Diabetes and Transplantation
New Onset Diabetes After Transplantation (NODAT)

Jagbir Gill MD MPH
Assistant Professor
University of British Columbia, St. Paul’s Hospital
Vancouver, Canada
Kidney Transplantation
“Stuck in a Rut”
Acute Rejection Rate is Decreasing with Time
Short-Term Graft Survival is Improving

Based on deceased donor transplants

USRDS Annual Data Report 2006
BUT Little Change in Overall Long-Term Graft Survival

Based on deceased donor transplants

USRDS Annual Data Report 2006
Death censored graft loss vs. Death with a functioning graft

USRDS Annual Report 2004
Causes of Death with a functioning graft

- CVD, 38.20%
- Malignancy, 10.60%
- Infection, 22.90%
- Other, 28.20%

USRDS ADR 2008 ADR

Major risk factors for CV death

- Diabetes Mellitus
- Hypertension
- Obesity
- Dyslipidemia
Outline

- What is New Onset Diabetes After Transplantation?
- How common is it?
- What are the outcomes from NODAT?
- Who is at risk for NODAT?
- How do we prevent NODAT?
- How do we treat NODAT?
“What’s in a name?”

- Post transplant Diabetes Mellitus (PTDM)
- New Onset Diabetes Mellitus (NODM)
- New Onset Diabetes After Transplantation (NODAT)
- Transplant Associated Hyperglycemia (TAH)
Definition of DM - CDA

- FPG ≥ 7.0 mmol/L
- Casual PG ≥ 11.1 mmol/L + symptoms of diabetes
- 2hPG in a 75-g OGTT ≥ 11.1 mmol/L

*Fasting = no caloric intake for at least 8 hours*
*Casual = any time of the day, without regard to the interval since the last meal Classic*
*Symptoms of diabetes = polyuria, polydipsia and unexplained weight loss or*
## Spectrum of disease

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>2 HR GLUC TOLERANCE (75G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Fasting Glucose (IFG)</td>
<td>6.1-6.9</td>
<td>NA</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
<td>&lt;6.1</td>
<td>7.8-11.0</td>
</tr>
<tr>
<td>IFG and IGT</td>
<td>6.1-6.9</td>
<td>7.8-11.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 7.0</td>
<td>≥11.1</td>
</tr>
</tbody>
</table>
Incidence of NODAT

- Variably reported incidence (2-40%) based on definitions and ability to exclude pre-existing diabetes prior to transplantation

- Cumulative incidence of NODAT reported at 9%, 16%, and 24% at 3, 12, and 36 months, respectively

- Incidence of NODAT attributable to factors related to transplantation per se is the incremental difference between the baseline rate among wait-listed patients and the observed rate after transplantation

- Woodward, et al. estimated the true incremental incidence of NODAT to be 8–10% during the first post-transplant year
NODAT now more common than AR

E. Cole, CJASN 2008
NODAT
Associated Outcomes
Kidney transplant recipients 1996-2000

- Graft failure: HR = 1.63, 95% CI (1.46-1.84)
- Death censored graft loss: 1.46, 95% CI (1.25-1.70)
- Mortality: HR = 1.87, 95% CI (1.60-2.18)

Kasiske et al. AJT 2003 3: 178
NODAT associated with patient death and allograft failure in liver transplant recipients

1 = preLTX DM, 2 = sustained NODM, 3 transient NODM, 4 normal
Moon J et al. Transplantation 2006: 82; 1625-28
What’s worse NODAT or AR?

- USRDS data
- First kidney only transplant recipients, 1995-2002, n = 28,053
- Excludes patients with known pre transplant diabetes
- Graft survival of at least 12 m
- NODAT identified in first 12 m using Medicare claims (like Kasiske)
- AR identified in first 12 m

E Cole et al, CJASN, 2008
AR and NODAT had similar impact on graft survival

CJASN 2008

[Graph showing the probability of all cause graft loss over time from transplantation (years). The graph compares outcomes for:
- Neither AR/NODAT
- NODAT
- AR
- Both AR + NODAT]
AR – mostly impacts graft
NODAT – mostly impacts patient

Death Censored Graft Loss

Death with a Functioning Graft

Neither AR/NODAT
NODAT
AR
Both AR + NODAT

AR
NODAT
Death

Graft loss
IFG and NODAT associated with increased CVD

490 Kidney recipients 1998-2002
Immunosuppression: Thymoglobulin induction, maintenance steroids, CNI or sirolimus, and MMF.

