ALBUMIN AND INFLAMMATION

IPRO ESRD Network of New England

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Disclosures

- I am employed by Fresenius Medical Care as the Lead Dietitian for New England and a Renal Dietitian at the Newburyport Dialysis Clinic
- I have no commercial relationships relevant to the topic being presented

Objectives

- Define albumin and inflammation and the relationship between the two specifically in the ESRD patient population.
- Answer the following questions:
  - Is albumin a good marker of nutrition status in the end stage renal disease (ESRD) patient population?
  - Is albumin an important prognostic lab value to be evaluated in the ESRD patient population?
  - What can the interdisciplinary team (IDT) do to positively impact albumin levels in our patient population?

Albumin

- Albumin, the body's predominant serum-binding protein, has several important functions.
- Albumin comprises 75-80% of normal plasma colloid oncotic pressure and 50% of protein content. When plasma proteins, especially albumin, no longer sustain sufficient colloid osmotic pressure to counterbalance hydrostatic pressure, edema develops.
- Albumin transports various substances, including bilirubin, fatty acids, metals, ions, hormones, and exogenous drugs. One consequence of hypoalbuminemia is that drugs that are usually protein bound are free in the plasma, allowing for higher drug levels, more rapid hepatic metabolism, or both.

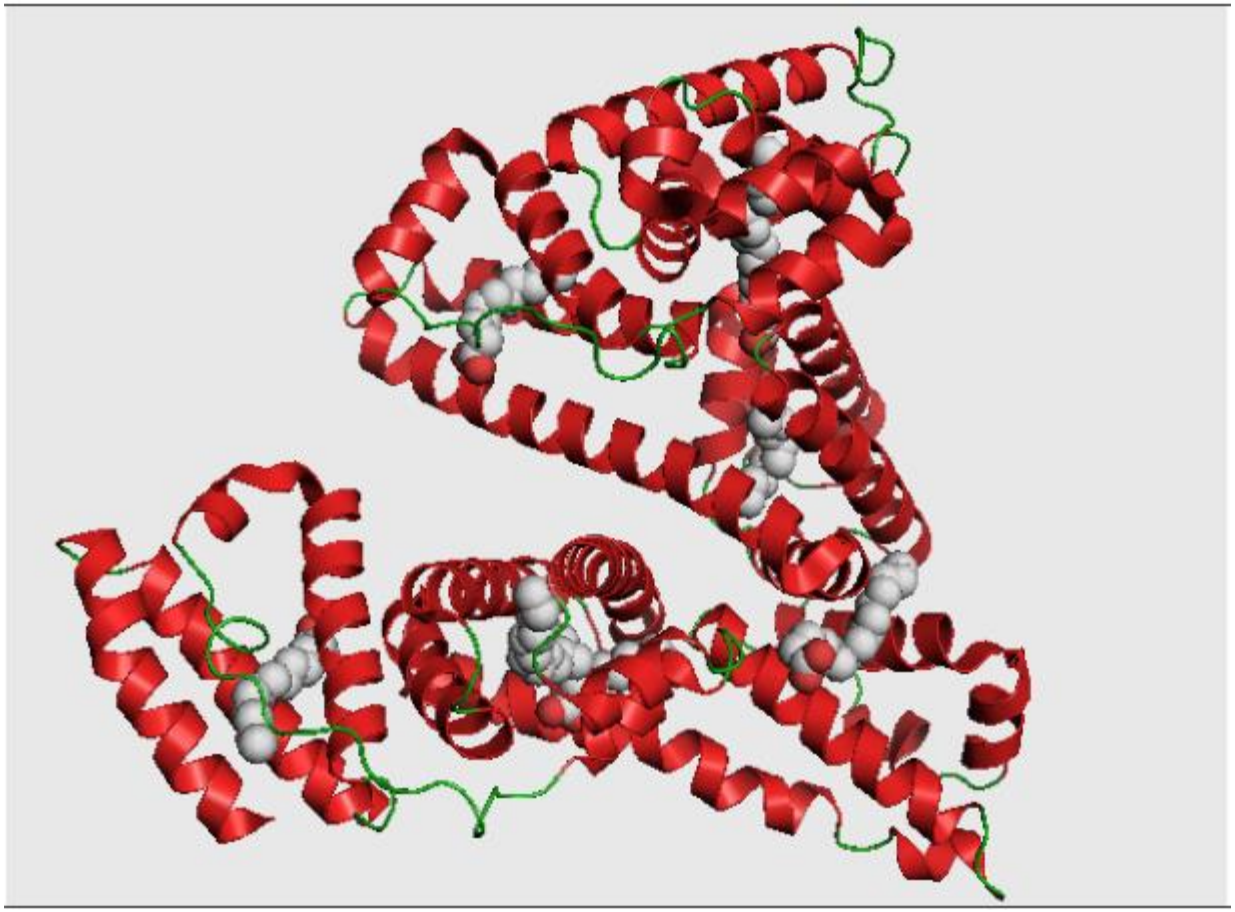
Peralta, R, “Hypoalbuminemia,” Medscape, April 1, 2015

Albumin

- Reference serum values range from 3.5-4.5 g/dL. Synthesis occurs only in hepatic cells at a rate of approximately 15 g/d in a healthy person, but the rate can vary significantly with various types of physiologic stress. The half-life of albumin is approximately 21 days.
- Hypoalbuminemia is a common problem among persons with acute and chronic medical conditions. At the time of hospital admission, 20% of patients have hypoalbuminemia. Hypoalbuminemia can be caused by various conditions, including nephrotic syndrome, hepatic cirrhosis, heart failure, and malnutrition; however, most cases of hypoalbuminemia are caused by acute and chronic inflammatory responses.
- Serum albumin level is an important prognostic indicator. Among hospitalized patients, lower serum albumin levels correlate with an increased risk of morbidity and mortality.

