Nutritional management in chronic kidney diseases and after transplantation

Bengt Lindholm
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Karolinska University Hospital, Stockholm, Sweden
Chronic kidney disease stages 1-5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Classification by Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with normal or ↑ GFR</td>
<td>≥ 90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with mild ↓ GFR</td>
<td>60-89</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>T if kidney transplant recipient</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>D if dialysis (HD, PD)</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
<td></td>
</tr>
</tbody>
</table>

Related Terms:
- Albuminuria
- Proteinuria
- Hematuria

Chronic renal failure, Early renal insufficiency

Chronic renal failure, Advanced renal insufficiency, Pre-ESRD

Renal failure, Uremia, ESRD

Abbreviations: GFR, glomerular filtration rate; ESRD, end-stage renal disease. Related terms for CKD Stages 3-5 do not have specific definitions, except ESRD.
Nutritional challenges in CKD

• The kidneys play a key role in maintaining fluid and electrolyte homeostasis, excretion of metabolic waste products, and regulation of various hormonal and metabolic pathways.

• Patients with chronic kidney disease (CKD) therefore display a variety of metabolic and nutritional abnormalities
Nutritional management in CKD is not easy: there will never be a silver bullet.
The internist knows everything but doesn´t do anything

The surgeon does everything but doesn´t know anything

The nephrologist knows everything and does everything - but too late!!
<table>
<thead>
<tr>
<th>Function of Kidney</th>
<th>Metabolic effect of Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excretion:</strong></td>
<td></td>
</tr>
<tr>
<td>Waste, fluid, excess minerals, metabolites</td>
<td>Accumulation:</td>
</tr>
<tr>
<td></td>
<td>Fluid, waste products (uremic toxins) eg urea, and minerals eg K⁺</td>
</tr>
<tr>
<td><strong>Regulation:</strong></td>
<td></td>
</tr>
<tr>
<td>Maintain homeostasis - fluid, acid- base &amp; electrolytes balance</td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td>Disturbed BP controlled/Uncontrolled HT</td>
</tr>
<tr>
<td></td>
<td>Lipid abnormality</td>
</tr>
<tr>
<td><strong>Endocrine:</strong></td>
<td></td>
</tr>
<tr>
<td>Vitamin D/Ca²⁺ Phosphate Metabolism</td>
<td>Renal bone disease-Osteodystrophy</td>
</tr>
<tr>
<td>Hb Synthesis/Erythropoietin</td>
<td>Anaemia</td>
</tr>
</tbody>
</table>

Slide courtesy of Maria Chan, Sydney, Australia
Accumulation of Na, P, K, H+ and H₂O

- Metabolic acidosis is a major factor for net protein catabolism due to protein breakdown and subsequent muscle wasting via stimulation of the ATP-ubiquitin-proteasome pathway.
- Correction of metabolic acidosis improves nitrogen balance.
- Metabolic acidosis - and in general accumulation of Na, P, K, H⁺ and H₂O - should always be monitored and corrected in CKD patients!
- In renal transplant patients, often need to supply P
Lipid disorders in CKD:
Hypertriglyceridemia, often normal cholesterol but low HDL cholesterol

Therapeutic lifestyle changes

- Reduced intake of saturated fat
- Increased physical activity
- Weight control

But beware of malnutrition!!!
Carbohydrate metabolism is a major issue in CKD

- Insulin resistance
- Glucose intolerance
- Metabolic syndrome
- Overt diabetes mellitus

*Plus: Diabetes is the most common cause of CKD*
Glucose intolerance/Insulin resistance
Hypertension
Atherogenic dyslipidemia
Proinflammatory/Prothrombotic state
Obesity

However, some of these risk factors may paradoxically be associated with improved survival in ESRD patients
Causes and consequences of insulin resistance in CKD

