LIVER TRANSPLANTATION FOR NASH:
Optimizing Post-Transplant Care

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Objectives

• Trends in liver transplantation for NASH
• Mortality in liver transplant recipients
• Impact of immunosuppression on metabolic diseases
• Optimizing care in patients with liver transplant for NASH
NAFLD is a Multisystem Disease

- Diabetes Mellitus
- Dyslipidemia
- Obesity
- Hypertension

Fatty Liver
Recognition of NAFLD in Clinical Practice is Sub-Optimal

NAFLD Care:
- 39% - Recognition of ALT increase
- 22% - Diagnosis of NAFLD/NASH
- 15% - Recommend lifestyle changes
- 10% Referral to specialist

NO NAFLD CARE

NAFLD is a Multisystem Disease

- Diabetes Mellitus
- Dyslipidemia
- Obesity
- Hypertension
- Atherosclerosis
- NASH with Fibrosis
- Renal Insufficiency
- Transplanted Liver
- Heart Failure
- Liver Transplantation
NASH as the listing diagnosis among new liver transplant waitlist registrants is rapidly increasing.

Wong et al. Gastro 2015
NASH as an indication for liver transplantation is increasing

Charlton et al. Gastroenterology. 2012
Survival in Liver Transplant Recipients is Improving

Watt KD. Nat. Review. Gastro 2015
Survival in Patients Transplanted for NASH are similar to other indications

Charlton et al. Gastroenterology. 2012
Survival in LTR is Lower Than Non-Transplant Population

Cardiovascular disease is one of the leading cause of death in liver transplant recipients

Watt et al. Am J Transplant. 2010
Risk of cardiovascular events increases with time after liver transplantation

Fussner et. al. Liver Transpl 2015
Causes of Long-term mortality in patients receiving a LT for NASH

- Cancer, Heart, Infection: 24.98%
- Other: 21.88%
- Liver: 18.78%
- Graft Cirrhosis: 9.39%

Bhati et al. AASLD 2016
Care of A Transplant Patient (Expectation)

Immunosuppression  Recurrent Liver Disease  Lipids  Obesity  HTN  Cancer Surveillance  T2DM

Hepatologist

Primary Care
Role of Primary Care in Managing Liver Transplant Recipients

- PCP feels comfortable: 73%
- Consult Transplant Center for only transplant related care: 55%
- Comfortable managing familiar disease: 36%
- Comfortable with ALL care: 9%
- Defer ALL care to LT center: 9%

McCashland, Liver Transplant, 2001
Care of A Transplant Patient (Reality)

- Immunosuppression
- Recurrent Liver Disease
- Lipids
- Obesity
- HTN
- Cancer Surveillance
- T2DM

Hepatology

Primary Care
Optimizing Care of Patients Receiving Liver Transplantation for NASH Cirrhosis

Pre-Transplant
- Patient Selection
- BMI
- CVD evaluation

Transplant
- Steroid free/Reduced Steroid
- Renal protective protocols
- Management of hyperglycemia

Post-Transplant
- Reducing rejection rates
- Limiting metabolic complications
- Reducing disease recurrence

Siddiqui and Charlton Gastro. 2016
Goals of Immunosuppression

- Reduce Rejection
- Role in Recurrent Liver Disease
- Reduce Complications
Consequences of Long Term Immunosuppression

• Metabolic Syndrome (its component)
  – Type 2 diabetes mellitus
  – Hypertension
  – Obesity
  – Hyperlipidemia
• Cardiovascular Disease
• Renal Disease
• De novo Cancer
Metabolic Syndrome is common post-transplant

Francioso et al. J of Hepatol. 2008
Components of metabolic syndrome are common after liver transplantation

- PTDM: 31%
- PTHTN: 50%
- PT Obesity: 40%
Metabolic syndrome increases cardiovascular mortality in general population

McCullough A. J Dig Dis. 2011
Post-transplant metabolic syndrome is associated with increased and accelerated vascular events.

