

# PRACTICE POINTS

## Natural history and epidemiology of post transplantation diabetes mellitus

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### Abstract

**Objective:** High patient mortality continues to be the major threat to the success of solid organ transplantation despite improvements in the control of immunologic phenomena post-transplantation with improvements in grafts survival. Post transplantation diabetes mellitus (PTD) occurring commonly in patients receiving immunosuppressives has been identified as a major culprit.

**Aim:** This paper reviews the current concepts of PTD.

**Methods:** A Medline literature search limited to research / review articles in English language, spanning 1984 January – 2004 June on post transplantation diabetes mellitus or hyperglycemia was done.

**Results:** Post transplantation diabetes mellitus is a heterogeneous condition of abnormal glucose tolerance with a variable onset, duration and severity. It is defined as a fasting plasma glucose = 7.0 mmol / L (126 mg / dL) and / or a 2 hour plasma glucose during an OGTT = 11.1 mmol / L (200 mg / dL), or a casual plasma glucose = 11.1 mmol / L (200 mg / dL), on 3 or more occasions over a period of at least 3 months. The risk factors predisposing to PTD are age, recipient's ethnicity, immunosuppressive regimen and family history of diabetes. The condition not only increases the risk of graft – related complications such as graft rejection, graft loss and infection, but also is a major determinant of the increased cardiovascular morbidity and mortality.

**Conclusions:** The most important risk factor predisposing to the development of PTD is the immunosuppressive drugs. The selection of immunosuppressive regimen should take into account individuals diabetes risk profile and the relative diabetogenicity and risk for diabetes of each immunosuppressant, balancing minimal risk of diabetes with effective immunosuppression.

**Keywords:** Current concepts, Definition, Diabetes, Epidemiology, Pathogenesis, Post transplantation, Management.

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### Introduction

Post transplantation diabetes mellitus (PTD) is a complication of solid organ transplantation, excluding pancreatic and islet cell transplantation. Despite the importance of this clinical condition, there was no consensus definition until recently. Evidence suggests that PTD has serious consequences for transplant recipients and threatens transplant outcomes. This condition increases the risk of graft – related

complications such as graft rejection, reduced graft function, graft loss and infection<sup>1,2,3</sup> and reduces the survival of transplant recipients<sup>4,5</sup>. It is also a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients<sup>6</sup>. Following kidney transplantation, the costs of developing PTD have been estimated to be \$12000 – \$13000 higher than for those without diabetes by the end of the first year with these costs rising to \$19000 - \$22000 by the end of the second year<sup>7</sup>. This paper reviews the current concepts of post transplant diabetes.

### Research design and methods

A Medline literature search limited to research / review articles in English language, spanning 1984 January – 2004 June on post transplantation diabetes mellitus or

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hyperglycemia was done. In reviewing the materials obtained, emphasis was on the definition, natural history, epidemiology and management of the condition.

### **Definition of post transplant diabetes mellitus**

Until recently there was no consensus regarding the definition of PTD, but the term excludes pancreatic and islet cell transplantations. A recent guideline defined the condition as the occurrence of DM requiring insulin post transplantation<sup>8</sup>. Some workers defined the condition as fasting hyperglycemia exceeding 7.8mmol/L and the need for insulin therapy<sup>9</sup>. Others used an oral glucose tolerance test (OGTT) to define PTD<sup>10</sup>. Post transplantation diabetes mellitus is a heterogeneous condition of abnormal glucose tolerance with a variable onset, duration and severity. The definition and diagnosis of the condition has recently been based on the revised definition of diabetes mellitus and IGT recently adopted by the American Diabetes Association<sup>11,12</sup>. A recent guideline defined the condition as the occurrence of DM requiring insulin post transplantation<sup>7</sup>. Post transplantation diabetes mellitus is thus defined as a fasting plasma glucose (FPG) = 7.0 mmol / L (126 mg / dL) with no calorie intake for at least 8 hours and / or a 2 hour plasma glucose during an OGTT (2 hr PG) = 11.1mmol / L (200 mg / dL), or a casual plasma glucose = 11.1 mmol / L (200 mg / dL), on 3 or more occasions over a period of at least 3 months<sup>8</sup>.

