Worldwide prevalence of protein energy wasting in patients with kidney disease: does the modality matter?

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Memphis, TN, USA
Disclosure

- Czech Health Research Council
- National Institute of Health (NIH) - USA
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Malnutrition (undernutrition), low nutrient intake

Comorbid conditions: DM, cardiovascular dz, infection, aging

Endocrine disorders, vitamin D deficiency, ↑PTH

Nutrient loss during dialysis,

Dialysis Rx related factors, AV graft, dialysis membrane

↓ clearance of inflammatory cytokines

Anorexia, acidosis, anemia

Oxidative & carbonyl stress

Volume overload

↓ nutrient intake, prescribed dietary restrictions

Comorbid conditions: DM, cardiovascular dz, infection, aging

Malnutrition (undernutrition), low nutrient intake

↓ albumin, transthyretin & lipids

↑ CRP & inflammatory cytokines

↓ weight, ↓ BMI, ↓ body fat, sarcopenia

Survival paradoxes

Atherosclerotic cardiovascular disease, vascular calcification

↓ mortality, ↑ hospitalization, ↓ quality of life

International Society of Renal Nutrition & Metabolism (ISRNM), Wasting in Kidney Disease Consensus paper (KI 2007)
A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease

D Fouque¹,¹⁷, K Kalantar-Zadeh²,¹⁷, J Kopple², N Cano³, P Chauveau⁴, L Cuppari⁵, H Franch⁶, G Guarnieri⁷, TA Ikizler⁸, G Kaysen⁹,¹⁰, B Lindholm¹¹, Z Massy¹²,¹³, W Mitch¹⁴, E Pineda¹⁵, P Stenvinkel¹¹, A Trevinho-Becerra¹⁵ and C Wanner¹⁶

Fouque et al, Kidney Int 2007
Criteria for the clinical diagnosis of Protein-Energy Wasting (PEW) in Kidney Disease

Serum Chemistry
- Serum albumin <3.8 g/dL (Bromcresol Green) †
- Serum prealbumin (transthyretin) <30 mg/dL (may vary according to GFR level) †
- Serum cholesterol <100 mg/dL †

Body Mass
- BMI or body weight <22 kg/m2 (under 65 years) <23 kg/m2 (>65 years)*
- Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
- Total body fat percentage <10%

Muscle Mass
- Muscle wasting (sarcopenia): Reduced muscle mass 5% over 3 months or 10% over 6 months
- Reduced mid-arm muscle circumference area **
- Creatinine appearance ***

Dietary Intake
- Unintentional low dietary protein intake (DPI) < 0.80 g/kg/day for at least 2 months‡
- Unintentional low dietary energy intake (DEI) < 25 Cal/kg/day for at least 2 months ‡

* International Society of Renal Nutrition & Metabolism (ISRNM), Wasting in Kidney Disease Consensus paper (KI 2007)
Mortality and BMI in 54,535 hemodialysis patients

Kalantar-Zadeh et al, AJKD 2005, & Kidney Int 2003 (& multiple other publications)
Change in WEIGHT over 6-months & 5-year mortality in 88,729 Hemodialysis Patients

Risk of Death by Change in BMI
Conventional Cox Model - Davita

Weight Gain              No Change              Weight Loss
Change in Weight (% per quarter)
> +3  +1 to +3  -1 to +1  -3 to -1  < -3

Relative Risk of All-Case Death
0.9  1  1.2  1.4  1.6
Unadjusted
Case-Mix
Case-Mix & MICS

No change in
Dry Weight
Gain in Dry Weight

Correction of Protein-Energy Malnutrition?

Gain in Dry Weight

Protein-Energy Malnutrition

Stable dry weight

Weight Loss

Kalantar-Zadeh et al,
Mayo Clinic Proceedings 2010
Arnold’s BMI: 37 kg/m² (1995)
Serum Creatinine in Dialysis Patients: Surrogate of MUSCLE?

Lowrie and Lew, AJKD, 1990
Mid-Arm Muscle Circumference and 5-Year Mortality (2001-06) in 792 hemodialysis patients

DEATH (Log hazard ratio) vs. MAMC percentile

If FAT is good, MUSCLE is better!

Noori N, CJASN, 2010
Mid-Arm Muscle Circumference and 3-Year Mortality in 892 prevalent kidney transplant recipients

Unpublished data
Change in CREATININE (muscle surrogate) over 6-months & 5-year mortality in 88,729 Hemodialysis Patients

Drop in creatinine (Muscle loss) → ↑Death
Rise in creatinine (MUSCLE Gain) → ↑Survival
Stable creatinine

All-Cause Mortality Hazard Ratio

- Unadjusted
- Case-Mix
- Case-Mix & MICS

Kalantar-Zadeh et al, Mayo Clinic Proceedings 2010
Low muscle mass and High body weight

High muscle mass and Low body weight

Molnar MZ et al., AJT, 2011
Fall in muscle mass and Fall in body weight

Rise in muscle mass and Rise in body weight

In waitlisted patients

Molnar MZ et al., AJT, 2011
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Hazard Ratio of Death for Reduced Appetite: 4.74 (95% CI: 1.85-12.16)
Cox p-value: 0.001; Kaplan-Meier p-value: 0.002

- Death
- Censored

Cumulative Proportion Surviving

Appetite status (dichotomized)
- Normal
- Anorexia

Low appetite $\rightarrow$ ↑ mortality
Good appetite $\rightarrow$ better survival

Kalantar-Zadeh et al, Am J Clin Nutr 2004

Low appetite $\rightarrow$ improvement in mortality
Good appetite $\rightarrow$ better survival
### Recommended Protein & Calorie Intakes for Dialysis Patients

<table>
<thead>
<tr>
<th></th>
<th>ESPEN (1)</th>
<th>NKF-KDOQI (2)</th>
<th>EBPG (3)</th>
</tr>
</thead>
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<tr>
<td><strong>Protein</strong></td>
<td>1.2 - 1.4</td>
<td>1.0-1.2</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>g/kg/day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>35</td>
<td>&lt; 60 y: 35</td>
<td>30-35</td>
</tr>
<tr>
<td><strong>kcal/kg/day</strong></td>
<td></td>
<td>&gt; 60 y: 30</td>
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*How much protein dialysis patients need?*

1.0 to 1.2 gm per kg (body weight) per day - KDOQI

---

1 - Clin Nutr, 2000  
2 - Am J Kidney Dis, 2000  
3 - Nephrol Dial Transplant, 2007
Over half of dialysis patients receive less than recommended protein intake (nPCR < 1.0 g/kg/day).

KDOQI Recommended range: 1.0-1.2 g/kg/day

Incident & Prevalent MHD Patients n= 98,489

Ravel V, Molnar MZ, et al., 2013, Journal of Nutrition
Risk of Controlling Phosphorus by Dietary Protein Restriction may Outweigh the Benefit*

Additional clinical trials are needed to determine the treatment protocols that offer the greatest survival advantage for dialysis patients and to ascertain whether nondietary control of phosphorus or restriction of nonprotein sources of phosphorus are safer and more effective.

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Serum Albumin: → STRONG, ROBUST, LINEAR Predictor of Survival

Protein-Energy Malnutrition: Over 60% of Dialysis Patients

N= 56,920 hemodialysis patients (7/2001-6/2003)


Serum Albumin:  STRONG, ROBUST, LINEAR Predictor of Survival
58,058 HD patients: 2001-2003, DaVita

N= 56,920 hemodialysis patients (7/2001-6/2003)

Rise in Serum Albumin → Greater Survival

Fall in Serum Albumin → Higher Mortality

All-Cause Death Hazard Ratio

Serum Albumin Change (g/dL per quarter)
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Body composition testing methods

- Underwater weighing
- DEXA
- Bioelectrical impedance (BIA)
- Near Infra-Red (NIR) Interactance
- Skinfold caliper (anthropometry)

Problems:
- Expensive
- Complicated
- Time-consuming
- Hard to perform in large cohort
### SGA: Subjective Global Assessment Score

- Most frequently used
- Easy to perform
- Overall validated
- Scoring result: A, B, C

#### SUBJECTIVE GLOBAL ASSESSMENT RATING FORM

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>ID #:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEIGHT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Weight:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Weight:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Wt loss past 6 mo:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% wt loss:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt change over past two weeks:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIETARY INTAKE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub optimal Intake:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Liquid:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL SYMPTOMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(*Frequency: Never, daily, 2-3 times/wk, 1-2 times/wk, &gt;2 weeks, &lt;2 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom:</td>
<td>Frequency *</td>
<td>Duration:</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td></td>
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<tr>
<td><strong>FUNCTIONAL CAPACITY</strong></td>
<td>Duration:</td>
<td></td>
</tr>
<tr>
<td>Description:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Function</td>
<td></td>
<td></td>
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<tr>
<td>Difficulty with ambulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty with activity (patient specific “normal”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed/chair ridden with little or no activity</td>
<td></td>
<td></td>
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<tr>
<td>Improvement in function</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIAGNOSIS/CO-MORBIDITIES RELATED TO NUTRITIONAL NEEDS</strong></td>
<td></td>
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<tr>
<td>Primary diagnosis:</td>
<td>Comorbidities:</td>
<td>Normal requirements:</td>
</tr>
<tr>
<td>Acute Metabolic Stress:</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td><strong>PHYSICAL EXAM</strong></td>
<td></td>
<td></td>
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<tr>
<td>Loss of subcutaneous fat:</td>
<td>Some areas</td>
<td>All areas</td>
</tr>
<tr>
<td>(below eye, triceps, biceps, chest)</td>
<td></td>
<td></td>
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<tr>
<td>Muscle wasting:</td>
<td>Some areas</td>
<td>All areas</td>
</tr>
<tr>
<td>(temples, clavicle, scapula, ribs, quadriceps, calves, knees, interosseous)</td>
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<tr>
<td>Edema (related to undernutrition/use to evaluate weight changes):</td>
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<tr>
<td><strong>OVERALL RATING</strong></td>
<td></td>
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<tr>
<td>6-7 = Very Mild risk to well nourished; most categories or significant/continued improvement</td>
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<tr>
<td>3-5 = Mild/Moderate; No clear sign of normal status or severe malnutrition</td>
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<tr>
<td>1-2 = Severely Malnourished; most categories/significant physical signs of malnutrition</td>
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Malnutrition Inflammation Score (MIS) (Kalantar-Zadeh)

A. Medical history
   A. Change in weight over past 3-6 months
   B. Dietary intake
   C. Gastrointestinal symptoms
   D. Functional capacity
   E. Comorbidity

B. Physical exam (according to SGA criteria)
   A. Decreased fat stores or loss of subcutaneous fat
   B. Signs of muscle wasting

C. Body mass index (BMI)
D. Laboratory results
   A. Serum albumin
   B. Serum transferrin

- PEW was assessed by the MIS developed by Kalantar-Zadeh on IHD.
- SGA: Subjective Global Assessment score.
Malnutrition (undernutrition), low nutrient intake

Comorbid conditions: DM, cardiovascular dz, infection, aging

Endocrine disorders, vitamin D deficiency, ↑PTH

Nutrient loss during dialysis, 

Dialysis Rx related factors, AV graft, dialysis membrane

↓ clearance of inflammatory cytokines

Anorexia, acidosis, anemia

Oxidative & carbonyl stress

Volume overload

↓ nutrient intake, prescribed dietary restrictions

↓ nutrient intake, prescribed dietary restrictions

Kidney Disease Wasting

Malnutrition (undernutrition), low nutrient intake

Protein-energy Wasting (PEW)

Cachexia

Uremic toxins

Hypercatabolism

↓ albumin, transthyretin & lipids

↑ CRP & inflammatory cytokines

↓ weight, ↓ BMI, ↓ body fat, sarcopenia

Survival paradoxes

Atherosclerotic cardiovascular disease, vascular calcification

↑ mortality, ↑ hospitalization, ↓ quality of life

* International Society of Renal Nutrition & Metabolism (ISRN), Wasting in Kidney Disease Consensus paper (KI 2007)
In CKD patients: Amparo FC et al., NDT, 2015

300 CKD St3-5 patients

In Tx recipients: Molnar MZ et al., AJKD, 2010

993 kidney transplant recipients
In CKD patients: Amparo FC et al., NDT, 2015

300 CKD St3-5 patients
**Malnutrition & Quality of Life**

**SF-36 Quality of Life** across Quartiles of Malnutrition-Inflammation Score in 809 Hemodialysis Patients

*Standardized SF-36 quality of life scores in the quartiles of malnutrition-inflammation score in 809 maintenance hemodialysis patients*

Malnutrition and Mortality in 809 Dialysis patients over 5 years

Rambod M, AJKD, 2009

Case-mix variables: age, gender, race/ethnicity, diabetes mellitus, log vintage, primary insurance, marital status, dialysis dose (Kt/V), and kidney residual urine (KRU)

MICS variables: erythropoietin dose, creatinine, hemoglobin, phosphorus, normalized protein catabolic rate (nPCR), bicarbonate, calcium, ferritin, WBC, lymphocyte percentage, and vitamin D dose

Inflammatory variables: CRP, IL-6, TNF-α
In Tx recipients: Molnar MZ et al., AJKD, 2010

993 prevalent kidney transplant recipients
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Rationale

In scientific publications, we generally find the same old statement of "15-75% of the patients on dialysis present symptoms of malnutrition".

This range may be too broad and the issue of prevalence needs revision and precision in the context of more contemporary population descriptions and of the ISRNM criteria.

Objective

To perform a meta-analysis of ALREADY PUBLISHED papers that report on PEW prevalence. Analyze the Global aspects reporting on continent-specific prevalence.

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Methods

• Systematic review and meta-analysis of contemporary cohort studies including >50 CKD patients and reporting on PEW prevalence by either subjective global assessment (SGA) or malnutrition-inflammation score (MIS).
• Searches were restricted to Jan 2000-Nov 2014.
• Reviewers independently identified articles from their assigned geographical regions. Two independent analysts processed and crossed-checked all searches, assessed report-quality and solved discrepancies by contacting the corresponding authors.
• Data was reviewed throughout different CKD strata (pediatric CKD, non-dialyzed CKD, dialysis, renal transplant (Tx) and acute kidney injury (AKI)).
• Because PEW may reflect country-specific malnutrition, studies including dialysis patients were analyzed after clustering by the countries’ Gross National Income (GNI).

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNLM, unpublished data
• No studies including AKI or pediatric patients fulfilled the inclusion criteria for meta-analysis.

• Two studies with a total of 1,067 Tx patients showed a PEW meta-prevalence of 30 (95%CI 28-33)%.

• Among twelve studies including 2,682 non-dialyzed CKD patients, the PEW meta-prevalence was 21(19-22)%.

• There were a total of 124 dialysis studies including 21,972 patients.
HD patients

- 81 eligible studies
- 15,793 enrolled patients
- Overall prevalence 39% (38%-39%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
• 38 eligible studies
• 5,593 enrolled patients
• Overall prevalence 47% (46%-49%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Objectives

1. Malnutrition & Wasting in CKD
2. Appetite & Protein Intake
3. Serum Albumin & Other Biomarkers
4. Nutrition Score & Outcomes in CKD
5. Prevalence of PEW by modalities
6. Worldwide prevalence of PEW by regions
7. Conclusions
North America

- 3 eligible studies
- 995 enrolled patients
- Overall prevalence 54% (51%-57%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
South America

- 16 eligible studies
- 3,146 enrolled patients
- Overall prevalence 46% (44%-47%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
16 eligible studies
3,234 enrolled patients
Overall prevalence 31% (29%-32%)
Southern Europe

- 6 eligible studies
- 618 enrolled patients
- Overall prevalence 38% (34%-42%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Western Europe

- 4 eligible studies
- 2,332 enrolled patients
- Overall prevalence 26% (24%-28%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Eastern Europe

- 3 eligible studies
- 474 enrolled patients
- Overall prevalence 23% (19%-27%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Africa

- 3 eligible studies
- 201 enrolled patients
- Overall prevalence 41% (34%-48%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
- 6 eligible studies
- 581 enrolled patients
- Overall prevalence 30% (27%-34%)

Oceania

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
• 40 eligible studies
• 6,306 enrolled patients
• Overall prevalence 44% (43%-45%)
South East Asia

- 11 eligible studies
- 1,195 enrolled patients
- Overall prevalence 69% (66%-71%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
West Asia

- 16 eligible studies
- 2,890 enrolled patients
- Overall prevalence 45% (44%-47%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Gross National Income – High Income

- HD patients
- 43 eligible studies
- 9,514 enrolled patients
- Overall prevalence 35% (34%-36%)

- PD patients
- 21 eligible studies
- 2,801 enrolled patients
- Overall prevalence 41% (40%-43%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Gross National Income
Upper-middle Income

- HD patients
- 35 eligible studies
- 5,844 enrolled patients
- Overall prevalence 42% (41%-44%)

- PD patients
- 18 eligible studies
- 3,079 enrolled patients
- Overall prevalence 50% (49%-52%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
Gross National Income
Lower-middle and low Income

- HD patients
- 6 eligible studies

558 enrolled patients

Overall prevalence 62% (58%-66%)

PD patients
- 2 eligible studies

299 enrolled patients

- Overall prevalence 74% (69%-78%)

Carrero JJ, Kovesdy CP, Molnar MZ and ISRNM, unpublished data
## Objectives

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Conclusions

- The clinical diagnosis of PEW based on laboratory results, body mass, muscle mass and dietary intake.
- PEW can be reliably assessed with available questionnaires such as MIS and SGA.
- There is a strong correlation between nutritional status and inflammatory markers in patients with kidney disease.
- PEW is common in patients with ESRD (Tx: 30%, HD: 38% and PD: 47%) and also common in patients with CKD (21%).
- The higher PEW prevalence among PD patients deserves further study.
- The prevalence of PEW is strongly correlate with countries’ Gross National Income (GNI).
- PEW is a strong and independent predictor of death and quality of life in patients with kidney disease as well as graft loss in kidney transplant recipients.
Questions?