

# New-Onset Diabetes After Transplantation 2003 International Consensus Guidelines

An endocrinologist's view

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ON BEHALF OF THE INTERNATIONAL EXPERT  
PANEL ON NEW-ONSET DIABETES AFTER  
TRANSPLANTATION\*

New-onset diabetes and impaired glucose tolerance (IGT) are among the most serious metabolic complications of solid organ transplantation. Despite the importance of these conditions to the outcome of transplant recipients, their precise incidence is difficult to determine. This is due to the fact that there has been, until recently, no consensus regarding the definition of new-onset diabetes after transplantation. Thus different studies described in the literature have used a variety of diagnostic criteria (1). Consequently, the reported incidence of new-onset diabetes after transplantation has varied between 2 and 53%, whereas the prevalence of diabetes in the general population is estimated at ~4% (2,3).

Although new-onset diabetes has been recognized as a complication of transplantation for 50 years (4), the significance of the condition has been grossly underestimated. This is largely due to the fact that diabetes in transplant recipients was generally thought not to be associated with the micro- and macrovascular complications of diabetes in the nontransplant population (5). It is now clear, however, that the development of new-onset diabetes after transplantation is a major determinant of the increased cardiovascular morbidity and mortality

seen in transplant recipients (6–8). Furthermore, studies indicate that the development of diabetes after transplantation has serious consequences for the patient, being associated with reduced graft function and patient survival and increased risk of graft loss (5,9,10). In addition, a recent analysis has revealed that the costs of developing new-onset diabetes after kidney transplantation are \$12,000–\$13,000 higher than for those with no diabetes by the end of the first year following transplantation. These costs rise to \$19,000–\$22,000 higher by the end of the second year (11).

Studies suggest that a number of risk factors exist that may predict the development of new-onset diabetes in transplant patients. In particular, the increased risk of diabetes in transplant recipients may be largely due to the immunosuppressive agents used to treat transplant recipients. Standard immunosuppressive therapy to prevent allograft rejection includes corticosteroids and calcineurin inhibitors (CNIs), both of which have been associated with diabetes. However, the diabetogenicity of these agents varies greatly, thus the choice of immunosuppressive therapy can considerably influence patients' risk of developing new-onset diabetes after transplantation. Moreover, it is

now recognized that early detection and appropriate treatment of transplant recipients who have already developed diabetes can ameliorate the long-term consequences of the condition. Nevertheless, clear guidelines outlining the appropriate management steps for transplant recipients at risk of developing diabetes were lacking. To meet this need, an expert panel meeting was recently convened, the proceedings of which have been published—New-Onset Diabetes after Transplantation 2003 International Consensus Guidelines (12). The present review summarizes the evidence on which these consensus guidelines were based and highlights the similarities and differences between the management of patients with diabetes in the general population and the transplant community.

## INCIDENCE OF NEW-ONSET DIABETES AFTER TRANSPLANTATION

The incidence of new-onset diabetes after transplantation has been greatly underestimated in the literature due to the lack of a standard definition of the condition. In some instances, new-onset diabetes after transplantation has been defined only by the patient's requirement for insulin without the use of oral glucose tolerance tests (OGTTs) to determine the exact incidence of glycemic abnormalities (13,14). Estimates of the incidence of new-onset diabetes after transplantation are further confounded by inconsistencies in identifying patients with diabetes before transplantation and monitoring the outcome of transplant recipients with type 2 diabetes. Furthermore, many studies underestimate the true incidence of the condition, since the observation periods are often too short (<1 year). However, the risk of developing new-onset diabetes has been shown to increase progressively post-transplant, with the condition being diagnosed in some patients up to 15 years after transplantation (15). In a retrospec-

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\*A complete list of the International Expert Panel members can be found in the APPENDIX.

