

# Risk factors for posttransplant diabetes mellitus: a review of the literature

The development of diabetes after solid organ transplantation is a known complication, and many published studies have examined prevalence rates and risk factors for specific categories of transplant recipients. However, fewer articles have compared rates of posttransplant diabetes and risk factors among different types of transplant recipients. This article provides an overview of the literature on this subject and compares similarities and differences related to posttransplant diabetes for different categories of organ transplant recipients. Awareness of the various risk factors for different organ transplant recipients will enhance transplant clinicians' knowledge related to this complication so that appropriate monitoring can be started. (*Progress in Transplantation*. 2007;17:295-301)

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## Notice to CE enrollees:

A closed-book, multiple-choice examination after this article tests your ability to accomplish the following objectives:

1. Describe the importance of early identification of development of posttransplant diabetes and the nursing implications for appropriate monitoring of transplant recipients
2. Identify risk factors that are similar and unique for transplant recipients, depending on which type of organ is transplanted
3. Discuss the challenges associated with accurate determination of the prevalence of posttransplant diabetes

**D**iabetes and impaired glucose tolerance have long been recognized as complications associated with organ transplantation. The development of diabetes after transplantation has been associated with increased graft loss and decreased graft and patient survival,<sup>1</sup> suggesting that diabetes is one of the most serious long-term complications associated with transplantation. In addition to these risks, patients with diabetes after transplantation are also at risk of development of the microvascular and macrovascular complications associated with diabetes, which are accompanied by increased healthcare costs.<sup>2</sup> The seriousness of diabetes as a posttransplant complication is receiving increasing attention. However, risk factors associated with the development of diabetes are not necessarily the same for all categories of organ transplant recipients.

Determining the prevalence of posttransplant diabetes has been difficult. One factor contributing to this problem is that patients are not always routinely screened for hyperglycemia after transplantation, leading to an underestimation of the prevalence. More importantly, however, is the fact that various diagnostic criteria have been used to identify posttransplant diabetes, which has contributed to the confusion associated with accurate identification of occurrence rates.<sup>2</sup> Researchers evaluating posttransplant diabetes have used widely varying definitions. Some studies included patients who had diabetes before transplantation,<sup>3,4</sup> many focused on patients with early-onset diabetes occurring within 3 months of transplantation,<sup>5,6</sup> while others limited inclusion to patients in whom signs of diabetes developed more than 6 months<sup>3,4</sup> or 12 months<sup>7</sup> after transplantation. Some studies limited inclusion to patients who required insulin only,<sup>8</sup> whereas others expanded the criteria to include patients who required oral hypoglycemic medications as well.<sup>9</sup> Such widely varying definitions of posttransplant diabetes make comparison of results of these studies difficult.

## Definitions

An international expert panel meeting was convened to address various issues related to posttransplant diabetes.<sup>2</sup> One outcome of this meeting was the development of the 2003 International Consensus

Table Definitions of diabetes and other glucose tolerance categories after transplantation<sup>2,10</sup>

Diabetes mellitus
Fasting plasma glucose level $\geq 126$ mg/dL
Random plasma glucose level $\geq 200$ mg/dL and symptoms of diabetes
2-hour plasma glucose level $\geq 200$ mg/dL during an oral glucose tolerance test (OGTT)
Normal glucose tolerance
Fasting plasma glucose level $< 110$ mg/dL
OGTT 2-hour plasma glucose $< 140$ mg/dL
Impaired fasting glucose
Fasting plasma glucose level $\geq 110$ mg/dL and $< 126$ mg/dL
Impaired glucose tolerance
OGTT 2-hour plasma glucose $\geq 140$ mg/dL and $< 200$ mg/dL

Guidelines, which recommended use of the criteria from the American Diabetes Association<sup>2,10</sup> for the diagnosis of posttransplant diabetes (see Table). In addition, the panel suggested that definitions for impaired glucose tolerance and impaired fasting glucose also be included in the guidelines because these conditions are important predictive factors associated with the development of diabetes and an increased risk of cardiovascular disease (see Table).