Risk Factors for NODAT

- Black or Hispanic ethnicity
- Family history of diabetes
- Age > 40 years
- Obesity
- Glucose intolerance
- Hepatitis C virus infection
- Immunosuppressive therapy
- Metabolic syndrome:
  - High triglycerides
  - Low HDL
  - Hypertension
  - Hyperuricemia

Increased risk for developing new-onset diabetes after transplantation.
Non-modifiable risk Factors for NODAT

- Black or Hispanic ethnicity
- Family history of diabetes
- Age > 40 years
- Increased risk for developing new-onset diabetes after transplantation
- Immunosuppressive therapy
- Obesity
- Glucose intolerance
- Hepatitis C virus infection
- Metabolic syndrome
  - High triglycerides
  - Low HDL
  - Hypertension
  - Hyperuricemia
Potentially modifiable risk factors for NODAT

- Black or Hispanic ethnicity
- Family history of diabetes
- Age > 40 years
- Obesity
- Glucose intolerance
- Hepatitis C virus infection

Increased risk for developing new-onset diabetes after transplantation

- Metabolic syndrome:
  - High triglycerides
  - Low HDL
  - Hypertension
  - Hyperuricemia

Immunosuppressive therapy
Immunosuppression

- Calcineurin inhibitors (Tacrolimus, Cyclosporine)
- Antimetabolites (Mycophenolate Mofetil, Azathioprine)
- Corticosteroids
- mTOR (Sirolimus)
Immunosuppression

- Calcineurin inhibitors (Tacrolimus, Cyclosporine)
- Antimetabolites (Mycophenolate Mofetil, Azathioprine)
- Corticosteroids
- mTOR (Sirolimus)
Tacrolimus is Associated with NODAT
Tacrolimus associated risk of NODAT did not vary by Age

Cox multivariate regression in steroid treated patients

Adjusted for: Sex, Race, Hispanic Ethnicity, BMI, donor type, cause of disease, comorbidities, time on dialysis, HLA mismatch

Tacrolimus associated risk of NODAT did not vary by Race

Cox multivariate regression in steroid treated patients

<table>
<thead>
<tr>
<th>Race</th>
<th>Adjusted Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.35</td>
<td>(1.13, 1.62)</td>
</tr>
<tr>
<td>Black</td>
<td>1.13</td>
<td>(0.88, 1.45)</td>
</tr>
<tr>
<td>Other</td>
<td>1.54</td>
<td>(0.91, 2.60)</td>
</tr>
</tbody>
</table>

Adjusted for: Age, Sex, Hispanic Ethnicity, BMI, donor type, cause of disease, comorbidities, time on dialysis, HLA mismatch

Cumulative Probability of NODAT by CNI

Steroids

Log-Rank $p=0.0004$

No Steroids

Log-Rank $p=0.1057$

Who should we not give tacrolimus to?
Who should we not give tacrolimus to?

Nobody…

…if we ONLY care about NODAT

…and DON’T care about rejection
Does the tacrolimus level matter?
Tacrolimus effect is dose dependent

<table>
<thead>
<tr>
<th>Trough level</th>
<th>10-25 ng/ml</th>
<th>8-16 ng/ml</th>
<th>8-12 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>NODAT</td>
<td>19%</td>
<td>6.5%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Year</td>
<td>1997</td>
<td>2000</td>
<td>2002</td>
</tr>
</tbody>
</table>
Reducing CNI levels may reduce risk of NODAT

