Diagnosis and Management of Metabolic Problems in Kidney Transplant Recipients

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associate professor

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Semmelweis University
Budapest, Hungary
• CKD in Tx
• DM
• Lipids
• Obesity
• Malnutrition/inflammation
• Bone – FGF23
• How to manage this...
The ESRD cycle

GFR ml/min/1.73 m²

transplantation → dialysis

120

15
Metabolic effects of common immuno-suppressive agents

<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>Dyslipidaemia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>NODAT</td>
<td>+</td>
<td>+ (+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

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
Figure 2. Cardiovascular mortality in kidney transplant recipients

cardiovascular disease management after renal transplantation

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Dyslipidemia
### Table 2. Effect of immunosuppressive drugs on lipid parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Everolimus</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prednisone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; TC—total cholesterol; TG—triglyceride.
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>54</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>30</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>57</td>
<td>44</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>Transplant patients</th>
<th>FHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥280</td>
<td>2.25</td>
<td>1.93</td>
</tr>
<tr>
<td>240-279</td>
<td>2.02</td>
<td></td>
</tr>
<tr>
<td>200-239</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td>160-199</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Lipid lowering strategies in transplant patients

- statins,
- fibrates,
- bile acid binding resins,
- cholesterol absorption inhibitors,
- nicotinic acid

Tx patients will have the same cardiovascular benefits from lipid lowering therapy achieving target or very low LDL-c levels (eg < 70 mg/dl) as non-transplant subjects
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
Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial


ITT, intent-to-treat population.

\[ P = 0.031 \]

Fluvastatin vs Placebo

SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022
Comparison of SHARP with other trials: Vascular Death

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocated LDL-C reduction</th>
<th>Allocated control</th>
<th>Risk ratio (RR) per mmol/L LDL-C reduction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>151 (8.52)</td>
<td>167 (9.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALERT</td>
<td>66 (1.23)</td>
<td>73 (1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURORA</td>
<td>324 (6.87)</td>
<td>324 (6.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHARP</td>
<td>361 (1.82)</td>
<td>388 (1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal: 4 renal trials</td>
<td>902 (2.85)</td>
<td>952 (3.01)</td>
<td>0.94 (0.85 - 1.04)</td>
<td>0.27</td>
</tr>
<tr>
<td>23 other trials</td>
<td>3679 (1.05)</td>
<td>4230 (1.21)</td>
<td>0.85 (0.81 - 0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All trials</td>
<td><strong>4581 (1.20)</strong></td>
<td><strong>5182 (1.36)</strong></td>
<td><strong>0.86 (0.83 - 0.90)</strong></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Difference between renal and non-renal trials: $\chi^2 = 3.8$ (p = 0.05)
Immunosuppressive protocols and dyslipidemia
MINIMIZING GLUCOCORTICOID USE

• Lower doses administered earlier after transplantation

• Complete withdrawal, which can either be performed early after transplantation (approximately three to six months post-surgery) or at a later time (after one year)

• Complete avoidance, which most frequently has been utilized with a calcineurin inhibitor-based immunosuppressive regimen and polyclonal antibody induction therapy
Steroid Avoidance or Withdrawal After Renal Transplantation Increases the Risk of Acute Rejection but Decreases Cardiovascular Risk. A Meta-Analysis

Simon R. Knight\textsuperscript{1,2} and Peter J. Morris\textsuperscript{1,3}

**TABLE 2.** Meta-analysis of cardiovascular risk factors in all studies and studies reporting intention-to-treat analysis only

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies reporting outcome</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies</td>
<td>Patients</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>2,833</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13</td>
<td>2,283</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>16</td>
<td>2,849</td>
</tr>
<tr>
<td>Intention-to-treat analysis only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>2,173</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9</td>
<td>2,055</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>10</td>
<td>2,346</td>
</tr>
</tbody>
</table>

CI, confidence interval; Random, random-effects analysis; Fixed, fixed-effects analysis; \(I^2\), \(I\)-squared statistic (measure of heterogeneity, see text).
Belatacept-Based Regimens Are Associated With Improved Cardiovascular and Metabolic Risk Factors Compared With Cyclosporine in Kidney Transplant Recipients (BENEFIT and BENEFIT-EXT Studies)

Yves Vanrenterghem, Barbara Bresnahan, Josep Campistol, Antoine Durrbach, Josep Grinyó, Hans-Hellmut Neumayer, Philippe Lang, Christian P. Larsen, Eduardo Mancilla-Urrea, José Medina Pestana, Alan Block, Tao Duan, Alan Glicklich, Sheila Gujrathi, and Flavio Vincenti
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