Peralta, R, “Hypoalbuminemia,” Medscape, April 1, 2015

Albumin



Peralta, R, “Hypoalbuminemia,” Medscape, April 1, 2015

Albumin in ESRD

- Albumin levels are lower in dialysis patients than among the general population and are a powerful predictor of mortality.
- There has been little or no progress in increasing albumin levels in the prevalent dialysis patient population in over 10 years, despite the wide introduction of biocompatible dialyzers and a trend toward increasing dialysis dose.
- Albumin levels are controlled by the rate of albumin synthesis, albumin fractional catabolic rate (FCR), and albumin distribution between the vascular and extravascular compartment. These in turn are affected by both nutrition and, since albumin is a negative acute-phase protein, by inflammation.
- Plasma volume expansion can dilute the plasma pool (hemodilution) in the dialysis patient.

Kaysen, Kidney International, Vol. 64, Supplement 87 (2003), pp. S92-S98

Albumin in ESRD

- Many studies have shown the predictive power of serum albumin for clinical outcomes especially in the ESRD population.
- Serum albumin levels below 2.5 g/dL have been associated with a risk of death 20 times greater as compared to the reference level of 4.0-4.5 g/dL in HD.
- Serum albumin levels of 3.5-3.9 g/dL were associated with double the risk of death.
- Serum albumin levels are considered indicators of quality of care at most dialysis facilities and may be included as a parameter of quality by the Centers for Medicare and Medicaid Services (CMS) in the future.

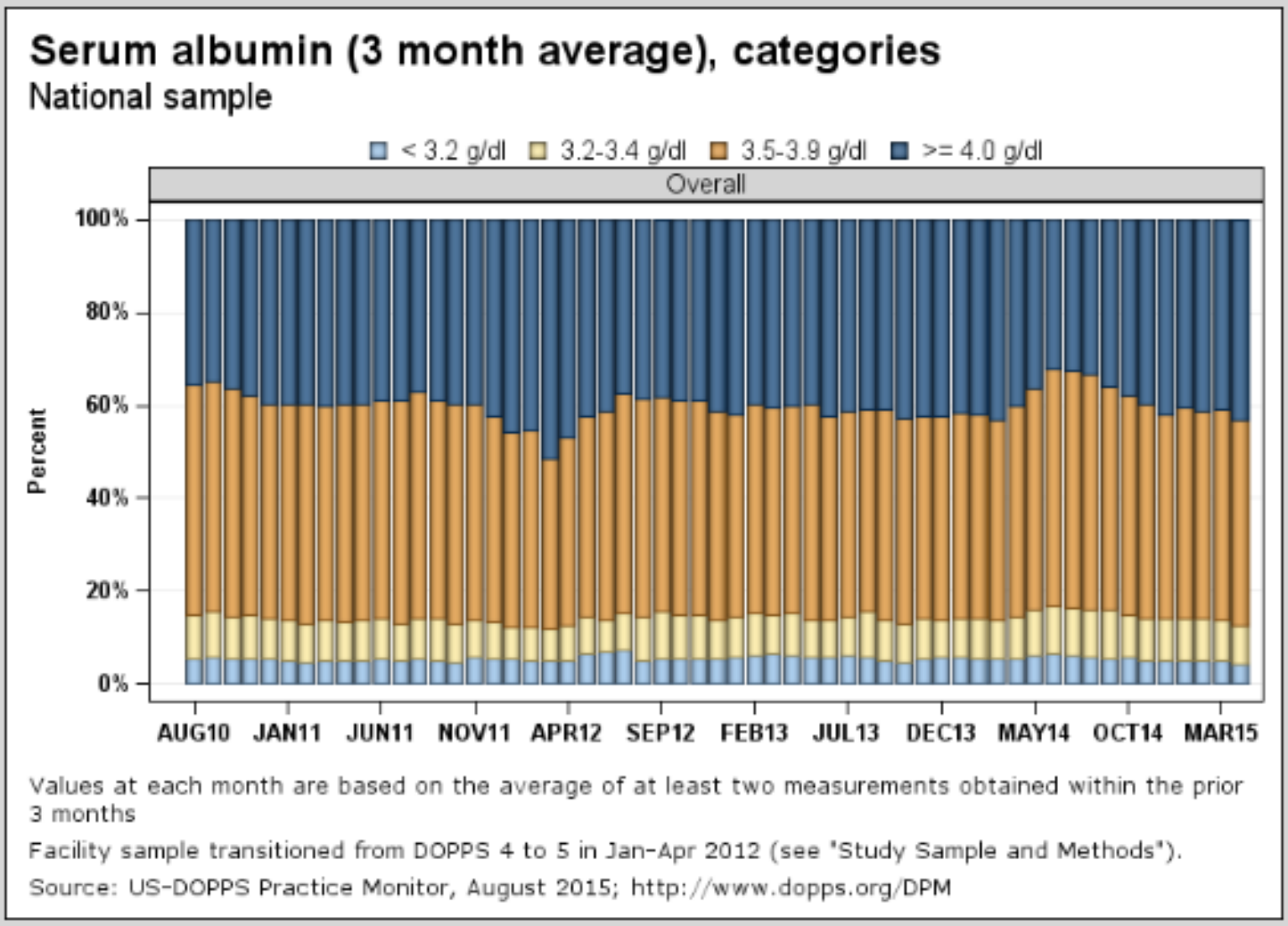
Nutritional Management of Renal Disease, Kopple et al, 3rd ed., 2013, pg. 140 and Sridhar and Josyula *BMC Nephrology* 2013, 14:242