### **Natural history and epidemiology of post transplantation diabetes mellitus**

Post transplantation diabetes mellitus develops insidiously in kidney, liver or heart transplant patients during the first 6 months of transplantation on the average, but the incidence increases progressively with time<sup>13-16</sup>. Similar to the natural history of type 2 diabetes mellitus patients, patients are exposed to the damaging effects of uncontrolled hyperglycaemia during this asymptomatic period. Post transplantation diabetes mellitus, however, may resolve spontaneously without therapy<sup>17</sup>.

Differences in diagnostic criteria of PTD have resulted in wide variations in the reported incidence of PTD. Such differences included non-exclusion of pre-existing diabetes mellitus, non-inclusion of OGTT in the definition and definitions based only on the patients' requirements for insulin. Another reason is that at times patients are observed for short periods, which underestimates the true occurrence

of the condition. Generally, the risk of developing PTD has been shown to increase progressively post transplant, with the condition being diagnosed in some patients up to 15 years after transplantation<sup>18</sup>. A retrospective analysis of Medicare beneficiaries in the United States showed that the cumulative incidence of PTD among 11,659 patients was 9.1, 16.0, and 24.0 % at 3, 6, and 36 months respectively<sup>5</sup>. Other reasons for variation may probably be related to differences in population demographics between studies: African – Americans and Hispanic populations have higher rates of both type 2 and PTD, related to genetic and, perhaps, pharmacokinetic factors, as there is reduced clearance of methylprednisolone in African – American compared to Caucasian men with PTD<sup>1</sup>.

Generally, incidence rates of PTD have ranged between 2.0% and 57.1 %<sup>1,19</sup>. Recent systematic review of literature found that PTD was observed in 13.5% of patients after kidney, liver or heart and lung transplantation<sup>7</sup>. The incidence of PTD has been demonstrated to show a bimodal pattern corresponding to the early kidney transplantation era using high dose corticosteroids in the 1960s and to the introduction of tacrolimus in the 1990s. In a recent analysis, the type of immunosuppressive regimen used was found to explain 74 % of the variability in the incidence.

The risk factors predisposing to the development of PTD after kidney, liver and heart transplantation include age, recipient's ethnicity, immunosuppressive regimen and family history of diabetes<sup>7,12,20,21</sup>. Recipient's age over 40 years is associated with increased prevalence of PTD. In a study by Cho et al, only the age at transplantation was associated future development of PTD on multiple logistic regression<sup>19</sup>. All patients over the age of 40 years developed PTD and the relative risk of age > 40 years in the development of PTD was 2.8 (95 % CI 1.39 – 5.66)<sup>19</sup>.

Non-white patients experienced a twofold increase in the risk of PTD (RR – 3.3, 95 % CI 1.6 – 7.0). Hricik et al reported that African Americans were more susceptible to PTD than Caucasians despite similar doses of corticosteroids and lower trough level of tacrolimus<sup>23</sup>. Another well established risk factor in the development of PTD is the immunosuppressive therapy used with corticosteroids being associated with the greatest risk<sup>24,25</sup>. The incidence of PTD depends on the dose administered and the duration of therapy. Hjelmesaeth et al in a single-center prospective cohort study involving a total of 173 consecutive previously nondiabetic renal transplant recipients, 167 of which underwent a 75 g OGTT ten weeks after transplantation showed that the actual daily prednisolone dose was strongly associated with the development of PTD<sup>24</sup>. The calcineurins (CNIs) cyclosporine and