<table>
<thead>
<tr>
<th></th>
<th>PTMS</th>
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<tbody>
<tr>
<td>ACS</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>MI</td>
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<td>0</td>
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<tr>
<td>TIA</td>
<td>6%</td>
<td>2%</td>
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</table>
Weight gain in post transplant period

Body Weight at the time of transplant

Richards et al. Transplant International. 2004
Weight gain in patients on Tacrolimus versus Cyclosporine

<table>
<thead>
<tr>
<th></th>
<th>Weight difference</th>
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<tr>
<td><strong>Cyclosporin</strong></td>
<td></td>
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<tr>
<td>At 3 months</td>
<td>−.05</td>
<td></td>
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<tr>
<td>At 6 months</td>
<td>2.60</td>
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<td>At 1 year</td>
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<tr>
<td><strong>Tacrolimus</strong></td>
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</tr>
<tr>
<td>At 3 months</td>
<td>−1.40</td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>.50</td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>3.95</td>
<td></td>
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<tr>
<td>At 2 years</td>
<td>7.20</td>
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<tr>
<td>At 3 years</td>
<td>9.10</td>
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</table>

p-value < 0.05

p-value NS
Weight Gain After Liver Transplantation

Mean BMI after LT

Prevalence of Obesity in LTR

Fussner et. al. Liver Transpl 2015
Post-Transplant diabetes (PTDM) is associated with increased risk of post-LT complications

![Bar chart showing comparison between PTDM and No DM for different complications]

- Cardiac: PTDM 48, No DM 24
- Major Infections: PTDM 41, No DM 25
- Minor Infection: PTDM 28, No DM 5
- Neurologic: PTDM 22, No DM 9
- Neuropsychiatric: PTDM 22, No DM 6
- ESRD: PTDM 18, No DM 10
Patient & Graft Survival based on sub classification of PTDM

1: Pre-transplant DM   2: Sustained NODM   3: Transient NODM   4: Normal

Moon et al. Transplantation. 2006
Tacrolimus is associated with increase incidence of PTDM

Incidence of PTDM at 6 months was 8.9% in CsA and 17% in Tac

Vincenti et al. Am J Transplant. 2007
Tacrolimus decreases insulin secretion

Beta-cell content was not increased

Cochrane Review – PTDM CsA v Tac

• 16 randomized controlled trials
• Tacrolimus associated with:
  – Reduced 1 year mortality (RR 0.85)
  – Reduced graft loss (RR 0.73)
  – Acute rejection (RR 0.81)
• Tacrolimus associated with more de novo insulin requiring diabetes (RR 1.38)
Post-transplant Dyslipidemia

• **Characterized by:**
  – Decreased HDL-C
  – Increased TG, Cholesterol, LDL-C

• **Cyclosporine use was associated with:**
  – Increased LDL-C
  – Total Cholesterol

Discontinuing CsA improves Lipid Profile

- Total cholesterol ↓ by 18%
- LDL-C ↓ 27%
- HDL-C was not affected

- Triglycerides ↓ by 23%
Tacrolimus as treatment for post-OLT dyslipidemia

Switch to Tacrolimus:
- Reduced total Cholesterol
- Modest reduction in LDL-C
- No change in HDL-C
- Reduction serum Triglycerides
Cyclosporine is associated with atherogenic lipoproteins

Chhatrala et al. Liver Transpl 2015
Steatosis and cyclosporine use are associated with atherogenic lipoprotein sub-particles

Subjects with steatosis

Idowu et al. Liver Transpl 2016
Renal Function in Patients who Received a Liver Transplant for NASH cirrhosis

Houlihan et al. Liver Transpl 2011
## Impact of Immunosuppression on Metabolic Conditions

<table>
<thead>
<tr>
<th></th>
<th>Calcenurin Inhibitors</th>
<th>Mycophenolate Mofetil</th>
<th>mTOR inhibitors</th>
<th>Steroids</th>
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<tbody>
<tr>
<td>Diabetes</td>
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<td>Potential Benefit</td>
<td>Potential Benefit</td>
<td>↑</td>
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<tr>
<td>Dyslipidemia</td>
<td>↑</td>
<td>Less than CNI</td>
<td>↑*</td>
<td>↑</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑</td>
<td>Less than CNI</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Malignancy</td>
<td>↑</td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Renal Injury</td>
<td>↑</td>
<td>Less than CNI &amp; mTOR inhibitors</td>
<td>Less than CNI</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>↑</td>
<td>Less weight gain than CNI</td>
<td>Less weight gain than CNI</td>
<td>↑</td>
</tr>
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Recurrence of NAFLD after LT and its association with liver enzymes
Rejection

• Rates of rejection:
  – Acute rejection 10-40%
  – Chronic Rejection 5%

• Rates of Rejection in NASH:
  – Acute rejection 12.6%
  – No chronic rejection
  – 2.9% of AR occurred after 1 year and none after 18 months
Suggestions

• NASH cirrhosis patients undergoing LT at highest risk of developing
  – Metabolic complications and CVD events
  – Renal dysfunction
• Post LT NASH patients have low risk of AR >1 year after LT
• Immunosuppression strategies:
  – Reducing CNI doses
  – Combination strategies
  – Individualize therapy