Chapter 15: Diabetes Mellitus

15.1: SCREENING FOR NEW-ONSET DIABETES AFTER TRANSPLANTATION

15.1.1: We recommend screening all nondiabetic KTRs with fasting plasma glucose, oral glucose tolerance testing, and/or HbA_{1c} *(1C)* at least:

- **weekly for 4 weeks *(2D)*;**
- **every 3 months for 1 year *(2D)*; and**
- **annually, thereafter. *(2D)***

15.1.2: We suggest screening for NODAT with fasting glucose, oral glucose tolerance testing, and/or HbA_{1c} after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids. *(2D)*

CNI, calcineurin inhibitor; HbA_{1c}, hemoglobin A_{1c}; KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s); NODAT, new-onset diabetes after transplantation.

Background

Diabetes is defined according to the WHO and American Diabetes Association (ADA) (Table 19).

New-onset diabetes after transplantation is diabetes defined by the WHO and ADA that develops for the first time after kidney transplantation.

Rationale

- The chances of reversing or ameliorating NODAT may be improved by early detection and intervention.
- Early treatment of NODAT may prevent complications of diabetes.
- The incidence of NODAT is sufficiently high to warrant screening.

Fasting plasma glucose, 2-h glucose tolerance testing (after a 75-g glucose load) and hemoglobin A_{1c} (HbA_{1c}) are probably suitable screening tests to detect NODAT in KTRs. The frequency of screening for NODAT is based on the incidence of NODAT at different times after kidney transplantation. The reported incidence varies by the definition of diabetes and the type of immunosuppressive medications used. However, the incidence of NODAT is highest in the first 3 months after transplantation. The cumulative incidence of NODAT by the end of the first year has generally been found to be 10–30% in adults receiving CsA or tacrolimus plus corticosteroids (468–479), and 3–13% in children (480,481). The high incidence of NODAT justifies frequent screening during the first year after transplantation. A number of risk factors increase the incidence of NODAT (Table 20), and patients with one or more of these additional risk factors may benefit from more frequent screening.

Since tacrolimus, CsA, mTORi and corticosteroids can cause NODAT, it is reasonable to screen for NODAT after starting, or substantially increasing the dose of one of these medications. Treating acute rejection with high-dose corticosteroids, for example, should prompt screening for NODAT.

Tacrolimus and CsA may cause NODAT by directly decreasing insulin secretion of pancreatic beta cells (489–493). Logically, reducing the dose or discontinuing these agents as soon as possible could potentially limit the damage to beta cells, although the clinical evidence is anecdotal (494,495). There is anecdotal evidence from case reports/series that NODAT may be reversed by reducing, replacing or discontinuing CsA, tacrolimus or corticosteroids (494,495). There are few data on the effects of corticosteroid reduction on reversing NODAT once it has occurred. Similarly, few, if any, data are available on whether discontinuing mTORi will reverse NODAT.

The relative effects of different immunosuppressive agents on NODAT are difficult to quantify, because RCTs use

Table 19: Criteria for the diagnosis of diabetes

1.	Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*
	OR
2.	Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia and unexplained weight loss.
	OR
3.	Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. 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.*

WHO, World Health Organization.
*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.
Modified with permission (467).

Table 20: Risk factors for NODAT[a]

Predictor	No. of subjects (range)	Association (No. of studies $p < 0.05$)	No association (No. of studies)
Tacrolimus (474–477,479,482–485)	100 418 (386–28 941)	7	2
CsA (479,484)	1066 (528–538)		2
Corticosteroids (477,478,484,486)	2035 (386–589)	2	2
Sirolimus (479,484,487,488)	22 525 (528–21 459)	2	2
Acute rejection (477–479)	1436 (386–528)	3	
Obesity/higher BMI (471,472,474,476–479,482,484,485,488)	97 702 (386–28 942)	9	2
African American ethnicity (471,472,474–476,479,482,485,488)	103 383 (528–28 942)	8	1
Hispanic ethnicity (US) (474)	15 787	1	
Older age (471,472,474–479,484,485,488)	94 487 (386–28 942)	9	2
Male (471,474,476–479,484,485)	64 090 (386–28 942)		8
HLA mismatch (474,476,478,485)	60 560 (522–28 942)	2	2
Deceased-donor kidney (471,474,476–478,485)	63 024 (386–28 942)	1	5
Hepatitis C (474,477,478,482,485,488)	63 805 (386–21 459)	5	1
HCV risk (D+/R−) (476)	28 942	1	
CMV risk (D+/R−) (477)	386		1
Beta-blockers	nd		
Thiazide diuretics	nd		
History of:			
Type 2 diabetes in family (478,484)	1060 (522–538)	1	1
Gestational diabetes	nd		
Impaired fasting glucose	nd		
Impaired glucose tolerance	nd		
HDL-C <40 mg/dL	nd		
Triglycerides >150 mg/dL (472)	1811	1	

BMI, body mass index; CsA, cyclosporine A; CMV, cytomegalovirus; D, transplant donor; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HLA, human leukocyte antigen; nd, no data; NODAT, new-onset diabetes after transplantation; R, transplant recipient.

