NEW ONSET DIABETES AFTER TRANSPLANTATION

SONIKA PURI
NEW ONSET DIABETES AFTER TRANSPLANTATION

- Overall incidence of NODAT ranges anywhere between 2-50% depending upon the criteria used for diagnosis.

- On average incidence is 14%-16% in 1st post transplant, cumulative incidence of 24% in the first 3 years.

- IFG/IGT was present in 33%-46% of patients one year post transplant.
Incidence of normal glucose tolerance (NGT), impaired glucose tolerance (IGT), new-onset diabetes (NODMM), and cumulative transplant-associated hyperglycemia (TAH) 1 yr after kidney transplant in 114 kidney transplant recipients who were confirmed to be eug...
Figure 1 | Kaplan-Meier estimates of renal transplant recipients free of cardiac events in the three different groups.

Figure 2 | Kaplan-Meier estimates of patient survival in the three different groups of renal transplant recipients.

Hjelmesaeth et al, KI 2006
Figure 3: Survival (with a functioning transplant) of patients who have an episode of acute rejection versus those developing NODAT, or both. After 1 year, a history of acute rejection has no effect on outcome. NODAT = new-onset diabetes after transplantation.
Table 2. Relationship of inpatient hyperglycemia and new onset diabetes mellitus after transplantation using various criteria to define NODAT

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Number of Patients</th>
<th>Total Cases with NODAT(^a) (%)</th>
<th>Total Cases with NODAT(^b) (%)</th>
<th>Total Cases with NODAT(^c) (%)</th>
<th>Total Cases with NODAT(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of inpatient hyperglycemia</td>
<td>27</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Random blood sugar &gt; 200 mg/dl but no insulin administered</td>
<td>23</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
<td>3 (13%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Insulin administered during hospitalization</td>
<td>327</td>
<td>98 (30%)</td>
<td>62 (19%)</td>
<td>91 (28%)</td>
<td>48 (15%)</td>
</tr>
<tr>
<td>Total</td>
<td>377</td>
<td>103 (27%)</td>
<td>65 (17%)</td>
<td>96 (25%)</td>
<td>49 (13%)</td>
</tr>
</tbody>
</table>

\(^a\)Cumulative composite definition of NODAT: NODAT was defined as either hemoglobin A1C \(\geq 6.5\)% or fasting venous serum glucose \(\geq 126\) mg/dl, or receiving diet or medical therapy for diabetes mellitus between 1 month and 1 year posttransplantation.

\(^b\)NODAT defined as either hemoglobin A1C \(\geq 6.5\)% or receiving diet or medical therapy for diabetes mellitus between 1 month and 1 year posttransplantation.

\(^c\)NODAT defined as either fasting venous serum glucose \(\geq 126\) mg/dl or receiving diet or medical therapy for diabetes mellitus between 1 month and 1 year posttransplantation.

\(^d\)NODAT defined as initiation of diet or medical therapy for diabetes mellitus between 1 month and 1 year posttransplantation.

Figure 1. Relationship of blood glucose and insulin requirement immediately after kidney transplantation to the incidence of NODAT.
RISK FACTORS FOR NODAT

NON MODIFIABLE

- Older age
- Race
- Genetic background
- Family history of DM
- Pre-transplantation IG tolerance
- Metabolic syndrome

MODIFIABLE

- Overweight/obesity
- HCV infection
- CMV Infection
- Immunosuppressive drugs

Rodrigo et al, JASN 2006, 17;S291-295
RISK FACTORS

• Compared to before 1995, since 1995 the incidence of PTDM had increased from 5.9% to 10.4% at the end of one year and 8.6% to 16yrs at the end of 3yrs.

- attributed to older age at the time of transplant / higher bmi, although pred dosing was lower. (Cosio et al, KI 2001)

• USRDS data –first transplant recipients between age 45-59yrs had RR of NODAT 1.9 CI 1.73-2.09, P <0.0001; age >60yrs had RR of 2.6 (CI 2.32-2.92)

• Pre-transplant glucose of 101-110 mg/dl conferred an OR of 1.5/ glucose between 111-125mg/dl conferred an OR of 7.9 for development of PTDM. (Cosio et al, KI 2005)
RR of developing PTDM if age >45yrs was 2.9

*Cosio et al, KI 2001*

Incidence of PTDM in patients classified according to their weight at the time of transplantation and race (dark bars –AA)
- 62% pts who developed NODAT had metabolic syndrome at baseline.

