NEW-ONSET DIABETES AFTER TRANSPLANTATION: 2003 INTERNATIONAL CONSENSUS GUIDELINES

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INTRODUCTION

Diabetes Mellitus

Diabetes mellitus is one of the most common chronic diseases in the world, with an estimated worldwide prevalence of over 176 million in 2000. Furthermore, the prevalence of the disease is expected to increase in the coming years as industrialized societies become older, more obese, and more sedentary, and it is predicted to rise to 370 million by 2030 (1). Acute metabolic complications of diabetes are associated with high mortality rates; in particular, hyperosmolar hyperglycemia (approximately 15%) and ketoacidosis (up to 5%). The prognosis in these conditions is substantially worse in older patients and those with coma or hypotension (2).

Following a review of epidemiologic and pathologic evidence, the American Heart Association has also classified diabetes a major independent risk factor for cardiovascular disease (CVD) (3–8). Manifestations of CVD include atherosclerotic coronary heart disease (CHD), heart failure (diabetic cardiomyopathy), myocardial infarction, stroke, and peripheral vascular disease (7). The risk for stroke has been reported to be two to four times higher in patients with diabetes (7, 9). Furthermore, patients with diabetes who develop CVD have a worse prognosis for survival than patients without diabetes (8–11). In fact, CVD is listed as the cause of death in approximately 65% of patients with diabetes (12).

In addition to the risk for macrovascular complications, diabetes is associated with long-term microvascular complications including neuropathy, retinopathy, nephropathy, and erectile dysfunction. Diabetic nephropathy is the most common single cause of end-stage renal disease in the United States and Europe (13). With respect to retinopathy, after 20 years with the condition, almost all individuals with type 1 diabetes and over 60% with type 2 diabetes have a degree of retinopathy that may progress to loss of vision (14). In fact, diabetes is now considered the leading cause of blindness in developed countries, causing 12,000 to 24,000 new cases each year (15, 16).

New-Onset Diabetes after Transplantation

Diabetes and impaired glucose tolerance occurring as a complication of organ transplantation have been recognized for many years. However, incidence figures for new-onset diabetes after transplantation across different studies have ranged between 2% and 53% (17). Precise figures have been difficult to determine because there has been no consensus regarding the definition of the condition and hence different clinical studies have used a variety of diagnostic criteria. Despite the apparently high incidence of new-onset diabetes after transplantation, transplant patients are not always routinely screened for hyperglycemia posttransplant and the condition is often underestimated (18). Nevertheless, it is clear that development of diabetes after transplantation has serious consequences for the patient and threatens the outcome of transplantation; studies suggest that diabetes developing after transplantation is associated with reduced graft function and patient survival, and increased graft loss (19–21).

In addition to other risk factors, studies suggest that immunosuppressive regimens may account for a large degree of the increased risk for development of diabetes after transplantation (22). However, currently used immunosuppressive therapies vary in the extent to which they induce diabetes and thus the choice of immunosuppressive therapy can have a major influence on patients’ risk for developing the condition.

In summary, diabetes is a serious complication that can adversely affect the survival of the transplant recipient, long-term survival of the graft, and the patient’s quality of life. It is suggested that appropriate screening and management of patients pre- and posttransplantation can minimize the risk for developing the condition. Furthermore, early detection and appropriate treatment of patients who have developed diabetes can ameliorate the long-term consequences of the condition.
This publication represents the proceedings of the International Expert Panel Meeting: the first part provides the evidence on which the following management guidelines were based, and the second part outlines the consolidated New-Onset Diabetes after Transplantation International Consensus Guidelines. It is hoped that use of these guidelines may assist in avoiding or reducing the incidence and impact of new-onset diabetes mellitus after transplantation.

PART I: LITERATURE REVIEW

1. The Impact of New-Onset Diabetes after Transplantation

Diabetes is one of the most serious long-term complications of transplantation, particularly if the condition is poorly controlled. Data from clinical trials suggest that transplant recipients who develop diabetes are at greater risk of graft-related complications, including graft rejection, graft loss, and infection (23). Furthermore, the chronic hyperglycemia associated with the condition carries a long-term risk of both microvascular and macrovascular complications. Development of new-onset diabetes also incurs substantial additional health care costs. A recent analysis of Medicare payments in the United States between 1994 and 1998 has revealed that the costs of developing new-onset diabetes after kidney transplantation are between $12,000 and $13,000 higher than for those with no diabetes by the end of the first year posttransplant, and between $19,000 and $22,000 higher by the end of the second year (24).

1.1. Incidence and prevalence of new-onset diabetes after transplantation

The prevalence of new-onset diabetes after transplantation has been greatly underestimated in the literature because of the lack of a standard definition for the condition. Most definitions for diabetes after transplantation are derived from random glucose testing or fasting glucose levels greater than 140 mg/dL, and clinical trials do not routinely include oral glucose tolerance tests (OGTT) to determine the exact incidence of glycemic abnormalities in transplant recipients. This heterogeneity has led to wide variations in the reported incidence of the disease (17, 25). The observation periods of many studies are also too short (some are <1 year) and underestimate the true incidence of the condition; risk of diabetes increases progressively posttransplant and patients may develop the condition many years posttransplant (26).

The incidence of new-onset diabetes after transplantation in adults was systematically reviewed by Montori et al. (17): 12-month cumulative incidence estimates of diabetes after transplantation for heart, liver, and kidney transplantation studies were reported to be within the range of 2% to 53% (17). In this analysis, the type of immunosuppressive regimen used was found to explain 74% of the variability in incidence, with high-dose steroids being associated with the highest incidences (17). More recently, in a retrospective analysis of Medicare beneficiaries in the United States, the cumulative incidence of new-onset diabetes after transplantation among 11,659 patients was 9.1%, 16%, and 24% at 3 months, 12 months, and 36 months, respectively (Fig. 1) (27).

1.2. Natural history of new-onset diabetes after transplantation

The natural history of diabetes after transplantation shares many similarities with type 2 diabetes in that the onset can be insidious; individuals may experience glucose intolerance and may be asymptomatic for years before symptoms clinically manifest (25, 28). Furthermore, posttransplant hyperglycemia and diabetes are not always permanent, and may normalize, sometimes without treatment, within weeks or months (29). However, abnormal OGTT may still be observed in some patients up to 26 months after remission from diabetes after transplantation (29). The potentially asymptomatic and/or transient nature of diabetes after transplantation can thus make the condition difficult to diagnose, underlining the importance of establishing a precise definition.

The posttransplant development of diabetes involves two distinct phases: (1) patients are initially at greatest risk during the first 6 months posttransplant; and (2) the number of patients developing diabetes increases progressively over time thereafter (26, 30). This has been illustrated by a study of 2,078 kidney allograft recipients in which 5.9% of patients developed diabetes in the first 6 months after transplantation, but then the percentage of cases increased linearly over time, leading to cumulative percentages at 1, 3, 5, 10, and 15 years of 7.1%, 10.4%, 13.2%, 20.5%, and 29.8%, respectively (Fig. 2) (26). Studies of only a few months’ duration are therefore likely to grossly underestimate the true incidence of the condition.

1.3. Graft survival

In patients without diabetes, the 10-year survival of patients’ functioning grafts increased from 55% to 60% in the 1970s to 86% between 1988 and 1997. In addition to these improved survival rates, the posttransplant mortality rate has continued to decline (31). A large proportion of these
death can be attributed to death with graft function, which also accounts for 43% of all kidney graft losses (31).

Reports have consistently shown that the development of diabetes is associated with impaired long-term graft function and survival in kidney transplant recipients (32). Roth et al. (33) have reported that the development of diabetes after transplantation was associated with a significant decrease in graft survival at 3 and 4 years, compared with control recipients (71% vs. 86% and 54% vs. 82%, respectively; \( P < 0.05 \)) (33). Similarly, patients with new-onset diabetes after kidney transplantation have been shown to have significantly impaired kidney function, assessed by serum creatinine level, compared with controls at 5 years (2.9 ± 2.6 vs. 2.0 ± 0.07 mg/dL, respectively; \( P = 0.05 \)). Twelve-year graft survival was also significantly worse in patients with diabetes compared with controls (48% vs. 70%, respectively; \( P = 0.04 \)), with new-onset diabetes being an independent predictor of graft loss (relative risk, 3.72; \( P = 0.04 \)) (19). The development of new-onset diabetes after transplantation has also been shown to result in a greater incidence of acute rejection in liver transplant recipients (50% vs. 30% in the control group) (34).