<table>
<thead>
<tr>
<th></th>
<th>NODAT (%)</th>
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<tbody>
<tr>
<td>Standard dose cyclosporine (trough level of &gt;200ng/ml in 1&lt;sup&gt;st&lt;/sup&gt; year)</td>
<td>6.4%</td>
</tr>
<tr>
<td>Low dose cyclosporine (trough level of ~ 100ng/ml in 1&lt;sup&gt;st&lt;/sup&gt; year)</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
Corticosteroids

- Increased insulin resistance
  - Decreased binding of insulin to insulin receptors
  - Increased hepatic gluconeogenesis

- Risk is dose related
  - 0.01 mg/kg/d increment in prednisolone 4% increase in glucose intolerance
  - Lower rates with low steroid maintenance doses
  - Effects of steroid withdrawal uncertain

1 Weir et al, AJKD 1999;34:1
2 Hjelmesaeth J et al. Transplantation 1997; 64:979
Reduced CV risk with Early CS withdrawal vs chronic CS

Meta-analysis of 34 studies including 5,637 patients receiving steroid withdrawal or avoidance regimens vs maintenance steroids

CV outcomes:

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<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Patients</th>
<th>Type</th>
<th>RR (95% CI)</th>
<th>P</th>
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<tr>
<td>HTN</td>
<td>15</td>
<td>2,833</td>
<td>Fixed</td>
<td>0.90 (0.85-0.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13</td>
<td>2,283</td>
<td>Random</td>
<td>0.76 (0.67-0.87)</td>
<td>&lt;0.0001</td>
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<tr>
<td>NODAT</td>
<td>16</td>
<td>2,849</td>
<td>Fixed</td>
<td>0.64 (0.50-0.83)</td>
<td>0.0006</td>
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Reduced CV risk with Early CS withdrawal vs chronic CS

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Relative risks of new-onset diabetes all significantly reduced
Steroid withdrawal – Astellas double blind trial

- 386 patients randomized post transplant day 3-7
- SCr <=30%
- No HD

- Steroid maintenance (CCS) n = 195
- Steroid withdrawal (CSWD) by day 7 n = 191
- Study was stratified Living vs Deceased and AA vs non-AA
Astellas trial 24 months

No difference between steroid w/d group and controls tapered to 5 mg of prednisone at 1 month

<table>
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<tr>
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<th>CCS</th>
<th>CSWD</th>
<th>P value</th>
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<tr>
<td>One FBS $\geq 126$ mg/dl</td>
<td>72 (53.3%)</td>
<td>72 (50.7%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Two FBS $\geq 126$ Mg/dl</td>
<td>43 (31.9%)</td>
<td>40 (28.2%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

3 yr data – insulin usage is slightly higher in CCS group
Which drug regimen is associated with the lowest risk of NODAT?
Multivariate Analysis – drugs at hospital discharge
Adjusted for: steroid use, age, race, ethnicity, gender, ESRD etiology, BMI, donor type, comorbidities, Hep C, era, duration of dialysis
JASN 2008

<table>
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<tr>
<th>Drug Combination</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA+MMF/Aza</td>
<td>1.00</td>
<td>(1.27,1.50)</td>
</tr>
<tr>
<td>TAC+MMF/Aza</td>
<td>1.38*</td>
<td>(1.07,1.64)</td>
</tr>
<tr>
<td>Rapa+MMF/Aza</td>
<td>1.33*</td>
<td>(1.33, 1.86)</td>
</tr>
<tr>
<td>Rapa+CSA</td>
<td>1.57*</td>
<td>(1.42, 1.92)</td>
</tr>
<tr>
<td>Rapa+TAC</td>
<td>1.65*</td>
<td>(1.42, 1.92)</td>
</tr>
</tbody>
</table>
Tacrolimus demonstrated superior efficacy in terms of acute rejection compared to cyclosporine.

