Prevention and Treatment of Protein Energy Wasting in Chronic Kidney Disease: a consensus statement by the International Society of Renal Nutrition and Metabolism

T. Alp Ikizler, MD
ISRNM Council Member – Past President
Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism

T. Alp Ikizler1, Noel J. Cano2, Harold Franch3, Denis Fouque4, Jonathan Himmelreich5, Kamyar Kalantar-Zadeh6, Martin K. Kuhlmann7, Peter Stenvinkel8, Pieter TerWee9, Daniel Teta10, Angela Yee-Moon Wang11 and Christoph Wanner12

1Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; 2CHU Clermont-Ferrand, Service de Nutrition, CINAH Aubergine, Clermont-Ferrand, France; 3Division of Nephrology, Department of Medicine, Emory University, Atlanta, Georgia, USA; 4Department of Nephrology, Hospital E.H.E.R.R.O.T, Lyon, France; 5Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington, USA; 6Division of Nephrology, Department of Medicine, University of California Irvine, Orange, California, USA; 7Division of Nephrology, Department of Medicine, Vivantes Klinikum im Friedrichshain, Berlin, Germany; 8Department of Renal Medicine, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden; 9Department of Nephrology, Vrije University Medical Center, Amsterdam, The Netherlands; 10Department of Medicine, Service of Nephrology, University Hospital CHUV, Lausanne, Switzerland; 11Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, People’s Republic of China and 12Department of Medicine, Division of Nephrology, University of Wuerzburg, Wuerzburg, Germany

Protein energy wasting (PEW) is common in patients with chronic kidney disease (CKD) and is associated with adverse clinical outcomes, especially in individuals receiving maintenance dialysis therapy. A multitude of factors can affect the nutritional and metabolic status of CKD patients requiring a combination of therapeutic maneuvers to prevent or reverse protein and energy depletion. These include optimizing dietary nutrient intake, appropriate treatment of metabolic disturbances such as metabolic acidosis, systemic inflammation, and hormonal deficiencies, and prescribing optimized dialytic regimens. In patients where oral dietary intake from regular meals cannot maintain adequate nutritional status, nutritional supplementation, administered orally, enterally, or parenterally, is shown to be effective in replenishing protein and energy stores. In clinical practice, the advantages of oral nutritional supplements include proven efficacy, safety, and compliance. Anabolic strategies such as anabolic steroids, growth hormone, and exercise, in combination with nutritional supplementation or alone, have been shown to improve protein stores and represent potential additional approaches for the treatment of PEW. Appetite stimulants, anti-inflammatory interventions, and newer anabolic agents are emerging as novel therapies. While numerous epidemiological data suggest that an improvement in biomarkers of nutritional status is associated with improved survival, there are no large randomized clinical trials that have tested the effectiveness of nutritional interventions on mortality and morbidity.

Kidney International advance online publication, 22 May 2013; doi:10.1038/sj.ki.5007342

KEYWORDS: dialysis; malnutrition; metabolism; nutrition; supplementation

Among the many risk factors that affect outcomes of chronic kidney disease (CKD) patients, especially ones with end-stage renal disease (ESRD) and on maintenance dialysis, a state of metabolic and nutritional derangements, more aptly called protein-energy wasting (PEW) of chronic kidney disease, plays a major role. Multiple studies now indicate that PEW is closely associated with major adverse clinical outcomes and results in increased rates of hospitalization and death in these patients.6,8 A significant number of factors affect nutritional and metabolic status in CKD, leading to multiple adverse consequences (Figure 1). Acutely, prevention and treatment of PEW of CKD should involve an integrated approach to limit protein and energy depletion, in addition to therapies that will avoid further losses and replenish already wasted stores. This article aims to provide a broad approach for the management of PEW, with a specific emphasis on interventions targeted on etiologic factors of PEW in CKD patients. The overarching aim is to describe methods to counteract the catabolic processes leading to PEW in CKD and provide means to treat the problem in patients already with PEW. In doing so, the rationale and
TAI: consultant for Abbott Renal Care, Abbott Nutrition, DSI, Baxter Renal, Amgen, Affymax, Fresenius Medical Care North America, Fresenius-Kabi, and Satellite Healthcare
NJC: research grants from Barry-Caillebaud, Baxter, B Braun, Danone, Fresenius Kabi, Lactalis, Nestle´, Nutricia, and Sanofi
HF: none
DF: consultant for Abbott Renal Care, Abbott Nutrition, Fresenius Kabi, and Danone
JH: consultant for Abbott Renal Care
KK-Z: consultant and/or speaker for Abbott Renal Care, Abbott Nutrition, Baxter Renal, Amgen, Fresenius-Kabi, Otsuka, Shire
MKK: speaker for Fresenius, Gambro, Baxter Renal, Fresenius Kabi, Abbott, Sanofi, Amgen, and Shire, and advisory board: Fresenius Kabi and Abbott;
PS: member of the scientific advisory board of Gambro and consultant for Abbott Renal Care and Takeda;
PT: advisory board member of AMGEN and Baxter Renal;
DT: consultant and/or speaker for Abbott Nutrition International, Fresenius Medical Care, Fresenius Kabi, and Shire;
AY-MW: advisory board member, speaker fee and grant from Sanofi, Baxter Renal, and speaker for Fresenius Kabi;
CW: scientific advisory board of Reata and Baxter Renal, speaker for Abbott Renal Care, Amgen, Fresenius Medical Care, and Mitsubishi Pharma.
PEW is present in 30 to 65% or more of dialysis patients around the world