**Abbreviations:** ACE, American College of Endocrinology; CNI, calcineurin inhibitor; CVD, cardiovascular disease; FPG, fasting plasma glucose; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

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**Table 1—RR for ischemic heart disease among transplant recipients >1 year after kidney transplantation (8)**

Risk factor	Men		Women	
	Control	Transplant recipient	Control	Transplant recipient
Age (years)	1.05	1.06*	1.40	1.10
Cholesterol (mg/dl)				
<160	0.52	0.00†	0.77	0.00†
160–199	1.00‡	1.00‡	1.00‡	1.00‡
200–239	1.19	2.39	1.23	2.07
240–279	1.66	2.02	1.28	2.44
>280	1.93	2.25	1.71	1.84
Blood pressure (mmHg)				
<120 and <80	1.00	0.25	0.59	0.56
120–129 or 80–84	1.00‡	1.00‡	1.00‡	1.00‡
130–139 or 85–89	1.33	1.05	0.93	1.26
140–159 or 90–99	1.68	1.19	1.30	1.63
≥160 or ≥100	1.86	1.47	1.59	0.31
Diabetes	1.53	2.78*	1.82	5.40*
Smoking	1.69	1.95*	1.34	1.82

A RR of  $\geq 1.00$  indicates a higher or lower risk for ischemic heart disease, respectively. Control subjects are from the Framingham Heart Study. \* $P < 0.05$  compared with reference risk values for transplant recipients; †too few patients were available to reliably assess this risk; ‡reference risks for cholesterol levels and blood pressure are indicated by 1.00.

tive analysis of Medicare beneficiaries in the U.S., the cumulative incidence of new-onset diabetes after transplantation among 11,659 patients was 9.1, 16.0, and 24.0% at 3, 6, and 36 months, respectively (16).

A further difficulty in assessing the incidence of new-onset diabetes after transplantation is that the risk of developing the condition depends on the immunosuppressive agent used. In a recent analysis, the type of immunosuppressive regimen used was found to explain 74% of the variability in incidence, with high-dose steroid regimens used during the 1970s being associated with the highest incidences (3).

### IMPACT OF NEW-ONSET DIABETES AFTER TRANSPLANTATION

Evidence suggests that new-onset diabetes after transplantation has serious consequences for transplant recipients, increasing the risk of graft-related complications such as graft rejection, graft loss, and infection (5,17–19). Numerous reports in the literature have demonstrated that the development of new-onset diabetes after transplantation is associated with impaired long-term graft function and survival in transplant recipients (18). In

one study, 12-year graft survival in kidney transplant recipients who developed diabetes after transplantation was reported as 48 vs. 70% in those with no development of diabetes (5). Similarly, in liver transplant recipients, the incidence of acute rejection episodes was found to be higher in patients who developed the condition (50 vs. 30% in the control group) (19).

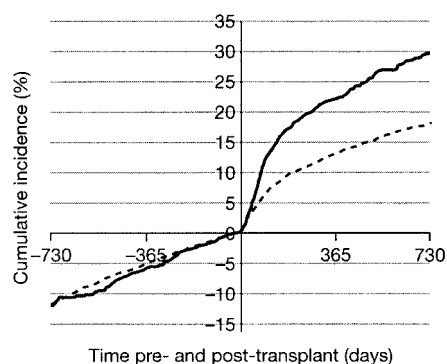
In addition to having adverse effects on grafts, new-onset diabetes after transplantation may also reduce the survival of transplant recipients (1,20–22). For example, one study has reported that the survival of kidney transplant recipients with new-onset diabetes was reduced at 2 years compared with those without diabetes (67 vs. 83%, respectively) (20). Development of the condition may also be detrimental to the long-term survival of transplant recipients, with a reported mean survival of 8.1 years for kidney recipients with new-onset diabetes versus 11.0 years for those without diabetes (1). Furthermore, it appears that survival of kidney transplant recipients is adversely affected by both preexisting diabetes and new-onset diabetes (23).

It is well established that patients with diabetes in the general population have an increased risk for cardiovascular mortal-

ity. Similarly, the risk of cardiovascular disease (CVD) is considerably higher in transplant recipients who develop diabetes after transplantation compared with those who do not develop the condition (6,8). In kidney transplant recipients, diabetes was found to be the most important risk factor for developing both cerebrovascular disease (independent RR 3.21) and peripheral vascular disease (independent RR 28.18;  $P < 0.05$ ) (7). In a further study, diabetes carried the highest relative risk for ischemic heart disease in kidney transplant recipients >1 year posttransplant (RR 2.78 for men and 5.40 for women), imposing a greater relative risk than hyperlipidemia, hypertension, or smoking (Table 1) (8). New-onset diabetes after transplantation not only predisposes transplant recipients to CVD, but also increases the risk of death from cardiovascular complications. Death following ischemic heart disease is 20.8 times higher in transplant patients with diabetes than in the general population (6).