Uwe Heemann¹, Daniel Abramowicz², Goce Spasovski³ and Raymond Vanholder⁴ for the European Renal Best Practice (ERBP) Work Group on kidney transplantation

16.2.1: Measure a complete lipid profile in all adult (≥18 years old) and adolescent (puberty to 18 years old) KTRs (based on KDOQI Dyslipidemia Recommendation 1):

• 2–3 months after transplantation;
• 2–3 months after a change in treatment or other conditions known to cause dyslipidaemias;
• at least annually, thereafter.

doi: 10.1093/ndt/gfr169
Advance Access publication 9 May 2011
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

Uwe Heemann\textsuperscript{1}, Daniel Abramowicz\textsuperscript{2}, Goce Spasovski\textsuperscript{3} and Raymond Vanholder\textsuperscript{4} for the European Renal Best Practice (ERBP) Work Group on kidney transplantation

16.2.2.1: For KTRs with fasting triglycerides $\geq 500$ mg/dL ($\geq 5.65$ mmol/L) that cannot be corrected by removing an underlying cause, treat with:

- Adults: therapeutic lifestyle changes and a triglyceride-lowering agent (based on KDOQI Recommendation 4.1);
- Adolescents: therapeutic lifestyle changes (based on KDOQI Recommendation 5.1).

doi: 10.1093/ndt/gfr169
Advance Access publication 9 May 2011
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

Uwe Heemann¹, Daniel Abramowicz², Goce Spasovski³ and Raymond Vanholder⁴ for the European Renal Best Practice (ERBP) Work Group on kidney transplantation

- Adults: If low density lipoprotein cholesterol (LDL)-C ≥100 mg/dL (≥2.59 mmol/L), treat to reduce LDL-C to <100 mg/dL (<2.59 mmol/L) (based on KDOQI Guideline 4.2);
- Adolescents: If LDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce LDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 5.2).

doi: 10.1093/ndt/gfr169
Advance Access publication 9 May 2011
Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative

Sheldon W. Tobe MD, James A. Stone MD PhD, Melissa Brouwers PhD, Onil Bhattacharyya MD PhD, Kimberly M. Walker BA, Martin Dawes MD PhD, Jacques Genest Jr MD, Steven Grover MD MPA, Gordon Gubitz MD, David Lau MD PhD, Andrew Pipe MD, Peter Selby MBBS, Mark S. Tremblay MD MSc, Darren E.R. Warburton PhD, Richard Ward MD, Vincent Woo MD, Lawrence A. Leiter MD, Peter P. Liu MD

Dyslipidemia

Treatment target is based on the person’s risk level.

- **High risk:** LDL-C < 2.0 mmol/L or 50% in LDL-C; alternate target: apoB < 0.80 g/L.
- **Moderate risk:** LDL-C < 2.0 mmol/L or 50% reduction in LDL-C; alternate target: apoB < 0.80 g/L.
- **Low risk:** if LDL-C ≥ 5.0 mmol/L, reduce LDL-C ≥ 50%; apoB < 0.90 g/L.
Obesity
Obesity is BAD!

1. Obesity is associated with increased morbidity and mortality, esp. Metabolic Syndrome and Diabetes mellitus, in the general population.
2. Obesity is a risk factor for the development of CKD and ESRD.
3. Obesity is a risk factor for CVD, CAD and CHF.
4. Obesity is associated with increased pro-inflammatory cytokines & oxidative stress.

\[
\text{BMI} = \frac{\text{Weight (kg)}}{\text{height (m)}^2}
\]

- <20: Lean (<18.5: Malnourished?)
- 20-25: Healthy ?
- 25-30: Overweight
- 30-35: Obese
- >35: Morbidly obese (>40 if no other risk)
Who will survive longer on dialysis?

Female: 28 y/o
weight 123 lbs
BMI 21 kg/m²
BP 110/65
Cholesterol 141 mg/dL

Female: 26 y/o
weight 241 lbs
BMI 43 kg/m²
BP 165/105
Cholesterol 220 mg/dL
BMI and Death Risk: General Population vs. Hemodialysis Patients

- General Population
- Hemodialysis Patients

Relative Risk of Death

BMI categories (kg/m²)

<18.5 18.5-20.4 20.5-21.9 22-23.4 23.5-24.9 25-26.4 26.5-27.9 28-29.9 30-31.9 32-34.9 35-39.9 ≥40
Aging → Risk Factor Reversal

> 65 years

65-75 years

> 75 years

Obesity-related excess mortality declines with age at all levels of obesity!