tacrolimus have also been associated with an increased risk for PTD with the latter being up to five times more diabetogenic than cyclosporine<sup>5,26,27</sup>. Tacrolimus was found to be an independent risk factor for PTD in a recent analysis of Medicare beneficiaries in the United States receiving kidney transplants between 1996 and 2000 (RR 1.53;  $p < 0.0001$ )<sup>5</sup>. The cumulative incidence of diabetes after transplantation at 3, 12 and 36 months for patients receiving tacrolimus were 13.5, 22.1, and 38.1 % respectively compared with 7.8, 14.2, and 21.9 % for those not receiving tacrolimus<sup>5</sup>. Tapering off of prednisolone but not cyclosporine A (CsA) also significantly improved glucose tolerance during follow-up period<sup>24</sup>.

There is strong evidence that individuals with a family history of diabetes among first degree relatives have an increased risk of developing PTD<sup>28,29</sup>. Hathaway et al in a prospective study including 86 patients followed for at least 18 months post transplantation reported that a family history of diabetes was an independent risk factor for PTD (OR 5.00)<sup>28</sup>.

Other not too-well established risk factors that have been associated with increased risk of PTD include abnormal glucose regulation pretransplantation or other components of the metabolic syndrome (for example, hypertriglyceridemia, hypertension, and hyperuricemia), acute rejection, higher body mass index (obesity), transplantation with a cadaveric kidney and transplant infection with hepatitis C virus particularly when patient is on tacrolimus<sup>8,13,30-32</sup>.

### **Health implications of posttransplantation diabetes**

Diabetes is the most common cause of end stage renal disease in Europe, United States and Japan. The development of the condition post transplant is associated with impaired long-term graft function and survival in transplant recipients. The development of PTD has been reported to be associated with a significant decrease in renal graft survival at 3 and 4 years, compared with recipients with no diabetes (3yr -71% vs 86%,  $p < 0.05$ ; 4yr - 54% vs 82%  $p < 0.05$ ; 12 yr - 48% vs 70%,  $p = 0.04$ )<sup>1,2</sup>. A recent meta-analysis has also revealed that the development of PTD was associated with a 63% increased risk of graft failure and a 46% increase in the risk of death-censored graft failure ( $p < 0.0001$  vs no diabetes for both comparisons)<sup>5</sup>. In liver transplant recipients, the incidence of acute rejection episodes was found to be higher in patients who

developed PTD (50 vs 30% in the control group)<sup>16</sup>. It has also been shown that the long term survival of kidney transplant recipients who developed PTD is reduced compared with those without PTD (8.1 years vs 11.0 years)<sup>4</sup>.

Post transplantation diabetes predisposes transplant recipients to cardiovascular disease and increases the risk of death from cardiovascular complications<sup>6</sup>. Death resulting from ischaemic heart disease is 20.8 times higher in transplant recipients with diabetes than in the general population<sup>34</sup>.

### **Pathogenesis**

Although the degree of diabetogenicity varies, immunosuppressants account for the greater majority of PTD<sup>35</sup>. Corticosteroids have the greatest risk of PTD after kidney<sup>24</sup>, liver and heart<sup>36</sup> transplantation. PTD due to the effects of corticosteroid therapy is related to both the dose and duration of treatment. The main pathogenesis is the development of insulin resistance evident as an increase in glucose production by the liver and a decrease in glucose uptake by the peripheral tissues<sup>1,9,24,36</sup>. Insulin response to oral glucose is also reduced following corticosteroid administration.

In the case of calcineurin inhibitors, both cyclosporine (CsA) and tacrolimus have diabetogenic effects, though the balance of evidence across all organs suggest that tacrolimus is more diabetogenic than CsA. The main mechanism underlying the diabetogenic effects of cyclosporine and tacrolimus are due to a number of mechanisms including pancreatic beta-cell toxicity, decreased insulin synthesis and decreased insulin secretion<sup>4</sup>. Drachenberg et al reported cytoplasmic swelling, vacuolization, apoptosis and abnormal immunostaining of islet cells in patients treated with CsA or tacrolimus<sup>37</sup>. Islet cell damage appears to be more severe in tacrolimus-treated group than the CsA-treated group<sup>37</sup>. Cyclosporine A inhibits both DNA and mRNA synthesis and tacrolimus disrupt the transcription of insulin mRNA<sup>4</sup>.

