Management of Post-transplantation Diabetes Mellitus (PTDM)

Chosun University Hospital
Lee Hae Jeong
Total treatment performed in the Korean to data (2013)

- Lung: 46
- Liver: 1,158
- Kidney: 1,759
- Pancreas: 61
- Bone: 86
- Corneal: 512
- Heart: 127
- Islet: 3
- Intestine: 5

Total: 3,757

KONOS data 2013
End stage renal disease with diabetes mellitus

Liver transplant from Jan 2004 to May 2007

Number

Liver transplant: 328
Post-transplant DM: 97

Estimated rate of post-transplant diabetes mellitus

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Type of Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-74%</td>
<td>Kidney transplants</td>
</tr>
<tr>
<td>7-30%</td>
<td>Liver transplants</td>
</tr>
<tr>
<td>11-38%</td>
<td>Heart transplants</td>
</tr>
<tr>
<td>6-45%</td>
<td>Lung transplants</td>
</tr>
<tr>
<td>15%</td>
<td>Bone marrow transplants</td>
</tr>
</tbody>
</table>

Transplant patient 5-years survival

5-year's

DM | non-DM
---|---
87% | 93%

average survival

DM | non-DM
---|---
8.1y's | 11y's

Transplantation 2000;70(11S):58-63
Patient survival after kidney transplant: effect of diabetes

% 100

Years after transplantation

N: 1811

Cosio et al, Kidney Int 62; 1440: 2002
Important to decrease the incidence of PTDM

- Avoid complications of PTDM in each individual transplant recipient
- Protect the social investment already made in the transplant recipient
- Optimize the distribution of a scarce resource
Criteria of Post-transplant diabetes mellitus

- **Fasting plasma glucose**
  - **Prediabetes**:
    - ≥ 110 mg/dL < 126 mg/dL
    - ≥ 126 mg/dL
  - **Normal**:
    - < 110 mg/dL

- **2 hours plasma glucose**
  - **Prediabetes**:
    - ≥ 140 mg/dL < 200 mg/dL
    - ≥ 200 mg/dL
  - **Normal**:
    - < 140 mg/dL

Diabetes Care;26:S5-20,2003
New onset diabetes after transplant (NODAT)

- Not all diabetes is “new” so may prefer term Post–Transplant Diabetes (PTDM)

### Criteria of Post-transplant diabetes mellitus

- Follows ADA criteria
- Doesn’t distinguish time from transplant
  - 1 month and 10 years considered same
- A1C less reliable so not an established criteria
- NODAT is spontaneous remission
- 50% people;
  Improvement in glucose tolerance after the immunosuppressive agents decrease or taper

*Diabetes Care 6:23-25*
Mechanism in the pathogenesis of PTDM

**Pre-transplant**
- Genetic variables
  - Older age
  - Family history of type 2 diabetes mellitus
  - Race
  - Hepatitis C
  - Obesity
  - Inflammation

**Post-transplant**
- Cessation of dialysis
  - Improved appetite
  - Relaxed diet/obesity

**Immunosuppression**
- Glucocorticoids
  - Increased hepatic glucose production
- Calcineurin inhibitors Sirolimus
- CMV infection

**Positive energy balance**

**Increased insulin resistance or decreased insulin sensitivity**

**Impaired \( \beta \) cell secretory capacity**

**Impaired glucose tolerance**

**New onset diabetes mellitus after kidney transplantation**

Diabetes care 36; 1406-1412; 2013
<table>
<thead>
<tr>
<th>Type of graft</th>
<th>Incidence estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>14-74%</td>
</tr>
<tr>
<td>Liver</td>
<td>7-30%</td>
</tr>
<tr>
<td>Heart</td>
<td>11-38%</td>
</tr>
</tbody>
</table>

Incidence varies with patient population and center immunosuppression used, diabetes screening protocol, interval of testing, who is looking at that data!

Pre-transplant
- Genetic variables
  - Older age
  - Family history of type 2 diabetes mellitus
  - Race
  - Hepatitis C
  - Obesity
  - Inflammation

Post-transplant
- Cessation of dialysis
  - Improved appetite
  - Relaxed diet/obesity

- Increased insulin resistance or decreased insulin sensitivity
- Positive energy balance
- Impaired \( \beta \) cell secretory capacity
- Impaired glucose tolerance
- New onset diabetes mellitus after kidney transplantation

Immunosuppression
- Glucocorticoids
- Calcineurin inhibitors Sirolimus
- CMV infection
- Increased hepatic glucose production

Diabetes care 36; 1406-1412; 2013
Glucocorticoid steroids stimulate glucose production and lipolysis, induce hyperglycemia, stimulate glucagon release, inhibit insulin secretion, and induce insulin resistance.

