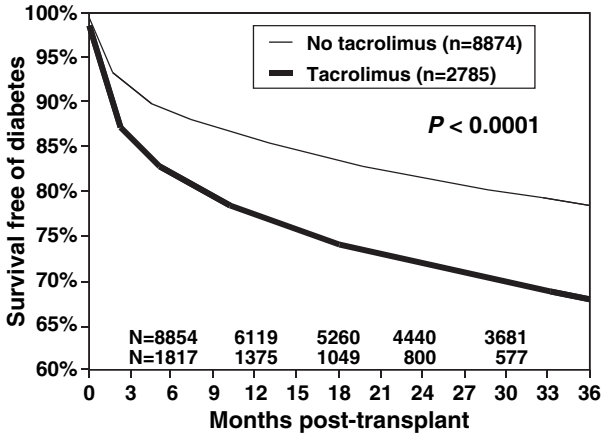

Figure 3 Survival free of new-onset diabetes mellitus for patients treated without (thin line) and with (thick line) tacrolimus as an initial maintenance immunosuppressive medication. Adapted from reference [6].

trial included mostly patients from Europe, where the incidence of obesity is lower.

Antiproliferative agents

First *et al.* analysed data from five transplant centers and concluded that the absence of treatment with an antiproliferative agent (i.e., mycophenolate mofetil or azathioprine) was associated with an increased risk of NODAT [51]. Similarly, Kasiske *et al.* showed that the use of these agents was associated with a lower risk of the disorder [6]. It is not clear whether such agents exert a directly beneficial effect on glucose intolerance or whether their adjunctive use simply allows the use of lower doses of corticosteroids and/or calcineurin inhibitors.

It is now clear that the target of rapamycin inhibitor, sirolimus, may also be diabetogenic. A number of studies in animals suggest that the drug may impair beta-cell proliferation *in vitro* and *in vivo* [52–54]. Clinically, the diabetogenic effects of sirolimus have been observed in patients converted from calcineurin inhibitors to this agent as part of 'conversion' protocols [55]. More recently, a registry analysis of 20,124 primary kidney transplants in the US convincingly demonstrated that sirolimus increased the risk of NODAT whether it was used in combination with either cyclosporine or tacrolimus [56].

Other risk factors

Ethnicity

In the United States, NODAT is more common in African Americans and Hispanics than in white or Asian patients. Sumrani *et al.* reported a 3.6% overall incidence in kidney transplant recipients: 4.8% incidence in Asians, 19.8% incidence in African Americans, and 21.3% incidence in Hispanics [15]. In two recent multivariate analyses, African American ethnicity emerged as one of the strongest independent correlates of NODAT [6,7]. The effect of African American ethnicity is magnified by the use of tacrolimus. In a U.S. multicenter phase III trial of tacrolimus therapy in kidney transplantation, the incidence of NODAT in African American patients treated with tacrolimus, azathioprine and prednisone was higher than in African Americans treated with cyclosporine, azathioprine, and prednisone (36.6% vs. 12.6%) [57].

Age

Considering the influence of advancing age on the incidence of diabetes mellitus in the general population, it is not surprising that increased age also is a risk factor for NODAT. Collective evidence from a number of studies suggests that the risk is increased in kidney transplant recipients over the age of 40 years [15,58]. A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) indicated that NODAT occurs in less than 3% of children [59]. However, more recent reports from single-centers report incidences in pediatric populations as high as 20% [59,60], possibly reflecting an increased use of tacrolimus. As is true in adults, African American ethnicity is associated with an increased incidence of NODAT in children [60].

Body weight

Because obesity is a known risk factor for type 2 diabetes mellitus, it is possible that higher rates of NODAT noted in some studies are related to the current epidemic of obesity in many western countries. Weight gain is common following kidney transplantation [61]. Furthermore, post-transplant obesity has been linked independently to reduced graft and patient survival [25,62]. Cosio *et al.* documented that the risk for developing NODAT increased by a factor of 1.4 for every 10 kg increase in body weight over 60 kg [14].

Family history

In many patients, NODAT reflects a genetic predisposition to diabetes mellitus influenced by multiple environmental factors and exposures. A family history of diabetes mellitus in first-degree relatives has been cited as a risk factor for NODAT in many studies, increasing the risk as much as sevenfold [15].