[a]NODAT was variously defined in studies identifying risk factors and having a sample size at least 100. To convert HDL-C mg/dL to mmol/L multiply by 0.02586; to convert triglycerides mg/dL to mmol/L multiply by 0.01129.

different regimens and doses, as well as different definitions of NODAT, all of which make comparisons difficult. Nevertheless, it appears that the risk of NODAT with tacrolimus is greater than with CsA. It is also clear that high doses of corticosteroids used immediately after transplantation, and in the treatment of acute rejection, are risk factors for NODAT. Sirolimus has not been as well studied. Some observational studies have found that sirolimus use was associated with an increased incidence of NODAT (487,496,497). Randomized trials have produced conflicting results (498–502). There is no evidence that azathioprine or MMF causes NODAT.

The risk of NODAT from immunosuppressive medications is no doubt higher in individuals with other risk factors, for example African American or American Hispanic ethnicity, obesity and age. Thus, the choice of immunosuppressive medications could be individualized to the risk for NODAT attributable to other risk factors in each individual patient. In addition, the risk of NODAT should be considered in light of the risk of acute rejection. Indeed, the occurrence of acute rejection and its treatment with corticosteroids is a risk factor for NODAT. Unfortunately, it is difficult to weigh the relative risks of rejection and NODAT in individual patients to determine the best immunosuppressive medication regimen.

By almost any definition, the risk of NODAT is increased by obesity. African American and Hispanic ethnicity are generally defined as self-reported. Since data on African American and Hispanic ethnicity are largely from the United States, it is unclear if ethnicities defined otherwise and in other countries have similar risk for NODAT. Older age is a risk factor that shows a linear relationship with risk, but there is no clear threshold. HCV infection is defined by the presence of antibody to the HCV at the time of transplantation.

A number of other risk factors for diabetes have not been rigorously studied in KTRs, but there is little reason to believe that they would not also be risk factors after transplantation. These risk factors include: family history (type 2 diabetes), gestational diabetes, impaired fasting glucose, impaired glucose tolerance and dyslipidemia (high fasting triglycerides and/or low HDL-C) (503–507).

Data from observational studies have shown that NODAT is associated with worse outcomes, including increased graft failure, mortality and CVD (474). It is possible that some of these associations result from unmeasured risk factors that are common to both NODAT and poor outcomes. However, it is certainly plausible that NODAT directly and indirectly contributes to worse outcomes. Untreated diabetes may increase the risk of metabolic complications, including hyperkalemia, and even ketoacidosis. However, there is no evidence from observational studies to suggest how frequently these complications occur after NODAT.

Research Recommendations

- Future RCTs of immunosuppressive medication regimens should measure fasting glucose, HbA_{1c} and/or glucose tolerance tests, and any treatments of diabetes, to determine the effect of the medication regimens on the incidence of NODAT.

15.2: MANAGING NODAT OR DIABETES PRESENT AT TRANSPLANTATION

15.2.1: If NODAT develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. *(Not Graded)*

15.2.2: Consider targeting HbA_{1c} 7.0–7.5%, and avoid targeting HbA_{1c} ≤6.0%, especially if hypoglycemic reactions are common. *(Not Graded)*

15.2.3: We suggest that, in patients with diabetes, aspirin (65–100 mg/day) use for the primary prevention of CVD be based on patient preferences and values, balancing the risk for ischemic events to that of bleeding. *(2D)*

CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; NODAT, new-onset diabetes after transplantation.

Background

The management of diabetes that is present at the time of transplantation may be complicated by severe autonomic neuropathy and other complications of long-standing diabetes that may make 'tight' control of blood glucose difficult to achieve. Therefore, we recommend avoiding intensive therapies targeting HbA_{1c} levels <6.0%. However, complications of long-standing diabetes that make the management of diabetes difficult are less likely to be present in patients with NODAT, and it is not clear whether NODAT can be safely and effectively managed within a narrow range of low blood glucose and HbA_{1c} targets.

Rationale

- The benefits and harm of altering the immunosuppressive medication regimen in response to the development of NODAT are unclear.
- In the general diabetic population, there is insufficient evidence for or against targeting a specific HbA_{1c} level to reduce CVD; however, recent data suggest that mortality may be increased in patients with type 2 diabetes by targeting HbA_{1c} levels that are <6.0%.
- In KTRs, attempting to reduce HbA_{1c} levels in order to reduce CVD may result in more complications than in the general diabetic population.
- Randomized trials in the general population suggest that aspirin prophylaxis may prevent CVD in patients with diabetes.