Protein Loss in Dialysis

- Hemodialysis:
  - Protein loss is dependent on the dialyzer type used (Reuse Dialyzers allow for higher protein loss)
  - Average Protein losses via hemodialysis 5-8 grams per HD session
  - Additional .6 – 1.6 gram protein loss related to expected blood loss of a regular dialysis session (5-10 mL of blood)
- Peritoneal Dialysis:
  - Varies considerably from patient to patient
  - Based on prescription and membrane transport
  - Potentially 2.0 to 15.0 g/day
  - However, the average loss is 6.0 to 8.0 g/day
  - Average protein loss of 10-25 g/day during peritonitis episodes

*Nutritional Management of Renal Disease, Kopple et al , 3rd ed., 2013 pg. 542-543.

Albumin in ESRD

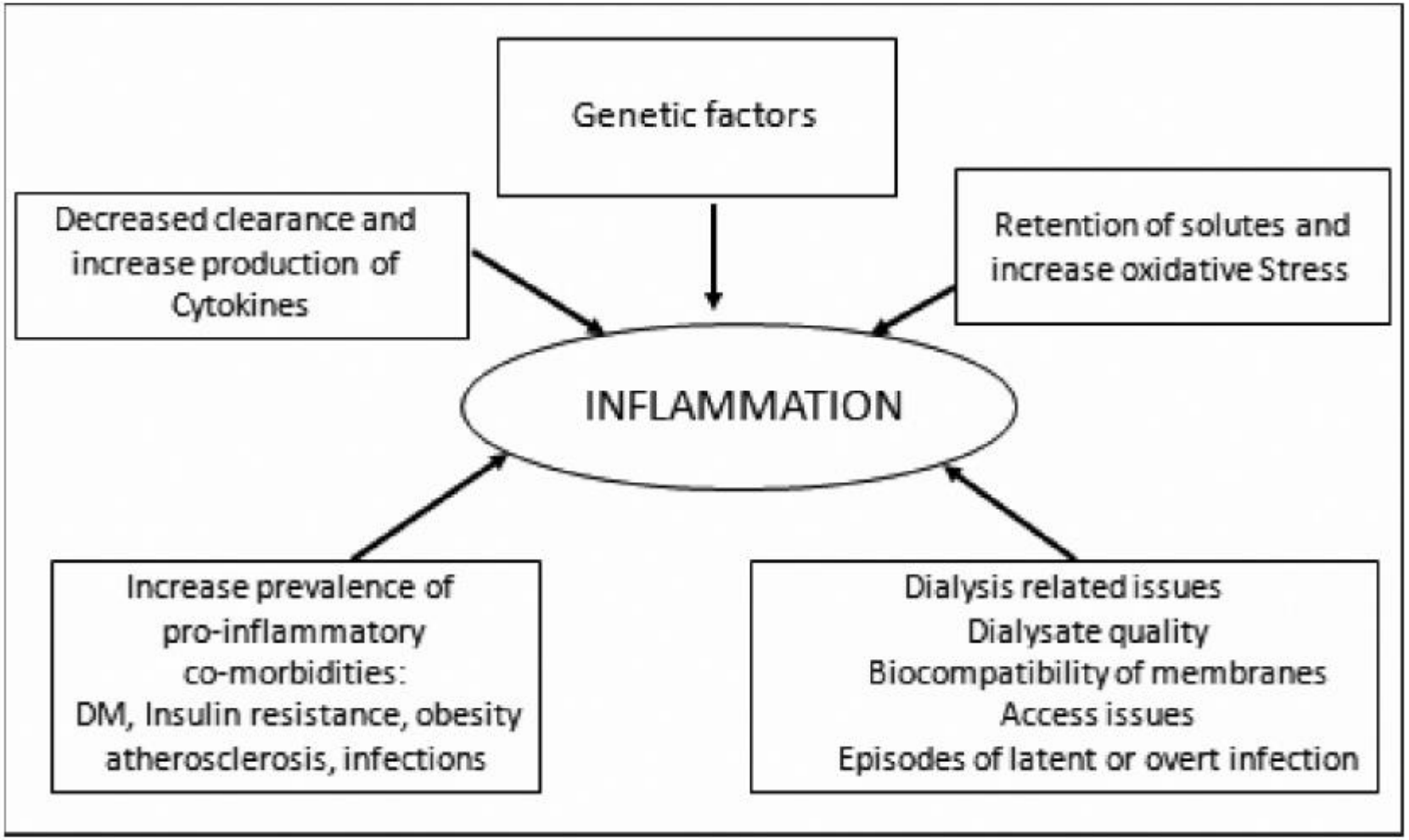


Inflammation

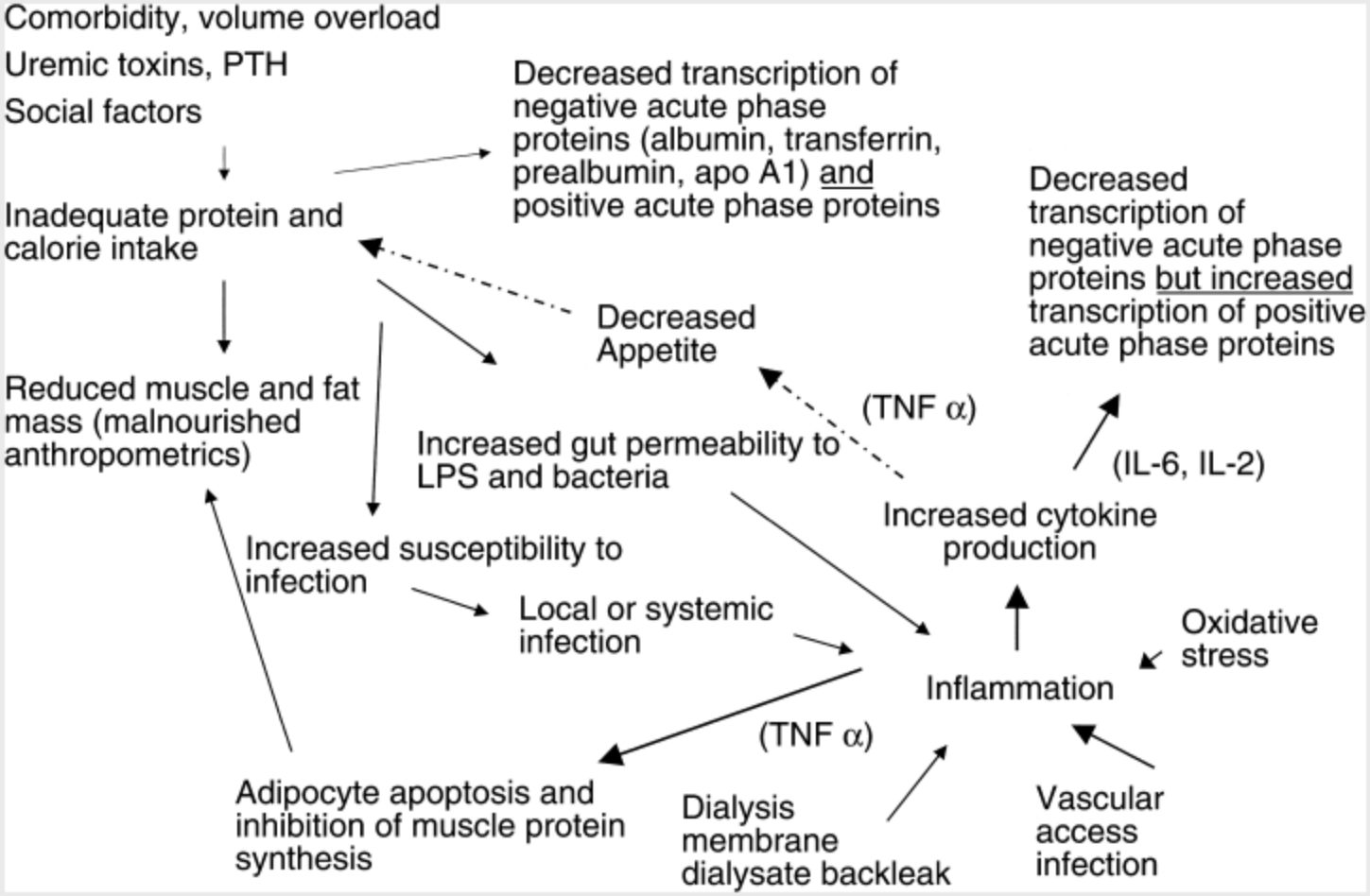
- Inflammation may be defined as a complex biologic response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.
- In ESRD there is a persistent low-grade inflammation, the systemic concentrations of both pro- and anti-inflammatory cytokines are several-fold higher than in the general population; due to both decreased renal clearance and increased production.
- Several factors, both dialysis related (e.g. membrane bioincompatibility) and non-dialysis related (e.g. infection, comorbidity, genetic factors, diet, etc.) may additionally contribute to a state of persistent inflammation

Persistent Inflammation as a Catalyst for Other Risk Factors in Chronic Kidney Disease: A Hypothesis Proposal, Carrero et al, Clin J Am Soc Nephol 4: S49-S55, 2009

Inflammation



Hung, A, Ikizler, ASeminars in Dialysis—Vol 21, No 5 (September–October) 2008 pp. 401–404



Relationships between inflammation, decreased nutrient intake, protein, malnutrition, and change in serum protein composition and muscle mass. Inflammation and malnutrition lead to decreased synthesis of visceral proteins. Cytokines, as well as uremic toxins, also reduce appetite, adding to the effect of inflammation on visceral protein levels. Tumor necrosis factor α (TFNα) also causes apoptosis of adipocytes and decreases muscle protein synthesis, impeding recovery from malnutrition.