Hemodialysis patients, USA, 47% (MIS)

Hemodialysis patients, • Sweden: 30 to 43% (SGA) • Netherlands: 28% (SGA)

Peritoneal dialysis patients, Brazil, 36 to 65% (SGA)

Peritoneal dialysis patients, China • 29 to 44% (SGA) • 60% (MIS)

Peritoneal dialysis patients, Korea, 40% (SGA)

Adapted from TNT Renal
Etiology and Consequences of Protein Energy Wasting in CKD

Co-Morbid Conditions (Diabetes, CVD, Depression)

Dialysis-Associated Catabolism

Dietary Nutrient Intake

Loss of Kidney Function

Uremic Toxins

Inflammation

Metabolic Derangements (Insulin Resistance, Metabolic Acidosis, IGF-1/GH Resistance)

Protein-Energy Wasting

Sarcopenia

Infection

CVD

Frailty

Carrero JJ et al on behalf of ISRNM; JREN 2013
Prevention and Treatment of Protein Energy Wasting in Chronic Kidney Disease: Consensus Statement

Historical Aspects

- Proposed to ISRNM Council and approved - 2010 Lausanne
- Outside funding obtained: Abbott Nutrition, Int
- Consensus meeting convened - Vancouver WCN 2011
  - Drs. Ikizler, Cano, Franch, Fouque, Himmelfarb, Kalantar-Zadeh, Kuhlmann, Stenvinkel, Ter Wee, Teta, Wang, Wanner – All ISRNM Council members
- 1st Draft completed - Hawaii 2012
- Electronic publication - May 2013
*Periodic Nutritional Screening
  SAlb, Weight, BMI, MIS, DPI, DEI

Nutritional Assessment (as indicated)
  SPrealb; SGA; Anthropometrics

Continuous Preventive Measures:
  Continuous Nutritional Counseling
  Optimize RRT-Rx and Dietary Nutrient Intake
  Manage co-morbidities (Acidosis, DM, Inflammation, CHF, Depression)

Indications for Nutritional Interventions Despite Preventive Measures:
  • Poor appetite and/or poor oral intake
  • DPI<1.2 (CKD 5D) or <0.7 (CKD 3-4); DEI < 30 Kcal/kg/d
  • Unintentional weight loss -> 5% of IBW or EDW over 3 months
  • Serum Albumin < 3.8 g/dL or Serum ^Prealbumin < 28 mg/dL
  • Worsening Nutritional Markers Over Time
  • Subjective Global Assessment in PEW range

Ikizler et al, on behalf of ISRNRM Kidney Int, 2013
Periodic Nutritional Screening
- SAlb, Weight, BMI, MNT, DPI, DEI

Nutritional Assessment (as indicated)
- SPrealb; SGA; MSI; Anthropometrics

Identify patients at risk

Diagnose and Treat

Ikizler et al, on behalf of ISRNK *Kidney Int*, 2013
*Periodic Nutritional Screening
SAIb, Weight, BMI, MIS, DPI, DEI

Nutritional Assessment (as indicated)
SPrealb; SGA; Anthropometrics

Continuous Preventive Measures:
Continuous Nutritional Counseling
Optimize RRT-Rx and Dietary Nutrient Intake
Manage co-morbidities (Acidosis, DM, Inflammation, CHF, Depression)