<table>
<thead>
<tr>
<th>Causes</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insulin secretion abnormalities</td>
<td>• Dyslipidemia</td>
</tr>
<tr>
<td>• Hyperparathyroidism</td>
<td>• Sodium retention</td>
</tr>
<tr>
<td>• Vitamin D deficiency</td>
<td>• Vascular calcification</td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td>• Muscle wasting</td>
</tr>
<tr>
<td>• Uremic toxins</td>
<td>• Hyperuricemia</td>
</tr>
<tr>
<td>• Anemia</td>
<td>• Renin activation</td>
</tr>
<tr>
<td>• Metabolic acidosis</td>
<td>• Ultimately hypertension and cardiovascular disease</td>
</tr>
<tr>
<td>• Inflammation</td>
<td></td>
</tr>
<tr>
<td>• Oxidative stress</td>
<td></td>
</tr>
<tr>
<td>• Muscle Loss</td>
<td></td>
</tr>
<tr>
<td>• Fructose</td>
<td></td>
</tr>
<tr>
<td>• Increased fat mass</td>
<td></td>
</tr>
<tr>
<td>• Physical inactivity</td>
<td></td>
</tr>
</tbody>
</table>

Treatment targeting

• Hyperparathyroidism
• Vit D deficiency
• ACEIs/ARBs?
• Glitazones?
• Metabolic acidosis
• Carbohydrate imbalance
• Uremia
Endocrine and hormonal alterations in CKD: Nutritional consequences

• Insulin resistance – Muscle wasting
• Erythropoetin deficiency - Anemia
• GH and IGF-1 resistance- Muscle wasting
• Testosterone deficiency – Muscle wasting
• Low thyroid hormones- ?
• Vitamin D deficiency- Bone disease etc
• Hyperparathyroidism- Bone disease
GH/IGF-1 axis in Chronic Kidney Disease

- CKD is a state of GH resistance because of:
  - Reduced IGF-1 synthesis
  - Reduced IGF-1 bioavailability, due to:
    - Impaired renal clearance and increased synthesis of IGFBP
  - Reduced IGF-1 receptor synthesis in the muscle

- As a result, HG/IGF-1 resistance in CKD contributes to sarcopenia

References:
- Powell et al. Endocrinology 1997; 138:938-946
- Sun et al. JASN 2004;15:2630-2646

Slide courtesy of Juan Jesus Carrero
CKD, a nonthyroideal illness

- TSH usually normal
- T4 normal or slightly low
- T3 usually low: Low T3 syndrome

Metabolic acidosis

Inflammation

↑ Iodine
As many as 50-70% of CKD stage-5 men have been reported to be hypogonadal.

Out of 260 male Swedish ESRD patients, 44% suffered from hypogonadism. Only 23% had normal testosterone levels.

Carrero et al. Nephrol Dial Transplant. 2010
Abnormally low testosterone values increase mortality risk in male dialysis patients.
Malnutrition in CKD - is often preventable

Screening by:
- Doctor
- Nurse
- Nutrition assistant

OR

Routine monitoring by dietitian

Identify patients at risk

Assessment & diagnosis

Intervention

Prevention and Early Intervention

Slide courtesy of Maria Chan, Sydney, Australia
Evaluation of Malnutrition/Wasting:
No single marker is enough

**Clinical**
- Weight loss
- Anorexia
- Fatigue
- Muscle wasting
- SGA

**Anthropometrics**
- BMI
- Skinfolds
- Midarm circumference
- Handgrip strength
- Waist circumference

**Biochemical markers**
- S-albumin
- Prealbumin
- IGF-1, IGFBP-1
- S-creat, S-chol
- nPNA

**More advanced**
- Bioimpedance
- DEXA
- Total body K or N
- CT or MR
Robust clinical nutritional indices in CKD

- Subjective global assessment of nutritional status (SGA)
- Appetite scoring (at SGA)
- Presence of muscle wasting (at SGA)
- Handgrip strength
- Biomarkers such as CRP and IL-6 add some information whereas serum albumin is a poor indicator of nutritional status.
S-alb is not a good marker of malnutrition

- Correlates well with poor prognosis.
- Correlates poorly with other markers of nutrition.
- Serum albumin is a negative acute phase reactant.
- Fluid overload, urinary losses and dialysate losses also result in hypoalbuminemia.

\[
R = -0.51 
\text{p}<0.0001
\]

<table>
<thead>
<tr>
<th>U-albumin (mg/24h)</th>
<th>F-ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-albumin</td>
<td>84,8</td>
<td>0.0001</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>19,9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>3,7</td>
<td>0.06</td>
</tr>
<tr>
<td>SGA</td>
<td>0,2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Slide courtesy of Peter Stenvinkel
Serum albumin is *not* a good nutritional marker

Serum albumin level was not related to Hand grip strength

Serum albumin level was not related to lean body mass (DEXA)

Serum albumin level was related to urinary albumin loss

115 incident ESRD pts (69 men, 46 women). Age 52 +/- 12 years. PEW 48%.