Stevens et al, NEJM, 1998
Bender et al. JAMA, 1999
Landi et al, Arch Int Med, 2000
Risk-adjusted five year survival in CHF patients for the BMI categories

Horwich et al, J Am Coll Cardiol 2001;38:789-795

Cumulative Survival

Months

- underweight n=164
- overweight n=168
- recommended weight n=692
- obese n=179
Arnold’s BMI: 37 kg/m² (1995)

<table>
<thead>
<tr>
<th>Actor or Athlete</th>
<th>Height</th>
<th>Weight in lbs. (in 2003)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sylvester Stallone</td>
<td>5'9&quot;</td>
<td>228</td>
<td>34</td>
</tr>
<tr>
<td>Arnold Schwarzenegger</td>
<td>6'2&quot;</td>
<td>257</td>
<td>33</td>
</tr>
<tr>
<td>Sammy Sosa</td>
<td>6'0&quot;</td>
<td>220</td>
<td>30</td>
</tr>
<tr>
<td>Harrison Ford</td>
<td>6'1&quot;</td>
<td>218</td>
<td>29</td>
</tr>
<tr>
<td>George Clooney</td>
<td>5'11&quot;</td>
<td>211</td>
<td>29</td>
</tr>
<tr>
<td>Bruce Willis</td>
<td>6'0&quot;</td>
<td>211</td>
<td>29</td>
</tr>
<tr>
<td>Mike Piazza</td>
<td>6'3&quot;</td>
<td>215</td>
<td>27</td>
</tr>
<tr>
<td>Brad Pitt</td>
<td>6'0&quot;</td>
<td>203</td>
<td>27</td>
</tr>
<tr>
<td>Michael Jordan</td>
<td>6'6&quot;</td>
<td>216</td>
<td>25</td>
</tr>
</tbody>
</table>

From: “Celebrity Height Weight Chart”
Body Mass Index, Waist Circumference and Mortality in Kidney Transplant Recipients

Figure 1: Kaplan–Meier curves of unadjusted (A) and waist circumference-adjusted (B) cumulative incidence of all-cause mortality in kidney transplant recipients grouped according to their body mass index.

C. P. Kovesdy\textsuperscript{a,b,*}, M. E. Czira\textsuperscript{c}, A. Rudas\textsuperscript{c}, A. Ujszaszi\textsuperscript{c}, L. Rosivall\textsuperscript{d}, M. Novak\textsuperscript{c,e}, K. Kalantar-Zadeh\textsuperscript{f}, M. Z. Molnar\textsuperscript{c,d,f} and I. Mucsi\textsuperscript{c,d,g}
Body Mass Index, Waist Circumference and Mortality in Kidney Transplant Recipients

Figure 2: Kaplan–Meier curves of unadjusted (A) and body mass index-adjusted (B) cumulative incidence of all-cause mortality in kidney transplant recipients grouped according to their waist circumference. Median waist circumference was 103 cm in males and 93 cm in females.

C. P. Kovesdy\textsuperscript{a,b,*}, M. E. Czira\textsuperscript{c}, A. Rudas\textsuperscript{c}, A. Ujszaszi\textsuperscript{c}, L. Rosivall\textsuperscript{d}, M. Novak\textsuperscript{c,e}, K. Kalantar-Zadeh\textsuperscript{f}, M. Z. Molnar\textsuperscript{c,d,f} and I. Mucsi\textsuperscript{c,d,g}

American Journal of Transplantation 2010; 10: 2644–2651
Associations of Pretransplant Weight and Muscle Mass with Mortality in Renal Transplant Recipients


CJASN ePress. Published on March 17, 2011
Adipocytokines → modulation of inflammation

- TNF-α
- IL-6
- Leptin
- Resistin

Bad Cytokines

Inflammation

Adiponectin

Good Cytokines

IL-10

?
Why is there an Obesity Paradox?

<table>
<thead>
<tr>
<th>Kidney Disease Wasting (Malnutrition-inflammation-complex syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time discrepancy between competitive risk factors: overnutrition vs. undernutrition</td>
</tr>
<tr>
<td>Unusual genetic constellation due to survival selection during CKD progression</td>
</tr>
<tr>
<td>Sequestration/storage of uremic toxins in fat tissue</td>
</tr>
<tr>
<td>Anti-inflammatory cytokines related to body mass, including adiponectins</td>
</tr>
<tr>
<td>Tumor necrosis factor alpha receptors</td>
</tr>
<tr>
<td>Endotoxin-lipoprotein hypothesis</td>
</tr>
<tr>
<td>Stability of hemodynamic status in obese patients</td>
</tr>
<tr>
<td>Neurohormonal alterations in obesity</td>
</tr>
<tr>
<td>Alteration of conventional risk factors in uremic milieu (“beyond Framingham”)</td>
</tr>
<tr>
<td>Reverse causation</td>
</tr>
<tr>
<td>Survival bias</td>
</tr>
<tr>
<td>Advantages of obesity in the history of man kind (the Ultimate Hypothesis)</td>
</tr>
</tbody>
</table>

Kalantar-Zadeh & Kopple, Contrib Nephrol 2006
16.4: OBESITY

16.4.1: Assess obesity at each visit. *(Not Graded)*
- Measure height and weight at each visit, in adults and children.
- Calculate BMI at each visit.
- Measure waist circumference when weight and physical appearance suggest obesity, but BMI is <35 kg/m².

