Post-Transplant Diabetes: Rationale for New Combination Therapy
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Disclosure
I have no relevant financial relationships with commercial interests to disclose.
Definition

PTDM: post transplant DM- Diabetes that develops post-transplant

NODAT: new-onset diabetes mellitus after transplant- Diabetes that develops post-transplant in previously non-diabetic patients

Objective

1. Familiar with the diagnosis of NODAT
1. Recognize the risks of NODAT
1. Be aware of the impact of NODAT
1. Discuss the management of NODAT
Diagnosis of NODAT

In 2003, the International Expert Panel set forth the International Consensus Guidelines for the diagnosis and management of NODAT. Recommended the diagnosis of NODAT should be based on the WHO and ADA guidelines.

- Fasting plasma glucose (FPG) ≥126 mg/dL,
- Symptoms of polyuria, polydipsia, or unexplained weight loss and a random plasma glucose concentration of ≥200 mg/dL,
- A 2 hour plasma glucose level of ≥200 mg/dL on an oral glucose tolerance test (75 gram OGTT)
- A1c value of ≥6.5 % (r/c start from 3 months post transplant)
Immunosuppressant

1. Corticosteroid: dose dependent
2. Calcineurin inhibitor: tacrolimus versus cyclosporine
3. Sirolimus: A mammalian target of rapamycin (mTOR) inhibitor. Early trials suggested that sirolimus was not diabetogenic but now its diabetogenicity has been well described.
4. The antimetabolites AZA and MMF have not been shown to be diabetogenic.
Incidence of NODAT at OSU

At 6 months, 5.9% of patients developed NODAT. Thereafter the cumulative percentage of NODAT at 1, 3, 5, 10, and 15 years was 7.1, 10.4, 13.2, 20.5, and 29.8%, respectively.

Older age, transplant after 1995, being African American and higher body weight were identified risk factors.

After 1995, NODAT has increased from 5.9 to 10.5% at one year and from 8.8 to 16.9% at three years, likely because those recipients also became significantly heavier and older.

Incidence of NODAT

Nine fold risk of diabetes in solid organ transplant recipients than their age matched controls [Ann Transplant. 2007;12(2):26-9].

Approximately one-third of non-diabetic kidney transplant recipients develop persistently impaired glucose metabolism by six months post-transplantation [Transplantation 2009; 88:429; Transplantation 2007; 84:50].

Renal Tx recipients: 4-25% (9-18%)  
Liver Tx recipients: 2.5-25% (20-30%)  
Heart Tx recipients: 4-40% (29%)  
Lung Tx recipients: 30-35% (26-40%)

Note: The incidence of diabetes for cyclosporine was 0.4% at 1 year and 0.4% at 2 years. The incidence of diabetes for tacrolimus was 1.1% at 1 year and 1.4% at 2 years.
NODAT or impaired fasting glucose (IFG) at 6 months, occurred in 73 CsA-ME patients (26.0%) and 96 tacrolimus patients (33.6%, $p = 0.046$)

Impact of NODAT: Patient Survival

One earlier study showed that one-year patient survival was 83% in those with NODAT and 98% in those without NODAT. [Transplantation. 1987;44(3):376–381]

A five-year survival with NODAT was reported as 87 versus 93 percent among non-diabetic patients [Transplant Proc 1991; 23:1249].

Mean patient survival post-transplantation was lower with NODAT (8.1 versus 11.0 years) [Transplantation 2000; 70:SS58].
Impact of NODAT: Patient Survival

The development of NODAT correlates with increased cardiovascular mortality, which is the most prevalent cause of poor long-term survival.

Impact of NODAT: Cardiovascular complication

<table>
<thead>
<tr>
<th>Cause of death (% of patients)</th>
<th>Total (n=201)</th>
<th>No diabetes (n=130)</th>
<th>New-onset PTDM (n=30)</th>
<th>Pretransplant diabetes (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death total (% of patients)</td>
<td>61 (30%)</td>
<td>28 (20%)</td>
<td>20 (67%)</td>
<td>13 (37%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>29 (14%)</td>
<td>11 (8%)</td>
<td>7 (20%)</td>
<td>11 (33%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (5%)</td>
<td>3 (2%)</td>
<td>2 (6%)</td>
<td>6 (21%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>16 (8%)</td>
<td>11 (8%)</td>
<td>4 (11%)</td>
<td>1 (4%)</td>
<td>0.562</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>5 (2%)</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
<td>0.241</td>
</tr>
</tbody>
</table>

Pearson χ² or Fisher’s exact test as appropriate.