NECOSAD: 700 incident dialysis patients starting HD or PD at 38 dialysis centers in The Netherlands. Mean age, 59 [+/15] years; serum albumin, 3.3 (0.7) g/dL; 60% men; 454 starting HD, and 246 starting PD.
The decision by nephrologists, renal dietitians, federal agencies, health care payers, large dialysis organizations, and the research community to embrace serum albumin as an important index of nutrition and clinical performance is based on numerous misconceptions.

Patients with analbuminemia are not malnourished and individuals with simple malnutrition are rarely hypoalbuminemic. Furthermore, nutritional supplementation has not been clearly shown to raise levels of serum albumin.

**Serum albumin is an unreliable marker of nutritional status in CKD.**
Serum albumin in CKD patients: Why measure it?

- Surrogate marker of inflammation? Yes
- Reveals well-being of the patient? Probably
- Predicts mortality? Yes
- Predicts nutritional status? No
Protein-energy wasting is common in CKD, HD and PD patients

- 14406 HD pats (DOPPS) - Lopes et al. 2007
- 223 HD pats - Carrero et al. 2007
- 34 HD pats - Muscaritoli et al. 2007
- 1846 HD pats (HEMO) - Burrowes et al. 2005
- 331 HD pats - Kalantar-Zadeh et al. 2004
- 307 HD pats - Curtin et al. 2002
- 73 HD pats - Virga et al. 1998
- 106 PD pats - Merkus et al. 1999
- 66 CKD 5 predialysis pats - Murtagh et al. 2007
- 238 CKD 5 predialysis pats - Curtis et al. 2002

35-60%

Courtesy of Juan Jesus Carrero
Spontaneous decrease of dietary protein intake

Protein and energy intakes decrease as appetite decreases during the course of CKD progression.

GFR less than 10-25% of normal

Retention of appetite depressants?

Increased dialysis dose improves feeding behavior


Courtesy of Juan Jesus Carrero
Accumulation of Anorectic Factors in Uremia

Aguilera et al Sem Dial 17: 44-52, 2004

**Anorexigens**
- CCK
- Leptin
- CRF
- NO deficiency
- Insulin
- Glucagon
- C-peptide
- TNF-α
- IL-1
- GIP
- PYY
- FTRP

**Orexigens**
- NPY
  - NPY negative correlation to TNF-α in PD pts (Aguilera et al NDT 1998)
- Ghrelin
  - Ghrelin is reduced by 3.86% glucose solution (Perez-Fontan M, et al. KI 2005)

PD (and inflammation) may accentuate this imbalance
Appetite stimulants?

**Megestrol acetate** improves the nutritional and inflammatory status, as well as anorexia in maintenance dialysis patients


**Nandrolone decanoate** (alone or in combination with resistance exercise training) has anabolic effects in CKD patients.


**Testosterone** in aged healthy men improve lean body mass and nutritional status in two recent randomized controlled trials.

Future approaches

Subcutaneous Ghrelin Enhances Acute Food Intake in Malnourished Patients Who Receive Maintenance Peritoneal Dialysis: A Randomized, Placebo-Controlled Trial

Katie Wynne,* Kalli Giannitsopoulou,* Caroline J. Small,* Michael Patterson,* Gary Frost,* Mohammad A. Ghaedi,* Edwina A. Brown,† Stephen R. Bloom,* and Peter Choi‡

*Department of Metabolic Medicine, Faculty of Medicine, Imperial College London, Hammersmith Hospital; and †Directorate of Renal and Transplant Medicine, Hammersmith Hospitals NHS Trust, Charing Cross Hospital, London, United Kingdom

9 PD patients with mild malnutrition.

Energy intake increased during a single meal test after administration of ghrelin (3.6 nmol/Kg) vs saline placebo

Sustained appetite improvement in malnourished dialysis patients by daily ghrelin treatment

Damien R. Ashby\textsuperscript{1,2}, Heather E. Ford\textsuperscript{1}, Katie J. Wynne\textsuperscript{1}, Alison M. Wren\textsuperscript{1}, Kevin G. Murphy\textsuperscript{1}, Mark Busbridge\textsuperscript{1}, Edwina A. Brown\textsuperscript{2}, David H. Taube\textsuperscript{2}, Mohammad A. G hatei\textsuperscript{1}, Frederick W.K. Tam\textsuperscript{2}, Stephen R. Bloom\textsuperscript{1} and Peter Choi\textsuperscript{2}