DIRECT trial – compared cyclosporine and tacrolimus with MMF, steroids, basiliximab induction – with primary outcome of NODAT/IFG:
- Lower incidence of NODAT with cyclosporine
- No significant difference in acute rejection rates at 6 months
- Limited by open-label design and non-standardized steroid doses
Thymoglobulin induction, reduced Cyclosporine exposure and early Corticosteroid reduction to reduce New-onset Diabetes and Acute rejection in Kidney Transplant Recipients

- Open-label, single arm, pilot
- N=49 recipients with PRA<20, first transplant, no overt DM (based on OGTT)
- Thymoglobulin induction
- Cyclosporine, MMF, low dose prednisone
6 MONTHS

- There was 1 death; no graft losses
- Two patients (4%) developed NODAT
- Four patients (8%) had impaired oral glucose tolerance testing at 6 months.
- One patient (2%) developed AR
LTA Study – Low Target Advagraf in A Steroid Free regimen to prevent NODAT

- Prospective, open label, randomized pilot study to examine the safety and efficacy of steroid withdrawal and low target tacrolimus

- TX ARM
  - Thymoglobulin induction/low target tacrolimus/MMF
  - Basiliximab induction/standard target tacrolimus/MMF

- 6 MONTH Outcomes
  - AR, NODAT
Obesity

- Weight gain is common following kidney transplantation
- Post-transplant obesity has been linked independently to reduced graft and patient survival
- Cosio et al. documented that the risk for developing NODAT increased by a factor of 1.4 for every 10 kg increase in body weight over 60 kg
- Multidisciplinary approach to weight management post-transplantation
DM has been reported to be more common in patients with hepatitis C than in other types of liver disease.

Several recent studies also suggest a strong association between hepatitis C infection and the development of diabetes mellitus after either kidney or liver transplantation.

Postulated mechanisms include a direct cytopathic effect of the virus on beta cells, insulin resistance mediated by a postreceptor signaling defect, and decreased hepatic glycogenesis.

Treatment of hepatitis C with interferon-alpha results in improved glycemic control.

Interferon-alpha increases the risk of rejection.
Prevention of NODAT

- Identify at risk population
- Tailor immunosuppressive therapies to minimize risk of NODAT
  - Steroid avoidance
  - Choice of CNI
- Mitigate additional risk factors
  - Obesity, dyslipidemia, hypertension
- Monitor for NODAT frequently post transplant
- Multidisciplinary approach
<table>
<thead>
<tr>
<th>Class</th>
<th>MOA</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (Metformin)</td>
<td>inhibit hepatic glucose production and increases peripheral glucose uptake</td>
<td>Low risk of hypoglycemia</td>
<td>Lactic Acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May help with weight loss</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurias (glyburide)</td>
<td>Increase insulin excretion</td>
<td>Effective as primary agent</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Meglitinides (Repaglanide)</td>
<td>Augments food-stimulated insulin secretion</td>
<td>Very short acting</td>
<td>P450 3A4 metabolized</td>
</tr>
<tr>
<td>Alpha-glycosidase inhibitors</td>
<td>Block carbohydrate digestion and decrease post prandial hyperglycemia</td>
<td>Effective as adjunctive agent</td>
<td>Malabsorption</td>
</tr>
<tr>
<td>(Acarbose)</td>
<td></td>
<td></td>
<td>GI SE</td>
</tr>
</tbody>
</table>
## Management

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Mechanism of Action</th>
<th>Efficacy</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazolidinediones</strong> (rosiglitazone, pioglitazone)</td>
<td>Increase sensitivity to insulin</td>
<td>Effective in NODAT</td>
<td>Metabolized by CYP450, associated with fluid retention, weight gain, associated with CV disease</td>
</tr>
<tr>
<td><strong>Incretins</strong></td>
<td>Glucagon-like peptide agonists - targets post-prandial hyperglycemia</td>
<td>Effective</td>
<td>Dose-adjust for renal function</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td>Effective</td>
<td>Labour intensive, Risk of hypoglycemia</td>
</tr>
</tbody>
</table>
Summary

- NODAT is now more common than acute rejection
- It is associated with increased risk of death
- Screening and identification of at risk population is important
- Risk factor modification (obesity, metabolic syndrome, ?HCV)
- Immunosuppressive adjustment considered on a case-by-case basis
- Routine monitoring, consideration of pros/cons of individual therapies, and consultation with endocrinology to optimize glycemic control post-transplant is key to minimize implication of NODAT