There are no RCTs testing whether changing to different immunosuppressive medication regimens reverses or ameliorates NODAT. There are uncontrolled (largely anecdotal) reports on the effects of changing immunosuppressive agents once NODAT has developed (494,495). Given the associations of NODAT with CsA, tacrolimus, mTORi and corticosteroids, it is plausible that reducing or eliminating these immunosuppressive medications may reverse or ameliorate NODAT. Changes in immunosuppressive medications that may reverse or ameliorate NODAT include:

i) reducing the dose of tacrolimus, CsA or corticosteroids;
ii) discontinuing tacrolimus, CsA or corticosteroids;
iii) replacing tacrolimus with CsA, MMF or azathioprine;
iv) replacing CsA with MMF or azathioprine.

We could find no published reports of reducing the dose or discontinuing a mTORi to reverse or ameliorate NODAT.

Optimal glycemic control to prevent microvascular disease complications has been defined in a number of guidelines for the general population. A recent systematic review of these guidelines concluded that the goal for glycemic control should be as low as feasible without incurring undue risk for adverse events (508). These authors concluded that a HbA_{1c} level <7% is a reasonable goal for many, but not all, patients in the general diabetic population.

While there is evidence in the general diabetic population that strict glycemic control reduces microvascular disease complications, there is less evidence that glycemic control reduces CVD. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial reported nonsignificant trends toward

Table 21: Pharmacological management of diabetes in KTRs

Class	Drug	Dose adjustment	Drug–drug interactions
First-generation sulfonylureas	Acetohexamide	Avoid (517)	↑ CsA levels
	Chlorpropamide	↓50% if GFR 50–70 mL/min/1.73 m^2 Avoid if GFR <50 mL/min/1.73 m^2 (517,518)	↑ CsA levels
	Tolazamide	Avoid	↑ CsA levels
	Tolbutamide	Use with caution (519,520)	↑ CsA levels
Second-generation sulfonylureas	Glipizide	No dose adjustment	↑ CsA levels
	Gliclazide	No dose adjustment	↑ CsA levels
	Glyburide (Glibenclamide)[a]	Avoid if GFR <50 mL/min/1.73 m^2 (521)	↑ CsA levels
	Glimepiride	Start at 1 mg/day	↑ CsA levels
	Gliquidone[b]	No dose adjustment	
	Glisentide[b]	Avoid if advanced CKD	
Alpha-glucosidase inhibitors	Acarbose	Avoid if Scr >177 μmol/L (2 mg/dL) (522–524)	
	Miglitol	Avoid if GFR <25 mL/min/1.73 m^2 (522–524)	
Biguanides	Phenformin	Contraindicated (522)	
	Metformin	Contraindicated if Scr ≥133 μmol/L (1.5 mg/dL) men, ≥124 μmol/L (1.4 mg/dL) women (522)	
Meglitinides	Repaglinide	Start 0.5 mg with meals if GFR <40 mL/min/1.73 m^2 and titrate carefully (522)	↑ Repaglinide levels with CsA (525)
	Nateglinide	Use with caution if advanced CKD (522)	
Thiazolidinediones[c]	Pioglitazone	No dose adjustment (522)	
	Rosiglitazone	No dose adjustment (522)	
Incretin mimetic	Exenatide	Avoid if GFR <30 mL/min/1.73 m^2 (522)	
Amylin analog	Pramlintide	No dose adjustment if GFR >20 mL/min/1.73 m^2	
DDP-4 inhibitor	Sitagliptin	↓50% if GFR 30–50 mL/min/1.73 m^2 ↓75% if GFR <30 mL/min/1.73 m^2	
	Vildagliptine	Avoid if advanced CKD on hemodialysis	

CKD, chronic kidney disease; CsA, cyclosporine A; DDP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; KTRs, kidney transplant recipients; Scr, serum creatinine.
[a]Glibenclamide is the same compound as glyburide (526).
[b]Gliquidone and glisentide are not currently available in the United States (522).
[c]Thiazolidinediones may cause fluid retention.

lower CVD with lower HbA_{1c} levels (509,510). A long-term follow-up of this trial reported that intensive insulin therapy reduced CVD (511). Similarly, in a 10-year follow-up of the UKPDS, there were reduced myocardial infarctions in the sulfonylurea–insulin and metformin intensive-therapy groups (compared to usual care) (512).