\textsuperscript{1}Department of Investigative Medicine, Imperial College London, London, UK and \textsuperscript{2}West London Renal and Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

RCT in 12 malnourished (PD and HD) patients

1-week intervention with subcutaneous ghrelin increased energy intake by 20%

Figure 2 | Energy intake with saline compared with ghrelin. (a) Study meals at the start of saline and ghrelin weeks showing an increase in energy intake after the first injection (individual values and mean \pm s.e., \(P<0.001\)); (b) study meals at the end of saline and ghrelin weeks showing persistence of the increase in energy intake \((P<0.001)\); and (c) food diaries during both weeks showing a consistent effect throughout the diurnal period (mean \pm s.e., \(P=0.040\)). *\(P<0.05\); **\(P<0.01\).

Recommended protein intake in non-dialyzed CKD *g/kg/day*

**ESPEN**

*GFR 25–70 ml/min*
- 0.55–0.60 (2/3 HBV)

*GFR < 25 ml/min*
- 0.55–0.60 (2/3 HVB)
  - or
- 0.28 +EAA or EAA +KA\(^a\)

**NKF**

*GFR 25–70 ml/min*
- N/A

*GFR < 25 ml/min*
- 0.60 or 0.75
  - (intolerance or inadequate energy intake)

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ESPEN, European Society for Clinical Nutrition and Metabolism; NKF, National Kidney Foundation; EAA, essential amino acids; GFR, glomerular filtration rate; HBV, high biological value; KA, ketoanalogues.

\(^a\) As EAA are not often used, very low protein diets are most often 0.3–0.4 g protein/kg/day + KA

### Restricted mineral intake in patients with CKD

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Daily Intake (mg/day) or (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>600–1000 mg/d&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>K</td>
<td>1.5–2.0 g/d&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Na</td>
<td>1.8–2.5 g/d&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluid</td>
<td>Not limited&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Depending on physical activity, lean body mass, age, gender, degree of malnutrition.

<sup>b</sup> Individual requirements can differ considerably.

Nutrition Support in CKD

**Functional GIT**

- **Enteral Nutrition (EN)**
  - Tube feeding (TF)
  - Oral (+edn & counseling):
    - Food fortification
    - Oral nutrition supplementations (ONS)

---

**Total Parenteral Nutrition (TPN)**

**Intradialytic PN (IDPN)**

**Intra-Peritoneal Nutrition**

---

**First Line**

**Psychosocial support**

---

**Multi-disciplinary Approach**

- **Dietitian**
  - Structured Care/Management plan

- **MD**
  - Control co-morbidities/inflammation
  - Medications/Appetite stimulants

- **Nursing**

- **Exercise training**

---

Slide courtesy of Maria Chan
# Oral Nutrition Support

<table>
<thead>
<tr>
<th>Diet Counseling (+ prescription &amp; meal plan)</th>
<th>(1) Food</th>
<th>±</th>
<th>(2) Food enriching/fortifications</th>
<th>±</th>
<th>(3) Oral Nutrition Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic/strategy</strong></td>
<td>• Use energy &amp; nutrient dense foods &amp; drinks</td>
<td></td>
<td>• adding protein, fat &amp; CHO to foods and drinks, e.g. egg, cheese, milk, milk powder sugars, fats</td>
<td></td>
<td>• Ready-made formula &amp; desserts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±</td>
<td>• commercial modules e.g. protein powder, tasteless sugars</td>
<td></td>
<td>• protein &amp; energy bar</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td>• economical</td>
<td></td>
<td>• economical</td>
<td></td>
<td>• easy to use</td>
</tr>
<tr>
<td></td>
<td>• familiar items:</td>
<td></td>
<td>• familiar items:</td>
<td></td>
<td>• convenient</td>
</tr>
<tr>
<td></td>
<td>• taste</td>
<td></td>
<td>• taste</td>
<td></td>
<td>• easy handling (in institutions) staff and hygiene</td>
</tr>
<tr>
<td></td>
<td>• texture</td>
<td></td>
<td>• texture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cultural specific</td>
<td></td>
<td>• cultural specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limitation</strong></td>
<td>“larger” volume</td>
<td></td>
<td>“larger” volume</td>
<td></td>
<td>• cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• acceptance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• taste</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• possible intolerance</td>
</tr>
</tbody>
</table>

Slide courtesy of Maria Chan, Sydney, Australia
Which parenteral nutrition (PN) formulae should be used in CKD patients?