The cause of impaired graft survival and function in transplant recipients with new-onset diabetes after transplantation is unclear. The development of diabetes-related nephropathy is one possibility because it has been clearly established that diabetic nephropathy can adversely affect allogenic kidney transplants and is associated with a high rate of allograft failure (35). However, diabetic nephropathy can take several years to develop and may not account for the early graft failure that can be associated with the development of diabetes. In kidney transplant patients, an alternative rationale may be that the presence of poorly controlled hypertension, which is common in transplant recipients with diabetes, may impact on graft function and survival by accelerating glomerular injury (25). The use of lower dosages of immunosuppressive regimens may also account for increased graft failure (19). However, it is also possible that other unmeasured factors in these retrospective studies caused both the higher incidence of new-onset diabetes and graft failure.

### 1.4. Patient survival

In addition to producing deleterious effects on graft function and survival, some studies (28, 36, 37) have reported that development of diabetes after transplantation reduces long-term survival of transplant recipients. Others have reported contradictory conclusions (19, 33, 38).

In one study, 1-year survival posttransplant was reported to be 83% for patients who developed diabetes after kidney transplantation compared with 98% for patients without diabetes (37). The survival of kidney transplant recipients developing diabetes is also reported to be reduced at 2 years compared with those without diabetes (67% vs. 83%, respectively) (36). Longer term survival of kidney transplant recipients with diabetes may also be reduced compared with non-diabetic recipients. In a study of 978 kidney transplant recipients, 6.7% of patients developed diabetes after transplantation, and the development of diabetes in these patients was found to be associated with significantly shorter patient survival compared with control patients (Fig. 3) (28). A further study has demonstrated that survival of transplant recipients is adversely affected by both preexisting diabetes and new-onset diabetes after kidney transplantation and that the development of diabetes posttransplant in recipients below the age of 55 years is associated with a particularly high risk of death (relative risk, 2.54; \( P < 0.001 \)) (39). Finally, a strong argument in favor of a deleterious effect of diabetes on posttransplant outcome is the fact that long-term survival of patients with diabetes who undergo simultaneous pancreas-kidney transplantation is superior to those with cadaveric kidney transplantation (8-year survival rates of 72% for pancreas-kidney recipients vs. 55% for cadaveric kidney recipients) (40). The development of new-onset diabetes after transplantation has also been shown to be an independent risk factor for mortality in liver transplant recipients (41). The reason why some studies have failed to demonstrate an effect of diabetes after transplantation on patient survival is
unclear, but may be related to the small numbers of patients involved (38) or improvements in patient management (19).

The increased incidence of infections, and associated increased risk for sepsis, in transplant recipients with diabetes may contribute toward the increased mortality. This hypothesis is supported by the findings of two studies conducted in kidney transplant recipients. Sumrani et al. (30) have reported that infections were a major complication in recipients with diabetes, with 54% experiencing infectious complications compared with 17% in the control group. Although no difference in mortality was found between the two groups, all five deaths in the group with diabetes were caused by sepsis compared with only one in the control group (30). Similarly, Miles et al. have reported that the frequency of sepsis as a cause of death was greater in kidney transplant recipients with diabetes compared with those with no diabetes (19). In a review of studies in liver transplant recipients, Benhamou and Penfornis reported that the incidence of acute rejection and the mortality rate within the first 2 years are significantly higher in patients with new-onset diabetes after transplantation (35). However, the precise association between the development of diabetes post-transplant and early mortality is difficult to define owing to the fact that rejection episodes are treated with corticosteroid boluses, which contribute substantially to the development of diabetes (35).

1.5. Diabetes as a risk factor for CVD

CVD is the most common cause of death after renal transplantation in the United States (42). The incidence of myocardial infarction is between three and five times more common in transplant patients than in the general population (43). It is therefore not surprising that the overall incidence of cardiovascular mortality is also considerably higher in transplant recipients than in nontransplant patients (43). Furthermore, conventional risk factors for CVD (e.g., diabetes, hypertension, dyslipidemia) are also risk factors for chronic graft rejection (44).

In addition to predisposing transplant recipients to CVD, diabetes after transplantation has a significant impact on the risk of death from cardiovascular complications. Death resulting from ischemic heart disease (IHD) has been shown to be 20.8 times higher in transplant recipients with diabetes than in the general population, compared with 6.4 times higher than the general population in transplant recipients without diabetes aged 55 to 64 years (Table 1) (45). This is not surprising because CVD is listed as the cause of death in approximately 65% of individuals with diabetes (12).

In one study conducted in kidney transplant recipients, diabetes was found to be the most important risk factor for developing both cerebrovascular disease (independent relative risk, 3.21) and peripheral vascular disease (independent relative risk, 28.18; P<0.05) (46). In a further study, diabetes mellitus carried the highest relative risk for IHD among kidney transplant patients more than 1 year post-transplant (Table 2) (47). This risk of IHD associated with diabetes was substantially higher for kidney transplant recipients than for the control population (Framingham Heart Study), particularly among women.

It therefore appears that individuals with diabetes in the general population have an increased risk for CVD mortality and that the risk of CVD is also substantially higher in transplant recipients who develop diabetes after transplantation compared with those who do not develop diabetes (45, 47). The reason for the increased risk of CVD mortality and morbidity in transplant recipients developing diabetes after transplantation is not entirely clear, although both hyperinsulinemia and glucose intolerance are reported to be independent risk factors for atherosclerosis in the general population (48–50). Furthermore, fasting blood glucose values in the upper normal range (86–108 mg/dL; 4.8–6.0 mM) are

### Table 1. Age-related IHD mortality after transplantation in a study of 1,347 kidney transplant recipients

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Ischemic heart disease death/1,000 patients/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Transplant recipient</td>
</tr>
<tr>
<td>25–34 yr</td>
<td>35–44 yr</td>
</tr>
<tr>
<td>Live donor</td>
<td></td>
</tr>
<tr>
<td>nondiabetic</td>
<td>1.05</td>
</tr>
<tr>
<td>Cadaver donor</td>
<td></td>
</tr>
<tr>
<td>nondiabetic</td>
<td>0.52</td>
</tr>
<tr>
<td>Live donor</td>
<td>1.19</td>
</tr>
<tr>
<td>with diabetes</td>
<td></td>
</tr>
<tr>
<td>Cadaver donor</td>
<td>1.66</td>
</tr>
<tr>
<td>with diabetes</td>
<td></td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>NA</td>
</tr>
<tr>
<td>General population</td>
<td>NA</td>
</tr>
</tbody>
</table>

The presence of diabetes appears to have a marked impact on the incidence of death from ischemic heart disease in all age groups post-transplant. The general population refers to Sweden. NA, Insufficient data available.


### Table 2. Relative risk for IHD among transplant recipients more than 1 year after kidney transplantation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Control</td>
<td>Transplant recipient</td>
</tr>
<tr>
<td>&lt;160</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>160–199</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>200–239</td>
<td>1.19</td>
<td>2.39</td>
</tr>
<tr>
<td>240–279</td>
<td>1.66</td>
<td>2.02</td>
</tr>
<tr>
<td>&gt;280</td>
<td>1.93</td>
<td>2.25</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120 and &lt;80</td>
<td>1.00</td>
<td>0.25</td>
</tr>
<tr>
<td>120–129 or 80–84</td>
<td>1.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>130–139 or 85–89</td>
<td>1.33</td>
<td>1.05</td>
</tr>
<tr>
<td>140–159 or 90–99</td>
<td>1.68</td>
<td>1.19</td>
</tr>
<tr>
<td>≥160 or &gt;100</td>
<td>1.86</td>
<td>1.47</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.53</td>
<td>2.78&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.69</td>
<td>1.95&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A relative risk of greater or less than 1.00 indicates a higher or lower risk for ischemic heart disease, respectively. Control subjects are from the Framingham Heart Study.

<sup>a</sup> P<0.05 compared with reference risk values for transplant recipients; <sup>b</sup> too few patients were available to reliably assess this risk; <sup>c</sup> Reference risks for cholesterol levels and blood pressure are indicated by 1.00.

associated with an increased risk for CVD mortality in non-diabetic, apparently healthy, middle-aged men (51). Transplant recipients tend to be insulin resistant because of impaired nonoxidative glucose disposal, and those who develop diabetes also have an impaired insulin secretion response (28). In addition, transplant recipients with diabetes also have an increased incidence of atherogenic dyslipidemia and hypertension. These factors are all thought to contribute to the higher risk for CVD mortality in this population (28, 35).