Clin j Am Soc Nephrol 2:343-355
### Immunosuppressant can cause hyperglycemia

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine A</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose intolerance</strong></td>
<td>+ 6%</td>
<td>+++ 8.4%</td>
<td>+ 6.6%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

N Engl J Med 2007;357:2562-75
Calcineurin inhibitors and sirolimus
Can cause hyperglycemia
Approach to management of PTDM
Central I type I 2 DM I and I PTDM

Impairment
insulin response
or secretion

Obesity
Inflammation

Increase
peripheral
insulin resistance

Central type 2 DM
Implicate development of PTDM

J Clin Invest 1981;68:1456-1467
Management aim of PTDM

- Type 2DM
  - Glucose control
  - Complication ↓

- PTDM
  - Glucose control
  - Complication ↓
  - Immunosuppressive agent

Individualized treatment
Prediction of hyperglycemia and risk of PTDM

- Older age
- Planned corticosteroid therapy after transplant
- Gout medicine
- High BMI
- Higher fasting glucose
- Higher triglycerides
- Family history of type 2 DM

Diabetes Care 34;2141-2145; 2011
Waiting transplant ...

- Document baseline blood glucose status
- Assess diabetes risk factors
- Identify high-risk subjects
- Initiate lifestyle intervention
  - Dietary counseling
  - Exercise counseling

J Clin Endocrinol Metab 2011;96(11):3289-3297
Post-transplant period

- Immunosuppressive regimen
  - Minimize steroid dose
  - Minimize calcineurin inhibitor exposure
- Treat hyperglycemia beginning in the peritransplant period
- Close follow-up of all patients, especially those with prediabetes

J Clin Endocrinol Metab 2011;96(11):3289-3297
Post-transplant period

• for those develop NODAT
  - diabetes education
  - appropriate medical therapy based of severity of hyperglycemia
• optimize insulin therapy during episodes of high-dose steroid exposure
Can lifestyle modification be adapted for prevention of PTDM?

Type 2DM

PTDM

Obesity!
Prevalence of obesity at the time of transplantation among transplant recipients

prevalence of obesity  BMI ≥30kg/m²

2001

1987

For the lower the incidence of NODAT

Insulin resistance
After transplantation

Obesity treatment
seems to reasonable
target for intervention

Higher BMI before transplantation
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Duration</th>
<th>Conclusions (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmo Feasibility study</td>
<td>181 IGT vs 193 IGT or NGT</td>
<td>5 and 12 y</td>
<td>37% ↓</td>
</tr>
<tr>
<td>Da Qing study</td>
<td>577 IGT</td>
<td>6 y</td>
<td>46% vs 67.7%</td>
</tr>
<tr>
<td>DPS</td>
<td>522 IGT</td>
<td>3.2 y</td>
<td>11% vs 23%</td>
</tr>
<tr>
<td><strong>DPP study</strong></td>
<td>3234 with IGT or IFG</td>
<td>2.8 y</td>
<td>58% ↓</td>
</tr>
<tr>
<td>Malmohus study</td>
<td>267 men with IGT</td>
<td>10 y</td>
<td>13% vs 29%</td>
</tr>
</tbody>
</table>
Percent developing diabetes (DPP study)

All participants

- Lifestyle (n=1079, p<0.001 vs. Met, p<0.001 vs. Plac)
- Metformin (n=1073, p<0.001 vs. Plac)
- Placebo (n=1082)

The DPP Research Group, NEJM 346:393-403, 2002
Lowering fat mass may be appropriate for the prevention of NODAT

Start: reduction of fat mass

Effect of higher muscle mass on survival in HD patients

High fat mass < higher muscle mass

- DM of renal failure
- coronary artery d's
- Cerebrovascular d's
- peripheral Vascular d's
- heart failure

High BMI (≥25Kg/m²) group by muscle mass

Lifestyle intervention similar to the diabetes prevention program

Safely reverse method?

Three times/week
For 3-4h’s treatment
Inactivity
anemia
hypervolemia
Uremic cachexia

J Nephrol Nurs 2011;38:139-147; quiz 148
Potential effectiveness of lifestyle intervention importance

Yet not easily substituted

Current Anti-rejection

- glucocorticoids
- CNIs
  - Tacrolimus
  - cyclosporine
- m TOR
  - Sirolimus
  - everolimus

J Nephrol Nurs 2011;38:139-147; quiz 148
Direction of lifestyle modification

- Limitation of calorie intake
- Regular exercise
- Weight control

Insulin resistance improvement

AACE system of intensive diabetes self-management -2000
# Treatment guideline for Post-transplantation diabetes mellitus

<table>
<thead>
<tr>
<th>Index</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>&lt;130mmHg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>&lt;80mmHg</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>&lt;100mg/dL</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>&gt;40mg/dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&lt;150mg/dL</td>
</tr>
</tbody>
</table>

ADA, JNC proposal of recommendation 2011
Self monitoring blood glucose

Maximization of curative effect

HbA1c <7.0%

OHA Therapy
Insulin therapy
Lifestyle modification

interval: 3 months
Especially attention:
Renal failure
anemia

J Korean Soc Transplant 2011;25:8-14
### ADA guidelines

<table>
<thead>
<tr>
<th>Setting</th>
<th>Glucose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>140-180 mg/dL</td>
</tr>
</tbody>
</table>
| Non-ICU         | Pre-meal ≤ 140 mg/dL  
|                 | Random ≤ 180 mg/dL |

Value of tighter control?

