End stage renal disease and Protein Energy wasting

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Introduction

Chronic kidney disease- increasing health burden in many countries. The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5%.

CKD is associated with increased risk of mortality, cardiovascular disease, and progression to renal failure.

Appendix 3: CKD – Stages of CKD

Kidney Function: Glomerular Filtration Rate (GFR) (Guidelines 1 and 2)

- **Stage 1**: Kidney Damage with Normal or ↑ Kidney Function
  - **At Risk**
  - If GFR < 60, assess:
    - Presence of anemia (Guideline 8): follow K/DOQI Anemia Guidelines
    - Nutritional status (Guideline 9): follow K/DOQI Nutritional Guidelines
    - Bone Metabolism (Guideline 10): follow K/DOQI Bone Metabolism Guidelines
    - Indices of functioning and well-being (Guideline 12)

- **Stage 2**: Kidney Damage with Mid ↓ Kidney Function
  - 130 120 110 100 90 80 70 60

- **Stage 3**: Moderate ↓ in Kidney Function
  - 50 40 30

- **Stage 4**: Severe ↓ in Kidney Function
  - 20 15 10 0

- **Stage 5**: Kidney Failure (ESRD)

If GFR < 30:
- Refer to nephrologist
- Prepare for Kidney Replacement Therapy (KRT)

If GFR < 15, consider initiation of KRT.
Patients who may benefit from KRT at Higher levels of kidney function:
- Living donor transplant recipients
- Older patients
- Those with diabetes (this group is at highest risk for ASCVD)
- Those with ASCVD
- Those with other comorbid conditions

Global maintenance dialysis population from 1990 to 2010

Prevalence of ESRD
(per million population), 2005

1. Taiwan  1,830
2. USA    1,585
3. Germany  1,057

7. HK  965
28. Malaysia  560

(Japan – no data - No. 1 in 2003)

USRDS 2007
Taiwan and Japan continued to report the highest rates of prevalent ESRD, at 2,584 and 2,260 per million population, respectively, in 2010. The next highest rate was reported by the United States, at 1,870, followed by Portugal, Singapore (2009), and Jalisco (Mexico) at 1,590, 1,524, and 1,402. The lowest rates were reported by Bangladesh and Russia, at 158 and 186.

1) Taiwan 2584 pmp
2) Japan 2260 pmp
3) USA 1870 pmp

25) Malaysia 812 pmp
Maurizio Nordio et al 2012, AJKD
Expected remaining lifetimes in adult CKD Stage 5 as compared to the General Population

- **Europe**
- **US Whites**
- **General Population**
- **Transplant**
- **Dialysis**

ERA-EDTA Registry data and USRDS data
If a cure is not achieved, the **kidneys** will pass on the disease to the **heart**

Huang Ti Nei Ching Su Wen
The Yellow Emperor’s Classic of Internal Medicine
~2000 B.C.
Cardiovascular Mortality

Dialysis Population (DP)

-General Population (GP)

Annual Mortality (%)

Age (y)

25-34  35-44  45-54  55-64  65-74  75-84  >85

GP Male  GP Female  GP Black  GP White  DP Male  DP Female  DP Black  DP White

### Table 3.1.2: Causes of Death on Dialysis 2001-2010

<table>
<thead>
<tr>
<th>Year Causes of Death</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>221</td>
<td>26</td>
<td>313</td>
<td>33</td>
<td>341</td>
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<tr>
<td>Died at home</td>
<td>228</td>
<td>27</td>
<td>212</td>
<td>22</td>
<td>290</td>
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<tr>
<td>Sepsis</td>
<td>134</td>
<td>16</td>
<td>148</td>
<td>15</td>
<td>197</td>
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<tr>
<td>PD peritonitis</td>
<td>30</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>14</td>
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<tr>
<td>GIT bleed</td>
<td>18</td>
<td>2</td>
<td>24</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Cancer</td>
<td>18</td>
<td>2</td>
<td>18</td>
<td>2</td>
<td>28</td>
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<tr>
<td>Liver disease</td>
<td>11</td>
<td>1</td>
<td>16</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>20</td>
<td>2</td>
<td>18</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Others</td>
<td>89</td>
<td>10</td>
<td>104</td>
<td>11</td>
<td>161</td>
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<tr>
<td>Unknown</td>
<td>81</td>
<td>10</td>
<td>90</td>
<td>9</td>
<td>100</td>
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<td>850</td>
<td>100</td>
<td>959</td>
<td>100</td>
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<table>
<thead>
<tr>
<th>Year Causes of Death</th>
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<th>2010</th>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td>Cardiovascular</td>
<td>517</td>
<td>28</td>
<td>516</td>
<td>26</td>
<td>682</td>
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<tr>
<td>Died at home</td>
<td>354</td>
<td>20</td>
<td>343</td>
<td>17</td>
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<tr>
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<td>235</td>
<td>13</td>
<td>222</td>
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<td>336</td>
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<tr>
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<td>22</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>25</td>
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<tr>
<td>GIT bleed</td>
<td>26</td>
<td>1</td>
<td>31</td>
<td>2</td>
<td>43</td>
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<tr>
<td>Cancer</td>
<td>41</td>
<td>2</td>
<td>34</td>
<td>2</td>
<td>53</td>
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<tr>
<td>Liver disease</td>
<td>35</td>
<td>2</td>
<td>37</td>
<td>2</td>
<td>44</td>
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<tr>
<td>Withdrawal</td>
<td>23</td>
<td>1</td>
<td>27</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Others</td>
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<td>552</td>
<td>28</td>
<td>366</td>
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<tr>
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<td>170</td>
<td>9</td>
<td>206</td>
<td>10</td>
<td>194</td>
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<tr>
<td>TOTAL</td>
<td>1815</td>
<td>100</td>
<td>1984</td>
<td>100</td>
<td>2190</td>
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</table>