1.6. Summary

In summary, development of new-onset diabetes after transplantation is associated with impaired long-term graft function and survival, reduced long-term survival of transplant recipients and increased risk of mortality and morbidity associated with CVD (Fig. 4).

2. Diagnosis of New-Onset Diabetes after Transplantation

2.1. Diagnosis of new-onset diabetes after transplantation in clinical studies

The major difficulty in estimating precisely the incidence for diabetes after transplantation has been the lack of consensus regarding the definition and diagnosis of the condition. Most definitions of the condition in the literature are derived from fasting or random glucose testing greater than 140 mg/dL (7.8 mM) or OGTT (25, 28). In clinical trials, the most commonly used definition is the requirement of insulin for a minimum period (usually 30 days) posttransplantation. This definition has resulted in an underestimate of the prevalence of diabetes after transplantation because it excludes patients treated with oral antidiabetic agents, as well as those with asymptomatic hyperglycemia and impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). In addition, this definition fails to address the long-term implications of diabetes after transplantation, as it does not identify patients with preexisting diabetes whose glycemic control worsens posttransplant. Finally, it does not distinguish between patients with new onset of disease from those with worsening of disease.

It has been suggested that the American Diabetes Association (ADA) criteria described below should also be recommended for the diagnosis of diabetes after transplantation, and that adoption of the criteria described in Table 3 may be the first step toward standardizing the definition of the condition (28). In this population, it may be particularly important to consider both IGT and IFG because these are likely to be important predictive factors for the development of diabetes.

2.2. Diagnosis of diabetes in the general population

2.2.1. Diagnostic criteria

The ADA has recently endorsed revised diagnostic guidelines for diabetes mellitus in accordance with the World Health Organization (WHO) in 1999 (52), which recommend that all types of diabetes be diagnosed through the criteria outlined in Table 3 (53). These guidelines are also in line with the criteria recommended by the International Diabetes Foundation (IDF) and the American College of Endocrinology (ACE) (54, 55).

A number of significant changes have been made to the diagnostic criteria and classification of diabetes over the past 20 years. The major and most recent changes to the diagnostic criteria include the following:

- Lowering of fasting plasma glucose values for diagnosis of diabetes from greater than or equal to 140 mg/dL (7.8 mM) to greater than or equal to 126 mg/dL (7.0 mM).
- Lowering of the plasma glucose level for diagnosis of impaired fasting glucose from greater than or equal to 120 mg/dL (6.7 mM) to greater than or equal to 110 mg/dL (6.1 mM).

The rationales for these revisions were to avoid the discrepancy between the fasting plasma glucose (FPG) and OGTT in identifying individuals at high risk for developing adverse effects of diabetes, such as microvascular complications, and to facilitate and encourage the use of a simpler and equally accurate test—FPG—for diagnosing diabetes (53). The new FPG criteria represent the upper end of the range that corresponds with the 2-hr postload concentration (that is unchanged in the revised recommendations). Thus, it is considered that the risk for microvascular complications is in...
increased in individuals with an FPG level greater than or equal to 126 mg/dL (7.0 mM) (52, 53). Furthermore, the WHO considers the risk for macrovascular disease to be increased in individuals with FPG values greater than or equal to 126 mg/dL (7.0 mM) even if 2-hr values are less than 140 mg/dL (7.8 mM) (52).

An intermediate group of individuals whose glucose levels do not meet the criteria for diabetes but cannot be considered normal have also been recognized in the recent changes to the diagnostic criteria (Table 3) (53). Although the FPG levels of people with impaired glucose tolerance or impaired fasting glucose are below diabetic thresholds, these individuals have a higher risk for the development of diabetes and CVD than the general population.

### 3. Risk Factors for Developing Diabetes after Transplantation

The ability to predict a patient’s risk for developing diabetes after transplantation would be of considerable benefit in selecting appropriate immunosuppressive regimens for individuals, and in identifying those who may need more intensive monitoring and risk-factor intervention. Although there are currently no clearly established risk factors for diabetes after transplantation, a number of characteristics have been identified that appear to predispose patients to the development of the condition (Fig. 5) (22). Consideration of such factors is an important step in the clinical assessment of patients before transplantation and may be used to individualize therapy and reduce the risk of developing diabetes after transplantation. Obviously, some of these risk factors, such as age and ethnicity, are not modifiable, although risk may have an additive effect and the evaluation of individual risk factors should play a significant role in the management of transplant recipients (27). Risk factors may also differ depending on the immunosuppressant agent used; immunosuppression therapies have changed greatly over the last two decades, which may account for discrepancies in risk factor assessment in the literature.

#### 3.1. Patient age

The incidence of diabetes after transplantation appears to be greater in older age patients. When taking the findings of a number of studies into account, risk of developing diabetes after transplantation appears to increase in patients over the age of 40 years (22, 30, 37, 56). Increased age is also reported to be associated with decreased patient and graft survival.
and increased morbidity from infections (30). In contrast, age does not appear to be a significant risk factor for the development of diabetes after liver transplantation (57).

### 3.2. Ethnic background

There is strong evidence that African American and Hispanic populations have a greater risk of developing new-onset diabetes after transplantation than white populations (Table 4) (21, 30). The differing incidence of new-onset diabetes after transplantation in patients of different ethnicity may reflect differential pharmacokinetics and diabetogenic effects of immunosuppressive agents (17). Compared with whites, African Americans require 37% higher doses of tacrolimus to achieve comparable blood concentrations, yet this agent is reported to be up to five times more diabetogenic than cyclosporine and has particularly potent diabetogenic effects in African Americans compared with whites (27, 58).

### 3.3. Family history

Type 2 diabetes is a complex condition involving a combination of genetic and environmental factors and studies suggest that such factors may also be involved in the development of new-onset diabetes after transplantation (59). For example, there have been some reports that a family history of diabetes may be a predictor for the development of diabetes after kidney transplantation, with one study showing a sevenfold increase in the condition in patients with a positive family history (29, 30). Similarly, significantly more heart transplant recipients who developed diabetes were found to have a family history of diabetes in first-degree relatives compared with those who remained free of the condition (46% vs. 15%, respectively; P<0.05) (60). These findings suggest that individuals with a history of diabetes among first-degree relatives should be identified early in the course of their treatment to monitor the development of diabetes and adapt their immunosuppressive therapy accordingly.

The incidence of diabetes after transplantation has been reported to be higher in individuals with certain histocompatibility leukocyte antigen (HLA) phenotypes; however, the results from these studies are contradictory and involve only small numbers of patients (30, 56, 61). Consequently, HLA phenotype cannot be considered as a reliable risk factor for new-onset diabetes after transplantation at this stage.

### 3.4. Patient body weight

Obesity frequently develops after transplantation and is associated with both reduced graft and patient survival (20, 62). Truncal obesity is also a risk factor for developing insulin resistance (63). Body weight has been shown to be associated with the development of diabetes after transplantation in most studies (19, 21, 27, 29, 37). However, some studies have found the association between development of diabetes post-transplantation and either body weight or body mass index (BMI) to be weak (17, 30). Nevertheless, obesity is a known risk factor for type 2 diabetes and it is possible that other indices such as intra-abdominal fat or waist-to-hip ratio may be more important risk factors for diabetes after transplantation than total body weight or BMI.

### 3.5. Hepatitis C virus status

The development of diabetes after liver transplantation appears to be associated with a pretransplant diagnosis of hepatitis C virus (HCV) infection (Fig. 6) (41, 64). Furthermore, new-onset diabetes after liver transplantation in patients with HCV infection is associated with an increase in both overall mortality and infection-related mortality (41).

HCV infection is also a significant comorbidity in kidney transplant recipients, occurring in 10% to 40% of patients, and again is associated with an increased risk of both graft failure and mortality (65). Furthermore, a strong association has been demonstrated between HCV status and the development of diabetes after kidney transplantation, particularly in patients receiving tacrolimus-based immunosuppression from the time of transplantation (65). In a recent study, unadjusted cumulative incidences at 3, 12, and 36 months for diabetes after kidney transplantation for patients who were HCV-positive at transplantation were 15.6%, 25.6%, and 35.4% compared with 8.8%, 15.4%, and 23.4% for patients who were HCV-negative at transplantation, respectively (P<0.0001) (27). Clearly, monitoring and prevention of diabetes, coupled with management of HCV infection with combination antiviral therapy, should be essential targets after transplantation, particularly in HCV-infected patients.