MVA - HR for MS was 1.34 (1.01-1.79, p<0.04)

- AA pts had greater Hep C positivity

- In multivariate analysis AA race had a HR of 1.35 (1.01—1.82) p <0.043)

-NODAT developed in 31.4% of recipients by the end of 1st post tx.
-58% of pts who developed NODAT during 5 yr follow up developed it during 1st yr

Bayer et al, Transplantation 2010, October 27
Activation of the T-cell receptor results in increased intracellular Ca^{2+}.

2. Activation of calcineurin, a Ca^{2+}-dependent phosphatase.

3. As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus.

4. NFATc associates with other nuclear components, leading to activation of genes encoding cytokines.

5. Release of IL-2.

T CELL
- Tacrolimus
- Cyclosporine
- Cyclophilin
- FK-binding proteins (FKBP)

CYTOPLASM
- Active NFATc
- IL-2 gene
- IL-2 mRNA

NUCLEUS
- Active NFATc
- IL-2 mRNA
- Cell cycle

Signal 1
- CD80:86
- T Cell receptor
- IL-2

Signal 2
- CD28
- IL-2

Signal 3
- mTOR
- Sirolimus

Cell-mediated immune response
DIRECT STUDY: CYCLOSPORINE VS TACROLIMUS

- Randomized, multicentric, open labelled trial - Denovo renal transplant
- Basiliximab, MMF, steroids and CsA (n=336) vs. Prograf (n=346)
- ITT group 682 pts, 567 non diabetics -80% caucasian
- Primary safety endpoint NODAT or IGT at 6mths (ADA/WHO)
- Primary efficacy endpoint: biopsy proven acute rejection; graft loss or death at 6mths
- CsA c2 level: 1600ng/mol -1st mth, 1400ng/ml-2-3rd mth, 1000ngm/ml 4th-6th mth
- Tacrol trough 10-15ng/ml -1-3mths, 5-10ng/ml for 4th-6th mth

AJT 2007, VINCENTI ET AL.
• Groups were well matched for age/underlying disease/duration of HD/PR/A/type of transplant

• Well matched for RF for DM, FBG data missing in 1/4 of patients.

• Median dose of steroids similar in both groups; statistically higher dose in pts who developed NODAT in CsA group vs those who did not.

- Primary safety point
NODAT or IFG: CsA vs Tacro – 26% vs. 33% (p0.046)

- Incidence of treated DM at the end of 6mths was lower in CsA group 8.9% vs 16.8%

- 24% vs.32% of caucasians in Csa/Tacro group developed primary end point.
-At the end of 6mths more number of people required Anti htn and lipid lowering therapy in both groups compared to baseline-11.9% vs. 43% in CsA group; 13.9% vs. 36% in Tacro group

Heisel et al, AJT 2004
ROLE OF FK506

-FK binds to FKBP-12 and inhibits calcineurin phosphatase whose function contributes to insulin production in beta cells.

-By inhibiting calcineurin phosphatase tacrolimus prevents phosphorylation of CREB (c-amp response binding protein)- an inducible transactivator of multiple genes involved in insulin signalling and beta cell survival.

*Araki et al, Transplantation 2006*

-presence of FK 506 was accompanied by dose dependant decrease in insulin mRNA and human insulin promoter CAT reporter gene.

*Redmon et al, JCI 1996*
**Figure 3.** Median fasting $K_G$ and parameters of glucose metabolism associated with pancreatic β-cell secretion capacity before and after steroid withdrawal and after tacrolimus trough level reduction. Right y-axis: $K_G$ (mmol/L per min). Left y-axis: C-peptide secretion (nmol × min/L) and insulin secretion (mU × min/L ÷ 10).