The terminology associated with posttransplant diabetes is also undergoing revision. Some authors now refer to posttransplant diabetes as “new-onset diabetes after transplantation” to distinguish it from onset of diabetes before transplantation. This phrase is sometimes shortened to NODM or NODAT.<sup>1,11</sup>

Patients with posttransplant diabetes may not exhibit overt clinical symptoms.<sup>1,2</sup> Routine monitoring of fasting plasma glucose levels is valuable in early identification of posttransplant diabetes. Patients with an elevated fasting plasma glucose level should undergo additional testing on a different day to confirm the diagnosis. Additional testing may be a repeat measurement of fasting plasma glucose level or an oral glucose tolerance test. Patients who have glucose levels consistent with impaired glucose tolerance or impaired fasting glucose should be monitored carefully for the development of posttransplant diabetes. The use of hemoglobin A<sub>1C</sub> testing is not recommended within the first 3 months after transplantation for diagnosis of posttransplant diabetes. Many patients receive blood transfusions at the time of transplantation, which makes hemoglobin A<sub>1C</sub> levels invalid until new hemoglobin is produced.<sup>1</sup> Anemia or kidney impairment can also contribute to inaccurate hemoglobin A<sub>1C</sub> levels.

**Rates of Posttransplant Diabetes**

The prevalence of posttransplant diabetes is thought to be greatly underestimated because of the lack of a standard definition for diagnosis.<sup>12</sup> Moreover, short observation periods have been common in many published studies. The greatest risk for development of posttransplant diabetes is thought to occur in the first few months after transplantation. However, posttransplant diabetes can develop at any time following transplantation. The few published studies examining