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence of new-onset diabetes after transplantation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>5/137 (3.6)</td>
</tr>
<tr>
<td>African American</td>
<td>22/111 (19.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10/47 (21.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>2/42 (4.8)</td>
</tr>
</tbody>
</table>

* a,b P<0.01 a vs. b.


**Figure 6.** Incidence of pretransplant diabetes and diabetes after liver transplantation in patients with and without hepatitis C virus infection. (From Baid S, Cosimi AB, Farrell ML, et al. Posttransplant diabetes mellitus in liver transplant recipients: Risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. Transplantation 2001; 72: 1066; with permission.)
3.6. Immunosuppressive therapies

Evidence from published studies suggests that immunosuppressive therapy increases the risk for developing diabetes after transplantation (22). Corticosteroids have clearly been associated with an increased incidence of impaired glucose tolerance and diabetes after transplantation (29, 36, 56, 66). With regard to other immunosuppressive therapies, tacrolimus is reported to be up to five times more diabetogenic than cyclosporine (27, 67–70). The impact of immunosuppressive therapies is discussed in section 4 of this review (see below).

3.7. Other factors

Abnormal glucose regulation before transplantation, defined as a fasting serum glucose level between 110 and 126 mg/dL, a postprandial serum glucose level between 140 and 200 mg/dL, or both, may increase the risk of developing diabetes after transplantation. The presence of other components of metabolic syndrome (e.g., hypertriglyceridemia, hypertension, hyperuricemia) may also be useful predictors of the condition, although the precise role of these markers is difficult to define because of the presence of organ failure before transplantation (35). Transplantation with a cadaveric kidney, as compared with a living donor kidney, may also increase the risk for diabetes after transplantation (30).

4. Effect of Immunosuppression on Risk for New-Onset Diabetes

Experimental and observational evidence suggests that currently used immunosuppressive regimens account for a large degree of the increased risk for development of diabetes after transplantation (71). However, different agents vary in the extent to which they induce diabetes.

The association between corticosteroid therapy and the development of diabetes after transplantation is clearly established (29, 36, 56, 66). The development of diabetes in transplant recipients receiving prednisolone has been reported to be as high as 46% (72); however, the diabetogenic effect of corticosteroids appears to be dose related (73). Incremental dose increases of 0.01 mg/kg prednisolone per day are associated with a 5% increased risk of diabetes after transplantation and a 4% increased risk of glucose intolerance (61). Conversely, reducing the prednisolone dose in kidney transplant patients to 5 mg/day at 1 year is associated with a reduction in the percentage of glucose-intolerant recipients from 55% to 34% (25, 73). The incidence of corticosteroid-induced diabetes is also related to the duration of therapy. In one study, 75.6% of kidney transplant recipients who developed new-onset diabetes manifest sustained hyperglycemia within 2 weeks of methylprednisolone treatment; however, the likelihood of patients developing hyperglycemia continued to increase the longer the methylprednisolone treatment continued (Table 5) (36).

It should be noted that, although corticosteroid withdrawal or dose reduction can reduce the incidence of diabetes post-transplant, this strategy has been associated with an increased risk for graft rejection, which may in turn increase steroid requirements and, potentially, the incidence of diabetes (25, 74, 75). In a study evaluating withdrawal of corticosteroids in 84 kidney transplant recipients, there was a 10% reduction in the frequency of diabetes compared with patients maintained on steroids. However, 26% of the patients withdrawn from corticosteroids subsequently resumed corticosteroid use because of the onset of rejection (75). Seven of eight kidney transplant recipients who developed diabetes after transplantation and were withdrawn from prednisolone were able to discontinue hyperglycemic therapy (insulin or oral agents) within 4 months of steroid cessation, although two of these patients developed acute rejection and had to resume steroid therapy (74).

Calcineurin inhibitors have also been associated with increased incidence of diabetes after transplantation. In a recent analysis, the unadjusted cumulative incidences for diabetes after transplantation in patients treated with tacrolimus were 13.5%, 22.1%, and 31.8% compared with 7.8%, 14.2%, and 21.9% in those who did not receive tacrolimus at 3, 12, and 36 months, respectively (Fig. 7) (27). After adjustment for multiple risk factors, this difference was found to be significant (P<0.0001).

Although both cyclosporine and tacrolimus have been associated with an increased risk for diabetes after transplantation, clinical studies indicate that tacrolimus is associated with a higher risk of impaired glucose tolerance and diabetes than cyclosporine in recipients of kidney, liver, pancreas, allogenic stem cell, and lung transplantation (69, 76–79). In a number of studies involving adult kidney transplant recipients, the risk for developing diabetes was found to be up to five times higher with tacrolimus at 1 year after kidney transplantation compared with cyclosporine (Table 6) (67–70). Moreover, high trough levels of tacrolimus during the first month after transplantation (especially >15 ng/mL) have been found to be a significant risk factor for the development of both IFG and new-onset diabetes after transplantation (80). 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 (24). This study found that by 2 years posttransplant, the incidence of new-onset diabetes was approximately 70% higher in tacrolimus-treated patients than in patients receiving cyclosporine (29.7% vs. 17.9%) (Fig. 8). The incremental increases in the incidence of new-onset diabetes after transplantation were 9.4% versus 15.4% at 1 year and 8.4% versus 17.7% at 2 years for cyclosporine and tacrolimus, respectively. This evidence suggests

<table>
<thead>
<tr>
<th>TABLE 5. Incidence of new-onset diabetes following administration of methylprednisolone treatment after kidney transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone treatment duration (days)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>0–7</td>
</tr>
<tr>
<td>8–14</td>
</tr>
<tr>
<td>15–21</td>
</tr>
<tr>
<td>22–28</td>
</tr>
</tbody>
</table>

Although most cases of new-onset diabetes developed within 2 weeks of methylprednisolone therapy, the longer the treatment was continued, the greater the likelihood of developing the condition, with new cases of the condition continuing to be observed up to 4 weeks after the initiation of treatment.


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that patients receiving tacrolimus, but not those taking cyclosporine, continue to develop new-onset diabetes at above baseline (pretransplant) rates in the second posttransplant. Furthermore, the estimated cost per patient of developing new-onset diabetes after transplantation (calculated by relating the incremental cost of each diabetes case to the incremental incidence of new-onset diabetes) was found to be almost doubled when tacrolimus was used for maintenance immunosuppression compared with cyclosporine: $2,205 versus $1,137 at 1 year and $3,308 versus $1,612 at 2 years posttransplant, respectively (24).

The incidence of diabetes after liver transplantation was reported to be 26.6% with tacrolimus and 16.1% with cyclosporine (76). There is also a higher frequency of hyperglycemia in liver transplantation after tacrolimus (47% for tacrolimus vs. 38% for cyclosporine) (81). In pancreas allograft recipients, hyperglycemia during the first year was more common with tacrolimus than cyclosporine (26.3% vs. 8.5%, respectively) (78). A twofold higher incidence of diabetes after transplantation has also been reported in lung transplant recipients receiving tacrolimus (57% vs. 23% for cyclosporine, $P<0.05$) (79).

In support of these findings, a recent meta-analysis by Heisel et al. (82) concludes from nine prospective kidney, liver, and heart transplant studies that the odds for developing diabetes after transplantation is four times less in patients receiving cyclosporine (24 of 806 patients vs. 116 of 1,000 tacrolimus) across all organ transplant groups (odds ratio, 0.25; 95% confidence interval [CI], 0.16–0.40; $P<0.00001$) (82).

African Americans appear to be particularly susceptible to the diabetogenic effects of tacrolimus. The incidence of diabetes after transplantation in adult African Americans has been reported as 36.6% in tacrolimus-treated kidney transplant recipients compared with 8.3% in those receiving cyclosporine (Table 7) (58). The diabetogenic effect of tacrolimus was reversible in some patients; at 2 years posttransplant, 70% of whites and 20% of African Americans were able to discontinue insulin.