**Figure 2.** Median fasting parameters of glucose metabolism associated with insulin resistance before and after steroid withdrawal and after tacrolimus trough level reduction. Right y-axis: fasting insulin (mU/L). Left y-axis: fasting C-peptide (nmol/L), homeostasis model assessment (HOMA-R) (mmol/L × mU/L), and insulin glucose ratio (mU/mmol).
### Table 3: Insulin secretion, sensitivity and disposition index at 6 months among normoglycemic patients and patients with NODAT who were not receiving hypoglycemic medication

<table>
<thead>
<tr>
<th></th>
<th>Normoglycemic patients (n = 300)</th>
<th>Untreated NODAT: CsA-ME (n = 29)</th>
<th>Untreated NODAT: tacrolimus (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin secretion (pmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>1146 (899–1359)</td>
<td>625 (279–920)</td>
<td>314 (124–581)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>304 (244–357)</td>
<td>187 (103–248)</td>
<td>116 (72–188)</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>0.076 (0.065–0.089)</td>
<td>0.043 (0.034–0.057)</td>
<td>0.049 (0.016–0.064)</td>
</tr>
<tr>
<td>Disposition index(^1)</td>
<td>100 (82–127)</td>
<td>26 (8–45)</td>
<td>9 (−1, 22)</td>
</tr>
</tbody>
</table>

\(^1\) Values are shown as medians (interquartile range).

\(^1\) Disposition index = (first and second phase insulin release) \times insulin sensitivity.
-Tacrolimus (n=11)/ Csa (n=12) + azathioprine ; all caucasians

-Tacro trough 10-15ng/ml for first 3mths, 7-10ng/ml after 3rd month
-Csa trough 100-200ng/ml for first 3mths, 100-150ng.ml thereafter
-solumderol 500mg iv on day 0, 125mg on day1, tapered to 5mg/day by week 6
-glucose metabolism studies performed at week3/mths 3,6/ year 1,2 and 3
- 6mth open labelled randomized trial, 260 pts Dac/MMF/Tac; 278 pts to MMF/Tac/steroids
- Incidence of NODAT 0.4% in steroid free group vs 5.4% in steroid group p<0.001

Rostaing et al, Transplantation 2005; corticosteroid free immunosuppression…
- Group 1- Cyclosporine (n=263), Group 2- Tacrolimus (n=60), Group 3- sirolimus (n=206)
- combination with MMF → FK -100%, CsA -84%, Sirolimus 99%
- well matched for age/sex/race- more DD transplants in Csa group (ns)
- more episodes of acute rejection in Csa group 22% vs 10% in group 2/ 5.3% in Group 3 (p<0.001)
- Greater cumulative dosing of steroids in Csa/Sirolimus group 2-3gm in first year due to higher rejection rate

| TABLE 2. Incidence of PTDM among the three study groups |
|---------------------------------|----------------|----------------|----------------|----------------|
|                               | Group I:        | Group II:       | Group III:      |                |
|                               | cyclosporine    | tacrolimus      | sirolimus       |                |
| n                               | 263            | 60             | 205             |                |
| All PTDM                        | 40             | 14             | 40              | 0.2378         |
| Insulin use plus FBS >126 mg/dl | 15.2%          | 23.3%          | 19.5%           |                |
| BS >200 mg/dl                   |                |                |                 |                |
| Insulin use only                | 20 (7.6%)      | 7 (11.7%)      | 12 (5.9%)       | 0.3120         |
| BS >200 mg/dl                   | 12 (4.5%)      | 5 (8.3%)       | 9 (4.3%)        |                |

FBS, fasting blood sugar; BS, blood sugar.
**Sirolimus Is Associated with New-Onset Diabetes in Kidney Transplant Recipients**