16.4.2: Offer a weight-reduction program to all obese KTRs. *(Not Graded)*
FGF23 in kidney transplant recipients
FGF-23

- Identified in 2000 as the responsible gene for ADHR
- Circulating glycosylated peptide, 32 kD, 251 amino acids
- Belongs to the FGF family of 22 peptides
- Main site of expression: osteocytes, osteoblasts, brain, parathyroid gland, thymus, liver
Clinical Spectrum Of Disordered Phosphate Homeostasis and Mineralization

FGF23 Excess
- Hereditary/Acquired Hypophosphatemic Rickets
- FGF23 administration to mice.
- FG23 overexpressing mouse models.
  - Hyp mice
  - Dmp1 null mice
  - FGF23 transgenic mice

FGF23 Deficiency
- Hereditary Tumoral Calcinosis
- FGF23 deficient mouse models

Phenotypes
- Low serum phosphate
- Aberrant vitamin D metabolism
- Rickets/Osteomalacia
- Hyperphosphatemia
- Elevated 1,25(OH)2D production
- Soft tissue calcifications
- Hyperosteoisis
Effect of FGF23 on renal PO4 transport

Relative levels of mRNA encoding renal Pi transporters in wild type and FGF23 overexpressing transgenic mice.

Increases urinary phosphate excretion

<table>
<thead>
<tr>
<th></th>
<th>Male (wild-type)</th>
<th>Male (FGF-23 transgenic)</th>
<th>Female (wild-type)</th>
<th>Female (FGF-23 transgenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pi (mM)</strong></td>
<td>2.75 ± 0.22</td>
<td>1.91 ± 0.27a</td>
<td>2.16 ± 0.15</td>
<td>1.19 ± 0.11a</td>
</tr>
<tr>
<td><strong>FEI(Pi)</strong></td>
<td>14.5 ± 2.5</td>
<td>34.8 ± 7.6a</td>
<td>14.0 ± 3.8</td>
<td>72.3 ± 31b</td>
</tr>
</tbody>
</table>

Endocrinology, July 2004, 145(7):3087–3094
CONTROL OF FGF23 LEVELS

Chronic dietary phosphate and serum phosphate concentration

Ferrari 2005
JCEM 90, 1519.

Serum calcitriol concentration

Burnett 2006
JBMR 21, 1187.

Liu 2006 JASN 17,1305
PTH increases FGF23 gene expression and mediates the high-FGF23 levels of experimental kidney failure: a bone parathyroid feedback loop

Vardit Lavi-Moshayoff, Gilad Wasserman, Tomer Meir, Justin Silver and Tally Naveh-Many

Sites and regulation of FGF23 expression

Systemic Factors
- ↑ 1,25(OH)$_2$D$_3$
- ↑ PO$_4^{2-}$
- ↑ PTH

Local Factors
- ↓ DMP-1
- ↑ MEPE
- ↓ PHEX

FGF23 receptors and Co-factors
- Pro-protein convertase
- Inactive FGF23 fragments

Possible target organs
- Parathyroid glands
- Kidney
- Pituitary & choroid plexus
- Other

Bone - osteocytes
- Brain
- Lymph node
- Thymus
- Bone Marrow

FGF23

Klotho independent effects?
Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Elevated:
- PTH
- Phosphorus

Decreased:
- 25(OH)D
- Calcitriol
- Calcium

- Coronary calcification
- Aortic calcification
- Calciphylaxis

- Abnormal bone histology
  - Mineralization
  - Turnover
  - Volume

- Decreased bone mineral density

FGF-23

KDIGO = Kidney Disease: Improving Global Outcomes.
KDIGO® is a registered trademark of Kidney Disease: Improving Global Outcomes, Inc.

KDIGO® Overview slide presentation at: http://www.kdigo.org/pdf/KDIGO%20Overview%20Slide%20Set.ppt
Temporal aspects of disordered mineral metabolism in CKD

1. Increased FGF-23 is the earliest alteration in mineral metabolism in CKD.
2. Gradually increasing FGF-23 levels cause early decline in 1,25D levels.
3. This frees PTH from feedback inhibition, leading to SHPT.
4. All these changes occur long before increases in serum P levels are evident.