5. New-Onset Diabetes in Pediatric Transplant Recipients

New-onset diabetes has also been described in pediatric transplant recipients, with reported incidences of up to 20% (18, 83, 84). In children, tacrolimus appears to be particularly associated with an increased risk for diabetes after transplantation. The incidence in pediatric kidney transplant recipients (aged 1–18 years) in the United States is reported to have increased markedly in recent years; 20% of children developed the condition between 1996 and 1999 compared with only 2% to 4% of children in the 9-year period before that (18). The increased incidence was considered to be associated with use of tacrolimus; the odds ratio for diabetes after transplantation, statistically adjusted for peritransplant hyperglycemia (blood glucose $>200$ mg/dL $\leq$2 weeks posttransplant), was 9.1 (95% CI, 1.1–76.0; $P=0.04$) for tacrolimus use at diagnosis compared with cyclosporine (18). In addition, in a retrospective analysis of 1,365 North American children receiving a kidney transplant between January 1992 and July 1997, 36 developed diabetes; of these children, 45% were receiving tacrolimus (83). However, a further study has reported a similar incidence of new-onset diabetes in tacrolimus- and cyclosporine-treated children after kidney transplantation (85).

The incidence of diabetes appears to be higher in pediatric transplant recipients of African American ethnicity (83). Furthermore, diabetes after transplantation is more likely to be transient in children (18). The incidence of diabetes in tacrolimus-treated pediatric thoracic transplant recipients is reported to be 17% (84).

PART II: NEW-ONSET DIABETES AFTER TRANSPLANTATION: INTERNATIONAL CONSENSUS GUIDELINES

These clinical guidelines contain a summary of recommendations based on the evidence in the literature reviewed in the previous sections of this report. The recommendations were validated through discussion at the International Expert Panel Meeting in Barcelona on 19 February 2003.

6. Definition and Diagnosis of New-Onset Diabetes after Transplantation

Patients developing new-onset glucose intolerance or new-onset diabetes after transplantation may not initially display any overt symptoms. However, this asymptomatic period increases the duration of exposure to the adverse effects of hyperglycemia and diabetes (35).

Previous definitions for diabetes after transplantation used in clinical trials (requirement of insulin for a minimum period [usually 30 days] posttransplantation) fail to identify patients with preexisting diabetes whose glycemic control worsens posttransplant, and do not distinguish between pa-
Patients with new onset of disease and those with worsening of disease. Although the FPG levels of people with IGT or IFG are below diabetic thresholds, these individuals have a higher risk for the development of diabetes and CVD than the general population. Thus, early diagnosis of patients with IGT, IFG, and diabetes after transplantation is essential so that the secondary complications of the condition can be reduced.

It is recommended that the definition and diagnosis of diabetes after transplantation should be based on the currently accepted definition of diabetes mellitus and IGT that has been most recently defined by the ADA, WHO, IDF, and ACE (Fig. 9) (52–55). In each case, in the absence of unequivocal hyperglycemia with acute metabolic decompensation, the criteria should be confirmed by repeat testing on a different day (53). The diabetes guidelines take into account the fact that IFG and IGT are associated with an increased risk for diabetes. New-onset diabetes is a heterogeneous condition

### TABLE 6. Incidence and risk for diabetes after transplantation with tacrolimus and cyclosporine

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of new-onset diabetes after transplantation</th>
<th>Patients</th>
<th>Cyclosporine 1-yr incidence (%)</th>
<th>Tacrolimus 1-yr incidence (%)</th>
<th>Odds ratio (95% CI/significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney transplant</td>
<td>Use of insulin &gt;1 wk</td>
<td>28 cyclosporine 67 tacrolimus</td>
<td>5.0</td>
<td>25.4</td>
<td>4.15 (0.5–34.04)</td>
</tr>
<tr>
<td>Vincenti et al., 1996 (67)</td>
<td>Use of insulin for ≥30 days with &lt;5-day medication gap</td>
<td>151 cyclosporine 151 tacrolimus</td>
<td>4.0</td>
<td>19.9</td>
<td>5.25 (1.94–14.20)</td>
</tr>
<tr>
<td>Pirsch et al., 1997 (69)</td>
<td>Use of insulin for ≥30 days with &lt;5-day medication gap</td>
<td>145 cyclosporine 303 tacrolimus</td>
<td>2.1</td>
<td>11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mayer et al., 1997 (68)</td>
<td>Use of insulin &gt;1 wk</td>
<td>28 cyclosporine 67 tacrolimus</td>
<td>5.0</td>
<td>25.4</td>
<td>4.15 (0.5–34.04)</td>
</tr>
<tr>
<td></td>
<td>Use of insulin for ≥30 days with &lt;5-day medication gap</td>
<td>151 cyclosporine 151 tacrolimus</td>
<td>4.0</td>
<td>19.9</td>
<td>5.25 (1.94–14.20)</td>
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</tr>
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</tr>
<tr>
<td></td>
<td>Use of insulin for ≥30 days with &lt;5-day medication gap</td>
<td>151 cyclosporine 151 tacrolimus</td>
<td>4.0</td>
<td>19.9</td>
<td>5.25 (1.94–14.20)</td>
</tr>
</tbody>
</table>

Test for heterogeneity* (70)  
Summary result† (70)  
\[ P > 0.80 \]  
5.03 (2.04–12.36)  

Azathioprine was also administered in all three studies. NS, not specified.

* Heterogeneity across studies was assessed with the Q statistic, with \( P \leq 0.1 \) considered significant.

† In the combined studies, treatment with tacrolimus was associated with a significant increase in the prevalence of new-onset diabetes after transplantation at 1 year (odds ratio 5.03).


### TABLE 7. Incidence and reversibility of diabetes by ethnicity with tacrolimus and cyclosporine for maintenance immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus (%)</th>
<th>Cyclosporine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African American (n=41)</td>
<td>White (n=82)</td>
</tr>
<tr>
<td>Developed diabetes</td>
<td>15 (36.6)</td>
<td>10 (12.2)</td>
</tr>
<tr>
<td>at 1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued insulin</td>
<td>1 (6.7)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>by 1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued insulin</td>
<td>3 (20.0)</td>
<td>7 (70.0)</td>
</tr>
<tr>
<td>by 2 yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. Transplantation 1998; 65: 515; with permission.
of abnormal glucose tolerance with a variable onset, duration, and severity. Consequently, patients should be closely monitored for the development of the condition posttransplant, with particular attention being paid to patients with IFG and IGT.

7. Management of the Transplant Patient

7.1. Pretransplant baseline evaluation

7.1.1. Screening

Despite the lack of consistency among studies, a number of factors have been identified that appear to predispose patients to the development of diabetes after transplantation (Table 8) (22, 27, 86). Consideration of such factors is an important step in the clinical assessment of patients before transplantation and may be used to individualize therapy and reduce the risk of developing diabetes (Fig. 10). A complete medical history, including documentation of glucose history (e.g., history of gestational diabetes) should also be taken from all patients at the pretransplant consultation and FPG levels tested at regular intervals. In addition, patients should be screened for the metabolic syndrome and other cardiovascular risk factors (e.g., smoking, family history of CVD, dyslipidemia), because such individuals have an increased risk of developing both diabetes and CVD (52). Ac-
following abnormalities:

- Serum triglyceride levels of at least 150 mg/dL (1.69 mM)
- High-density lipoprotein (HDL) cholesterol levels of less than 40 mg/dL (1.04 mM) in men and 50 mg/dL (1.29 mM) in women
- Blood pressure of at least 130/85 mm Hg
- Serum glucose levels of at least 110 mg/dL (6.1 mM)

7.1.2. Counseling

Before transplant surgery, all patients should be informed of their risk of developing diabetes after transplantation and advised that their appetite is likely to increase posttransplant, which may result in weight gain and hence may further increase this risk. Patients should thus be counseled on the importance of weight control, following an appropriate diet, and engaging in a higher level of physical activity to help prevent the development of the condition (Fig. 10).

These recommendations are particularly important for those with an increased risk for new-onset diabetes (e.g., those with abnormal glucose tolerance), and such individuals should be referred for additional nutritional education from a dietitian. During ongoing counseling, patients should also be made aware that the long-term survival of their graft depends on their compliance with medications and that no change in their immunosuppressive regimen should be attempted without involvement of the transplant team (88).

7.2. Individualization of immunosuppressive therapy

The selection of an appropriate immunosuppressive regimen must be considered carefully for each individual patient (Fig. 11). Because there is evidence that some immunosuppressant therapies are more diabetogenic than others, selection of an appropriate immunosuppressive regimen should be considered, taking into account the individual’s diabetes and CVD risk profile, the relative diabetogenicity and risk for diabetes of each immunosuppressant, and the efficacy of each agent.

