Protein-Energy Kaybinin Etyolojisinde Beslenmenin, Renal Replasman Tedavisinin ve Inflamasyonun Rolu

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Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease.
Simplified flow schedule of uremia and its complications

Renal failure

Retention of Na and water
- Edema
  - Arterial hypertension
    - Ocular disturbances
      - Peripheral neuropathy
      - Malnutrition
      - Pruritus
      - Immune depression
      - Convulsions
      - Gall. rhythm.
      - Infectious diseases
      - Pulmonary edema
      - Pseudo-gout

Retention of potassium
- Potassium intoxication
  - Arrhythmias
    - Anorexia
      - Anemia
  - Hypertriglyceridemia
    - Hypertension
      - Ocular disturbances
      - Pruritus
      - Immune depression
      - Convulsions
      - Gall. rhythm.
      - Infectious diseases
      - Pulmonary edema

Retention of phosphate
- Renin excess
  - Glucose intolerance
    - Erythropoietin deficiency
      - Bone dissolution
        - Deficient conversion of vitamin D into active products
          - Resistance to PTH
            - Resistance to vitamin D
              - Osteitis fibrosa
                - Bone pain
                  - Decreased insulin metabolism
                    - Osteomalacia
                      - Rickets

Retention of toxic metabolites
- Hemolysis
  - Bleeding tendency
    - Hypocalcemia
      - Secondary hyperparathyroidism
        - Osteosclerosis
          - Skeletal deformities
            - Pericarditis
              - Peripheral ischemia
                - Arteriosclerosis
                  - Cardiac failure
                    - Gastrointestinal bleeding
                      - Cardiac tamponade
                        - Spontaneous bone fractures
Uremik Protein Energy Kaybina Hedefli yaklaşımda:

**Dialytic Factors**
- Bioincompatibility ✅
- Inadequate Dose of Dialysis ✅
- Nutrient Losses ❌
- Increased Energy Expenditure ✅

**“Inadequate” Nutrient Intake**
- ✅
- ❌

**Protein-Energy Wasting**

**Other Factors**
- Co-morbidities
  - Inflammation, DM ❌
- Frequent Hospitalizations ❌
- Metabolic & Hormonal Derangements ❌
Uremik Ultrafiltrate ve Agizdan Besin (Protein) Alimi

Modified from Anderstam, Mamoun & Bergstrom JASN 1996
Dietary Protein Intake and Daily Creatinine Excretion During Progression of Renal Disease

Ikizler JASN 1995
Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients

Kamyar Kalantar-Zadeh, Giadyz Block, Charles J McAllister, Michael H Humphreys, and Joel D Kopp
Membranların biyokimyasal yapısı
- HD membranları ile ilişkili kompleman aktivasyonu ile birlikte protein katabolizmasında artış
  - Gutierrez & Bergstrom Kidney Int 1990

Membran porlarının boyutu
- Hemodiyaliz sırasında amino asit kaybı (? Daha geniş porlardan daha yüksek kayıplar)
  - Wolfson & Kopple Kidney Int 1989
  - İkizler & Hakim Kidney Int 1994
Dializ Esnasında Onlenemez Amino Acid Kaybi: Degisik Dializorlerin Etkisi

İkizler & Hakim 1994 Kidney Int
Arterial Plasma Essential Amino Acids (µmol/L)

Arterial Plasma Total Amino Acids (µmol/L)

Ikizler et al, AJP, 2002
Hemodializ’e Bagli Net Tum-Vucut Protein Kaybi

<table>
<thead>
<tr>
<th></th>
<th>proteolysis</th>
<th>synthesis</th>
<th>net balance</th>
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<tbody>
<tr>
<td>B</td>
<td>10%</td>
<td>11%</td>
<td>*</td>
</tr>
<tr>
<td>D</td>
<td>96%</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>PD</td>
<td>21%</td>
<td></td>
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</table>

Ikizler et al, AJP, 2002
Plazma arteriyel aminoasit konstantrasyonları
Intradialytik Nutrusyon ile artmaktadır

- Total AA
- Esansiyel olmayan
- Esansiyel AA
- Dalli zincirli AA ($\mu$mol/L)

![Graph](image)

Pupim et al, JCI, 2002
Figure 1 | Schematic representation of the causes and manifestations of the protein–energy wasting syndrome in kidney disease.
Prevalence of malnutrition, inflammation and atherosclerosis in predialysis patients

- Malnutrition: 44%
- Inflammation: 32%
- Carotid plaque: 72%

53% with inflammation
32% with malnutrition
72% with inflammation and malnutrition

