The complex management of kidney transplanted patients - beyond immunosuppression

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University of Toronto, Canada
• The ESRD cycle
• CKD in the kidney transplant (Tx) population
• Cardiovascular disease in the Tx population
• Post-transplant anemia
• Post-transplant metabolic disorders (diabetes, lipids)
• Depression and quality of life in the Tx population
• The multidisciplinary model
The ESRD cycle

GFR ml/min/1,73 m2

120

15

transplantation
dialysis
CKD STAGES IN KIDNEY TRANSPLANTED PATIENTS
Majority of transplant recipients have kidney function equivalent to stage 3 CKD or worse (UK data)

19,074 adult patients with a functioning kidney transplant at the end of 2005
Renal function in Tx patients – Hungarian data

<table>
<thead>
<tr>
<th>Std</th>
<th>V</th>
<th>IV</th>
<th>III</th>
<th>II</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>2</td>
<td>14</td>
<td>58</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>GF R</td>
<td>12.7 ±1.6</td>
<td>23.9 ±4.1</td>
<td>45.4 ±8.1</td>
<td>69.9 ±7.7</td>
<td>98.9 ±8.2</td>
</tr>
</tbody>
</table>
Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines

Levey As, et al. Kidney Int 87:2089, 2005

- Consider all kidney transplants recipients to have CKD, irrespective of GFR level or presence or absence of markers of kidney damage.

- The rationale for this is based on damage to native kidneys, presumed damage to the kidney transplant based on studies of "protocol biopsies," and need for life-long care caused by complications of prior CKD and chronic allograft nephropathy.
Progression of CKD

- No Treatment
- Current Treatment
- Early Treatment

GFR vs Time (years)

Kidney Failure
Outcomes with CKD in Managed Care

N = 27,998, 5 year F/U, mean age stage 2: 61, stage 3-4: 72

- Stage 2, no proteinuria
- Stage 2, proteinuria
- Stage 3
- Stage 4

Keith DS et al. Arch Intern Med 164; 659-663: 2004
Renal function versus SF-36 scores

- eGFR >60
- eGFR 30-60
- eGFR<30

“#” = p<0.05, Mann-Whitney U test
A vesefunkció és a túlélés kapcsolata

![Graph showing cumulative survival with GFR (ml/min) and follow-up time (months).]

- GFR (ml/min)
  - >60
  - 30-60
  - <30

Cumulative survival with different GFR categories:

- Blue line: censored
- Green line: censored
- Red line: censored

Follow-up time (months): 0.00, 10.00, 20.00, 30.00, 40.00, 50.00.
CARDIOVASCULAR DISEASE IN KIDNEY TRANSPLANTED PATIENTS
Cause of Death in Renal Transplant Recipients With Functioning Transplants

Total CVD: 45.7%

- Cerebrovascular disease: 21.0%
- Myocardial infarction: 7.4%
- Other cardiovascular: 13.0%
- Infection: 25.3%
- Malignancy: 13.0%

Caveat:
Cardiovascular Disease remains a significantly greater risk for renal transplant recipients compared to infection and malignancy.
Figure 1  Prevalence of cardiovascular disease in patients with renal disease
Cardiovascular mortality in kidney transplant recipients

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Table 4. Traditional and nontraditional risk factors for CVD in renal transplant recipients

<table>
<thead>
<tr>
<th>Traditional Risk Factors</th>
<th>Nontraditional Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Decreased kidney function</td>
</tr>
<tr>
<td>Male gender</td>
<td>CNI</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Anemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>low HDL</td>
<td>Advanced glycation end products</td>
</tr>
<tr>
<td>high LDL</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Menopause</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Thrombogenic factors</td>
</tr>
<tr>
<td>Modifiable/potentially modifiable</td>
<td>Traditional Risk Factors</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>obesity</td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>smoking</td>
<td></td>
</tr>
<tr>
<td>Nonmodifiable</td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td></td>
</tr>
<tr>
<td>family history</td>
<td></td>
</tr>
</tbody>
</table>
## Immuno-suppression and atherogenesis

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>TAC</th>
<th>SRL</th>
<th>MMF</th>
<th>AZA</th>
<th>Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>NODAT</strong></td>
<td>+</td>
<td>+ (+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

How to improve outcome in kidney transplanted patients?