The risk of diabetes is highest with corticosteroids, and combination with tacrolimus may confer additional risk for children or individuals of black ancestry (18, 25). Thus, corticosteroid doses should be reduced as early as possible and a reduction in calcineurin inhibitor dosage should also be considered, particularly for high-risk patients. The risk of developing new-onset diabetes should be weighed against the risk of acute rejection when choosing a calcineurin inhibitor for any individual patient. Steroid-sparing regimens (e.g., induction antibody adjunct treatment) should also be considered to allow rapid corticosteroid withdrawal or avoidance.

7.3. Ongoing monitoring for the transplant patient

FPG should be monitored in all patients throughout the posttransplant period, regardless of current or previous diabetic status (Fig. 12). Patients who have previously been diagnosed with diabetes but whose symptoms have resolved should be particularly closely monitored, as such individuals are at increased risk for the development of subsequent diabetes. In these patients, the detection of IGT and abnormal lipid profiles should lead to the implementation of intensive prevention strategies. FPG testing should be performed on samples of venous blood taken in the morning after an 8-hr period without caloric intake.

Data from a number of recent studies conducted in the general population have indicated that elevated 2-hr OGTT levels may be more predictive of increased risk of CVD and mortality than FPG testing, particularly in individuals with IGT (89–94). Furthermore, the OGTT criteria to diagnose IGT (140–200 mg/dL; 7.8–11.1 mM) will identify more individuals with IGT than the criteria for FPG (110–126 mg/dL; 6.1–7.0 mM) (53). Because such individuals may have the greatest attributable risk of death, the use of OGTT may provide additional prognostic information to FPG testing. Although the predictive value of OGTT has not been assessed in transplant patients, the use of this test should be considered in subjects with normal FPG levels (<110 mg/dL; 6.1 mM). Further research is required to assess fully the value of OGTT in transplant recipients.

8. Management of Diabetes after Transplantation

The following guidelines outline the rationale and recommended steps for managing patients who do develop diabetes after transplantation to minimize the impact of the disease. The key aims for managing patients are to resolve the symptoms of diabetes through adjustment of immunosuppressive therapy and to prevent complications of diabetes through appropriate management of diabetes (i.e., monitoring, treatment, and patient education). Patients with IGT or IFG should be identified and treated early because this condition is thought to be a risk factor for the development of diabetes mellitus (73).

8.1. Management of immunosuppressive therapy

Reducing the dose of corticosteroids is a further therapeutic approach for transplant recipients who are at risk of
During initial consultation for transplantation, the following assessments should be made:

- Documentation of complete medical history
- All potential transplant recipients should be screened for abnormal glucose regulation by determination of fasting plasma glucose (FPG) levels at the following intervals:
  - individuals with FPG <110 mg/dl (6.1 mmol/l) – testing every 3 years
  - individuals with FPG 110–126 mg/dl (6.1–7.0 mmol/l) – annual testing
- Determination of risk factors for diabetes after transplantation:
  - individuals of African American or Hispanic ethnicity
  - history of diabetes among first-degree relatives
  - hepatitis C viral infection
  - history of gestational diabetes
  - CV risk factors
  - age >40 years
  - other risk factors (i.e. obesity).
- Potential transplant recipients should be informed of their risk profile for diabetes post-transplant and counseled on the importance of weight control, diet and regular exercise. Patients at high risk for developing diabetes should be referred to a dietician for further advice on diet.

*The committee recognizes that the percentage of individuals with abnormal glucose regulation in this population is likely to be higher than in the general population, though data to support this opinion are lacking; further research is thus required to assess this situation.

**Figure 10. Recommendations: Pretransplant screening and counseling.**

**Figure 11. Recommendations: Pretransplant individualization of immunosuppressive therapy.**

Immunosuppressive therapy should be individualized using the following guidelines.*

- Plan to reduce corticosteroids doses as early as possible in individuals with CV and diabetes risk factors.
- Steroid-sparing regimens should be considered to allow lower corticosteroid doses to be used.
- The risk of developing new-onset diabetes after transplantation should be weighed against the risk of acute rejection when choosing an immunosuppressive regimen for any individual patient.

*These guidelines are based on review of the available data describing the diabetogenic risk associated with different immunosuppressive therapies; however, it is recognized that further studies are required to determine the impact of different initial immunosuppressive therapies on the risk for diabetes.

developing new-onset diabetes, because this strategy has been shown to significantly improve glucose tolerance during the first year after kidney transplantation (73). Decreasing the dose of prednisolone to 5 mg/day at 1 year is associated with a reduction in the percentage of glucose-intolerant recipients from 55% to 34% (73). The dose of prednisolone is
also an independent risk factor for the development of diabetes after transplantation, with every 0.01-mg/kg/day increase in dose being associated with a 5% increased risk of new-onset diabetes and a 4% increased risk of glucose intolerance (61). However, any reduction in corticosteroid dose should be balanced against the possible increased risk of rejection associated with such treatment (Fig. 13) (75).

Data in liver transplant recipients have suggested that switching to cyclosporine may be beneficial in tacrolimus-treated patients who develop diabetes after transplantation (95). In this study, reducing the dose of tacrolimus was not effective in the management of patients with new-onset diabetes after transplantation; however, all patients with diabetes who were switched to cyclosporine responded to the change in therapy, with 15 patients becoming nondiabetic. For recipients who develop diabetes after transplantation and are receiving calcineurin-inhibitor therapy, switching from tacrolimus to cyclosporine may be considered in patients whose diabetes is difficult to control.

In summary, management of the transplant patient should involve pretransplant baseline evaluation and careful consideration and selection of an appropriate immunosuppressive therapy for each individual patient, particularly those at high risk for developing diabetes after transplantation. In addition, patients should be routinely monitored after transplantation, with particular attention given to patients with abnormal glucose metabolism (Figs. 14 and 15).

8.2. Management of diabetes mellitus after transplantation

Management of diabetes developing after transplantation should follow the ADA guidelines for the treatment of patients with type 2 diabetes (35, 53). There is strong evidence that intensive blood glucose control in patients with type 1 or type 2 diabetes confers significant benefits in terms of preventing complications (96, 97).

In addition to monitoring the FPG of patients routinely during the posttransplant management, lipid levels and A1C levels should also be assessed regularly (Fig. 16). Transplant recipients who develop diabetes after transplantation should also receive regular checkups for the development of diabetic complications, including retinopathy and neuropathy. Consideration may also be given to screening for the presence of microalbuminuria, although the validity of such screening has not been verified (see section 8.2.1.5.).

8.2.1. Monitoring the patient who develops diabetes after transplantation

8.2.1.1. Self-monitoring of blood glucose. The ability of patients with diabetes to monitor daily changes in blood glucose has markedly improved the ability to control glucose levels. Self-monitoring should thus be an essential component of the therapeutic plan of all patients taking oral agents

* Reduce the dose of steroids as soon as possible.*
* Consideration of the risk of developing new-onset diabetes after transplantation should be weighed against the risk of acute rejection when choosing an immunosuppressive regimen for any individual patient.
* Switching from tacrolimus to cyclosporine may be beneficial if diabetes has developed and is difficult to control.

*Complete withdrawal of steroids remains controversial and is not recommended at this stage. Further research into steroid-free regimens is warranted.*
or insulin. Self-monitoring may also be useful for patients whose diabetes is controlled by diet therapy alone (53, 98).

8.2.1.2. Lipid levels. Evaluation of the target lipid levels for patients with diabetes depends on the number of risk factors present; all three target values (low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglycerides) in each case (Table 9). Variation from these target levels requires patient reassessment and readjustment of therapy.

**Figure 14.** Algorithm 1: Management of diabetes after transplantation.

**Figure 15.** Algorithm 2: Management of diabetes after transplantation.
The following steps are recommended for patients who develop diabetes after transplantation.

- **Self-monitoring:** should be an essential component of the therapeutic plan of all patients taking insulin therapy or oral agents. Self-monitoring may also be useful for patients whose diabetes is controlled by diet therapy alone.

- **Lipid levels:** should be monitored throughout the post-transplant period in accordance with Table 9.

- **A1C levels:** should be measured every 3 months. An A1C level of 6.5% or higher is recommended for therapeutic intervention.

- **Diabetic complications:** all patients should be screened annually to detect the development of the long-term complications associated with diabetes, including retinopathy and neuropathy.