**Diagnosis**

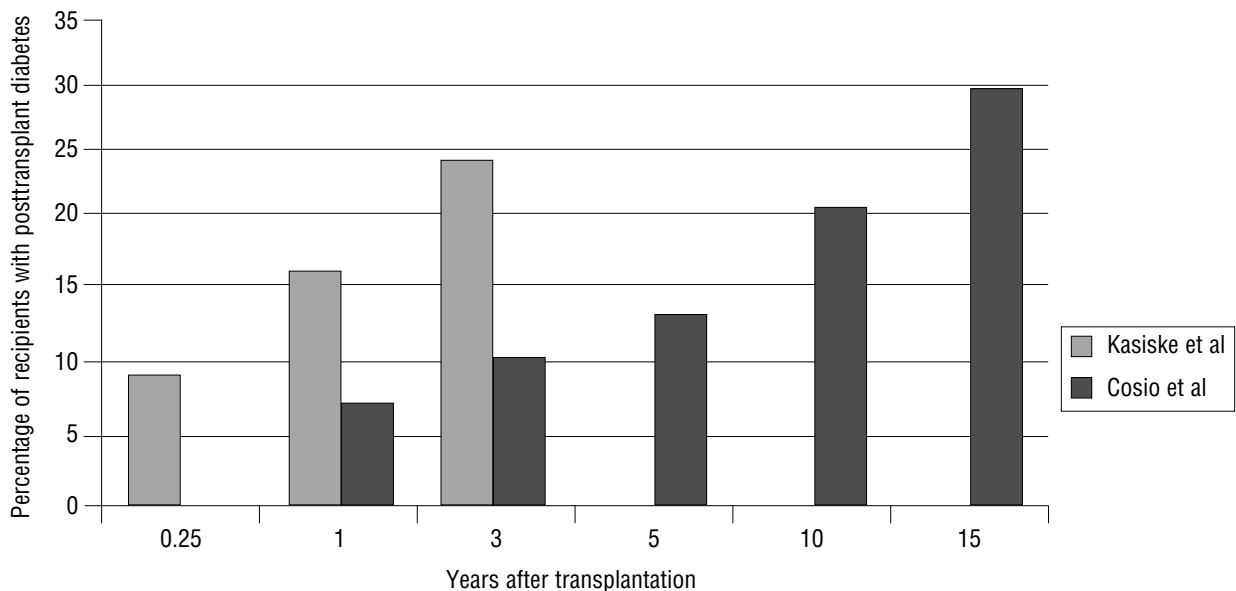


Figure 1 Cumulative rates of posttransplant diabetes in kidney transplant recipients. Kasiske et al<sup>16</sup> report on rates up to 3 years after transplantation and Cosio et al<sup>14</sup> provide data up to 15 years after transplantation. Results of both studies indicate that the risk of posttransplant diabetes developing increases with time after transplantation.

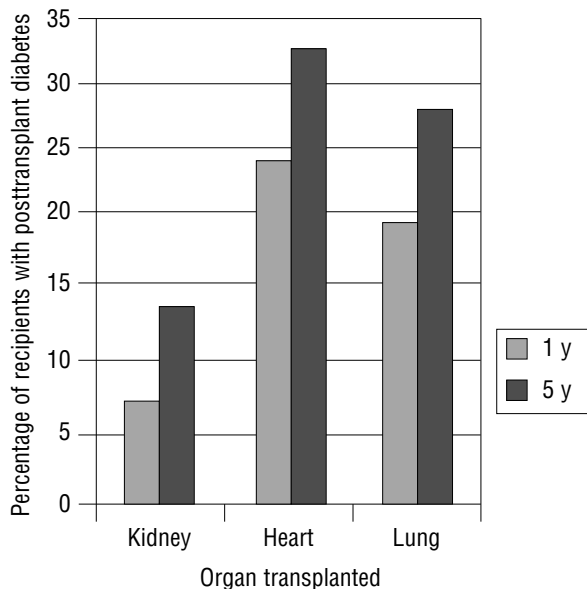


Figure 2 A direct comparison of rates of posttransplant diabetes between kidney,<sup>14</sup> heart,<sup>15</sup> and lung<sup>6</sup> transplant recipients is difficult due to varying factors unique to each type of organ transplantation. However, these studies demonstrate that for each group of organ transplant recipients, the rate of posttransplant diabetes increases with time from transplantation.

posttransplant diabetes rates over longer periods show that the risk for development of posttransplant diabetes increases with time from transplantation.<sup>6,13-15</sup>

Several investigators have reported rates of posttransplant diabetes in kidney transplant recipients over several years (Figure 1).<sup>14,16</sup> In each case, the risk of posttransplant diabetes developing increased with time from transplantation. This pattern also holds true for heart and lung transplant recipients, for whom 5 year posttransplant data are available (Figure 2).<sup>6,14,15</sup> Fewer studies<sup>9,13</sup> have examined long-term rates of posttransplant diabetes for liver transplant recipients, but a comparison between 1- and 3-year posttransplant rates also shows increased risk with time from transplantation (Figure 3).

### Pathogenesis

The mechanisms by which posttransplant diabetes develops are not completely understood. Although many studies have examined risk factors associated with posttransplant diabetes, fewer have evaluated the biological mechanisms of this condition. Many studies support the idea that posttransplant diabetes is most similar to type 2 diabetes and is associated with increased insulin resistance and decreased insulin secretion.<sup>17</sup> However, multiple mechanisms may be involved in the development of posttransplant diabetes. In addition, the impact of insulin resistance or decreased insulin sensitivity may vary in the presence of different risk factors.