Kaysen, Kidney International, Vol. 64, Supplement 87 (2003), pp. S92-S98

Albumin and Inflammation

- It is unusual to find serum albumin decreased to values less than 3.0 g/dL in the absence of both inflammation and malnutrition.
- Consider the controlled Minnesota study, and what is described for subjects with pure anorexia nervosa, as nPCR declines in dialysis patients, so does serum albumin concentration, and the quantity of this decline is dependent upon the incident level of CRP. These observations suggest that dialysis patients are subject to stresses beyond protein and calorie restriction alone, and that one important factor in this relationship is that imparted by inflammation.

Kaysen, Kidney International, Vol. 64, Supplement 87 (2003), pp. S92-S98

The Minnesota Experiment

- Study done and the University of Minnesota 1944-45 to investigate the effects of severe and prolonged dietary restrictions and re-feeding strategies.
- Subjects were mostly conscientious objectors to WWII.
- Results not published until 1950 but preliminary results were used by aid workers in Europe and Asia after the war.
- 32 healthy volunteers were subjected to semi-starvation (1500 kcal/ 24 h) for 6 months.
- Despite a 23% reduction in body weight (from 69.3 to 53.6 kg, BMI from 21.7 to 16.4) and muscle mass, serum albumin decreased only moderately (from 4.28 to 3.86 g/dL)
- This study suggests that when serum albumin concentration was reduced to very low levels that additional processes contribute.

Kaysen, Kidney International, Vol. 64, Supplement 87 (2003), pp. S92-S98 and Friedman et al, J Am Soc Nephrology 2010

Acute Phase-Reactant Markers in ESRD

Positive Acute-Phase Reactants	Negative Acute-Phase Reactants
Proinflammatory cytokines	Nutritional markers
IL-6	Albumin
TNF-α (cachechtin)	Transferrin or TIBC
Other interleukins (IL-1β, etc)	Prealbumin (transthyretin)
Other positive acute-phase reactants	Cholesterol
CRP	Leptin?
Serum amyloid A	Other negative acute-phase reactants
Ferritin	Histidine-rich glycoprotein
Fibrinogen, α_1-antitrypsin T, haptoglobin	

Kalantar-Zdeh at el AJKD vol 42, #5 (November) 2002

C-Reactive Protein (CRP)

- CRP is a positive acute-phase reactant (APR) that correlates negatively with serum visceral protein concentrations.
- During inflammatory processes there is release of cytokines, which mediate an increase in hepatic synthesis of APR as CRP and suppression of the synthesis of negative-phase reactants, such as albumin.
- In chronic inflammation, CRP (Normal range <1mg/L) may be slightly but persistently increased which can predispose to an increased risk of atherosclerotic cardiovascular disease (CVD; CRP 1-3 mg/L).
- In many maintenance HD patients, CRP levels are persistently between 5 and 50 mg/L, although they may fluctuate widely (CRP half life 19 hrs).

KDIGO: CRP Guidelines

- Guideline VII.5.2
- A. Patients with CRP >8 mg/L should be screened for silent infection of hemodialysis access grafts, periodontitis or any low-grade infection.

  (Evidence level: B)
- B. In patients with elevated CRP >8 mg/lL biocompatibility of dialyzer membrane and hemodialysis fluid quality should be checked (see Sections III and IV).

  (Evidence level: B)

Pro-inflammatory Cytokines

- Il-6: from T-cell and macrophages to stimulate immune system response to stress/trauma
- TNF-α: a cytokine involved in a systemic inflammation, it regulates the immune cells, and induces apoptosis (process to program cell death)
  - Acute inflammation
  - Inhibition of tumor genesis
  - Inhibition of viral replication
- Cytokines are not limited to their immune-modulatory role. For instance, cytokines are also involved in several developmental processes during embryo development.

Gregory CD, Devitt D; Immunology 2004, Sept 113(1):1-14

Table 3. Possible Causes of Inflammation in Patients With CKD and ESRD

- Causes of inflammation from CKD or decreased glomerular filtration rate
  - Decreased clearance of proinflammatory cytokines
  - Volume overload*
  - Oxidative stress (eg, oxygen radicals)*
  - Carbonyl stress (eg, pentosidine and advanced glycation end products)
  - Decreased levels of antioxidants (eg, vitamin E, vitamin C, carotenoids, selenium, glutathione)*
  - Deteriorating protein-energy nutritional state and food intake*
- Coexistence of comorbid conditions
  - Inflammatory diseases with kidney involvement (eg, systemic lupus erythematosus; AIDS)
  - Increased prevalence of comorbid conditions (eg, cardiovascular disease; diabetes mellitus; advanced age)*
- Additional inflammatory factors related to dialysis treatment
  - Hemodialysis:
    - Exposure to dialysis tubing
    - Dialysis membranes with decreased biocompatibility (eg, cuprophane)
    - Impurities in dialysis water and/or dialysate
    - Backfiltration or backdiffusion of contaminants
    - Foreign bodies (such as polytetonfluoroethylene) in dialysis access grafts
    - Intravenous catheter
  - Peritoneal dialysis:
    - Episodes of overt or latent peritonitis*
    - Pcritoneal dialysis catheter as a foreign body and its related infections
    - Constant exposure to peritoneal dialysis solution