### Figure 16. Recommendations: Monitoring for the transplant patient with new-onset diabetes.

#### Table 9. Evaluation of plasma lipid levels in people with diabetes

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL cholesterol, mg/dL (mM)</th>
<th>HDL cholesterol, mg/dL (mM)</th>
<th>Triglycerides mg/dL (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥130 (&lt;2.38)</td>
<td>&lt;40 (&lt;1.02)</td>
<td>≥400 (4.53)</td>
</tr>
<tr>
<td>Borderline</td>
<td>100–129 (2.60–3.35)</td>
<td>40–59 (&lt;1.02)</td>
<td>150–399 (1.70–4.52)</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;100 (&lt;2.60)</td>
<td>≥60 (≥1.53)</td>
<td>&lt;150 (≤1.70)</td>
</tr>
<tr>
<td>Optimal levels in adults with diabetes</td>
<td>&lt;100 (&lt;2.60)</td>
<td>&gt;40 (&gt;1.02)</td>
<td>&lt;150 (&gt;1.70)</td>
</tr>
</tbody>
</table>

* For women, HDL cholesterol values should be increased by 10 mg/dL (0.26 mM).


(99). According to the latest ADA position statement, LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides should be measured every year in adult patients because of frequent changes in glycemic control in patients with diabetes and the effect of this on lipoproteins (99).

8.2.1.3. A1C (glycosylated hemoglobin). All patients with diabetes after transplantation should have A1C (previously termed HbA1c) tests performed routinely to determine whether or not blood glucose control is improving, with the A1C assay standardized according to the Diabetes Control and Complications Trial to be used in all cases (96). The frequency of testing should depend on the treatment regimen used and the judgment of the clinician. For transplant patients developing diabetes posttransplant, it is recommended that A1C is measured routinely every 3 months.

Maintaining a patient’s A1C levels below 7% is likely to be related to minimal long-term complications but may be difficult to achieve in most patients. Suboptimal A1C levels may be achievable in most patients but may not be adequate to prevent complications. Inadequate A1C levels are related to an increased risk for long-term complications, and require reassessment and readjustment of therapy. The optimal or target A1C level above which intervention may be required varies according to different guidelines for the management of diabetes (Table 10) (53–55). Thus, to take the proposals of each guideline into account it is recommended that an A1C level of 6.5% or higher should indicate the need for therapeutic intervention.

It should be noted that A1C testing is not recommended for diagnosis of new-onset diabetes after transplantation because it is not sensitive enough for this purpose. Furthermore, A1C levels in patients with anemia or kidney impairment should be interpreted with caution because such conditions can interfere with the assay and the results may thus be inaccurate.

#### Table 10. Recommended target levels for A1C

<table>
<thead>
<tr>
<th>Level of glucose control</th>
<th>A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4–6</td>
</tr>
<tr>
<td>Target levels for patients with diabetes</td>
<td>≤6.5 (54, 55)</td>
</tr>
<tr>
<td></td>
<td>≤7.0 (53)</td>
</tr>
</tbody>
</table>

8.2.1.4. Diabetic complications. The natural history of new-onset diabetes after transplantation shares many similarities with type 2 diabetes and it is thus presumed that transplant recipients who develop new-onset diabetes would also be at risk of the long-term complications of diabetes, such as retinopathy and neuropathy. Consequently, it is recommended that all patients diagnosed with new-onset diabetes are screened annually for diabetic complications, including an eye test and a foot checkup.

8.2.1.5. Microalbuminuria. The presence of microalbuminuria in the urine is an early marker of nephropathy in patients with type 1 and type 2 diabetes, and is a marker for significantly increased cardiovascular morbidity and mortality. Microalbuminuria is thus an indication for screening for vascular disease and aggressive intervention in these populations to reduce cardiovascular risk factors (e.g., reducing LDL cholesterol, antihypertensive therapy, stopping smoking, exercise) (13).
Annual screening for microalbuminuria is currently recommended for all patients with diabetes (at diagnosis for type 2 diabetes and after 5 years for type 1 diabetes) to allow early identification of nephropathy (13). Although the importance of microalbuminuria screening has not been validated in transplant patients, such monitoring may also be considered in transplant recipients who have developed new-onset diabetes to prevent the progression of nephropathy. However, it should be noted that many transplant recipients have renal insufficiency and may have proteinuria without diabetes. In addition, microalbuminuria levels may be difficult to interpret in kidney recipients with early chronic rejection. Further studies are thus required to assess fully the utility of microalbuminuria screening in transplant recipients with new-onset diabetes.

8.2.2. Step-wise approach to managing diabetes after transplantation

Management of patients with diabetes after transplantation should follow a step-wise approach, similar to that followed for patients with type 2 diabetes (Figs. 17 and 18) (35, 100).

8.2.2.1. Non-pharmacologic therapy. One of the most important therapeutic strategies for the management of patients with IGT and potentially transient diabetes after transplantation involves weight loss and maintenance of weight loss through a healthy diet, as this approach can reduce insulin resistance. Physical activity has also been shown to decrease peripheral insulin resistance, plasma triglyceride levels, and very-low-density lipoproteins in patients with type 2 diabetes (98). Thus, the following lifestyle changes and educational elements are recommended as the first step in the management of type 2 diabetes.

- Lifestyle modifications:
  - Nutrition therapy (consultation with a dietician)
  - Adequate physical activity
  - Avoidance of smoking
- Education:

<table>
<thead>
<tr>
<th>A step-wise approach: should be adopted for the management of patients who develop diabetes after transplantation (see Algorithm 2). The following progressive steps should be taken if individualized glycemic control targets are not achieved.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Non-pharmacologic therapy</td>
</tr>
<tr>
<td>- Lifestyle modification</td>
</tr>
<tr>
<td>- Education</td>
</tr>
<tr>
<td>2. Oral agent monotherapy</td>
</tr>
<tr>
<td>- Choice of agent should be tailored to the individual patient:</td>
</tr>
<tr>
<td>- Alpha-glucosidase inhibitor</td>
</tr>
<tr>
<td>- Biguanide</td>
</tr>
<tr>
<td>- Meglitinide</td>
</tr>
<tr>
<td>- Sulfonylurea</td>
</tr>
<tr>
<td>- Thiazolidinedione</td>
</tr>
<tr>
<td>3. Oral combination therapy*</td>
</tr>
<tr>
<td>- If target glucose levels have not been reached, a combination of the above agents may be used to the maximum dose of agent for each class.</td>
</tr>
<tr>
<td>4. Insulin ± oral agents*</td>
</tr>
<tr>
<td>- Insulin may be in the form of a single injection of intermediate-acting insulin at bedtime, and may be given concomitantly with oral agents as above.</td>
</tr>
<tr>
<td>- Better glucose control may be achieved with a low insulin dose plus oral agent</td>
</tr>
<tr>
<td>5. Insulin monotherapy</td>
</tr>
<tr>
<td>- Insulin injections should be administered and adjusted to achieve target glucose levels.</td>
</tr>
<tr>
<td>- Oral agents may be added to the insulin regimen on occasion.</td>
</tr>
</tbody>
</table>

*The use of oral combination therapy with or without insulin is commonly used in patients with type 2 diabetes but has not been assessed in patients with new-onset diabetes after transplantation.
Teach diabetes self-care, including self-monitoring of blood glucose level (13).

8.2.2. Oral-agent monotherapy. If adequate blood glucose control is not achieved with diet and exercise, pharmacologic monotherapy intervention is required. Once the decision to initiate therapy has been made, the agent should be chosen primarily on the basis of safety, although other agent-specific factors (e.g., potency, duration of action, side-effects, cost) and patient-specific factors (e.g., age, weight, level of glycemic control) should also be taken into account (100). The choice of an oral agent may be an alpha-glucosidase inhibitor (e.g., acarbose), biguanide (metformin is the most commonly used biguanide), a meglitinide (e.g., repaglinide), a sulfonylurea, or a thiazolidinedione (e.g., rosiglitazone); use of each of these agents is associated with specific advantages and disadvantages (see Table 11) (100). Drug selection must also consider the following points.

- In the case of transplant recipients with impaired kidney function, it is important to consider the possibility of serious adverse effects such as lactic acidosis (e.g., with metformin) and hypoglycemia (e.g., with sulfonylurea).
- Standard immunosuppressant treatment is associated with an increase in the risk factors for CVD (e.g., dyslipidemia, hypertension, obesity) (28).
- Weight gain and hypoglycemia are less common with biguanides compared with sulfonylureas or thiazolidinediones.
- Gastrointestinal side effects are more common with biguanides.
- Particular care is required in the selection of oral agents for elderly transplant patients and lower doses should be used. Meglitinides may be the agents of first choice in this population.