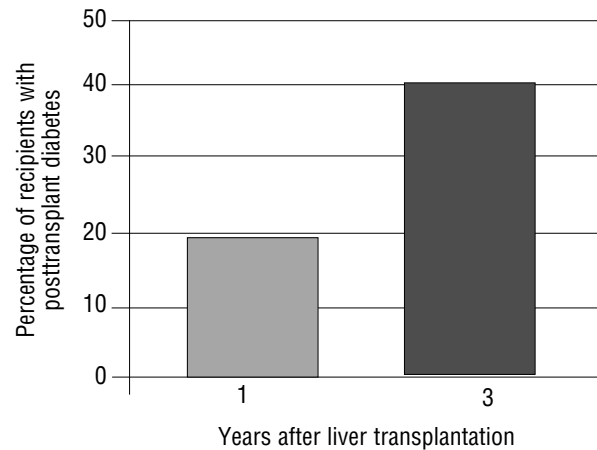


Figure 3 Findings from 2 different studies reporting rates of diabetes at 1 year<sup>9</sup> and 3 years<sup>13</sup> after liver transplantation. Rates of posttransplant diabetes increase with time after transplantation. Currently, no data are available on 5-year rates of posttransplant diabetes in liver transplant recipients.

### Risk Factors

The risk factors associated with posttransplant diabetes have been examined in many studies. Some risk factors (eg, age, ethnicity, and immunosuppression) are similar for different organ transplants. However, conflicting information exists for other risk factors such as family history of diabetes, weight, and vital status of the organ donor.<sup>18</sup> Most published studies examining risk factors for posttransplant diabetes report findings from kidney transplant recipients. Fewer published studies have examined posttransplant diabetes in liver, lung, and heart transplant recipients.<sup>6,19</sup> Findings for liver, kidney, lung, and heart transplant recipient studies are incorporated in the discussion of risk factors that follows.

### Patient's Age

The risk of posttransplant diabetes developing appears to be greater for patients who are older at the time of transplantation.<sup>2</sup> However, the effect of age can vary by organ transplant. Kidney transplant recipients more than 40 years of age are at greater risk of posttransplant diabetes developing than are younger recipients. Older heart transplant recipients are also at increased risk.<sup>19</sup> However, the influence of age as a risk factor for liver transplant recipients is less convincing. In several studies,<sup>4,9,20</sup> researchers reported no relationship between age and posttransplant diabetes. However, in one study,<sup>13</sup> researchers identified age greater than 50 years as a risk factor. That study<sup>13</sup> had a larger sample size ( $n = 492$ ) than the other studies had (range,  $n = 115-177$ ). Additional factors that may contribute to differences in findings include the following: liver transplant recipients seem to vary less in age than other transplant recipients, and few studies

have examined age as a risk factor because many case control studies match subjects by age.

### **Ethnicity**

The risk of posttransplant diabetes developing is greater for nonwhite populations.<sup>2</sup> Patients of different ethnicities may have different pharmacokinetic responses that alter the diabetogenic impact of immunosuppressive medications. African American and Hispanic kidney transplant recipients are at greater risk for diabetes than are white recipients,<sup>16,21</sup> with a 2-fold increased risk for kidney transplant recipients of nonwhite ethnicity reported in one study.<sup>18</sup> Evidence of increased risk for liver transplant recipients of nonwhite ethnicity is less well defined. In many studies,<sup>3,4,20</sup> ethnicity has not been evaluated as a risk factor for posttransplant diabetes. Researchers in several studies<sup>8,9,22</sup> have reported no association between ethnicity and posttransplant diabetes. All of these studies had a high percentage of white subjects (>80%), which may limit the ability to detect differences related to ethnicity. A higher rate of posttransplant diabetes in African American liver transplant recipients than in white recipients was reported in one study.<sup>7</sup> However, that case-control study was designed to look at differences in outcomes of liver transplant recipients with posttransplant diabetes rather than to identify risk factors for this complication. No published reports specify ethnicity as a risk factor for posttransplant diabetes in heart or lung transplant recipients.