18th MDTR report 2010, Malaysia
**TRADITIONAL RISK FACTORS**
- Age
- Male sex
- Hypertension
- Smoking
- Left ventricular hypertrophy
- Diabetes
- Dyslipidemia

**NOVEL AND UREMIA RELATED RISK FACTORS**
- Oxidative stress
- Sympathetic activation
- Subclinical hypothyroidism
- Uremic bone disease
- Volume overload
- Protein-energy wasting
- Insulin resistance
- Uremic toxins
- Fat mass: adipokine imbalance
- Genetics/epigenetics
- Coagulation disorders
- Atherosclerotic plaque
Protein-energy wasting (PEW) is common in patients with chronic kidney disease (CKD). The International Society of Renal Nutrition and Metabolism (ISRNMI) expert panel has defined PEW as a, “state of decreased body stores of protein and energy fuels (body protein and fat masses)”
Other terms used

Uremic malnutrition,
uremic (renal) cachexia,
protein–energy malnutrition,
malnutrition–inflammation atherosclerosis syndrome, or
malnutrition–inflammation complex (or cachexia) syndrome
# CKD and Malnutrition

<table>
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<tr>
<th>Complication</th>
<th>GFR category (ml/min/1.73 m²)</th>
<th>F</th>
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<tr>
<td></td>
<td>&lt; 90</td>
<td>60-89</td>
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<tr>
<td>Anemia¹</td>
<td>4.0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Hypertension²</td>
<td>18.3%</td>
<td>41.0%</td>
</tr>
<tr>
<td>25(OH) Vit D deficiency³</td>
<td>14.1%</td>
<td>9.1%</td>
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<tr>
<td>Acidosis⁴</td>
<td>11.2%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Hyperphosphatemia⁵</td>
<td>7.2%</td>
<td>7.4%</td>
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<tr>
<td>Hypoalbuminemia⁶</td>
<td>1.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Hyperparathyroidism⁷</td>
<td>5.5%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Kidney international, 2013, 73-90
Surveys using classic measures of nutritional status indicate that approximately 18–75% of patients with CKD undergoing maintenance dialysis therapy show evidence of wasting.
Malnutrition is Common in Dialysis Patients

HEMO Study (2002): Nutritional status of 1000 patients analyzed.

- 76% had mean energy intake below KDOQI standard of care (28kcal/kg/d)
- 61% had a mean protein intake below the KDOQI standard of care (1g/kg/d)
- 79% had a mean serum albumin level < 4.0g/dL
- 28% had a mean serum albumin level < 3.5g/dL

Pre-albumin levels and patient survival both drop with increasing time on dialysis

Potential causes of protein-energy wasting syndrome in kidney disease

- Anorexia, acidosis, anemia
- Endocrine disorders, vitamin D deficiency, ↑PTH, diabetes, decreased insulin / IGF signalling
- ↑ Production of inflammatory cytokines
- Oxidative and carbonyl stress
- Volume overload
- ↓ Nutrient intake, prescribed dietary restrictions
- Nutrient loss during dialysis
- Dialysis treatment-related factors, AV graft, dialysis membrane
- Comorbid conditions: DM, cardiovascular disease, infection, aging
Markers of Malnutrition and Inflammation are Independent Predictors of Mortality

Peter Stenvinkel. Blood Purification 2001
Association of Albumin and Mortality

Lowrie et al \textit{(Am J Kidney Dis 1990)}

12,000 US hemodialysis patients were evaluated.
Serum albumin $< 4g/dL$ was the variable most highly associated with death.
2/3 had low albumin.