### PREDICTIVE FACTORS FOR NEW-ONSET DIABETES AFTER TRANSPLANTATION

Studies suggest that some of the risk factors identified for type 2 diabetes (e.g., age) may also be involved in the development of new-onset diabetes after transplantation. However, it is clear that additional factors (e.g., immunosuppression agent and hepatitis C virus infection) are also involved in the pathogenesis of the condition (24–26). There is strong evidence that individuals with a family history of diabetes among first-degree relatives, and those of African-American or Hispanic ethnicity, have an increased risk of developing new-onset diabetes after transplantation (20,27–29). The age of transplant recipients also appears to be an important predictor of new-onset diabetes, with risk increasing over the age of 40 years (21,24,28). Individuals with abnormal glucose regulation before transplantation or other components of the metabolic syndrome (e.g., hypertriglyceridemia, hypertension, and hyperuricemia) may have a higher risk of developing diabetes posttransplant (25). Transplantation with a cadaveric kidney may also increase the risk (28). However, the relative importance of other risk factors, such as obesity, is unclear due to inconsistencies in the published data.



**Figure 1**— Incidence of diabetes before and after transplantation in patients receiving tacrolimus (—) or cyclosporine (---). At 1 year posttransplant, the incidence of new-onset diabetes was significantly lower in patients receiving cyclosporine than in those receiving tacrolimus (14.1 vs. 22.9%;  $P < 0.0001$ ). (From Woodward RS, Schnitzler MA, Baty J, et al.: Incidence and cost of new onset diabetes mellitus among U.S. waitlisted and transplanted renal allograft recipients. *Am J Transplant* 3:590–598, 2003, with permission from Blackwell Publishing Ltd.)

One of the most well-established risk factors for the development of new-onset diabetes is the immunosuppressive therapy used, with corticosteroids being associated with the greatest risk. The incidence of new-onset diabetes in transplant recipients receiving prednisolone has been reported to be as high as 46% and is related to both the dose administered and the duration of therapy (20,30, 31). The CNIs cyclosporine and tacrolimus have also been associated with an increased risk for diabetes after transplantation, although tacrolimus is reported to be up to five times more diabetogenic than cyclosporine (14,16,32–34). The greater diabetogenicity of tacrolimus compared with cyclosporine has been confirmed in a recent study investigating the incidence of new-onset diabetes before and after kidney transplantation (11). By 2 years posttransplant, the incidence of new-onset diabetes was higher in tacrolimus-treated patients than in patients receiving cyclosporine (29.7 vs. 17.9%) (Fig. 1). This evidence suggests that patients receiving tacrolimus, but not those taking cyclosporine, continue to develop new-onset diabetes at above baseline (pretransplant) rates in the second year posttransplant.

A recent analysis of Medicare beneficiaries in the U.S. receiving kidney trans-

plants between 1996 and 2000 found tacrolimus to be an independent risk factor for new-onset diabetes after transplantation (RR 1.53;  $P < 0.0001$ ) (16). In this study, the percentage of patients with a functioning graft posttransplant that remained free from diabetes was consistently greater in the group not receiving tacrolimus compared with those receiving tacrolimus for initial maintenance immunosuppression (16). The cumulative incidences for diabetes after transplantation at 3, 12, and 36 months for patients receiving tacrolimus were 13.5, 22.1, and 31.8%, respectively, compared with 7.8, 14.2, and 21.9% for those not receiving tacrolimus (16).

The predictive factors described above can be used to screen potential transplant recipients before transplantation to identify those at high risk of developing new-onset diabetes (24,35). Although some of the risk factors identified for the condition are not modifiable (e.g., age), their presence may add to an individual's chance of developing the disease. Risk factors should, therefore, be taken into consideration when tailoring immunosuppressive therapy to each individual patient. In particular, the varied diabetogenicity of current immunosuppressive agents suggests that transplant recipients at high risk of developing diabetes may benefit from switching to a less diabetogenic immunosuppressive regimen. Indeed, as diabetes carries the highest risk for CVD in transplant recipients (8), minimizing the risk for developing diabetes after transplantation is paramount.