The main issue for long term outcomes is to reduce ISU toxicity and to manage CV disease.

• Before Tx:
  – Dialysis vintage
  – CV management
  – CV interventions

• After Tx: medical management
  – Anemia
  – Dyslipidaemia
  – Hypertension
  – NODAT
  – Smoking
  – Obesity
cardiovascular disease management after renal transplantation

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BLOOD PRESSURE
Blood Pressure One Year after Kidney Transplantation and Graft Outcome

Measures of care in adult renal transplant recipients in the United Kingdom (Chapter 11)

Fig. 11.11. Percentage of patients with renal transplants in different renal units who achieve the RA standards for BP.
BP control in Budapest

![Graph showing frequency distribution of RRsys1 with mean = 143.04, std. dev. = 20.471, N = 991]
BP management after the first posttransplant year

- **Stage 1 HTN(+)**
  - SBP 140-159 or DBP 90-99
  - ACE-I, ARB, CCB, BB, diuretics
  - Or Combinations

- **Stage 2 HTN(+)**
  - SBP > 160 or DBP > 100
  - Start with 2 drugs: ACE-I, ARB + CCB, BB, diuretics

- Not at goal
  - Optimize Dose
  - Add new Drug
  - Consider work-up for resistant HTN

**Urine P:C Ratio**
- Goal < 200 mg/g

**BP not at goal ≤130/80 mmHg**
- All patients: Lifestyle Modifications
- Drug Therapy

**Not at goal**
- ACE-I, ARB preferred
  - Caution if K > 5.6, Hematocrit < 30 or renal artery stenosis
DIABETES
| Table 5. Risk factors for NODAT$^a$
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient characteristics</td>
</tr>
<tr>
<td>older age (&gt;45 yr)</td>
</tr>
<tr>
<td>higher body mass index (≥30)</td>
</tr>
<tr>
<td>black race</td>
</tr>
<tr>
<td>family history of diabetes</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
</tr>
<tr>
<td>education (no college degree)</td>
</tr>
<tr>
<td>Donor</td>
</tr>
<tr>
<td>deceased donor</td>
</tr>
<tr>
<td>male gender</td>
</tr>
<tr>
<td>Transplant era (after 1995)</td>
</tr>
<tr>
<td>Tacrolimus use</td>
</tr>
<tr>
<td>HLA mismatch</td>
</tr>
<tr>
<td>Acute rejection</td>
</tr>
<tr>
<td>HCV infection</td>
</tr>
</tbody>
</table>

$^a$HCV, hepatitis C virus; NODAT, new-onset diabetes after transplantation.

Disordered CH metabolism

Patient Survival and Cardiovascular Risk After Kidney Transplantation: The Challenge of Diabetes

Figure 1: Left: Kaplan–Meier plots of patient survival after transplantation in recipients without DM (—) and those with DM (……..) (log-rank, p < 0.0001). Right: Kaplan–Meier plots of the incidence of fatal and nonfatal posttransplant CV events in recipients without DM (—) and those with DM (……..) (log-rank, p < 0.0001).
Diabetes management after the first posttransplant year

<table>
<thead>
<tr>
<th>Oral Agent</th>
<th>Target Population</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>DM2 &lt; 5 year duration</td>
<td>↓ cost</td>
<td>↑ Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▼ Rapid effect</td>
<td>↑ hypoglycemia</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Recent DM2</td>
<td>↓ hypoglycemia</td>
<td>↑ cost</td>
</tr>
<tr>
<td></td>
<td>↑ PPG</td>
<td>short acting</td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Overweight/Obese</td>
<td>No ↑ weight</td>
<td>GI side-effects</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td>↓ hypoglycemia</td>
<td>Lactic acidosis (rare)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Overweight/Obese</td>
<td>↓ Insulin requirement</td>
<td>↑ Cost, weight</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td>↓ hypoglycemia</td>
<td>↑ Liver toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slow onset of action</td>
</tr>
<tr>
<td>α-glucosidase</td>
<td>↑ PPG</td>
<td>↓ hypoglycemia</td>
<td>GI side-effects</td>
</tr>
<tr>
<td>inhibitor</td>
<td></td>
<td></td>
<td>↑ cost</td>
</tr>
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</tr>
</tbody>
</table>