Ikizler et al, on behalf of ISRNM Kidney Int, 2013
✧ Only 6.5% of the dieticians did biannual dietary assessment
✧ Up to 62% “estimated” intake
✧ Median number of patients under care of a dietitian was 100 (IQR 70-130)
Dedicating dietitian time to development of MNT plan

Prioritize work based on clinical importance and evidence

The regulatory, logistical and administrative requirements should also be considered as applicable
## Protein Intake Recommendations in CKD

<table>
<thead>
<tr>
<th></th>
<th>Non-dialysis CKD</th>
<th>Hemodialysis</th>
<th>Peritoneal Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Kidney Foundation K/DOQI</td>
<td>0.6-0.75 g/kg/day</td>
<td>&gt;1.2 g/kg/day</td>
<td>1.2-1.3 g/kg/day</td>
</tr>
<tr>
<td>British Dietetic Association</td>
<td>N/A</td>
<td>&gt;1.1 g/kg/day</td>
<td>&gt;1.2 g/kg/day</td>
</tr>
<tr>
<td>ESPEN (Nutrition Support)</td>
<td>0.6-0.8 g/kg/day</td>
<td>1.2-1.4 g/kg/day</td>
<td>1.2-1.5 g/kg/day</td>
</tr>
<tr>
<td></td>
<td>Illness 1.0g/kg</td>
<td>Illness &gt;1.5g/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

- >50% of High Biological Value (ie complete protein sources, containing the full spectrum of EAA)
- Clear goals with supporting education and follow up helps support compliance
### Summary of CKD nutrition recommendations

<table>
<thead>
<tr>
<th></th>
<th>Non-dialyzed CKD</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy</strong></td>
<td>30 – 35 kcal/kg/d</td>
<td>35 kcal/kg/d</td>
<td>35 kcal/kg/d including dialysate kcal</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>Low&lt;br&gt;0.6 – 0.8 g/kg/d&lt;br&gt;Illness: 1.0 g/kg/d</td>
<td>High&lt;br&gt;≥ 1.2 g/kg/d</td>
<td>High&lt;br&gt;≥ 1.2 g/kg/d&lt;br&gt;Peritonitis: ≥ 1.5 g/kg/d</td>
</tr>
<tr>
<td><strong>Sodium</strong></td>
<td>≤ 2 g/d</td>
<td>≤ 2 g/d</td>
<td>≤ 2 g/d</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>&lt; 1 mmol/kg if elevated</td>
<td>&lt; 1 mmol/kg if elevated</td>
<td>Not usually an issue – monitor</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td>800 – 1000 mg/d + binders if elevated</td>
<td>800 – 1000 mg/d + binders if elevated</td>
<td>800 – 1000 mg/d + binders if elevated</td>
</tr>
</tbody>
</table>

Indications for Nutritional Interventions Despite Preventive Measures:

- Poor appetite and/or poor oral intake
- DPI < 1.2 (CKD 5D) or < 0.7 (CKD 3-4); DEI < 30 Kcal/kg/d
- Unintentional weight loss - > 5% of IBW or EDW over 3 months
- Serum Albumin < 3.8 g/dL or Serum ^Prealbumin < 28 mg/dL
- Worsening Nutritional Markers Over Time
- Subjective Global Assessment in PEW range

Ikizler et al, on behalf of ISRN M Kidney Int, 2013
Prognostic Ability of Nutritional Markers

ALBUMIN

PREALBUMIN

Survival Distribution Function

Cohort years

Months

* p-value < .0001

Subjective Global Assessment
Malnutrition-Inflammation Score
• Start CKD-Specific Oral Nutritional Supplementation:
  • CKD 3-4: DPI target of > 0.8 g/kg/d (± AA/KA or ONS)
  • CKD 5D: HD& PD: DPI target > 1.2 g/kg/d
    (ONS at home or during dialysis; in-center meals)

Salb > 3.8; SPrealb > 28; Weight or LBM gain

Maintenance Nutritional Therapy Goals:
• Salb > 4.0 g/dL
• SPrealb > 30 mg/dL
• DPI > 1.2 (CKD-5D)
  & > 0.7 g/kg/d (CKD 3-4)
• DEI 30-35 Kcal/kg/d

Intensified Therapy
• Dialysis Rx alterations
• Increase quantity of oral therapy
• Tube feeding or PEG
• Parenteral interventions:
  • IDPN (esp. if Salb <3.0 g/dL)
  • TPN