Impact of NODAT: Cardiovascular complication

Figure 1 | Kaplan-Meier estimates of renal transplant recipients free of cardiac events in the three different groups.


Cost of NODAT Among U.S. Wait-Listed and Transplanted Renal Allograft Recipients

American Journal of Transplantation 2003 (3) 590-598.
Management of NODAT

• Prevention:
  • Pre-transplant screening;
  • Post-transplant monitoring;
  • Life style intervention;
  • Treat risk factors

• Treatment:
  • Non-pharmacologic therapy, including diet, weight reduction and exercise
  • Oral monotherapy, combination therapy,
  • Insulin

Treatment of NODAT: Non-insulin Therapy

Sulfonylureas: More experience, low cost, toxicity if RF. Lower HbA1c 0.8-2%, weight gain. Glipizide: short half life. Glyburide. Risk of hypoglycemia if RF.

Meglitinides: Nateglinide (Starlix) or Repaglinide (Prandin), not contraindicated with renal or liver insufficiency. No adverse drug interactions, increased expense.

Dipeptidyl peptidase-4 inhibitor: Linagliptin (Tradjenta), Sitagliptin (Januvia). Adjust dose for renal insufficiency, does not cause hypoglycemia; but may prolong the QT interval especially if used with cyclosporine.

GLP-1 agonist: Exenatide (Byetta, bydureon), Liraglutide (Victoza)
Treatment of NODAT: Non-insulin Therapy

Alpha-glucosidase inhibitors: less effective, expensive and GI side effects. Acarbose (Percose) or Miglitol (Glyset)

Amylin analog: Pramlintide (Symlin)

Thiazolidinediones: Pioglitazone

Biguanide: Metformin: risk of lactic acidosis with RF.

SGLT2 inhibitor: Canagliflozin

Other: Bromocriptine (Cycloset), Welchol (colesevelam)

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Treatment of NODAT

Sitagliptin increases insulin secretion and reduces fasting and postprandial plasma glucose in renal transplant recipients with NODAT. The short-term treatment was well tolerated, and Sitagliptin seems safe in this population. [Nephrol Dial Transplant. 2014, Jan. [Epub ahead of print]]

A small study showed the addition of Sitagliptin to NODAT patients after renal transplant whom glycemia was not controlled adequately by oral hypoglycemic agents was able to achieve glycemic control similar to insulin Glargine but with a slightly weight advantage. [Exp Clin Transplant. 2013;11(6):494-8.]
Treatment of NODAT- Insulin therapy

Many patients will require institution of insulin.

Long acting Insulin: Glargine (Lantus) or Detemir (Levemir). Adjust to control the morning fasting glucose.

Intermittent insulin: Novolin N: NPH

Novolin R

Mixed insulin preparation

Short-acting insulin aspart (Novolog), lispro (Humalog), Glulisine (Apidra). Based on premeal glucose and anticipated carbohydrate ingestion.

Insulin pump: basal rate, CR and SSI

Treatment of NODAT-Steroid Use

Patients who are receiving steroids have diurnal glucose patterns that is differ among those who are not.

Typically a late afternoon or early evening peak in blood glucose concentration that is often much higher than the two-hour postprandial blood glucose concentration.

NPH in the morning, adjusted to control the late afternoon or early evening glucose increases after steroids given in the morning.
New Treatment of NODAT

Early basal insulin therapy decreases NODT after renal transplantation

![Graph showing OGTT outcomes at 3, 6, and 12 months after transplantation. Patients receiving antidiabetics were counted as diabetic (without OGTT being performed). Generalized estimating equations were used to determine overall odds ratios over the 1-year follow-up period, accounting for within-patient repeated measures. Boldface numbers indicate findings with P<0.05. CI, confidence interval; imp. gic. tol., impaired glucose tolerance.]


Treatment of NODAT

Table 4 Management of NODAT

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2011:4