### SIMILARITIES BETWEEN NEW-ONSET DIABETES AND TYPE 2 DIABETES

The natural history of new-onset diabetes after transplantation appears to be similar to that of type 2 diabetes (25). Like type 2 diabetes, the onset of new-onset diabetes after transplantation can be insidious, and individuals may be asymptomatic for years before symptoms clinically manifest (1,36). In the case of both type 2 and new-onset diabetes, this asymptomatic period exerts deleterious effects on the individual, since it increases the duration of exposure to the adverse effects of hyperglycemia and diabetes before treatment is initiated (25). The metabolic abnormality that causes type 2 diabetes in the general population is often permanent but in

some instances may resolve (e.g., in cases of drug-induced or obesity-related diabetes) over time (37). Similarly, in the transplant population, posttransplantation hyperglycemia and diabetes are not always permanent states and may normalize, possibly without treatment, within a few weeks of their development (27). However, such patients remain at high risk of subsequently developing diabetes, since abnormal glucose tolerance tests can still be seen in these individuals as long as 26 months after remission (27). Moreover, the risk of developing the condition has been shown to increase progressively for the remainder of the patient's life (15,28). These factors can make diabetes in the transplant population difficult to diagnose and therefore highlight the importance of establishing a precise definition of the condition in order to help clinicians adopt appropriate management steps for patients posttransplant.

The similarities between type 2 and new-onset diabetes after transplantation have led to the development of a standard definition by the International Consensus Guidelines committee (12). These guidelines recommend that the diagnosis of the condition should be based on the definition of diabetes and IGT recently defined by the American Diabetes Association (ADA), World Health Organization (WHO), International Diabetes Federation (IDF), and American College of Endocrinology (ACE) (37–40). As with the recommendations for diabetes in the general population, the guidelines on new-onset diabetes after transplantation recommend that, in the absence of unequivocal hyperglycemia with acute metabolic decompensation, the diagnosis should be confirmed by repeat testing on another day (12). This recommendation takes into account the fact that individuals with IGT or impaired fasting glucose have a higher risk for the development of diabetes and CVD than the general population. It is thus particularly important that such individuals are diagnosed early, so that the long-term complications of the conditions can be minimized.

### MANAGEMENT OF PATIENTS WITH NEW-ONSET DIABETES AFTER TRANSPLANTATION

It has been recommended that patients who develop new-onset diabetes after

**Table 2—Different aspects of the management of transplant recipients with new-onset diabetes and differences from management of patients with diabetes in the general population**

Management aspect	Recommendation/frequency of testing	Comments/similarity with general management of type 2 diabetes
FPG testing	<ul style="list-style-type: none"> <li>● Weekly for first month posttransplant</li> <li>● At 3, 6, and 12 months</li> <li>● Annually after the first year</li> </ul>	<ul style="list-style-type: none"> <li>● Used to identify patients with abnormal glucose regulation</li> </ul>
OGTT testing	<ul style="list-style-type: none"> <li>● Consider for patients with normal FPG or those with IGT</li> </ul>	<ul style="list-style-type: none"> <li>● Utility of test not validated in this population</li> </ul>
Tailoring immunosuppressive therapy	<ul style="list-style-type: none"> <li>● Decrease corticosteroids as soon as possible</li> <li>● Consider switch to cyclosporine in poorly controlled tacrolimus-treated patients</li> </ul>	<ul style="list-style-type: none"> <li>● Complete withdrawal of corticosteroids not recommended due to risk of acute rejection</li> </ul>
Self-monitoring of blood glucose	<ul style="list-style-type: none"> <li>● Essential component of management for patients receiving oral agents/insulin</li> <li>● Useful for patients on nonpharmacologic therapy</li> </ul>	<ul style="list-style-type: none"> <li>● Similar to recommendation for patients with type 2 diabetes</li> </ul>
Lipid levels	<ul style="list-style-type: none"> <li>● Evaluate annually</li> </ul>	<ul style="list-style-type: none"> <li>● Similar to recommendation for patients with type 2 diabetes</li> </ul>
A1C	<ul style="list-style-type: none"> <li>● Measure every 3 months; intervention for A1C <math>\geq</math>6.5%</li> </ul>	<ul style="list-style-type: none"> <li>● Same target as IDF and ACE</li> <li>● Interpret test with care in patients with anemia/kidney impairment</li> </ul>
Diabetic complications	<ul style="list-style-type: none"> <li>● Screen annually</li> </ul>	<ul style="list-style-type: none"> <li>● Similar to recommendation for patients with type 2 diabetes</li> </ul>
Microalbuminuria	<ul style="list-style-type: none"> <li>● Consider annual screening</li> </ul>	<ul style="list-style-type: none"> <li>● Not validated in this population</li> </ul>
Oral agent monotherapy	<ul style="list-style-type: none"> <li>● Make choice of agent mainly on safety</li> </ul>	<ul style="list-style-type: none"> <li>● Comparative efficacy of agents not investigated in this population</li> </ul>
Combination therapy	<ul style="list-style-type: none"> <li>● Consider possibility of serious adverse events in patients with kidney impairment</li> <li>● Use same combinations as used for patients with type 2 diabetes</li> </ul>	<ul style="list-style-type: none"> <li>● No combinations tested in this patient population</li> </ul>
Insulin + oral agents	<ul style="list-style-type: none"> <li>● Consider for patients poorly controlled with combination therapy</li> </ul>	<ul style="list-style-type: none"> <li>● Not tested in this patient population</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>● Aggressive lipid-lowering as detailed by NCEP</li> </ul>	<ul style="list-style-type: none"> <li>● All patients considered at high risk of CHD</li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>● Reduction of blood pressure &lt;130/80 mmHg</li> </ul>	<ul style="list-style-type: none"> <li>● Same target recommended by ADA</li> <li>● Value of blood pressure lowering not tested in this population</li> </ul>