Olwyn Johnston,* Caren L. Rose,* Angela C. Webster,† and John S. Gill*

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Table 1. Patient characteristics and comparison of patients treated with various immunosuppressant medications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 20,124)</th>
<th>CSA + MMF/AZA (n = 9095)</th>
<th>TAC + MMF/AZA (n = 8431)</th>
<th>Sir + MMF/AZA (n = 619)</th>
<th>Sir + CSA (n = 800)</th>
<th>Sir + TAC (n = 1179)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr; mean [SD])</td>
<td>47.0 (14.6)</td>
<td>47.0 (14.8)</td>
<td>47.1 (14.4)</td>
<td>49.0 (14.5)</td>
<td>45.3 (14.6)</td>
<td>46.1 (14.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>59.4</td>
<td>60.9</td>
<td>57.0</td>
<td>61.2</td>
<td>63.5</td>
<td>61.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>68.5</td>
<td>72.0</td>
<td>65.6</td>
<td>68.0</td>
<td>70.6</td>
<td>60.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>black</td>
<td>25.7</td>
<td>21.7</td>
<td>28.7</td>
<td>29.1</td>
<td>24.3</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>5.8</td>
<td>6.3</td>
<td>5.7</td>
<td>2.9</td>
<td>5.1</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>12.5</td>
<td>11.3</td>
<td>12.8</td>
<td>12.0</td>
<td>19.5</td>
<td>15.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute rejection in first year</td>
<td>11.8</td>
<td>14.9</td>
<td>8.9</td>
<td>7.6</td>
<td>12.2</td>
<td>8.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2. Factors associated with NOD

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA + MMF/Aza</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC + MMF/Aza</td>
<td>1.40</td>
<td>1.29 to 1.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sirolimus + MMF/Aza</td>
<td>1.36</td>
<td>1.09 to 1.69</td>
<td>&lt;0.0100</td>
</tr>
<tr>
<td>Sirolimus + CSA</td>
<td>1.61</td>
<td>1.36 to 1.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sirolimus + TAC</td>
<td>1.66</td>
<td>1.42 to 1.93</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Cumulative incidence of NOD within the first 3 yr posttransplantation by drug combination at hospital discharge from transplantation.
Higher rate of rejection in Group c → use of higher doses of steroids
-higher overall incidence of NODAT could be sec to predominant AA/hispanic population

Postulated Mechanism for NOD sec. to Sirolomus include:
---Ectopic triglyceride deposition which causes insulin resistance
---Direct Beta cell toxicity
---Impairment of insulin mediated suppression of hepatic gluconeogenesis.
BENEFIT AND BENEFIT-EXT – USE OF BELATACEPT

- More diabetics in CsA group in Benefit-EXT study 21% vs 16% vs 29% (MI/LI/CsA)
Table 3: Secondary outcomes: cardiovascular/metabolic endpoints

<table>
<thead>
<tr>
<th>Month 12 endpoints</th>
<th>Belatacept MI (n = 219)</th>
<th>Belatacept LI (n = 226)</th>
<th>Cyclosporine (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of NODAT, n (%)</td>
<td>11 (7)</td>
<td>7 (4)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>-2.8 (-10.2, 4.4)</td>
<td>-5.7 (-12.6, 0.5)</td>
<td>-</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.4825</td>
<td>0.0687</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Cardiovascular/metabolic outcomes

<table>
<thead>
<tr>
<th>Month 12 endpoints</th>
<th>Belatacept MI (n = 184)</th>
<th>Belatacept LI (n = 175)</th>
<th>Cyclosporine (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of NODAT, n (%)</td>
<td>3 (2)</td>
<td>7 (5)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Difference from cyclosporine (97.3% CI)</td>
<td>-7.1 (-15.0, -0.6)</td>
<td>-4.2 (-12.5, 3.2)</td>
<td>-</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.0308</td>
<td>0.2946</td>
<td>-</td>
</tr>
</tbody>
</table>
HCV AND NODAT

- Meta-analysis of 9 papers with 2502 patients reporting PTDM in association with Hepatitis C status
- 60% of papers reported adjusted OR – adjusted for age/family history of diabetes, immunosuppression, BMI
- Definition of PTDM was variable; ADA criteria, or use of insulin therapy
- IS regimen combination of aza/CsA, or FK/MMF or FK/CsA
- Race was not reported in all papers