N = 109

Stenvinkel et al. 
*Kidney Int* 1999
SDB Hastalarında Inflamasyona Yol Acan Sebepler

INFLAMMATION

- Uremic Toxins
  - Loss of Kidney Function

- Oxidative Stress
  - Insulin Resistance

Co-Morbidities

- Atherosclerosis
- Infections
- Diabetes Mellitus

Renal Replacement Therapy

- Endotoxin
- Vascular Access
- Bioincompatibility
Inflammation is Associated with Loss of Kidney Function

Pupim, Himmelfarb, Ikizler
Kidney Int 2004
Inflammatory Signals Associated With Hemodialysis

Caglar, Pupim, Ikizler, *KI*, 2002
Hemodializ’e Bagli Net Tum-Vucut Protein Kaybi

Inflamasyon’un katkısı

Ikizler et al, AJP, 2002
Systemic Inflammatory Response Syndrome

Tissue Injury

Activation of IL-1, TNF, IL-6

Activation of other cytokines

Acute phase response
CRP, Albumin, SAA

Biological activities
Metabolic Effects of Inflammation

- Muscle Loss
- Anorexia
- Increased REE
- Uremia
- Complement Activation
- Fever
- Increased SNS Activity
- Immune System Modulation
- App Synthesis
Continuous IL-1 Infusion Leads to Decreased Food Intake

Fig. 2. Daily food intake (g) during experimental period for saline (□), semistarved (●), and chronic IL-1 (○) groups of rats. Values are means ± SE; n = 8/group.

* P < 0.0001 vs Semi-starved and Chronic-IL-1

Ling et al
JCI 1996
Serum **Interleukin-6** and Appetite in 331 Hemodialysis Patients

![Graph showing serum interleukin-6 levels in normal and diminished appetite categories.](image)

ANOVA

\[ p = 0.004^* \]

(*logarithmic scale)

Potential Pharmacological Strategies Using Inflammation and Oxidative Stress as a Target

- Statins
- Tocopherols

Randomized double-blind placebo controlled trial
- 57 HD-pts completed the study
- 8 weeks
- 308 mg $\gamma$-tocopherol and 800 mg docosahexaenoic acid (DHA)

An Anti-Inflammatory and Antioxidant Nutritional Supplement for Hypoalbuminemic Hemodialysis Patients: A Pilot/Feasibility Study

**Figure 1.** Serum albumin changes in both groups of hypoalbuminemic MHD patients.

Kamyar Kalantar-Zadeh, MD, PhD, MPH, *,† Amy Broglio, RD, ††
Joanne Chow, RD, †† Oum Kwon, MD, PhD, *,†† Noriko Kawae, MD, *‡
Sara Coleman, RD, § David B. Cockram, PhD, RD, || and Joel D. Koppal, MD, *¶
IL-1 Beta Inhibition Improves Chronic Inflammation in Hemodialysis Patients

Hung & Ikizler et al. JASN 2010 in press
IL-1 Beta Inhibition Improves Chronic Inflammation in Hemodialysis Patients

Hung, Ikizler JASN. 2011 Mar;22(3):437-42
Nutritional Biomarkers at Baseline and Post Intervention by Randomization Group

**Prealbumin, mg/dl**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post</th>
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<tbody>
<tr>
<td>IL-1ra</td>
<td>38.16</td>
<td>46.43</td>
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<tr>
<td>Placebo</td>
<td>31.86</td>
<td>33.57</td>
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**Albumin, g/dl**

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<tbody>
<tr>
<td>IL-1ra</td>
<td>4.03</td>
<td>4.26</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.93</td>
<td>3.95</td>
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</table>

**Lean Body, gm**

<table>
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<th>Baseline</th>
<th>Post</th>
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</thead>
<tbody>
<tr>
<td>IL-1ra</td>
<td>55.73</td>
<td>59.13</td>
</tr>
<tr>
<td>Placebo</td>
<td>50.57</td>
<td>50.38</td>
</tr>
</tbody>
</table>

Hung, Ikizler JASN. 2011 Mar;22(3):437-42
Üremik protein enerji kaybı sendromunun etiyolojisi multifaktoriyeldir.

↓ diyetin azalması + HD ilişkili katabolizma + Inflamasyon + Insulin resistance -> tüketme -> mortalite ve morbiditede ↑

Nutrisyonel müdahaleler -> uygun ve emniyetli;
IDPN ve Oral besinler HD ilişkili katabolizması parsiyel olarak geri döndürebilir
(primer olarak aminoasit havuzunu yeniden doldurarak)
Metabolic Paradigm for Uremic Wasting and Treatment Options