Iseki et al \textit{(Kidney International 1993)}

1982 Okinawan dialysis patients were recruited between 1971-1990 and observed until 1992.
Albumin (along with age, male sex and serum creatinine) was identified as a significant predictors of death (52% died of cardiovascular causes).
Patients had incrementally higher survival rates when albumin went from $<3.5g/dL$ (HR1) to 3.5-3.9 g/dL (HR0.4) to 4 (HR0.27).

Readily utilizable criteria for the clinical diagnosis of protein energy wasting in chronic kidney disease criteria

1. Serum chemistry
   Serum albumin < 3.8 g 100 ml⁻¹ (Brom cresol Green)a
   Serum prealbumin (transthyretin) < 30 mg 100 ml⁻¹ (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5)a
   Serum cholesterol < 100 mg 100 ml⁻¹a

2. Body mass
   BMI < 23b
   Unintentional weight loss over time: 5% over three months or 10% over six months
   Total body fat percentage < 10%

3. Muscle mass
   Muscle wasting: Reduced muscle mass 5% over three months or 10% over six months
   Reduced mid-arm muscle circumference area² (reduction > 10% in relation to the fiftieth percentile of reference population)
   Creatinine appearance²

4. Dietary intake
   Unintentional low DPI < 0.80 g kg⁻¹ day⁻¹ for at least two months c for dialysis patients or < 0.6 g kg⁻¹ day⁻¹ for patients with CKD stages 2–5
   Unintentional low dietary energy intake (DEI) < 25 kcal kg⁻¹ day⁻¹ for at least two months c
   At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease–related PEW. Optimally, each criterion should be documented on at least three occasions, preferably two-to-four weeks apart.

   Dietary energy intake (DEI), dietary protein intake (DPI), nPCR normalized protein catabolic rate, and nPNA normalized protein nitrogen appearance,
   a. Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines
   b. A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight
   c. Measurement must be performed by a trained anthropometrist
   d. Creatinine appearance is influenced by both muscle mass and meat intake
   e. Can be assessed by dietary diaries and interviews, or by protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR), as determined by urea kinetic measurements
Simplified Assessment

1) Biochemistry- Albumin level, serum cholesterol (38g-bromcresol green technique and 2.59umol)

2) BMI or body fat content (<23 and < 10%)

3) Muscle mass- reduced mid arm circumference
4) Dietary intake- protein intake less than 0.8g/kg for 2 months in dialysis patients or energy intake of less than 25 kcal/kg/day.

Must be 3 out of 4 criteria above
Selected nutritional parameters for varying levels of kidney disease

<table>
<thead>
<tr>
<th>Nutritional Parameter</th>
<th>Stages 1 – 4 CKD</th>
<th>Stage 5 Hemodialysis</th>
<th>Stage 5 Peritoneal Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal / kg / d)</td>
<td>35 &lt; 60 years</td>
<td>35 &lt; 60 years</td>
<td>35 &lt; 60 years, include kcals from dialysate</td>
</tr>
<tr>
<td></td>
<td>30 – 35 ≥ 60 years</td>
<td>30 – 35 ≥ 60 years</td>
<td>30 – 35 ≥ 60 years</td>
</tr>
<tr>
<td>Protein (g / kg / d)</td>
<td>0.6 – 0.75</td>
<td>1.2</td>
<td>1.2 – 1.3</td>
</tr>
<tr>
<td>Fat (% total kcal)</td>
<td>For patients at risk for CVD, &lt; 10% saturated fat, 250 – 300 mg cholesterol / d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mg / d)</td>
<td>2000</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>Potassium (mg / d)</td>
<td>Match to laboratory values</td>
<td>2000 – 3000</td>
<td>3000 – 4000</td>
</tr>
<tr>
<td>Calcium (mg / d)</td>
<td>1200</td>
<td>≤ 2000 from diet and medicines</td>
<td>≤ 2000 from diet and medicines</td>
</tr>
<tr>
<td>Phosphorus (mg / d)</td>
<td>Match to laboratory values</td>
<td>800 – 1000</td>
<td>800 – 1000</td>
</tr>
<tr>
<td>Fluid (mL / d)</td>
<td>Unrestricted with normal urine output</td>
<td>1000 + urine</td>
<td>Monitor; 1500 – 2000</td>
</tr>
</tbody>
</table>

*Represents initial guidelines; individualization to patient’s own metabolic status, and coexisting metabolic conditions are essential for optimal care

American Dietetic Association guidelines
Albumin = Marker of Nutrition?