Adjunct Therapies
• Anabolic hormones
  • Androgens, GH
• Appetite stimulants
• Anti-inflammatory interventions
  • Omega 3; IL-1ra
• Exercise (as tolerated)

Ikizler et al, on behalf of ISRNK Kidney Int, 2013
Start CKD-Specific Oral Nutritional Supplementation

- **CKD 3-4**: DPI target of $> 0.8$ g/kg/d ($\pm$ AA/KA or ONS)
- **CKD 5D**: HD & PD: DPI target $> 1.2$ g/kg/d

(ONS at home or during dialysis; in-center meals)

**Short-term Nutritional Therapy Goals:**
- Salb $> 3.8$
- SPrealb $> 28$
- Weight or LBM gain

**Maintenance Nutritional Therapy Goals:**
- Salb $> 4.0$ g/dL
- SPrealb $> 30$ mg/dL
- DPI $> 1.2$ (CKD-5D) & $> 0.7$ g/kg/d (CKD 3-4)
- DEI 30-35 Kcal/kg/d

Ikizler et al., on behalf of ISRN M Kidney Int, 2013
### Oral supplements: Randomized Clinical Trials in HD/PD patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Design</th>
<th>Days</th>
<th>Nutritional significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acchiardo et al. (1982)</td>
<td>15</td>
<td>RCT: ONS vs control groups</td>
<td>105</td>
<td>↑ albumin, transferrin, bone density</td>
</tr>
<tr>
<td>Allman et al. (1990)</td>
<td>21</td>
<td>RCT: ONS vs control groups</td>
<td>180</td>
<td>↑ BW, LBM</td>
</tr>
<tr>
<td>Tietze et al. (1991)</td>
<td>19</td>
<td>RCT, crossover, ONS vs control periods</td>
<td>120</td>
<td>↑ BW, arm muscle circumference</td>
</tr>
<tr>
<td>Eustace et al. (2000)</td>
<td>47</td>
<td>RCT: ONS vs control groups</td>
<td>90</td>
<td>↑ albumin, grip strength, SF12 mental health</td>
</tr>
<tr>
<td>Hiroshige et al (2001)</td>
<td>44</td>
<td>RCT, crossover, ONS vs control periods</td>
<td>180</td>
<td>↑ DEI, DPI, fat mass, fat free mass, albumin</td>
</tr>
<tr>
<td>Sharma et al. (2002)</td>
<td>40</td>
<td>RCT: ONS vs control groups</td>
<td>30</td>
<td>↑ albumin</td>
</tr>
<tr>
<td>Leon et al. (2006)</td>
<td>180</td>
<td>RCT: ONS vs control groups</td>
<td>365</td>
<td>↑ DEI, DPI, albumin</td>
</tr>
<tr>
<td>Cano et al. (2007)</td>
<td>186</td>
<td>RCT: ONS vs ONS+IDPN groups</td>
<td>365</td>
<td>↑ nPNA, BMI, SA1b, prealbumin in both groups</td>
</tr>
<tr>
<td>Fouque et al. (2008)</td>
<td>86</td>
<td>RCT: ONS vs control groups</td>
<td>90</td>
<td>↑ DEI, DPI, SGA, QOL</td>
</tr>
<tr>
<td>Moretti et al. (2009)</td>
<td>49</td>
<td>RCT: ONS vs control groups</td>
<td>365</td>
<td>↑ nPNA, albumin</td>
</tr>
</tbody>
</table>

*Slide Courtesy of Dr. Daniel Teta; Ikizler et al, *Kidney Int*, 2013*
Oral nutrition supplementation provides benefits for HD or PD patients

Hemodialysis and peritoneal patients using ONS experience:

- Increased calorie and protein intake
- Improved serum albumin, serum prealbumin levels
- Improved nutritional status (SGA)
- Increased body weight or BMI
- Increased lean body mass and bone density
- Improved physical function (grip strength)
- Improved quality of life and mental health scores

Over the past 3 decades, 10 studies have shown outcome benefits of ONS therapy for CKD patients on dialysis

Receipt of Oral Supplements During Dialysis is Associated with Improved Survival in MHD Patients

![Graph showing survival distribution function for patients who received oral supplements and those who did not.](Image)
Receipt of Oral Supplements is Associated with Improved Hospitalization in MHD Patients