- Because no data are available on specific PN formulae, standard PN mixtures should be used if PN is indicated (C).
- In patients receiving PN without any oral or enteral supply, vitamins and trace elements should also be administered intravenously (C).
- If the patients need PN for a period exceeding two weeks, accumulation of vitamin A and trace elements should be considered (C).
Uremic symptoms diminish or disappear (especially nausea, vomiting)
Reduce the burden of uremic toxins (urea, H+, K+, phosphate, other)
Slow progression of renal failure?
Reduce proteinuria
Improve nutritional status (supplemented with EAA or EAA/KAA)
Increases insulin sensitivity and glucose tolerance
Antioxidant effect
Keto Acid/Amino Acid-Supplemented Protein- Restricted Diets

**Protein restriction** 0.3/0.4 to 0.6 g protein/kg body weight/ day, depending on stage of CKD (i.e., stages 3 to 5);

**Keto acid/amino acid supplementation** 10-15-20 tablets (0.1 g/kg body weight/day);

**Energy** 30 - 35 kcal/kg body weight/day;

**Phosphate** 5 - 7 mg/kg body weight/day; <800 mg/day;

**Sodium** at <2 g/day

**Vitamins and trace elements** (e.g., iron).

Multiple Causes of Malnutrition/Wasting in CKD

<table>
<thead>
<tr>
<th>Renal disease per se</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual renal function</td>
</tr>
<tr>
<td>Uremic toxins</td>
</tr>
<tr>
<td>Endocrine abnormalities</td>
</tr>
<tr>
<td>Amino acid abnormalities</td>
</tr>
<tr>
<td>Acidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake</td>
</tr>
<tr>
<td>Energy intake</td>
</tr>
<tr>
<td>Vitamin intake</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/Inflammation</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Vascular disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Other comorbidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Genetics</td>
</tr>
<tr>
<td>Drugs (corticosteroids)</td>
</tr>
<tr>
<td>Social factors</td>
</tr>
<tr>
<td>Protein assimilation</td>
</tr>
</tbody>
</table>

Dialysis related

- Nutrient losses: Protein/AA
- Infections:
- Glucose load: good and bad
- Bioincompatibility?

Courtesy of Peter Stenvinkel
Malnutrition (undernutrition), low nutrient intake

Production & Clearance of inflammatory cytokines

Anorexia, acidosis, anemia

Volume overload

Nutrient loss during dialysis

Dialysis Rx related factors, AV graft, dialysis membrane

Co-morbid conditions: DM, CVD, infection, aging

Endocrine disorders, vitamin D deficiency, ↑PTH, ↓insulin/IGF signaling

Oxidative & carbonyl stress

↓nutrient intake, prescribed dietary restrictions

↓nutrient intake, prescribed dietary restrictions

Kidney Disease Wasting

Malnutrition (undernutrition), low nutrient intake

Uremic toxins

Protein-Energy Wasting (PEW)

Hypercatabolism

Inflammation

↓Albumin, transthyretin & Lipids, ↑CRP

↓weight, ↓BMI, ↓body fat, sarcopenia

Survival paradoxes

Atherosclerotic cardiovascular disease, vascular calcification

↑Mortality, ↑hospitalization, ↓quality of life

I. Evaluate and treat intercurrent events and co-morbidities that may cause inflammation

- Infectious complications and intercurrent clinical events
- Silent ischemic heart disease
- Periodontal disease

- Failed kidney transplant
- Volume overload
- Inflammatory diseases

II. Evaluate and if possible handle potential dialysis related causes of inflammation

**Hemodialysis**
- Central dialysis catheter
- Unpure dialysate
- Infectious complications of hemodialysis access
- Thrombosed fistula or graft
- Bioincompatible membranes
- Hemodiafiltration
- Volume overload

**Peritoneal dialysis**
- Bioincompatible dialysis fluids
- Peritonitis
- Exit-site infection
- Volume overload
- Glucose degradation products

III. Consider possible anti-inflammatory treatment strategies

- Physical training
- Nutritional interventions
  - Omega-3 fatty acids
  - Gamma tocopherol
  - Soy isoflavones
  - Genistein
  - Green tea

- Non-specific immunomodulation
  - Statins
  - D-vitamin
  - ACEI/ARBs
  - Pentoxifylline
  - Heparin (?)