Albumin influenced by nutrition as well as inflammation

Albumin may be Low even in apparently well nourished patients suggesting it is not a pure marker of nutritional status

Albumin is regulated by multiple factors including protein malnutrition, inflammation and external losses

Inflammation via acute phase proteins (ie. CRP) are correlated with reductions in serum albumin

Halliwell B. *Haemostasis* 23 (Suppl 1), 1993
<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>Sr. Albumin (g/L)</th>
<th>Patient Distribution</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
<td>LQ</td>
</tr>
<tr>
<td>1997</td>
<td>1644</td>
<td>40.9 ± 6.2</td>
<td>41</td>
<td>37.7</td>
</tr>
<tr>
<td>1998</td>
<td>2075</td>
<td>41.2 ± 6.5</td>
<td>41</td>
<td>37.5</td>
</tr>
<tr>
<td>1999</td>
<td>2755</td>
<td>39.7 ± 6.1</td>
<td>39.7</td>
<td>36.3</td>
</tr>
<tr>
<td>2000</td>
<td>3731</td>
<td>38.6 ± 7</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>2001</td>
<td>4666</td>
<td>39 ± 5.6</td>
<td>38.5</td>
<td>36</td>
</tr>
<tr>
<td>2002</td>
<td>5568</td>
<td>39.2 ± 5.6</td>
<td>39</td>
<td>36.5</td>
</tr>
<tr>
<td>2003</td>
<td>6524</td>
<td>39.9 ± 5.4</td>
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<td>37</td>
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<td>2005</td>
<td>8706</td>
<td>40 ± 5.2</td>
<td>40.3</td>
<td>37.5</td>
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<td>40</td>
<td>37</td>
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<tr>
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<td>39.4 ± 5.1</td>
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<td>18757</td>
<td>38.9 ± 4.9</td>
<td>39.3</td>
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<td>2011</td>
<td>21830</td>
<td>38.7 ± 5</td>
<td>39</td>
<td>36.3</td>
</tr>
<tr>
<td>2012</td>
<td>24789</td>
<td>38.7 ± 5</td>
<td>39.2</td>
<td>36.3</td>
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</table>
Figure 1 | Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease.
Oral Nutritional Supplements: Useful!

All HD patients with
  albumin ≤3.5 g/dL
  >4000 matched pairs

Nepro, or pure protein supplement at dialysis

Survival improved in the supplement group by 9% (ITT) or 34% (as-treated) compared with matched controls

Subjects with serum albumin <3.5 g/dL who were prescribed and received supervised ONSP exhibited significantly better one-year survival

KM survival curves – As Treated

Strategies to enhance oral intake

- Avoid diet restrictions in patients with poor intake
- Offer oral liquid supplements and snacks
- Treat gastroparesis and other gastrointestinal conditions
- Achieve glycemic control
- Correct electrolyte abnormalities
- Evaluate for and address depression
Guidelines for Nutrition Intervention

PEW is one of the strongest predictors of mortality in CKD patients.

Provision of meals or oral nutritional supplements improves outcomes as well as patient adherence and satisfaction to dietary recommendations.

Diets and enteral supplements for improving outcomes in chronic kidney disease


Nutrition Intervention now Supported by Nephrology Societies

Expert recommendations:

<table>
<thead>
<tr>
<th>Nutrition Support</th>
<th>KDOQI¹</th>
<th>ESPEN²</th>
<th>EBPG³</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Individuals undergoing maintenance dialysis who are unable to meet their protein and energy requirements with food intake for an extended period of time <strong>should receive nutritional support</strong></td>
<td>Special formula products for HD treatment can be useful, especially in malnourished patients who are not able to increase their nutrient intake</td>
<td>Oral nutritional supplements should be prescribed if nutritional counseling does not achieve an increase in nutrient intake to a level that covers minimum recommendations. <strong>Products specifically designed for dialysis patients should be prescribed</strong></td>
</tr>
</tbody>
</table>

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THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

**European Best Practice Guidelines**
Assisted Enteral Feeding

The hospitalized patients may benefit from a period of nasogastric feeding until the acute illness resolves.

If the feeding tube placement is discussed as an important and beneficial part of their overall care, a patient is much more likely to agree to NGT placement.
Parenteral Nutrition

Parenteral nutrition should be reserved only for those patients who are unable to receive enteral nutrients.
Clinical studies have shown that renal-specific nutrition offers advantages over standard nutrition.

- Phosphorus levels were lower with the renal-specific nutrition than with the standard nutrition\(^1\)
- Less fluid and potassium in renal-specific nutrition offers advantages over standard nutrition\(^2\)

SUMMARY
Summary

Protein Energy wasting is common among chronic kidney disease patients and it is multifactorial.

PEW in CKD/dialysis patient is linked to increased CV disease, atherosclerosis, and mortality.

Various strategies can be employed to treat PEW and studies show promising results in improving survival.
The Wheels of Life

Thank You