GFR (mL/min/1.73 m²) vs. Time post-transplant (months)

- cFGF-23 (RU/mL)
- 1,25D (pg/mL)
- PTH (pg/mL)
- P (mg/dL)

Normal PTH range
Normal P range

Dialysis

cFGF-23, C-terminal Fibroblast Growth Factor-23
Tertiary ‘Hyperphosphatonism’ Accentuates Hypophosphatemia and Suppresses Calcitriol Levels in Renal Transplant Recipients

P. Evenepoel*, M. Naesens, K. Claes, D. Kuypers and Y. Vanrenterghem

FGF23 Actions and Feedback Loops

Collateral Damage
- CKD progression
- Left ventricular hypertrophy
- Endothelial dysfunction
- Vascular stiffness
- Death

Malnutrition and Inflammation in Transplant – Hungary (MINIT-HU) study

Prospective cohort study to assess the association between PEW, post-transplant anemia, energy and bone metabolism; to assess the association of these factors with clinical outcomes

- Malnutrition-Inflammation in Transplant (MINIT-HU) study: 993 stable prevalent kidney transplant recipients followed at the Semmelweis University, Budapest
- Baseline clinical and laboratory assessment 2007 February – August and annual follow-up visits x3
- Cytokines, adipokines, bone markers and FGF23 was determined from frozen sera
- Participants underwent prospective follow-up until they died, returned to dialysis
- Outcomes assessed were all-cause mortality or graft loss necessitating return to dialysis
Elevated Fibroblast Growth Factor 23 is a Risk Factor for Kidney Transplant Loss and Mortality

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![Graph showing cumulative incidence and mortality over analysis time.](image-url)
FGF23 Tertiles & Risk of Allograft Loss

Cumulative Incidence, Allograft Loss (%)

Analysis time (years)

Outcomes – potential mechanisms
### FGF23 and Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Model</th>
<th>Increase in mean LVMI (95% CI) per 1-SD increase in Log FGF-23, %</th>
<th>p</th>
<th>OR (95% CI) of LVH pr 1-SD increase in Log FGF-23</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted model</strong></td>
<td>12 (4-18)</td>
<td>&lt;0.001</td>
<td>2.0 (1.2-3.4)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Multivariable-adjusted model</strong>*</td>
<td>11 (3-18)</td>
<td>0.01</td>
<td>2.3 (1.2-4.2)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Plus active vitamin D use</strong></td>
<td>11 (4-18)</td>
<td>0.005</td>
<td>2.2 (1.2-4.3)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Plus phosphorus binder use</strong></td>
<td>11 (4-18)</td>
<td>0.003</td>
<td>2.2 (1.2-4.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race, BMI, eGFR, diabetes, hypertension, and serum phosphate

LVH=left ventricular hypertrophy; LVMI=left ventricular mass index

FGF23 induces left ventricular hypertrophy


FGF23 and FGF2 use different signaling pathways to induce hypertrophy of NRVMs.

Klotho-deficient and klotho heterozygous mice develop LVH
Proposed mechanism of FGF23 induced LVH

Multidisciplinary care
An important issue for long term patient outcomes is to reduce ISU toxicity and to manage CV disease.

**Before Tx:**
- Dialysis vintage
- CV management
- CV interventions

**After Tx: medical management**
- DM
- Dyslipidaemia
- Obesity
- Smoking
- Inflammation
- Anemia
- Bone
- ...
CAD treatment gap in the community

Provider awareness does not equal successful implementation

NCEP = National Cholesterol Education Program

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
Multidisciplinary care

- Education program
- Protocollized clinic f/u
- Protocollized lab
- Regular audits/CQI

- Nephrologist
- Nurse practitioner
- Social worker/psychologist
- Dietician
- Pharmacist
- Physiotherapist
Summary and conclusion

• Multiple metabolic derangements are prevalent in KTx patients and they are associated with increased mortality/CV events
• Screening for impaired glucose and lipid metabolism using OGT is necessary
• Lifestyle modifications and statins are likely to improve outcomes
• The association between obesity and cardiovascular outcomes among kidney transplant recipients is controversial; however, physical activity, healthy diet are advisable to maintain a close to ideal body composition
• Tailoring immunosuppression to the metabolic characteristics of the individual patient is a potential consideration
• Multidisciplinary “risk management clinics” may be necessary to target all these metabolic problems among kidney transplant recipients to improve patient outcomes