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Malnutrition-Inflammation Complex Syndrome (MICS)

- Protein-energy malnutrition or wasting and inflammation that occur concurrently and coexist in maintenance dialysis patients.
- Low appetite and a hypercatabolic state are common features.
- MICS is believed to be the main cause of erythropoeietin hyporesponse.
- Possible causes of MICS:
  - Comorbid illnesses
  - Oxidative and carbonyl stress
  - Nutrient loss through dialysis
  - Anorexia and low nutrient intake
  - Uremic toxins

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Table 1. Causes of Wasting and PEM in Dialysis Patients

- Inadequate nutrient intake
  - Anorexia* caused by
    - Uremic toxicity
    - Impaired gastric emptying
    - Inflammation with/without comorbid conditions*
    - Emotional and/or psychological disorders
  - Dietary restrictions
    - Prescribed restrictions: low-potassium low-phosphate regimens
    - Social constraints: poverty, inadequate dietary support
    - Physical incapacity: inability to acquire or prepare food or to eat
- Nutrient losses during dialysis
  - Loss through hemodialysis membrane into hemodialysate
  - Adherence to hemodialysis membrane or tubing
  - Loss into peritoneal dialysate
- Hypercatabolism caused by comorbid illnesses
  - Cardiovascular diseases*
  - Diabetic complications
  - Infection and/or sepsis*
  - Other comorbid conditions*
- Hypercatabolism associated with dialysis treatment
  - Negative protein balance
  - Negative energy balance
- Endocrine disorders of uremia
  - Resistance to insulin
  - Resistance to growth hormone and/or IGF-1
  - Increased serum level of or sensitivity to glucagons
  - Hyperparathyroidism
  - Other endocrine disorders
- Acidemia with metabolic acidosis
- Concurrent nutrient loss with frequent blood losses

*The given factor may also be associated with inflammation.

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(November) 2003

Malnutrition-Inflammation Complex Syndrome (MICS)