- Future treatment with anti-cytokine therapy
  - IL-1 receptor antagonists
  - Soluble TNF receptors
  - Antibodies against TNF
  - Chemokine antagonism

Slide courtesy of Peter Stenvinkel
Post-transplant Health Issues

• Transplantation:
  – Corrects: uraemia & side effects of dialysis
  – Induces: new problems, esp. side effects of immunosuppressive medications

• Health issues:
  – Acute and chronic phases
  – Short and/or long term

• In the literature:
  – Increase in body weight of 10%-35%
  – High cholesterol in 30-60%
  – High triglycerides 20-35%
  – Up to 20% develop diabetes
  – Hypertension
  – Decrease in bone mineral density in 60%

Slide courtesy of Maria Chan, Sydney, Australia
Effects of immunosuppression

• Transplant recipients are required - by necessity - to receive immunosuppression, which further exacerbates the metabolic syndrome.

• Calcineurin inhibitors (mainly cyclosporine and tacrolimus), sirolimus, and glucocorticoids all contribute to further metabolic derangements complicating the previous uremic state and the metabolic milieu of liver and cardiac failure.
Protein-energy wasting in renal transplant patients

• Up to 15% of renal transplant recipients may display signs of malnutrition\(^a\).

• Protein-calorie malnutrition often occur in the early postoperative weeks when glucocorticoid doses are highest and the protein catabolic rate (PCR) is accelerated due to surgery or rejection.

\(^a\) Sezer S, et al Transplant Proc 38:517-520, 2002
Protein Requirements

Background:
• It changes from early to chronic transplant phase:
  – Early: higher protein catabolic rate according to glucocorticoids doses
  – Later: chronic allograft nephropathy/rejection, excess protein intake is undesirable

Guidelines:
• No recommendations possible based on Level I or II evidence.

Suggestions for clinical care:
• Immediate post-transplant period: 1.3-1.5g/kg/d:
  – may reverse negative nitrogen balance
  – May ↑ muscle mass
• Chronic: restricting dietary protein may be beneficial with respect to kidney function. Magnitude of the benefit and a safe level is to be identified:
  – 0.75 g/kg body weight for females
  – 0.84 g/kg body weight for males

RDI levels as per general population

Slide courtesy of Maria Chan, Sydney, Australia
Diet control in kidney transplantation

**Early phase**
- Energy 30–35 kcal/kg
- Protein 1.3–2.0 g/day
- NaCl 6.0–7.0 g/day

**Late phase**
- Energy 35 kcal/kg
- Protein 0.8–1.0 g/day
- NaCl 6.0–7.0 g/day

Renal transplantation and metabolic syndrome

• During the pretransplant period, CKD patients often display features of the metabolic syndrome.

• The proatherogenic environment in uremia combined with steroids and immunosuppressive drugs amplify many metabolic syndrome components.

• Also, CKD patients have pre-existing co-morbidities such as ischemic heart disease, diabetes mellitus, and obesity and display features of the metabolic syndrome which also carry over into the posttransplant period.
Metabolic Syndrome After Kidney Transplantation

- Avoid body weight increase the first years after transplantation,
- Low-protein diet to keep hyperfiltration under observation,
- Low-lipid, low-calorie diet,
- Exercise daily,
- Control inflammation,
- Reduce insulin resistance

Posttransplant diabetes mellitus (PTDM) is common

• 15% to 20% of solid organ transplant recipients.
• Influenced by the choice of immunosuppressive
• Glucocorticoids, cyclosporine, and tacrolimus may contribute to the onset of PTDM.
• Conversion from tacrolimus to cyclosporine may improve PTDM.
• Steroids clearly increase hepatic gluconeogenesis and aggravate insulin resistance by contributing to increased fat mass.