Apart from insulin, the safest agents for use in transplant patients with renal impairment may be meglitinides, because they are not contraindicated in patients with either renal or liver insufficiency and do not interact with calcineurin inhibitors. It should be noted, however, that no comparative trials of oral antidiabetic agents have been conducted in posttransplant patients to date.

8.2.2.3. Oral combination therapy. If adequate control is not obtained with a single agent, then a combination of agents with different mechanisms of action could be considered. As with monotherapy, the choice of agent depends on individual characteristics. Presently, the following combination therapies are used in the management of patients with type 2 diabetes:

- Sulfonylurea plus biguanide or thiazolidinedione or alpha-glucosidase inhibitor
- Biguanide plus meglitinide

### Table 11. Target populations, and advantages and disadvantages of common antidiabetic agents

<table>
<thead>
<tr>
<th>Antidiabetic agent</th>
<th>Target population</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Recent type 2 diabetes diagnosis</td>
<td>Rapid FPG reduction</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes &lt;5 yr duration</td>
<td>Low cost</td>
<td>Increased risk of hypoglycemia</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Recent type 2 diabetes diagnosis</td>
<td>Reduced risk of hypoglycemia</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td>Elevated PPG</td>
<td>Short-acting</td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Overweight/obese</td>
<td>No weight gain</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>Insulin resistant</td>
<td>Reduced risk of hypoglycemia</td>
<td>Rare lactic acidosis</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Insulin resistant</td>
<td>Reduced amount of insulin</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td>Overweight/obese</td>
<td>Reduced risk of hypoglycemia</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Alpha-glucosidase</td>
<td>Elevated PPG</td>
<td>Reduced risk of hypoglycemia</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td>inhibitor</td>
<td></td>
<td></td>
<td>Issue of liver toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GI side effects</td>
</tr>
</tbody>
</table>

FPG, Fasting plasma glucose; GI, gastrointestinal; PPG, postprandial glucose.
• Biguanide plus thiazolidinedione
• Biguanide plus alpha-glucosidase inhibitor
• Sulfonylurea plus biguanide plus thiazolidinedione
• Sulfonylurea plus biguanide plus alpha-glucosidase inhibitor

Clearly, the use of any of the above combinations must follow local license approval. It should also be noted that none of these combinations has been investigated in randomized, controlled trials in transplant recipients. Acarbose may be added to nutritional therapy, biguanide, or sulfonylurea treatment to improve glycemic control; however, gastrointestinal side effects may be a limiting factor.

8.2.2.4. Insulin therapy with or without oral agents. Concomitant use of insulin and oral agents is commonly used in patients with type 2 diabetes, although this approach has not been investigated in patients with new-onset diabetes after transplantation. Administration of insulin may be required when use of oral agents is unsafe, or if blood glucose levels do not fall to less than 120 mg/dL (6.7 mM) before meals and to less than 160 mg/dL (8.9 mM) after meals, with an A1C level less than 6.5%.

Insulin may be in the form of a single injection of intermediate-acting insulin at bedtime. Poor glucose control despite insulin therapy can be improved by the addition of acarbose or metFORMIN.

8.2.2.5. Insulin monotherapy. If at any point the patient becomes metabolically decompensated (symptomatic hyperglycemia, particularly when accompanied by ketosis), insulin injections must be administered. Patients may also be switched to insulin if therapeutic goals are not met with previous therapies. Insulin doses and number of daily injections should be adjusted to achieve target glucose levels. Individuals receiving insulin injections should be referred to an endocrinologist or diabetologist for ongoing management.

8.2.3. Treatment of dyslipidemia and hypertension

8.2.3.1. Treatment of dyslipidemia. It is suggested that aggressive therapy of diabetic dyslipidemia will probably reduce the risk of chronic heart disease in patients with diabetes (53). Because all patients with new-onset diabetes after transplantation are at high risk of CVD, it is recommended that such patients also receive aggressive lipid-lowering therapy in accordance with the NCEP guidelines (Table 12; Fig. 19) (87), including:

- In patients with LDL ≥130 mg/dL (3.38 mM) requiring rapid lipid lowering:
  - Primary therapy using statins
  - Concomitant medical nutritional therapy (53).
- In patients with LDL 100 to 129 mg/dL (2.60–3.35 mM):
  - Medical nutritional therapy should be attempted first
  - Statins also may be administered (53).

Guidelines on the treatment of dyslipidemia in patients with kidney disease, including renal transplant recipients, have recently been published (101). Trials investigating the

<table>
<thead>
<tr>
<th>Risk category</th>
<th>10-yr risk for chronic heart disease (%)</th>
<th>Level at which to consider drug therapy, mg/dL (mM)</th>
<th>Primary goal of drug therapy, mg/dL (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple (2+) risk factors</td>
<td>&gt;20% (includes all chronic heart disease risk equivalents&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>≥130 (3.38)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;130 (3.38)</td>
</tr>
<tr>
<td>10–20%</td>
<td></td>
<td>≥160 (4.16)</td>
<td>&lt;130 (4.16)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td></td>
<td>≥190 (4.94)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;160 (4.94)</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Most patients with chronic heart disease risk equivalents have multiple risk factors and a 10-yr risk >20%. They include patients with noncoronary forms of clinical atherosclerosis, diabetes, and multiple (2+) risk factors with a 10-yr risk >20% by Framingham scoring.

<sup>b</sup> When LDL cholesterol is ≥130 mg/dL, a cholesterol-lowering drug can be started concomitantly with therapeutic lifestyle changes (TLC). If baseline LDL cholesterol is 100–129 mg/dL, TLC should be started immediately. Concomitant use of drugs is optional; several options for drug therapy are available (e.g., statins, fibrates, nicotinic acid).

<sup>c</sup> When LDL cholesterol is in the range of 130–159 mg/dL, drug therapy can be used if necessary to reach the LDL cholesterol goal of <130 mg/dL, after an adequate trial of TLC.

<sup>d</sup> When LDL cholesterol is in the range of 160–189 mg/dL, use of cholesterol-lowering drugs is optional, depending on response to TLC diet.
value of C-reactive protein and homocysteine as predictors of chronic heart disease are ongoing.

8.2.3.2. Treatment of hypertension. Elevated blood pressure is reported to lower the life expectancy of patients with diabetes in the general population and is associated with an increased risk of cardiovascular death (9). Consequently, a number of guidelines for the management of patients with diabetes have recommended that blood pressure should be lowered in such patients to certain target levels (Table 13) (102–104).

Although no studies to date have evaluated the effect of lowering blood pressure in patients with new-onset diabetes after transplantation, such an approach may be expected to be of value. Because there is good evidence from large cohort studies of people with diabetes and proteinuria in the general population that lowering blood pressure below current target levels (130/80 or 130/85 mm Hg) (103, 104) is associated with a further reduction in cardiovascular morbidity and mortality, a target of 130/80 mm Hg is thus recommended for patients with new-onset diabetes after transplantation (Fig. 19) (105, 106).

Antihypertensive therapy may be initiated with an angiotensin-converting enzyme inhibitor with addition of further agent(s) to reduce blood pressure to the target level depending upon individual characteristics. In addition, angiotensin-converting enzyme inhibitors may contribute to a significant reduction of left ventricular mass in hypertensive renal allograft recipients (107, 108). Although no antihypertensive agents are currently contraindicated in transplant patients, further studies are required to assess the efficacy of these agents in this population. Consideration should be given to the use of aspirin to further reduce the risk of cardiovascular events.

8.3. Summary: Management of new-onset diabetes after transplantation

The data presented in the first part of these guidelines highlight the importance of diabetes as a major complication of transplantation and depict the role that standard immunosuppressive therapies may play in its development. However, experimental evidence suggests that a number of pre-transplant factors may predict the development of diabetes in susceptible patients. Furthermore, early detection and appropriate treatment can lessen the long-term complications of the condition.

These guidelines have been developed to establish a standard definition and diagnosis of new-onset diabetes after transplantation and to describe predictive factors for development of the condition that can be used to screen potential transplant recipients. Use of these tools will assist clinicians in prospectively identifying patients at risk of developing diabetes after transplantation so that immunosuppressive therapy can be individualized early in the treatment regimen. Adoption of these management strategies can be expected to reduce the patient’s risk of developing new-onset diabetes after transplantation and diminish the long-term consequences associated with the condition (Fig. 20).

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