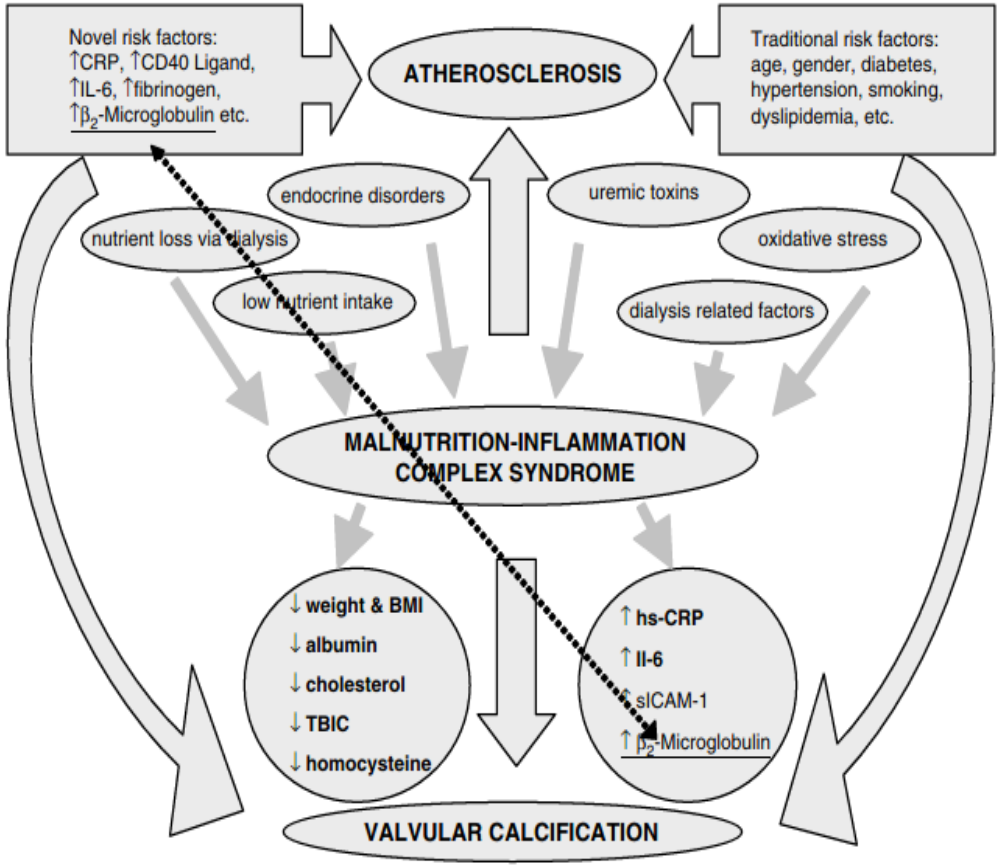
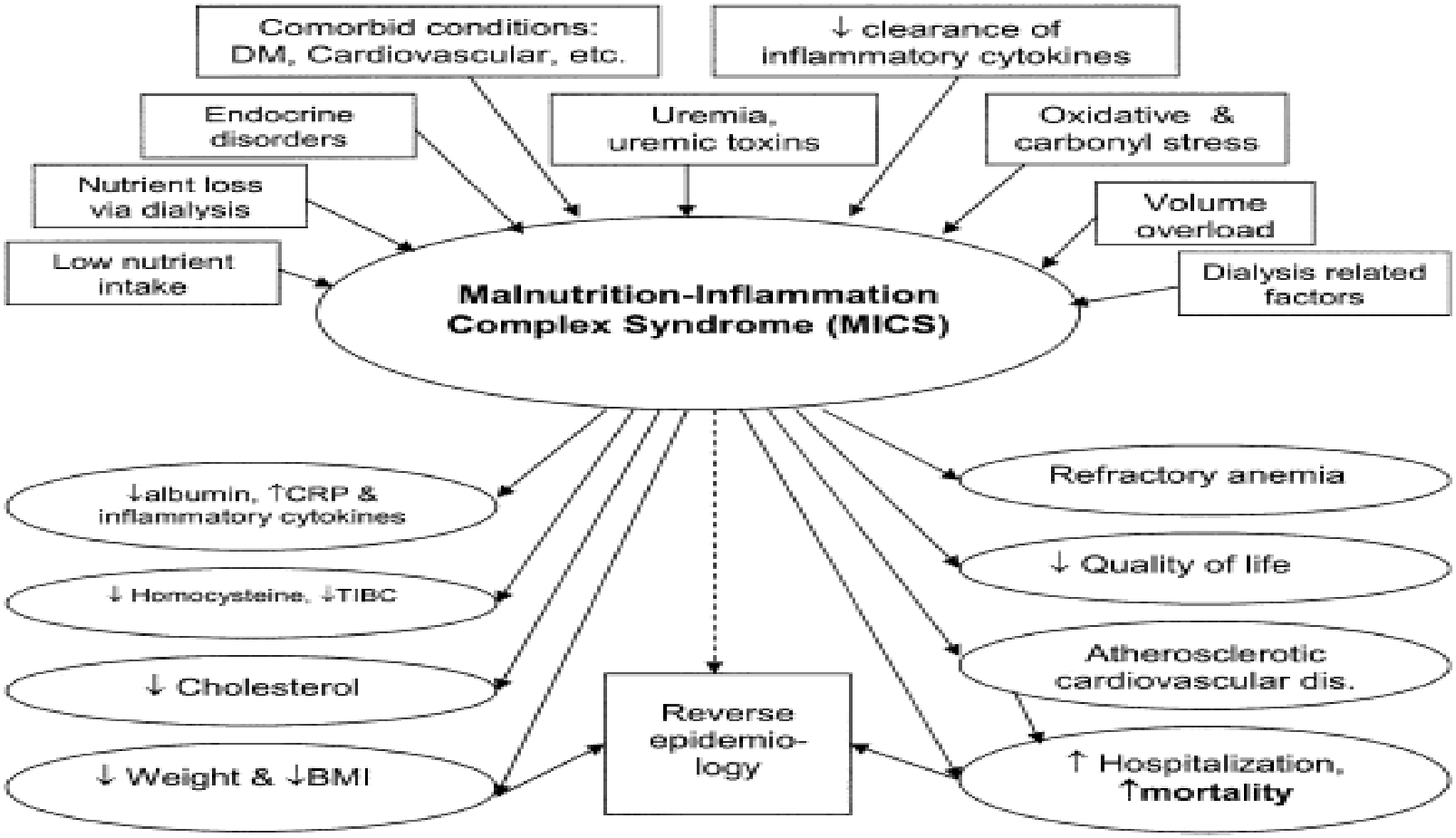


Figure 2 Association between malnutrition–inflammation complex syndrome and atherosclerosis and valvular calcification in dialysis patients with ESRD.

Malnutrition-Inflammation Complex Syndrome (MICS)