Ward HJ: J Renal Nutrition 19: 111–122, 2009:
Diabetes Mellitus

Background:
• ~ 20% developed new-onset diabetes after transplantation (NODAT) one year post transplantation.
• life-long problem and not a temporary aberration driven by high dose of steroid exposure in the acute phase
• key modifiable risk factors: (1) Obesity (2) Choice of immunosuppressive regimen

Guidelines:
• No recommendations possible based on Level I or II evidence

Suggestions for clinical care:
• Priority- weight management strategies to reduce the risk
• Dietary guidelines/ healthy eating ± the management of type 2 diabetes as per the general population

Slide courtesy of Maria Chan, Sydney, Australia
Dyslipidaemia

Background:
• ~ 60% developed dyslipidaemia
• positive association between cholesterol and atherosclerotic cardiovascular disease.

Guidelines: No recommendations possible based on Level I or II evidence

Suggestions for clinical care:
• Patients with elevated serum total cholesterol, LDL-cholesterol and triglycerides, encouraged a diet rich in:
  – wholegrain
  – low glycaemic index
  – high fibre carbohydrates
  – vitamin E
  – monounsaturated fat
• Healthy eating / weight control as per general population

Slide courtesy of Maria Chan, Sydney, Australia
Dyslipidemia

• Elevated total and LDL cholesterol (about 60%) and hypertriglyceridemia (35%).
• Glucocorticoids and calcineurin inhibitors, especially cyclosporine, can worsen the lipid profile.
• Sirolimus is probably the most potent immunosuppressive drug in its ability to aggravate dyslipidemia.
• **Management**: Dietary intervention, HMG-CoA reductase inhibitors (statins), and careful, but more rapid, tapering of steroids
Overweight/Obesity:

**Background:**
- Weight gain is common
- Is associated with serious health complications:
  - steroid induced diabetes
  - cardiovascular disease risk factors
  - poor graft function and graft survival

**Guidelines:**
- No recommendations possible based on Level I or II evidence

**Suggestions for clinical care:**
- referral to a dietitian as soon as practicable after transplantation, for written and verbal advice for preventing weight gain
- regular follow-up until the desired weight loss is achieved

Slide courtesy of Maria Chan, Sydney, Australia
Hypophosphataemia

Background:
• Early phase (up to ~ 93% in 4/12) & long-term
  – Cause: Urinary loss, tubular dysfunction and persistent hyperparathyroidism
  – Exacerbated by immunosuppressive medications
• Complications at various phases and severity e.g.:
  – bone disorders osteomalacia (early) and osteodystrophy (later)
  – Muscle weakness

Guidelines: No recommendations possible based on Level I or II evidence

Suggestions for clinical care:
• Encouraged phosphorous rich diet once graft functions well
• Physicians beware:
  – PO$_4$ supplementation has the potential to worsen hyperparathyroidism
  – To consider PO$_4$ supplementation if hypophosphataemia persists despite adequate dietary intake
  – dose of replacement unclear and clinical judgment is required
Bone disease after renal transplantation

- Loss of bone volume
- Mineralization defects that can be extensive
- Low bone turnover.
Bone Disease (prevention)

Background:
- At transplant: CKD causes significant abnormalities of bone remodeling
- After transplantation - further weakening of bones due to:
  - Prednisone - reduction of calcium absorption
  - Hyperparathyroidism

Guidelines:
- Kidney transplant recipients should be advised to take a vitamin D (or analogue) supplement at a dose of at least 0.25 µg daily.
  (Level I and II)

Suggestions for clinical care:
- Medications/ supplements – physician prescription (consider other BMD)
- Diet – Calcium & Vitamin D at RDI levels as per general population assuming minimal sunlight exposure
Treatment of CKD Patients with Signs of Protein-Energy Wasting

1. Provide adequate nutrition, treat co-morbidities and correct hormonal alterations

   - Acidosis?
   - Infectious complications?
   - Ischemic heart disease
   - Intercurrent clinical events
   - Peridontal disease
   - Failed kidney transplant
   - Volume overload
   - Inflammatory diseases

2. Evaluate and treat potential *dialysis related* causes of PEW

   Check
   - Infections access related
   - Other infectious complications
   - Unpure dialysate
   - Bioincompatible membrane

3. Nutritional interventions

   Others

   - Enteral supplements
   - Parenteral supplements
   - Physical training
   - Pharmacological intervention?

Staff at Div of Renal Medicine & Baxter Novum

“Art is I – Science is We”