**Table 3: Baseline characteristics of studies included in analysis**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Anti-HCV positive recipients, n (%)</th>
<th>PTDM recipients, n (%)</th>
<th>Time after RT, months (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gursoy M et al.</td>
<td>40 (16.2)</td>
<td>40 (16.2)</td>
<td>39.1±19.6</td>
</tr>
<tr>
<td>Yildiz A et al.</td>
<td>47 (54.6)</td>
<td>43 (50)</td>
<td>NR</td>
</tr>
<tr>
<td>Bloom RD et al.</td>
<td>71 (16.6)</td>
<td>63 (14.7)</td>
<td>41.9±2.2/38.7±1.0</td>
</tr>
<tr>
<td>Gentil MA et al.</td>
<td>177 (50)</td>
<td>28 (7.9)</td>
<td>44.4±21/43.7±23</td>
</tr>
<tr>
<td>Gentil MA et al. (1)</td>
<td>96 (29.1)</td>
<td>36 (10.9)</td>
<td>95.6±47</td>
</tr>
<tr>
<td>Gentil MA et al. (2)</td>
<td>27 (11.3)</td>
<td>19 (7.9)</td>
<td>32.1±17</td>
</tr>
<tr>
<td>Finni PES et al.</td>
<td>23 (34.8)</td>
<td>22 (33.3)</td>
<td>9.6±1.5/9.8±1.2</td>
</tr>
<tr>
<td>Foo SM et al.</td>
<td>89 (28.1)</td>
<td>42 (13.3)</td>
<td>125.6±60/65.6±15.5</td>
</tr>
<tr>
<td>Gourishankar S et al.</td>
<td>11 (3.0)</td>
<td>35 (9.8)</td>
<td>44.2±1 (92)</td>
</tr>
<tr>
<td>Sens YAS et al.</td>
<td>25 (50)</td>
<td>9 (18)</td>
<td>29.4±16/28.7±15.8</td>
</tr>
</tbody>
</table>

**Table 6: Anti-HCV seropositive status and diabetes mellitus after RT: multivariate analysis adjusted odds ratio (aOR) and 95% CI.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>aORs</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yildiz A et al.</td>
<td>17.44</td>
<td>2.48–122.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Bloom RD et al.</td>
<td>6.76</td>
<td>2.36–19.38</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gentil MA et al.</td>
<td>1.778</td>
<td>0.768–4.125</td>
<td>NS</td>
</tr>
<tr>
<td>Gentil MA et al. (1)</td>
<td>5.65</td>
<td>2.6–12.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gentil MA et al. (2)</td>
<td>1.232</td>
<td>0.256–5.984</td>
<td>NS</td>
</tr>
<tr>
<td>Gourishankar S et al.</td>
<td>3.4</td>
<td>1.02–11.2</td>
<td>0.047</td>
</tr>
<tr>
<td>Overall random</td>
<td>3.97</td>
<td>1.83–8.61</td>
<td></td>
</tr>
</tbody>
</table>

Figures are given as post-transplant diabetes mellitus (PTDM) positive or negative recipients, respectively. NR: not reported (information needed was not available).

Fabrizi et al, AJT 2005
ROLE OF GENETIC FACTORS
DIAGNOSIS

• Identification of patients at risk of NODAT

• Weekly FG check for first month, followed by quarterly till 12th mth, then annual

• Positive FG should be confirmed with OGTT.

• Valderhaugh et al looked at 1571pts with previous normal FBG levels 10 weeks post tx.

• OGTT performed -213pts diagnosed with PTDM
  --51% positive OGTT
  --32% positive OGTT/FBG
  --only 17% positive FBG
  --FBG (95mg/dl)/ hba1c 5.8 had 80% sensitive
ROSIGLITAZONE

- single centre study, 107 pts post liver transplant/ 8pts post RT who developed NODAT according to ADA criteria
- 40 prospectively enrolled, predominantly causian/hispanic, 38% hep c positive ; 83% -tacrolimus
- 40% of patients prednisone was withdrawn after 26wks.
- Rosiglitazone started at 4mg/day, then titrated
- no appreciable weight gain ; 13% reported peripheral edema, no pulmonary edema

Villaneuva and Baldwin, Transplantation 2005
REPAGLINIDE

- Short acting insulin secretagogues, facilitate insulin secretion during early phase insulin release

- Metabolized through Cyp450 CYP3A4 /CYP2C8 -CYP3A4 which is also involved in metabolism of Tacrolimus/CsA.

- 14/23 patients (m/f 10/13) responded to Repaglinide; mean Hba1c 7.6+/0.6; 9 required change to insulin- higher hba1c levels

- 3 patients were on sirolimus

- 4 patients on dual Rosiglitazone/replaglinide responded well.

Turk et al, AJT 2006