CHD, coronary heart disease; NCEP, National Cholesterol Education Program.

transplantation should be managed in a similar way to those with type 2 diabetes (12). In particular, the management strategy for this population should focus on intensive blood glucose control, as this has been shown to confer significant benefits in preventing long-term complications for patients with type 1 or type 2 diabetes (12,41,42). However, there are some important differences between new-onset diabetes after transplantation and type 2 diabetes. These differences mean that some aspects of the management of diabetes are particularly important in transplant recipients, while the validity of other management options recommended for patients with type 2 diabetes have yet to be verified in the transplant population (Table 2). The recommended

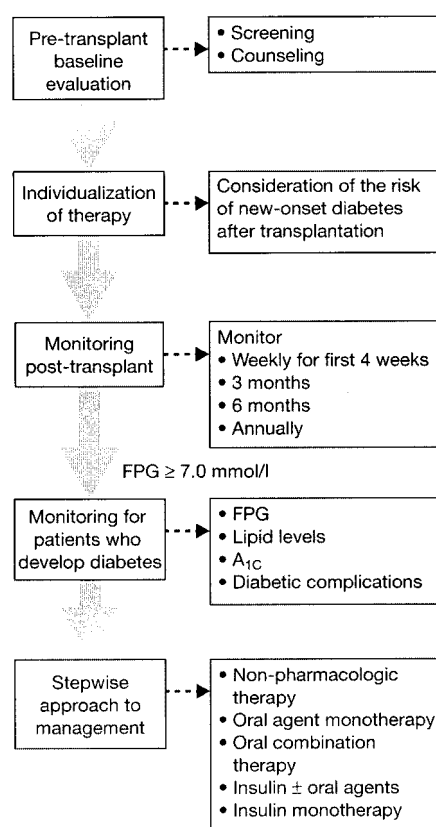
management of patients with new-onset diabetes after transplantation is summarized in Fig. 2.

### Pretransplant management

Careful management of patients before transplantation and individualization of immunosuppressive therapy can minimize the transplant recipient's risk of developing new-onset diabetes after transplantation (12). Many studies investigating new-onset diabetes after transplantation fail to distinguish between patients with preexisting diabetes whose glycemic control worsens posttransplant and those with new-onset disease (32, 33). It is thus important that fasting plasma glucose (FPG) levels are tested regularly in patients before transplanta-

tion to identify those with abnormal glucose control. The results of these tests can then be reviewed posttransplant in patients diagnosed with diabetes to clearly differentiate those with new-onset diabetes after transplantation.