### **Weight**

Gaining weight after transplantation is common, and weight gain is a risk factor for the development of insulin resistance.<sup>2</sup> In addition, increased body weight after transplantation has been associated with the development of posttransplant diabetes, particularly among kidney transplant recipients. However, the role of posttransplant weight gain as a risk factor for liver transplant recipients is confusing and less convincing. Low body mass index was reported as a risk factor in one small study.<sup>8</sup> In 2 other larger multicenter studies, researchers have reported increased risk for posttransplant diabetes when the patient's body mass index exceeds 25.<sup>2,22,23</sup> Interestingly, researchers in one of these studies<sup>22</sup> also noted that recipients with hepatitis C were more likely to have a body mass index greater than 25 than were recipients without hepatitis C. Thus, increased body mass index as a risk factor for posttransplant diabetes may actually be a confounding factor associated with infection with hepatitis C virus. Other researchers<sup>7,9</sup> report no relationship between weight gain and posttransplant diabetes. Heart transplant recipients with a higher body mass index are also at increased risk of developing posttransplant diabetes.<sup>19</sup>

### **Family History of Diabetes**

A family history of diabetes has been associated with increased risk for posttransplant diabetes in some populations; this finding has been reported more for kidney transplant recipients than for other organ transplant recipients.<sup>2</sup> Heart transplant recipients with a family history of diabetes, however, are also at increased risk for posttransplant diabetes.<sup>19,24</sup> Yet, family history was not associated with increased risk for posttransplant diabetes for liver transplant recipients.<sup>9,23</sup>

### **Hepatitis C**

An association between posttransplant diabetes and infection with the hepatitis C virus has been reported in multiple studies.<sup>2-4,9,13,22,23,25</sup> This association is most commonly seen in liver transplant recipients, among whom hepatitis C is the leading indication for transplantation.<sup>3,4,9,13,22,23</sup> However, a strong association between hepatitis C and posttransplant diabetes in kidney transplant recipients has also been reported.<sup>2,25</sup>

### **Immunosuppression**

Evidence supports a strong link between immunosuppression regimens and the development of posttransplant diabetes.<sup>2</sup> Early studies showed an association between corticosteroid use and posttransplant diabetes.<sup>26</sup> Newer immunosuppressive agents such as the calcineurin inhibitors also increase risk for posttransplant diabetes, with tacrolimus increasing the risk more than cyclosporine does.<sup>16</sup> Fewer studies have examined the effect of sirolimus on development of posttransplant diabetes; however, the risk does not appear significantly different from that of the other calcineurin inhibitors.<sup>27</sup> Immunosuppression as a risk factor for posttransplant diabetes has been reported for kidney, liver, heart, and lung transplant recipients.<sup>2</sup>

### **Rejection**

Rejection has been identified as a risk factor for posttransplant diabetes.<sup>18</sup> A link between rejection and posttransplant diabetes has been identified in kidney<sup>28</sup> and liver transplant recipients.<sup>7</sup> Heart transplant recipients with more rejection episodes have increased risk for posttransplant diabetes as well.<sup>19</sup> This association, however, may actually be more of a reflection of the use of pulse corticosteroids or higher immunosuppression doses rather than a relationship between rejection and posttransplant diabetes.

### **Cytomegalovirus Infection**

Infection with cytomegalovirus as a risk factor for the development of posttransplant diabetes has not been widely reported, though cytomegalovirus infection was identified as a risk factor in kidney transplant recipients in several studies.<sup>29,30</sup> This association was also reported in liver transplant recipients in at least one study.<sup>9</sup>