Hepatitis C

In the general population, diabetes mellitus has been reported to be more common in patients with hepatitis C than in other types of liver disease [63,64]. Several recent studies also suggest a strong association between hepatitis C infection and the development of diabetes mellitus after

either kidney- [65,66] or liver transplantation [23]. Treatment of hepatitis C with interferon-alpha results in improved glycemic control [67]. However, use of this agent is relatively contraindicated after transplantation because of the risk of promoting allograft rejection. The pathophysiologic mechanisms linking hepatitis C infection to hyperglycemia remain unclear. Postulated mechanisms include a direct cytopathic effect of the virus on beta cells, insulin resistance mediated by a postreceptor signaling defect, and decreased hepatic glycogenesis [68].

The risk factors noted above can be categorized as those that are modifiable (e.g. body weight, type of immunosuppression, and perhaps hepatitis C infection) and those that are nonmodifiable (e.g., age, ethnicity, and family history). In the analysis of Kasiske *et al.* [6], the relative risks (RR) of NODAT associated with these factors, in descending order of importance, were: age >60 years (RR 2.60), age 45–59 (RR 1.90), obesity (defined as body mass index >30 kg/m^2) (RR 1.73), African American ethnicity (RR 1.68), use of tacrolimus (RR 1.53), Hispanic ethnicity (RR 1.35), and presence of hepatitis C antibodies (RR 1.33).

Risk factors in extra-renal transplantation

Risk factors for NODAT in extra-renal transplant recipients are similar to those in kidney recipients. Dean *et al.* reported that the pretransplant insulin dose, body mass index and number of acute rejection episodes were significant predictors of NODAT in pancreas transplant recipients treated with a tacrolimus-based regimen [21]. In lung transplant recipients, Ollech *et al.* found NODAT to be more frequent based on body mass index, acute rejection and infection with cytomegalovirus [69]. An analysis of more than 500 liver transplant recipients indicated that the overall incidence of NODAT was 26.6% vs. 16.6% in patients treated with tacrolimus versus cyclosporine, respectively [70]. Clearly, the incidence of NODAT is much higher in patients with hepatitis C, ranging from 40 to 60% [23,67,71]. Driscoll *et al.* reported that infection with cytomegalovirus within the first post-transplant year also predicted NODAT in liver recipients [72]. Among heart transplant recipients, body mass index, age, urgency for transplant, number of rejection episodes, tacrolimus-based immunosuppression, family history of diabetes and pretransplant blood glucose all have been reported as independent risk factors for NODAT [73–75].

Prevention and screening

Pretransplant screening and counseling

Consideration of the risk factors listed above should be considered in assessing the pretransplant risk of NODAT, and is essential in future research endeavors designed to characterize the natural history of this disorder. Some assessment of glucose tolerance is warranted prior to transplantation, as frank glucose intolerance prior to transplantation is a likely correlate of NODAT. Current guidelines suggest a measurement of fasting plasma glucose on initial evaluation and a 2-h oral glucose tolerance test in patients with normal fasting levels [76]. In addition, it has been recommended that all candidates for transplantation be screened for other cardiovascular risk factors (i.e. smoking, family history of coronary artery disease, hyperlipidemia) and for evidence of the metabolic syndrome. Patients with such risk factors and those with the metabolic syndrome have a higher risk of developing diabetes mellitus as well as cardiovascular disease.

The risk of NODAT should be discussed with all candidates for kidney transplantation. Those at higher risk should certainly be counseled regarding the importance of weight control, diet, and physical activity. It is tempting to suggest that pretransplant assessment of risk for NODAT should serve as a guide to choosing a patient's immunosuppression regimen. However, the benefits of designing relatively nondiabetogenic immunosuppression protocols must be weighed against the risks of acute or chronic allograft rejection on a case-to-case basis.

Post-transplant screening

Monitoring of fasting plasma glucose concentrations (obtained after no less than 8 h of fasting) remains the standard of practice for NODAT screening in many transplant centers [77]. There is no consensus about the frequency of testing, but it is certainly sensible to screen more frequently during the 6 months following transplantation (when the risk of NODAT is highest) and to increase the frequency of testing in patients with multiple risk factors for NODAT. Studies in the general population suggest that an elevated 2-h plasma glucose obtained during an oral glucose tolerance test is more closely associated with a risk of cardiovascular disease than an elevated fasting plasma glucose [78,79]. Recently Armstrong *et al.* suggested that IGT detected on oral glucose tolerance testing was more predictive of subsequent NODAT than an elevated fasting plasma glucose [80]. However, the long-term implications of abnormal postprandial blood glucose in transplant recipients are unknown and the role for routine oral glucose tolerance testing thus remains controversial.