Recently, the blood glucose control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) was stopped early, because participants in the intensive-treatment group had experienced increased mortality (513). In ACCORD, 10 251 adults with long-standing (average 10 years) type 2 diabetes, and either heart disease or two or more other risk factors for heart disease, were randomly allocated to target HbA_{1c} <6.0% vs. standard treatment targeting HbA_{1c} 7.0–7.9%. Half of the participants in the intensive-treatment group achieved a HbA_{1c} of <6.4%, and half of the participants in the standard treatment group achieved a HbA_{1c} of <7.5%. The Data Safety Monitoring Board halted these diabetes control arms of the trial 18 months early, because of a higher mortality rate in the group targeting lower HbA_{1c} levels. In the intensive-treatment group 257 died, compared with 203 in the standard-treatment group. This was a difference of 54 deaths, or 3 per 1000 participants per year, over an average of almost 4 years of treatment. For both the

intensive- and standard-treatment groups in ACCORD, clinicians could use all major classes of diabetes medications available. Extensive analyses did not determine a specific cause for the increased deaths, and there was no evidence that any medication or combination of medications was responsible.

Similarly, the Action in Diabetes and Vascular Disease (ADVANCE) study (514) failed to demonstrate that more intensive glycemic control compared to standard practice reduced CVD events. The ADVANCE study achieved a median HbA_{1c} of 6.3% in the intensive-management group compared with 7.0% in the standard-intervention group. The results from ACCORD and ADVANCE studies may not apply to patients with type 1 diabetes, patients with recently diagnosed type 2 diabetes or those whose cardiovascular risk is different than the participants studied in ACCORD and ADVANCE. In particular, the results may not apply to patients with CKD or to KTRs. Nevertheless, the results of the ACCORD and ADVANCE trials cast serious doubt on the advisability of targeting low HbA_{1c} levels to reduce CVD. Additional trials in the general diabetic population may help to determine the optimal strategy for managing diabetes (515).

Kidney transplant recipients with diabetes, especially if the diabetes was the cause of CKD stage 5, often have difficult-to-control diabetes, with advanced autonomic neuropathy causing diabetic gastroparesis and hypoglycemic unawareness. In a RCT comparing intensive glucose control with usual care in 99 KTRs, the incidence of severe hypoglycemia was significantly higher in the intensive glucose-control arm (516). Therefore, it may be more difficult to achieve a HbA_{1c} level $<7.0\%$ without undue risk and burden in many KTRs. In addition, some medications used to treat diabetes may need dose reduction, or should be avoided in patients with reduced kidney function (Table 21).

Patients with difficult-to-control type 1 diabetes may be candidates for pancreas transplantation. There has never been a randomized trial of pancreas transplantation vs. kidney transplantation alone, but there is little question that a successful pancreas transplantation can improve the quality of life of patients with difficult-to-control diabetes (527–529). Whether pancreas transplantation reduces the risk for CVD is unknown. Pancreas transplantation is best performed either simultaneously with, or subsequent to, a living-donor kidney transplantation in patients who are already taking immunosuppressive agents (530). Islet transplantation is still experimental, and long-term survival of islets has yet to be achieved (531). In addition, the multiple infusion of islet cells required may sensitize the recipient to a number of major histocompatibility antigens that can make it difficult to find a compatible solid organ for transplantation when one is needed (532).

Evidence that the benefits of aspirin (e.g. preventing of CVD events) outweigh the harm (e.g. bleeding complications) for patients with diabetes, but without known CVD, is not strong. Therefore, while some guidelines in the general population suggest that aspirin be used for primary prevention in all patients with diabetes, others do not. For example, the ADA currently recommends:

- Use aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia or albuminuria). (*C*)
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD. (*A*)
- Aspirin therapy should not be recommended in people under 30 years of age due to lack of evidence of benefit, and is contraindicated in patients under the age of 21 years because of the associated risk of Reye's syndrome. (*E*)

where *A* indicates 'Clear evidence from well-conducted, generalizable, randomized clinical trials that are adequately powered . . .,' *C* indicates 'Supportive evidence from poorly controlled or uncontrolled studies . . .' and *E* indicates 'Expert consensus or clinical experience . . .' (533).

A recent RCT in patients with type II diabetes and peripheral vascular disease (PVD) reported that aspirin prophylaxis had no effect on CVD events (534). Another small trial of low-dose aspirin for primary prevention of atherosclerotic events in Japanese patients with type II diabetes failed to show clear benefit from aspirin (535). The results of these trials have cast doubt on the use of aspirin in patients with diabetes to prevent first CVD events. Thus, it is unclear whether the benefits outweigh the harm for aspirin use in KTRs with diabetes. The results of other pending trials with aspirin prophylaxis in the general population may help to clarify the benefits and harm of aspirin for primary prevention in patients with diabetes.

Research Recommendations

- A RCT is needed to examine aspirin prophylaxis in KTRs with and without diabetes.