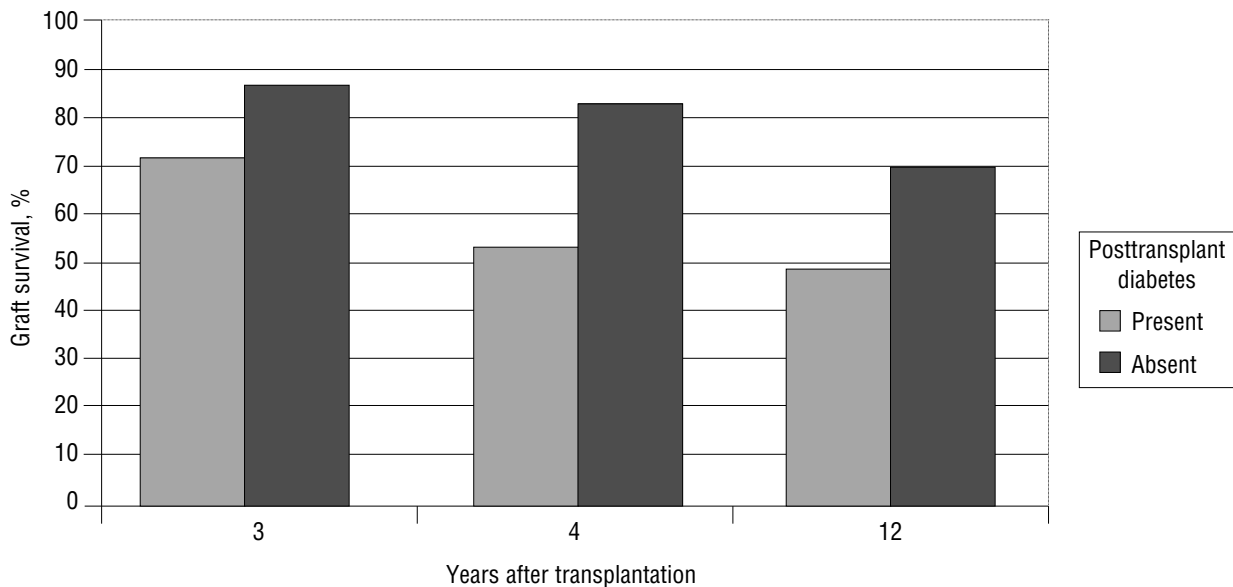


Figure 4 Graft survival rates for kidney transplant recipients at 3, 4, and 12 years after transplantation. Recipients in whom posttransplant diabetes developed consistently had lower survival rates than did recipients in whom posttransplant diabetes did not develop.<sup>2</sup>

### Underlying Disease

Associations between the underlying disease leading to transplantation and posttransplant diabetes have been identified. As previously mentioned, hepatitis C increases the risk of posttransplant diabetes in liver and kidney transplant recipients.<sup>9</sup> In addition, other diagnoses such as alcohol-induced liver disease also increase risk in liver transplant recipients.<sup>20</sup> Lung transplant recipients with cystic fibrosis are at higher risk than recipients receiving transplants for other diagnoses.<sup>6</sup>

### Prognosis

The development of posttransplant diabetes may alter a recipient's prognosis. A small increase in mortality has been reported for recipients with posttransplant diabetes.<sup>18</sup> However, data regarding patients' survival related to posttransplant diabetes are conflicting. The overall prognosis for posttransplant survival has improved with time. Yet reduced graft survival has also been reported (Figure 4).<sup>2</sup> The development of posttransplant diabetes may also increase the risk of other comorbidities.<sup>18</sup> Examples of comorbidities with increased relative risk associated with posttransplant diabetes include cardiovascular (relative risk 3.0), stroke (relative risk 1.9), infection requiring hospitalization (relative risk 1.9-2.0), cytomegalovirus (relative risk 2.0), and fatal sepsis (relative risk 4.8-11.6).<sup>2,18</sup>

### Conclusion

Posttransplant diabetes is an important complication of transplantation. The continued success of transplantation has helped focus attention on compli-

cations of transplantation, such as posttransplant diabetes, that can affect the quality of life of transplant recipients. The role of immunosuppression therapies in the development of posttransplant diabetes has been well described. However, the similarities and differences in risk factors for posttransplant diabetes depending on which organ was transplanted are less well described. Most published studies have focused on kidney transplant recipients.

As highlighted in this article, a careful comparison of data for kidney transplant recipients with data for liver, heart, and lung transplant recipients reveals some common risk factors. Further, not all of the risk factors for kidney transplant recipients have data to support them as risk factors for the other organ transplant recipients. Therefore, it is important to recognize contributing risk factors that are similar or unique for transplant recipients depending on which type of organ transplant recipient is evaluated. Doing so allows clinicians to determine which transplant recipients are at greater risk of posttransplant diabetes developing so that appropriate monitoring and preventive measures can be started after transplantation.