In a report generated from an international consensus conference, Davidson *et al.* recommended that transplant recipients be screened for hyperglycemic disorders by determination of fasting plasma glucose at least once a week for the first 4 weeks post-transplant, at 3, 6 and

12 months post-transplant, and annually after the first year [81]. The same authors recommended that oral glucose tolerance tests be considered for screening in patients with normal fasting plasma glucose levels and in those with impaired glucose tolerance suggested by elevated random plasma glucose concentrations [81]. Measurement of hemoglobin A_{1C} (HbA_{1C}) is not sensitive enough to be recommended as a screening test for NODAT.

Management

The goals of managing the patient with NODAT are (i) to prevent symptoms of uncontrolled hyperglycemia and (ii) to prevent the microvascular complications of diabetes mellitus. To that end, use of guidelines developed by the ADA and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (see Table 3) for the management of patients with type 2 diabetes mellitus has been recommended [82]. However, several aspects of guidelines may be less relevant to the transplant recipient than to a diabetic patient in the general population. For example, annual screening for microalbuminuria is recommended for all patients with diabetes mellitus in the general population. Microalbuminuria may be difficult to interpret in patients with chronic allograft nephropathy, recurrence of underlying renal disease, diseased native kidneys that continue to excrete protein. Thus, the importance of screening for microalbuminuria in transplant recipients remains to be proven. In addition, the ADA guidelines suggest routine monitoring of lipid levels (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) and aggressive treatment of hyperlipidemia [82]. While the incidence and severity of post-transplant hyperlipidemia tend to be even greater than that observed in the general population [83], transplant patients may exhibit a unique lipid profile and it is not at all clear that the target lipid levels recommended by the ADA are levels that correlate with reduction of cardiovascular risk in the transplant population. Finally and most importantly, the ADA guidelines do not deal with management of the immunosuppressive drugs that play a pivotal role in the pathogenesis of NODAT.

Table 3. Recommended goals for the treatment of patients with type 2 diabetes mellitus

Variable	Value
Glucose	
Hemoglobin A_{1C}	<7%
Fasting plasma glucose (mg/dl)	90–130
Peak postprandial glucose (mg/dl)	<180
Blood pressure	
Systolic (mmHg)	<130
Diastolic (mmHg)	<80
Lipids	
Low-density lipoprotein cholesterol (mg/dl)	<100
High-density lipoprotein cholesterol (mg/dl)	>45
Triglycerides (mg/dl)	<200

Blood glucose monitoring

There is now abundant evidence suggesting that intensive control of blood glucose can prevent the complications of both type 1 and type 2 diabetes mellitus. Aggressive self-monitoring of blood glucose has markedly improved the ability to control glucose levels. In the general population, blood glucose monitoring has proven to be useful, not only in insulin-dependent patients, but in those managed with oral agents or diet alone [8,84]. It is reasonable to recommend self-monitoring of blood glucose to patients with NODAT.

HbA_{1C} levels should be monitored every 3 months in patients with documented NODAT, keeping in mind that severe anemia or advanced renal failure may influence the HbA_{1C} assay. Based on results of the Diabetes Control and Complications Trial that demonstrated a benefit of glycemic control in preventing complications of diabetes mellitus in the general population [85], a target HbA_{1C} level of <7.0% is a reasonable recommendation for patients with PTDM.

Nonpharmacologic therapy

In the general population, caloric restriction and weight loss may reduce insulin resistance and are recommended for obese patients (body mass index >30 kg/m^2) with diabetes mellitus. Even in the absence of obesity or post-transplant weight gain, regular exercise has been shown to decrease insulin resistance and to reduce lipid levels [84]. Sharif *et al.* recently demonstrated that aggressive lifestyle modification based on dietary changes, weight loss, and exercise reduced the incidence of NODAT in kidney transplant recipients with early laboratory signs of TAH [86]. These life-style modifications are recommended irrespective of whether patients require pharmacologic treatment for hyperglycemia and may be sufficient to achieve acceptable glycemic control without drug therapy. Nonpharmacologic therapy is the first consideration in a stepwise approach to NODAT delineated in Fig. 4.

Pharmacologic therapy

Some diabetologists have argued that early treatment of type 2 diabetes mellitus with insulin monotherapy, prior to the use of oral hypoglycemic agents, may prevent the

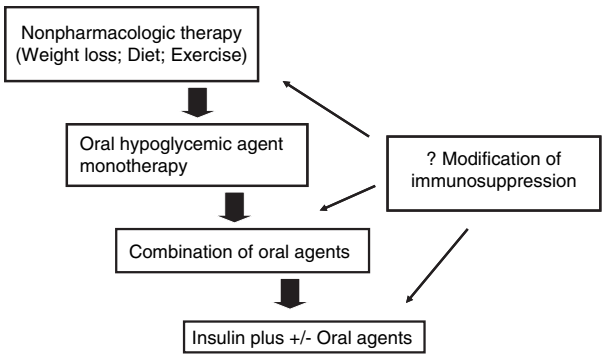

Figure 4 Stepwise approach to management of new-onset diabetes mellitus after transplantation. Whether and when to modify immunosuppression as part of the algorithm remains controversial.

metabolic exhaustion of beta cells that contributes to progressive beta-cell dysfunction [87]. However, no randomized controlled trials have been performed to test this strategy in patients with NODAT or other forms of type 2 diabetes mellitus. Thus, the traditional approach of using oral hypoglycemic drugs as first line agents (Fig. 4) remains the standard practice.