- **Kidney Transplant RCT:** 70-100 vs <180 mg/dL
- More hypoglycemia, rejections → no benefit

*Diabetes Care 36 Suppl 1; S11-66, 2013*

*JCEM 97; 4399, 2012*
Insulin therapy

Several stressors after trans-plant surgery

- Surgical procedure
- High-dose corticosteroids
- Initiation of CNIs

Pancreatic β-cell

Thus

Treatment goals
Resting the β-cell with Basal insulin and β-cell
Protection with near-normo-glycemic control
: reduce IGT and NODAT

Insulin therapy

Used widely

Basal insulin, split-mix, basal-bolus

Flexibility and creativity
<table>
<thead>
<tr>
<th>Oral /SQ agent</th>
<th>Effective Post-TX?</th>
<th>Potential limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas &amp; repaglinide</td>
<td>Yes</td>
<td>Drug-durg interactions with cyclosporine, risk of hypoglycemia with GFR ↓, less with repaglinide</td>
</tr>
<tr>
<td>Metformin</td>
<td>Yes</td>
<td>Contraindicated in hospital with GFR ↓, LFTs ↑, CHF, infection</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Not studied</td>
<td></td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Yes</td>
<td>Reduce dose for most with GFR ↓</td>
</tr>
<tr>
<td>TZDs</td>
<td>Yes</td>
<td>Risk of LFTs ↑, CHF, weight gain</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Yes</td>
<td>Avoid with GFR ↓, ineffective as single agent</td>
</tr>
</tbody>
</table>
Hypoglycemia can

- Induce seizure and arrhythmia
- Triggers adrenergic discharge
- Expression of pro-inflammatory cytokines

Adverse outcomes in high-risk patients

Metabolism 2009;58:443-48
Dyslipidemia

- Calcineurin inhibitors:
  increase cholesterol level
  Preferentially pravastatin, fluvastatin

- Sirolimus and glucocorticoids:
  increase hypertriglyceridemia
  Be used fibrate, fish oil

Drugs 2009;69:2227-43
Hypertension

- Premorbid hypertension

- Recommends BP: 130/80 mmHg ↓

- β-blockers, calcium channel blockers to be effective

- ACE inhibitors, ARB are associated decreases in GFR and hyperkalemia

Transition to home: always tricky

• Diet
• Exercise
• Sick day management
• Self-blood glucose monitoring
• Insulin injection method

Check list
Sticker

Diary of diet/exercise
SMBG

Make sure
Feed back!!
Fiber-rich meal
Food is insipid
Standard body weight

Regular diet
Attention to monosaccharides
Attention to fatty food

You are what you eat!
What about foods high in carbohydrates?

- Come from sugars and starches
- provide fuel and energy
- Take steroid medication, it’s difficult for your body to use extra carbohydrates

For these reasons

- Fewer “simple” carbohydrates
- Moderately “complex” carbohydrates
What about cholesterol and triglyceride levels?

- Limit
- Lose weight
- Egg yolks
- Frying foods
- Alcoholic beverages
- All types of fat and oils
- Use lean meats, poultry or fish

www.kidney.org
Still need to follow a low-salt diet?

- Transplant medications, Steroids may cause to retain fluid
- Salt makes this problem worse, increasing fluid retention and raising blood pressure

www.kidney.org
소금이 거의 없는 향신료 사용
식품 자체의 신선한 맛 활용
1일 소금 사용량 점차적으로 감소
먹기 직전에 간을 함
국 및 찌개류, 김치류, 해조류는 특히 싱겁게 조리
볶음, 튀김 등 소금함량이 적어도 맞있는 조리법 이용
음식에 간을 할 때 소금, 간장 적게 사용
먹기 직전에 간을 함
소금이 거의 없는 양식료 사용
음식에 간을 할 때 소금, 간장 적게 사용
What about protein?

- Especially...
- It builds and repairs muscles and tissues
- It helps you heal after surgery
- 1.0g~1.2g/Kg (15~20%/ day)
Take care of the meal

- Calcium-rich foods
- Food rich dietary fiber

• Not eat the health supplements food

American of transplantation 2009;9:S64-S70
Many people have a better appetite after they get a transplant, and gain unwanted weight. 

Avoid high-calorie foods, fatty foods, sweets, pastries, sugar 

Important to controlling weight 
Help to: exercise and regular physical activity plan 

American of transplantation 2009;9:S64-S70
Knowing is not enough; We must apply.

Willing is not enough; We must do.

-Goethe-
Thank you for your attention