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**CE Test** Test ID 4000-J51: Risk factors for posttransplant diabetes mellitus: a review of the literature

**Learning objectives:** 1. Describe the importance of early identification of development of posttransplant diabetes and the nursing implications for appropriate monitoring of transplant recipients 2. Identify risk factors that are similar and unique for transplant recipients, depending on which type of organ is transplanted 3. Discuss the challenges associated with accurate determination of the prevalence of posttransplant diabetes

1. The 2003 International Consensus Guidelines recommended the use of what organization's diagnosis criteria for diabetes mellitus and other glucose tolerance categories?

- a. The International Society of Transplant Surgeons
- b. The Centers for Disease Control
- c. The International Institute of Health
- d. The American Diabetes Association

2. Which of the following *best* describes the reason for difficulty in accurately comparing the results of studies focused on the prevalence of posttransplant diabetes?

- a. Very few studies have examined prevalence rates and risk factors for development of diabetes after solid organ transplant.
- b. Transplant recipients are not always routinely screened for hyperglycemia after transplantation.
- c. A large percentage of the transplant recipients studied had diabetes before transplantation.
- d. There are widely varying definitions of posttransplant diabetes.

3. Routine monitoring of which of the following is most valuable in early identification of posttransplant diabetes?

- a. Fasting blood glucose levels
- b. Oral glucose tolerance test measurements
- c. Hemoglobin A1C levels
- d. Overt clinical symptoms of impaired glucose tolerance

4. The influence of age as a risk factor in the development of posttransplant diabetes is most questionable in current study results for recipients of which transplanted organ?

- a. Heart
- b. Liver
- c. Lung
- d. Kidney

5. Lung transplant recipients with what underlying disease are at higher risk for developing posttransplant diabetes?

- a. Obesity
- b. Alcohol-induced liver disease
- c. Anemia
- d. Cystic fibrosis

6. In order to distinguish posttransplant diabetes from diabetes that is present before transplantation, what is the revised terminology some authors are using to describe it?

- a. "New onset diabetes after transplantation"
- b. "Posttransplantation onset diabetes mellitus"
- c. "New onset impaired glucose tolerance"
- d. "New onset transplant-associated diabetes mellitus"

7. When are hemoglobin A1C levels valid in patients who have received blood transfusions during their organ transplant procedures?

- a. Immediately
- b. 3 weeks after transfusion
- c. When new hemoglobin has been produced
- d. Once anemia has resolved

8. Which of the following is appropriate for a transplant recipient with an elevated fasting plasma glucose level 1 week after transplantation?

- a. Additional glucose tolerance testing 3 months after transplantation
- b. An oral glucose tolerance test within 24 hours
- c. Evaluation for clinical signs and symptoms of impaired glucose tolerance
- d. A repeat fasting plasma glucose level measured on a different day

9. Which of the following risk factors is most associated with development of insulin resistance after organ transplantation?

- a. Weight gain
- b. Immunosuppression medications
- c. Infection with the hepatitis C virus
- d. Alcohol-induced liver disease

10. Which of the following has been reported as a risk factor for development of posttransplant diabetes for all solid organ transplant recipients?

- a. Immunosuppression
- b. Weight gain
- c. Family history of diabetes
- d. Age

11. According to the 2003 International Consensus Guidelines, which of these findings is indicative of a diagnosis of diabetes mellitus?

- a. Fasting plasma glucose level  $\geq 140$  mg/dL and  $< 126$  mg/dL
- b. 2-hour plasma glucose level  $\geq 140$  mg/dL during an oral glucose tolerance test
- c. Random plasma glucose level  $\geq 200$  mg/dL and symptoms of diabetes
- d. Two consecutive fasting plasma glucose levels of  $\geq 110$  mg/dL and  $< 126$  mg/dL

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