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Prevalence of Hyperlipidemia in Renal Transplant Patients Based on CKD Stage

Karthikeyan V, Am J Transplant 4:262-269, 2004

- Cholesterol > 200 mg/dl
- Triglycerides > 150 mg/dl
- Lipid Lowering Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>Lipid Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>48</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>67</td>
<td>50</td>
</tr>
</tbody>
</table>
Hypercholesterolemia: Relative Risk for Ischemic Heart Disease in Patients More Than One Year After Renal Transplantation

Relative Risk of IHD in Males From the Framingham Heart Study (FHS) or Transplant Patients

<table>
<thead>
<tr>
<th>Cholesterol (mg/dL)</th>
<th>FHS</th>
<th>Transplant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥280</td>
<td>1.93</td>
<td>2.25</td>
</tr>
<tr>
<td>240-279</td>
<td>2.02</td>
<td>2.39</td>
</tr>
<tr>
<td>200-239</td>
<td>1.66</td>
<td>2.39</td>
</tr>
<tr>
<td>160-199</td>
<td>1.19</td>
<td>2.39</td>
</tr>
<tr>
<td>&lt;160</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

ALERT: Assessment of Lescol in Renal Transplantation

- Randomized, double blind, placebo controlled multicentric study, 2102 Tx patients
- Fluvastatin (40 mg/d - 80 mg/d) or placebo
- Outcome: cardiac mortality, AMI, coronary intervention
Cardiac mortality

<table>
<thead>
<tr>
<th>Years (years)</th>
<th>Fluvastatin (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>0.5</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5</td>
<td>4.0</td>
<td>4.5</td>
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<tr>
<td>2.0</td>
<td>5.0</td>
<td>5.5</td>
</tr>
<tr>
<td>2.5</td>
<td>6.0</td>
<td>6.5</td>
</tr>
<tr>
<td>3.0</td>
<td>7.0</td>
<td>7.5</td>
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<tr>
<td>3.5</td>
<td>8.0</td>
<td>8.5</td>
</tr>
<tr>
<td>4.0</td>
<td>9.0</td>
<td>9.5</td>
</tr>
<tr>
<td>4.5</td>
<td>10.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>

$P=0.031$

Fluvastatin vs Placebo: 38% decrease in cardiac mortality.
Dyslipidemia management after the first posttransplant year

- **Total cholesterol > 200 mg/dL**
  - LDL > 100 mg/dL
  - Non-HDL chol > 130 mg/dL
  - **Statin**
  - **Lifestyle modifications**
  - Lipid profile in 3 months

- **Hypert triglyceridemia**
  - TG > 300 mg/dL
  - **Fibates**
  - **Lifestyle modifications**
  - Lipid profile in 3 months

- **At goal?**
  - TG < 150 mg/dL
    - **Yes**
      - Lipid profile every 6M
    - **No**
      - ↑Fibates
      - Lipid profile in 3M

- **LFTs at 1, 4, 6 wks**
  - **Normal**
    - LFTs every 6M
  - **Abnormal**
    - Revise treatment
POST-TRANSPLANT ANEMIA
Prevalence and Management of Anemia in Renal Transplant Recipients: A European Survey

Yves Vanrenterghem\textsuperscript{a}, Claudio Ponticelli\textsuperscript{b}, José Maria Morales\textsuperscript{c}, Daniel Abramowicz\textsuperscript{d}, Keshwar Baboolal\textsuperscript{e}, Björn Eklund\textsuperscript{f}, Volker Kliem\textsuperscript{g}, Christophe Legendre\textsuperscript{h}, Antonio Luis Morais Sarmento\textsuperscript{i} and Flavio Vincenti\textsuperscript{i}