Screening for all identified risk factors for new-onset diabetes after transplantation should form an important part of the clinical assessment pretransplant, with particular attention being paid to cardiovascular risk factors and family history of diabetes (12). The diabetes and CVD risk profiles of the patient can then be used to tailor the immunosuppressive therapy they receive. Selection of an appropriate immunosuppressive regimen must be considered carefully, due to the varying diabetogenicity of immunosuppressive



**Figure 2**— Algorithm summarizing the recommended management for transplant recipients with new-onset diabetes. (From Davidson JA, Wilkinson A, Dantal J, et al.: *New-onset diabetes after transplantation: 2003 international consensus guidelines*. Transplantation 75:SS3–SS24, 2003, with permission from Lippincott Williams & Wilkins.)

agents. Risk appears to be highest with corticosteroids, with tacrolimus being the more diabetogenic of the CNIs (14,16, 30,31,34). One further essential aspect of the management of patients pretransplant is the counseling of patients on the importance of weight control and exercise (12). Although such nonpharmacological therapies form an important part of the management of patients with diabetes in the general population, they appear to be particularly important in transplant recipients. This is due to the fact that such patients are prone to weight gain post-transplant, potentially increasing their risk of developing diabetes (43,44).

## Posttransplant management

### Monitoring of the transplant recipient.

Screening for the development of diabetes among transplant recipients should follow that recommended for individuals at

risk of the condition in the general population (12). In particular, FPG should be monitored in patients posttransplant at least weekly in the first 4 weeks after transplantation, then at 3-, 6-, and 12-month intervals, and annually thereafter. Evidence suggests that OGTT levels may be more predictive of an increased risk of CVD than the FPG test, especially in individuals with IGT (45–47). Although the association between OGTTs and CVD has not been investigated in transplant recipients, the test may also be of value in this population in patients with normal FPG levels (<110 mg/dl, 6.1 mmol/l) (12). This is due to the fact that the diabetes and abnormal glucose regulation that develop posttransplant can, unlike that experienced in the general population, resolve over time. However, such individuals are at increased risk for the development of subsequent diabetes and should be particularly closely monitored.

### Management of the transplant recipient.

Consideration of the immunosuppressive therapy administered appears to be an important component of the management of transplant recipients who develop diabetes posttransplant (12). In particular, reducing the dose of corticosteroids has been shown to improve significantly patient's glucose tolerance during the first year after transplantation. The dose of corticosteroids should, therefore, be reduced as soon as possible in patients at risk of developing diabetes. Any reduction in corticosteroid dose should be balanced against the possible increased risk of graft rejection associated with such treatment, and complete withdrawal of corticosteroids is not recommended at present (31,48). Transplant recipients who develop diabetes after transplantation while receiving the CNI tacrolimus may also benefit from a switch to the less diabetogenic agent cyclosporine. This approach should be considered particularly for individuals whose diabetes is difficult to control (12).

Monitoring of transplant recipients with diabetes should follow similar lines to that recommended for patients with type 2 diabetes (12). For example, self-monitoring of blood glucose should form an essential component of the therapeutic management of patients receiving oral agents or insulin and may be useful for those controlling their diabetes by non-pharmacological means (37,49). Lipid levels (LDL, HDL, and total cholesterol

and triglycerides) should be evaluated yearly, as recommended by the ADA (50). Patients should also be screened annually for diabetic complications (e.g., retinopathy), as transplant recipients who develop diabetes are expected to have a similar risk of such long-term problems as patients with type 2 diabetes (12). A1C levels should be monitored every 3 months in patients with new-onset diabetes after transplantation, with the standard assay used in the Diabetes Control and Complications Trial (DCCT) to be used in all cases (41). An A1C of 6.5% or higher has been recommended for therapeutic intervention, which is in line with the recommendations of both the IDF and ACE (12,39,40). However, care must be taken in interpreting A1C levels in transplant patients, as conditions such as anemia or kidney impairment may affect the validity of the use of A1C in these patients. Annual screening for microalbuminuria is recommended for all patients with diabetes in the nontransplant population, as it is an early marker for both nephropathy and increased cardiovascular morbidity and mortality (51). Such monitoring may also be of value in transplant patients, though its utility in this population has not been validated. Indeed, many transplant recipients have renal insufficiency and may have proteinuria without diabetes. Furthermore, microalbuminuria levels may be difficult to interpret in kidney recipients with early chronic rejection (12).