N = 470

p* < 0.01
No Improvement or Deterioration

Intensified Therapy
• Dialysis Rx alterations
  • High-flux; Hemofiltration; FH; NH
• Increase quantity of oral therapy
• Tube feeding or PEG
• Parenteral interventions:
  • IDPN (esp. if Salb <3.0 g/dL)
  • TPN

Ikizler et al, on behalf of ISRNM *Kidney Int*, 2013
Effects of IDPN on nutritional outcomes in MHD patients in randomized clinical trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Design</th>
<th>Days</th>
<th>Nutritional significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guarnieri et al. (1980)</td>
<td>18</td>
<td>RCT, 3 groups: control, and 2 groups with different AA solutions</td>
<td>60</td>
<td>↑ Body Weight in treated patients</td>
</tr>
<tr>
<td>Cano et al. (1990)</td>
<td>26</td>
<td>RCT: IDPN vs controls</td>
<td>90</td>
<td>↑ DEI, BW, AMC, TSF, serum albumin, prealbumin, creatinine</td>
</tr>
<tr>
<td>Navarro et al. (2001)</td>
<td>17</td>
<td>RCT: IDPN vs controls</td>
<td>90</td>
<td>↑ TSF, serum albumin, nPCR</td>
</tr>
<tr>
<td>Cano et al. (2006)</td>
<td>35</td>
<td>RCT: two IDPN groups differing by fat émulsions, olive vs soya)</td>
<td>35</td>
<td>In the two groups: ↑ nPCR, serum albumin, prealbumin, creatinine</td>
</tr>
<tr>
<td>Cano et al. (2007)</td>
<td>186</td>
<td>RCT: IDPN+ONS vs ONS</td>
<td>365</td>
<td>No advantage of IDPN addition to ONS. ↑ nPNA, BMI, serum albumin, prealbumin in both groups</td>
</tr>
</tbody>
</table>

Table Courtesy of Dr. Noel Cano; Ikizler et al, *Kidney Int*, 2013
Exercise and steroids were both effective when more precise measures are used.

Changes in quadriceps muscle area (cm²) over 3 months, with resistance exercise and steroid (nandrolone)

![Graph showing changes in quadriceps muscle area](image)

Periodic nutritional screening
SAIb, weight, BMI, MIS, DPI, DEI

Nutritional assessment (as indicated)
SPreaB, SGA, anthropometrics

Continuous preventive measures
- Continuous nutritional counseling
- Optimize RRT-Rx and dietary nutrient intake
- Manage comorbidities (acidosis, DM, Inflammation, CHF, depression)

Indications for nutritional interventions despite preventive measures
- Poor appetite and/or poor oral intake
- DPI < 1.2 (CKD 3–4) or < 0.7 (CKD 3–4); DEI < 30 kcal/kg/day
- SAIb < 3.5 g/dl or SPreaB < 25 mg/dl
- Unintentional weight loss > 5% of IBW or ECW over 3 months
- Worsening nutritional markers over time
- SGA in PEW range

Start CKD-specific oral nutritional supplementation
- CKD 3–4: DPI target of > 0.8 g/kg/day (as AA/KA or ONS)
- CKD 5d: DPI target > 1.2 g/kg/day (ONS at home or during dialysis treatment; in-center meals)

Maintenance nutritional therapy goals
- SAIb > 4.0 g/dl
- SPreaB > 30 mg/dl
- DPI > 1.2 (CKD 3–4) and > 0.7 g/kg/day (CKD 3–4)
- DEI 30–35 kcal/kg/day

Intensified therapy
- Dialysis prescription alterations
- Increase quantity of oral therapy
- Tube feeding or PEG if indicated
- Parenteral interventions:
  - IDPN (esp. if SAIb < 3.0 g/dl)
  - TPN

Adjunct therapies
- Anabolic hormones
- Androgens, GH
- Appetite stimulants
- Anti-inflammatory interventions
- Omega 3, IL-11a
- Exercise (as tolerated)
Acknowledgements

- Writers and Editors
  - Noel J. Cano, Harold Franch, Denis Fouque, Jonathan Himmelfarb, Kamyar Kalantar-Zadeh, Martin K. Kuhlmann, Peter Stenvinkel, Pieter TerWee, Daniel Teta, Angela Yee-Moon Wang and Christoph Wanner

- ISRNM Council

- Unrestricted grant support from Abbott Nutrition, International