Blackwell Munksgaard
Prevalence of anemia by gender – Transqlol-HU 2002

Male patients (n=3260)
- No anemia: 11%
- Mild anemia: 13%
- Moderate anemia: 21%
- Severe anemia: 55%

Female patients (n=2003)
- No anemia: 7%
- Mild anemia: 25%
- Moderate anemia: 56%
Anemia and CKD stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Anaemia</th>
<th>Hb&lt;110</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD1+2</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>CKD3</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>CKD4</td>
<td>68</td>
<td>31</td>
</tr>
<tr>
<td>CKD5</td>
<td>79</td>
<td>52</td>
</tr>
</tbody>
</table>
Cardiovascular events are more common in anaemic patients

404 type 1 diabetic ESRD who underwent either cadaveric kidney transplantation alone or simultaneous pancreas-kidney transplantation

Anemia Is Associated with Mortality in Kidney-Transplanted Patients—A Prospective Cohort Study

M. Z. Molnar\textsuperscript{a,b,c}, M. Czira\textsuperscript{a}, C. Ambrus\textsuperscript{b,c}, L. Szeifert\textsuperscript{a}, A. Szentkirály\textsuperscript{a}, G. Beko\textsuperscript{d}, L. Rosivall\textsuperscript{e}, A. Remport\textsuperscript{f}, M. Novak\textsuperscript{a,g} and I. Mucs\textsuperscript{i}\textsuperscript{a,b,e,*}

\textbf{Cumulative Survival}

Follow-up time (months)

Log Rank: p<0.0001

\textbf{Cumulative Graft Survival}

Follow-up time (months)

Log Rank: p<0.0001

\textit{American Journal of Transplantation 2007; 7: 818–824}
Blackwell Munksgaard
Common causes of posttransplantation anemia

Anemia and MICS

Tertiles of MICS score

- CKD1+2: 14 (Anaemia), 2 (Hb<110)
- CKD3: 21 (Anaemia), 3 (Hb<110)
- CKD4+5: 38 (Anaemia), 12 (Hb<110)
Difference in centers

Severity of anemia

No anemia
Mild anemia
Moderate anemia
Severe anemia

On ESA therapy
Not on ESA therapy
Depression and QoL
Significance of depression

- A major predictor of QoL in different Pt groups
- High prevalence, large social and economic burden
- Treatment adherence
- Rehabilitation
- Association with CV diseases, diabetes, outcome
Depression (CESD) and QOL

- High risk for depression
- Low risk for depression

Phys fctn
Role phys
General health
Social fctn
Vitality
Emotional wb
Pain
Depression and return to dialysis

Age, gender, education, eGFR, alb, Hb, diabetes, HTN, CRP, tx vintage
Depression and mortality

Age, gender, education, eGFR, alb, Hb, diabetes, HTN, CRP, tx vintage
MULTIDISCIPLINARY CARE
Multidisciplinary care

- Education program
- Protocollized clinic f/u
- Protocollized lab
- Nephrologist
- Nurse practitioner
- Social worker
- Dietician
- Pharmacist
- Physiotherapist
Provider awareness does not equal successful implementation

NCEP = National Cholesterol Education Program

Drug utilization - Budapest

- Acei/ARB 29%
- Plt aggreg. Inhibitors 39%
- Statins 30%
Steno 2: Intensive Therapy

NB: combined cardio/renal protection

• Multidisciplinary team (MD, nurse, dietician)
• Diet
• Exercise 30 minutes 3 – 5x/wk
• Smoking cessation courses
• ACEI/ARB independent of BP
• Vitamin – mineral supplement
• ASA
• Glycemic control
• BP control
• Lipid control

Gaede P et al. NEJM 2003; 348: 383-393
Steno 2: Outcomes

- Hazard ratio = 0.47 in favor of intensive group (.24 - .73, p=0.008)
- Absolute RR = 20%
- NNT 5 patients to prevent one CV event in 7.8 years

Gaede P et al. NEJM 2003; 348: 383-393
The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes.
Role of Remission Clinics in the Longitudinal Treatment of CKD

JASN Express. Published on March 19, 2008 as doi: