Nutritional Resilience and Competence:
Predicting Outcomes from Patient Nutritional Trajectories

Michelle Wong, MD, MSc, FRCPC
Renal Research Institute, New York, NY

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**Nutritional competence**
- Being in a state of adequate nutrition
  - No single measurement that provides a complete assessment of nutritional status
  - Therefore, a combination of parameters is necessary

**Nutritional resilience**
- Maintaining an adequate nutritional status in the face of stressors (e.g., intercurrent illness, hospitalization, etc.)
- A dynamic measure
Identifying HD patients at nutritional risk

- At many HD clinics in USA, oral nutritional supplements are administered at dialysis sessions to patients based on albumin criterion.

- Serum albumin has several limitations as a marker of nutritional status:
  - Albumin fluctuates with inflammation and fluid status and has weak correlations with other nutritional parameters.

- There is a need to develop improved strategies for assessing risk of malnutrition/protein-energy wasting and identifying evidence-based criteria for nutritional intervention.
Malnutrition and Wasting in ESRD

“Malnutrition”
- Consequence of insufficient nutrient intake
- Predominantly loss of fat mass

“Protein-energy wasting”
- Occurs in 18% to 75% in adult hemodialysis patients
- Loss of body protein store and energy fuels
- Nutrient intake, inflammation, neuropeptide signaling, insulin resistance, acidosis contribute
- Criteria based on:
  - serum chemistry (albumin, prealbumin, cholesterol)
  - body mass (BMI, body fat %)
  - muscle mass (muscle wasting, mid-arm muscle circumference)
  - dietary intake (low protein and energy intake)

Fouque et al. KI 2008; 73:391-398
Causes of protein-energy wasting

Fouque et al. KI 2008; 73:391-398
How do we assess nutritional competence?

- Nutritional assessment tools:
  - Dietary assessment (interviews, diaries)
  - Body mass index
  - % usual post-dialysis body weight
  - % standard (NHANES II) body weight
  - Subjective global assessment
  - Normalized protein nitrogen appearance
  - Serum albumin, prealbumin, cholesterol, urea, creatinine index
  - Anthropometry: mid arm circumference; skin fold thickness
  - Technical investigations (eg. Bioimpedance, DEXA)
  - Other: creatinine kinetic modelling

KDOQI Guideline on Nutrition, 2000
# Nutritional competence: Guideline targets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>&gt;23 kg/m²*</td>
</tr>
<tr>
<td>Normalized protein nitrogen appearance</td>
<td>&gt;1.0g/kg ideal body weight/day *</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&gt;4.0 g/dL*</td>
</tr>
<tr>
<td>Serum prealbumin</td>
<td>&gt;0.03 g/dL *</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>Above minimal laboratory threshold *</td>
</tr>
<tr>
<td></td>
<td>&gt; 150 to 180 mg/dL **</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt;10 mg/dL**</td>
</tr>
</tbody>
</table>

**KDOQI Guideline on Nutrition, 2000
### Relative risk for mortality by nutritional indicators

<table>
<thead>
<tr>
<th>Nutritional indicator (vs. reference group or per one SD increase)</th>
<th>Adjusted relative risk for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malnutrition by modified subjective global assessment (vs. normal)</td>
<td>1.25 (p&lt;0.05)</td>
</tr>
<tr>
<td>Neutrophil count (per 2800 cells/mm³)</td>
<td>1.09 (p&lt;0.05)</td>
</tr>
<tr>
<td>BMI (per 10%)</td>
<td>0.88 (p&lt;0.001)</td>
</tr>
<tr>
<td>Creatinine (per 3.7 mg/dL)</td>
<td>0.85 (p&lt;0.001)</td>
</tr>
<tr>
<td>Albumin (per 0.56 g/dL)</td>
<td>0.78 (p&lt;0.001)</td>
</tr>
<tr>
<td>Change in albumin (per 20%)</td>
<td>0.78 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Pifer et al. KI 2002 62:2238-45 (DOPPS)
Albumin and Hazard Ratios of Mortality

Source: 2011 Mortality Study, FMC NA, N=116,259
Nutritional Resilience and trajectory of serum albumin

- An important determinant of outcomes is not only the absolute serum albumin level but also the trajectory of albumin

Therefore, the slope of albumin change is an indicator of nutritional resilience

Trends in Albumin

Source: RRI, N = 3054
Incident patients divided into declining, stable, and increasing albumin levels between months 7 to 12 from start of dialysis.

8% of patients are clearly “increasers”.
Most patients are stable.
4% of patients are clearly “decliners”.

Source: FMCNA KC patients
Outcomes in patients with stable albumin levels

Source: MONDO
N=12,952

Hazard Ratio

<table>
<thead>
<tr>
<th>Albumin</th>
<th>USA</th>
<th>Latin America</th>
<th>Europe</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5</td>
<td>1.8</td>
<td>0.8</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>0.7</td>
<td>1.0</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Patients with declining albumin levels have poorer outcomes.

Source: MONDO
N=12,952
Other nutritional parameters during 1\textsuperscript{st} year of HD

**Creatinine**

- Survived
- Died

**Phosphorus**

- Survived
- Died

**enPCR**

- Survived
- Died

Source: Renal Research Institute patients
Other nutritional parameters during 1\textsuperscript{st} year of HD

**Volume of distribution of urea**

- **Survived**
- **Died**

![Graph showing the volume of distribution of urea over months before event.](image)

**Pre-HD weight**

- **Survived**
- **Died**

![Graph showing pre-HD weight over weeks before event.](image)

Source: Renal Research Institute patients
Serum albumin and neutrophil/lymphocyte ratio over 1st year of HD

Serum albumin

Neutrophil to Lymphocyte ratio = NLR

NLR = a marker of inflammation

Source: Renal Research Institute patients
Evolution of Nutritional Parameters Over the First Two Years on Hemodialysis

- Albumin
- Creatinine
- Interdialytic weight gain
- Phosphorus
- enPCR

Month 1
Month 6
Month 12
Month 24
A Simple Composite Nutritional Score

A composite nutritional score was created by converting the raw component variables to z scores and generating a linear composite.

The component variables used were:
- Albumin
- Creatinine
- Phosphorus
- enPCR
- IDWG

The evolution of this Nutritional Score (converted to percentiles) was tracked in incident patients over the first two years on HD and over two years before death in patients who died.
Evolution of Nutritional Composite Score in First Two Years on Hemodialysis
(using albumin, creatinine, phosphorus, IDWG and enPCR)

N=21,754 HD patients who survived ≥ 4 years on HD
Evolution of nutritional score before death

Evolution of Nutritional Score in HD patients before death

N=12,104 patients who survived ≥ 4 years on HD
Body composition and survival in incident HD patients

- Estimated subcutaneous adipose tissue mass
- Estimated muscle mass

Source: RRI, N=1598 African American pts
Body Composition and mortality

- Analysis of data from FMC European Clinical Database, N=566 with body composition data
  - Median age 65 yr
  - Median vintage 1.85 yr
  - 58% male

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard ratio for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.032 (p=0.006)</td>
</tr>
<tr>
<td>Vintage (years)</td>
<td>1.059 (p=0.029)</td>
</tr>
<tr>
<td>Fat mass (% of weight)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Lean tissue mass (% of weight)</td>
<td>0.960 (p=0.001)</td>
</tr>
</tbody>
</table>

Source: FMC EuCliD data from Dr. Daniele Marcelli
Nutritional Resilience

Nutritional Resilience is the ability to resist the negative consequences of any challenges to the maintenance of Nutritional Competence.
Analyzing nutritional resilience

- How does a physiologic stress, such as hospitalization, affect nutritional status?
- What are predictors of those who decline in nutritional status vs. those who are nutritionally resilient with hospitalization?

Population:
- N = 15347 Fresenius Medical Care North America hemodialysis patients with vintage ≥2.5 years, and first hospitalization for 7-14 days during 2006-2011

Outcome/analysis:
- Change in albumin, creatinine, phosphate, IDWG, enPCR over 6 months prior to and after hospitalization
- Change in composite Z-score over 6 months prior to and after hospitalization
- Subgroup analyses: hospitalization diagnosis grouping and patients with re-hospitalization
Changes in albumin (>5%) with type of hospitalization

Source: FMCNA, 2007-2011, N=31632 patients with hospitalization. Changes in albumin within 30 days before and after 1st admission
Nutritional Parameters Around Hospitalization Event

Units
Albumin: g/dL
Creatinine: mg/dL
Phosphorus: mg/dL
Interdialytic weight gain: kg
enPCR: g/kg/d
± 95% confidence interval
N=12,249 HD patients
Time Course of Nutritional Composite Score Around Hospitalization Event
(using albumin, creatinine, phosphorus, IDWG, enPCR)

N=14791 HD patients
Trajectories by hospitalization diagnosis

- Infectious
  - N=3424
- Circulatory system
  - N=2958
- Digestive system
  - N=1603
Nutritional trajectories of Rehospitalized vs. non-rehospitalized patients

Rehospitalized within 6 months
N=8784

Not rehospitalized within 6 months
N=5967
Nutritional Scores
# Nutritional scores in dialysis patients

<table>
<thead>
<tr>
<th>Nutritional Score</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite nutritional index</td>
<td>Harty 1994</td>
</tr>
<tr>
<td>Dialysis Malnutrition score</td>
<td>Kalantar-Zadeh 1999</td>
</tr>
<tr>
<td>Protein-Energy Malnutrition score</td>
<td>Herselman 2000</td>
</tr>
<tr>
<td>Malnutrition-Inflammation Score</td>
<td>Kalantar-Zadeh 2001</td>
</tr>
<tr>
<td>Geriatric nutritional risk index</td>
<td>Yamada 2008</td>
</tr>
<tr>
<td>Objective score of nutrition</td>
<td>Beberashvili 2010</td>
</tr>
<tr>
<td>Composite score of protein-energy nutritional status</td>
<td>Mazairac 2011</td>
</tr>
<tr>
<td></td>
<td>Composite nutritional index</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Albumin</td>
<td>√</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Transferrin or TIBC</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
<tr>
<td>nPNA</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>√</td>
</tr>
<tr>
<td>(triceps, subscapular)</td>
<td></td>
</tr>
<tr>
<td>Arm circumference or muscle area</td>
<td>√</td>
</tr>
<tr>
<td>% reference weight</td>
<td>√</td>
</tr>
<tr>
<td>Fat mass &amp; Fat-free mass</td>
<td>√</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
</tr>
<tr>
<td>Loss of subcutaneous fat</td>
<td>√</td>
</tr>
<tr>
<td>Weight change</td>
<td>√</td>
</tr>
<tr>
<td>Dietary intake</td>
<td>√</td>
</tr>
<tr>
<td>GI symptoms</td>
<td></td>
</tr>
<tr>
<td>Functional capacity</td>
<td>√</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td></td>
</tr>
</tbody>
</table>
Longitudinal performance of nutritional scores

- Very limited data

- Recent study of N=75 chronic HD patients in Israel that performed serial monitoring of 2 nutritional scores over 18 months:
  - **Malnutrition-inflammation score** (0 = normal, 30=severely malnourished): Longitudinal changes correlated with nutritional biomarkers and were significantly associated with hospitalization (HR 1.14, 95% CI 1.06-1.22 for each 1-unit increase in score) and mortality (HR 1.12, 95% CI 1.01-1.24)
  - **Geriatric nutritional risk index** (score <90 indicates poor nutritional status) Associated with hospitalization (HR 0.98, 95% CI 0.97-0.99 for each 1-unit increase in score) but not with mortality

Goals of developing a new nutritional score

- To combine several nutritional parameters into separate scores in prevalent (vintage ≥ 12 months) and incident patients that predict hospitalization and mortality over 1 year.
- To aid in identifying hemodialysis patients at highest nutritional risk.
- To provide groundwork for future randomized controlled trials assessing the optimal use of nutritional supplements and other interventions.
Methods

- Large retrospective study of FMCNA patients on chronic hemodialysis
- Nut
- Outcomes assessed over 1 year (2012)
- Cohort divided 2:1:1 for model development, cut-off determination, & testing, respectively
  - N=25,539 for mortality dataset
  - N=27,451 for hospitalization dataset
- Statistical modeling:
  - Generalized linear model (GLM)
  - Generalized additive model (GAM)
  - Machine learning methods
Nutritional score variables

- age
- gender
- diabetes comorbidity
- CHF comorbidity
- GI bleeding comorbidity
- vintage
- residual renal function
- race

- serum creatinine
- serum albumin
- serum phosphorus
- equilibrated normalized PCR
- IDWG
- BMI
- post-HD weight
- serum BUN
- volume of distribution of urea
- serum prealbumin
- serum cholesterol
- Serum bicarbonate
- Neutrophil-to-lymphocyte ratio
- Trajectories of above parameters
Results: Mortality prediction

Best model included the following variables:
- Neutrophil-to-lymphocyte slope
- Serum bicarbonate slope
- Serum albumin
- Serum creatinine
- Serum phosphate
- Sex
- Age
- Dialysis vintage
- Residual renal function
Results: Hospitalization prediction

- Best model included the following variables:
  - NLR slope
  - Serum bicarbonate slope
  - Serum phosphate slope
  - IDWG slope
  - Pre-HD urea slope
  - Serum phosphate slope
  - Serum creatinine slope
  - NLR
  - enPCR
  - Serum creatinine
  - Serum albumin
  - IDWG
  - Post-HD weight
  - Volume of distribution of urea
  - Dialysis vintage
  - Age
  - Sex
  - Diabetes
  - GI bleeding
  - Congestive heart failure

- Hospitalization rate of 6 per year had best predictive power
How does these models perform in comparison to current criteria for oral nutritional supplements?

<table>
<thead>
<tr>
<th></th>
<th>Area under the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best prediction model</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.84</td>
</tr>
<tr>
<td>Hospitalization (&gt;6 hospitalizations/year)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* Current criterion for oral nutritional supplements at Fresenius North America clinics
Potential advantages of the new nutritional score

- Large sample size
- Outcome-based score
- Distinct nutritional scores for incident patients and prevalent patients
- Can incorporates slopes of nutritional parameters into prevalent patient score
  - Eg. albumin trajectory over past 6 months
Challenges to developing a nutritional risk score

- Nutrition is just one component associated with patient outcomes
  - **Cardiovascular disease & inflammation** affect nutrition & also have direct impact on outcomes
  - Socioeconomic factors also play a role
Conclusions

- **Nutritional Competence** refers to having an adequate nutritional status, which must be assessed using multiple nutritional parameters.

- **Nutritional Resilience** is the ability to resist the negative consequences of any challenges to the maintenance of Nutritional Competence.

- **Low absolute serum albumin** and **trajectory of albumin** are associated with mortality and hospitalizations, but albumin has limitations as a marker of nutritional status.

- **Body composition** is a nutritional parameter that is related to outcomes.

- A **new nutritional score** incorporating multiple nutritional parameters and their trajectories (slopes) can assist in predicting hospitalization and mortality.
Thank you

- Dr. Stephan Thijsse
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- Leslie Xiao
- Dr. Peter Kotanko
- Dr. Franklin W. Maddux