Oral hypoglycemic agents

A variety of oral agents is now available for patients who continue to exhibit hyperglycemia despite lifestyle changes (see Table 4). The sulfonylureas (which stimulate insulin secretion) and the guanides (which decrease hepatic glucose production) are the oldest classes of oral hypoglycemic agents, each capable of reducing HbA1C levels by 1.5% [87]. Biguanides such as metformin are contraindicated in patients with impaired renal function because of an increased risk of lactic acidosis. Thus, they should be used with great caution in kidney transplant recipients who generally exhibit glomerular filtration rates below the values of subjects with two normal kidneys. The glitinides have a faster onset of action and shorter duration of action when compared with the sulfonylureas [88], but generally achieve comparable degrees of glycemic improvement [87]. The thiazolidinediones are peroxisome-proliferator-activated receptor antagonists that increase peripheral glucose uptake. These agents are only moderately effective when used as monotherapy and most often are used in combination with other oral agents and/or insulin [89]. The alpha-glycosidase inhibitors work by inhibiting the absorption of carbohydrates in the small intestine and also are used most commonly as adjunctive agents [90]. Drugs that promote glucagon-like peptide-1 (GLP-1) receptor activation or that inhibit degradation of GLP-1 have recently been approved for clinical use, but experience with these agents in organ transplant recipients has been limited.

Insulin

Use of insulin is generally indicated in patients with NODAT if lifestyle changes and the use of oral agents fail to decrease fasting plasma glucose to less than 120 mg/dl, postprandial blood glucose to less than 160 mg/dl, or HbA1C to less than 7%. A wide variety of rapid-acting, intermediate-acting, and long-acting insulin preparations is now available [85], and their use in various combinations is beyond the scope of this review. Concomitant use of insulin with oral agents is now a common practice in patients with type 2 diabetes mellitus, but there is little data available regarding the wisdom of this approach in patients with NODAT. Considering the large degree of individualization required in prescribing insulin, a low threshold for referral to a diabetologist is recommended for most patients with insulin-dependent NODAT.

Table 4. Available oral hypoglycemic agents.

	Sulfonylureas and glitinides	Biguanides (metformin)	Alpha-glycosidase inhibitors	Thiazolidinediones
Main mechanism	Increase insulin secretion	Decrease hepatic glucose production	Delay gastrointestinal absorption of carbohydrates	Increase insulin sensitivity
Typical reduction in HbA_{1C} (percent)	1.0–2.0	1.0–2.0	0.5–1.0	0.5–1.0
Typical dose range	Glyburide 1.25–20 mg/day Glipizide 2.5–40 mg/day Nateglinide 60–120 mg before meals Repaglinide 0.5–4.0 mg before meals	Metformin 500–2550 mg/day	Acarbose 25–100 mg with meals Miglitol 50–100 mg with meals	Rosiglitazone 4–8 mg/day Pioglitazone 7.5–45 mg/day
Most common side effects	Hypoglycemia, weight gain	Gastrointestinal upset, lactic acidosis	Flatulence, other gastrointestinal upset, weight gain	Edema, weight gain

Modification of immunosuppression

The role of altering immunosuppression in an effort to improve glycemic control in patients with NODAT remains controversial. Matas *et al.* recently compared the outcomes of kidney transplant recipients based on the presence or absence of acute rejection and NODAT, and concluded that prevention of acute rejection was more important than prevention of NODAT in preserving long-term kidney function [91]. Thus, any potential benefit of avoiding or reversing NODAT based on a change of immunosuppressants must be weighed against the risk of precipitating acute or chronic rejection with such changes. For example, the benefits of reducing or discontinuing corticosteroids in patients with NODAT certainly must be weighed against the risk of acute rejection associated with steroid withdrawal and against the possibility that NODAT may recur or persist despite elimination of steroids. Similarly, the benefits of reducing, eliminating or switching calcineurin inhibitors to treat NODAT remain to be proven. Further studies are needed before recommending any of these strategies as a standard of practice in the care of patients with NODAT.

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