Similar to that recommended for patients with type 2 diabetes in the general population, management of patients with new-onset diabetes after transplantation should follow a stepwise approach. In particular, management should begin with nonpharmacologic therapy (weight loss, exercise, and stopping smoking) and progress, if necessary, to oral agent monotherapy, oral combination therapy, then insulin therapy with or without oral agents (see for example 52,53; summarized in 12). The safety and tolerability profile of oral agents should be the most important factor in their selection for transplant recipients; however, other factors should also be taken into consideration. In particular, the possibility of serious adverse events such as lactic acidosis and hypoglycemia with agents like metformin and the sulfonylureas should be considered when selecting an oral agent for transplant recipients with impaired kidney function (12). Meglitinides

may be the safest agents (apart from insulin) for transplant patients with renal disease, as they do not interact with CNIs and are not contraindicated in patients with renal or liver insufficiency. Meglitinides may also be the agents of first choice for elderly transplant patients, though lower doses are recommended.

However, when considering an appropriate oral agent for transplant recipients, it should be noted that the comparative efficacy of these agents in transplant recipients is unknown, as no comparative trials have been conducted to date in this population. For transplant recipients in whom adequate control has not been achieved with oral monotherapy, oral combination therapies are recommended (12,53). Use of such combinations should be considered carefully, however, since they have not been tested in this patient population. Further research is thus required to determine the most effective oral combinations for such patients. Similarly, the concomitant use of insulin and oral agents, which is a commonly used approach for patients with type 2 diabetes, has not been evaluated in transplant recipients. As with the management of type 2 diabetes, the final step in the management of transplant recipients with new-onset diabetes, if therapeutic goals are not met, should be the consideration of a switch to insulin monotherapy (12). Transplant recipients requiring insulin injections to treat their diabetes should be referred to an endocrinologist for ongoing management. Most transplant teams, while multidisciplinary, do not currently involve an endocrinologist. However, the inclusion of such specialists within the broader transplant team has the potential to optimize management of patients with new-onset diabetes after transplantation, overcoming many long-term problems associated with this condition.

**Dyslipidemia and hypertension.** As previously mentioned, diabetes is the most significant risk factor for CVD and ischemic heart disease in transplant recipients (8). Furthermore, transplant recipients who develop new-onset diabetes consequently have an increased risk for atherogenic dyslipidemia and hypertension (1,25). Thus, following individualization of immunosuppressive therapy and initiation of a stepwise approach for treatment of diabetes, it has been recommended that patients receive aggressive

lipid-lowering therapy as detailed in the National Cholesterol Education Program (NCEP) guidelines (12,54). In particular, patients with LDL cholesterol  $\geq 130$  mg/dl (3.38 mmol/l) who require rapid lipid lowering should receive statins as primary therapy concomitant with medical nutritional therapy (37). Those with LDL cholesterol levels between 100 and 129 mg/dl (2.6–3.35 mmol/l) should be managed initially with medical nutritional therapy, although statins may also be considered. Guidelines on the treatment of dyslipidemia in patients with kidney disease, including renal transplant recipients, have recently been published (55).

To date, no studies have investigated the value of blood pressure lowering in posttransplant patients with new-onset diabetes, and the efficacy of antihypertensive agents has not been investigated in this population. However, raised blood pressure reduces the life expectancy of patients with diabetes in the general population, and thus recent guidelines for the management of diabetes outlined by the ADA and the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure have recommended a reduction of blood pressure to  $<130/80$  and  $<130/85$  mmHg, respectively (56,57). It is also likely that blood pressure lowering would be of value in transplant recipients with diabetes. Thus, a target of 130/80 mmHg has been recommended for transplant recipients who develop the condition (12).

## SUMMARY

New-onset diabetes is a major complication of transplantation that appears to have a high incidence. The condition is currently under diagnosed due to a previous lack of a standard definition; however, the recent International Consensus Guidelines for New-Onset Diabetes after Transplantation will help to establish a standard definition and assist in the diagnosis of the condition. New-onset diabetes after transplantation shares many similarities with type 2 diabetes, and recent guidelines thus recommend that its management should follow many of the therapeutic and preventative steps taken for type 2 diabetes (12) (Fig. 2). However, important therapeutic differences exist between the two conditions, and transplant recipients should not be considered comparable with patients with diabetes in the general population. It is important

that endocrinologists are aware of the similarities and differences between diabetes in the transplant and general populations. Adoption of appropriate management strategies may reduce the transplant recipient's risk for developing new-onset diabetes after transplantation and thus minimize the long-term consequences associated with the condition.

## APPENDIX

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