### **Management**

#### *Pretransplantation*

Patients should be screened for risk factors for PTD enumerated earlier. Because transplant patients also have an increased risk of developing cardiovascular disease, they should be screened for cardiovascular risk factors and metabolic syndrome<sup>8</sup>. The information so obtained will help in selecting the appropriate immunosuppressive therapy. Selection of an appropriate immunosuppressive regimen should take into account individuals diabetes risk profile and the relative diabetogenicity and risk for diabetes

of each immunosuppressant, balancing minimal risk of diabetes with effective immunosuppression. Patients should be counseled on the importance of weight control and exercise since they are prone to weight gain post transplant which potentially increases their risk of developing PTD<sup>38,39</sup>.

#### *Post transplantation*

Fasting plasma glucose should be monitored in patients post transplant at least weekly in the first 4

weeks after transplantation, then at 3-, 6-, and 12-month intervals and annually thereafter<sup>8</sup>. In patients at risk of developing PTD, the dose of corticosteroids should be reduced as soon as possible since this has been shown to improve patient's glucose tolerance. This reduction, however, should be balanced against the possible increased risk of graft rejection associated with such reduction<sup>25</sup>. Patients who develop PTD on tacrolimus can be switched CsA which is less diabetogenic. Table 1 summarizes the recommendations of IDF on the management of patients with PTD<sup>11</sup>.

**Table 1: Recommendations of IDF on the management of patients with PTD**

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#### **Monitoring**

- Blood pressure monitoring. Target 130/80mmHg. No antihypertensive is contraindicated.
- Self-monitoring of blood glucose
  - Check FBG in the morning (target 90-130 mg/dl) and before bedtime (target 110-150mg/dl).
  - FPG should be monitored initially weekly for a month, then at 3,6,12 months post transplant. If high, OGTT is indicated.
- Lipid levels
  - Measure annually, ADA targets recommended.
  - Evaluate risk of CHD
- A1C levels
  - Measure every three months
  - A level of 6.5% or higher recommended for therapeutic intervention
- Diabetic complications
  - Annual screening

#### **Immunosuppressive therapy**

- Reduce the dose of steroids as soon as possible.
- Consideration of the risk of developing PTD should be weighed against the risk of acute rejection.
- If glycaemic control cannot be established, consider CNI discontinuation involving a MPA derivative- or proliferation signal inhibitor-based regimen.
  - Reduce CNI exposure
  - Consider switching tacrolimus-treated patients to CsA
  - If glycaemic control cannot be established, consider CNI discontinuation involving a MPA derivative- or proliferation signal inhibitor-based regimen

#### **Management of Diabetes**

- Acute hyperglycemia
    - Casual plasma glucose levels  $\geq 250$  mg/dL
    - Treat patients with a continuous infusion of insulin (50IU)/hour to maintain a morning blood glucose level of between 80 and 110mg/dL
    - When the condition has stabilized, implement a convectional maintenance level and adopt a treat-to-target approach to therapy.
  - Chronic hyperglycemia
    - Set individual blood glucose targets for each patient
    - Adopt a treat-to-target approach and adjust therapy accordingly
    - The precise intervention required to achieve optimum blood glucose control will vary with each individual patient.
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## Conclusion

Post transplantation diabetes mellitus is a heterogeneous condition of abnormal glucose tolerance with a variable onset, duration and severity. Differences in definition have resulted in wide variations in the reported incidence. The most important risk factor predisposing to the development of PTD is the immunosuppressive drugs. Patients with PTD have poorer outcomes including impaired graft function and survival.

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