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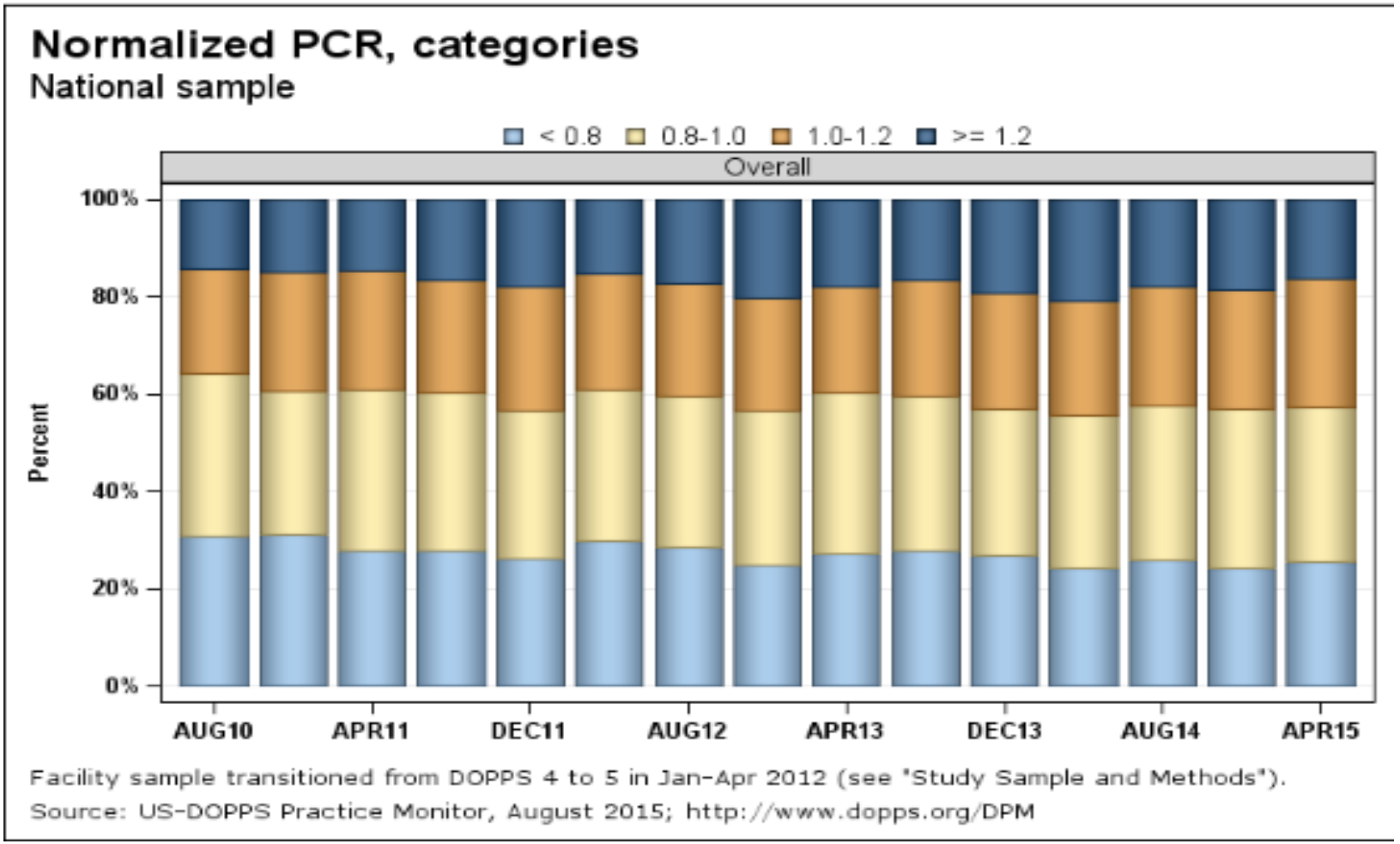
Normalized Protein Catabolic Rate (nPCR) or Normalized Protein Nitrogen Appearance (nPNA)

- nPNA or nPCR is closely correlated with Dietary Protein Intake (DPI) in the steady state; ie, when protein and energy intake are relatively constant.
- It's an accurate when there are little or no internal or external stressors, when the dose of dialysis is constant, if residual urine output is included in the calculation.
- nPCR/nPNA are inaccurate when the patient is in a anabolic or catabolic state
- It may be reasonable to assume that nPNA or nPCR reflects the DPI.
- Levels of 1.0-1.4 g/Kg per day are associated with the best survival outcomes.

NKF KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure 2000

Normalized PCR Trends



Metabolic Acidosis Correction in ESRD

(Cochrane Review)

- In health, protein and amino acids remain in equilibrium however in CKD this balance is disturbed. Metabolic acidosis has been shown to have negative effects on protein balance, leading to a negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, and reduced albumin synthesis, and hence is associated with protein energy malnutrition, loss of lean body mass and muscle weakness.
- This review found three small trials in adult hemodialysis patients (n = 117). The evidence for the benefits and risks of correcting metabolic acidosis is very limited with no RCTs in pre-ESRD patients and none in children. These trials suggest there may be some beneficial effects on protein metabolism but the trials were underpowered to provide strong evidence.

Roderick PJ, Willis NS, Blakeley S, Jones C, Tomson C. Correction of chronic metabolic acidosis for chronic kidney disease patients. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD001890. DOI: 10.1002/14651858.CD001890.pub3

Interventions to Improve and Albumin and Mitigate Inflammation

- **Teamwork!!**
- The Interdisciplinary Team (MD, RN, RD, and MSW) need to review all patients with suboptimal albumin levels regularly.
- All members of the IDT need to fully understand how multi-factorial hypoalbuminemia is and increasing protein intake or supplementing protein may not significantly improve albumin levels unless the underlying infection, inflammation, or psychosocial factors are addressed.
- Every member of the IDT should be invested in the plan to improve our patients albumin levels.

Traditional Nutrition Interventions

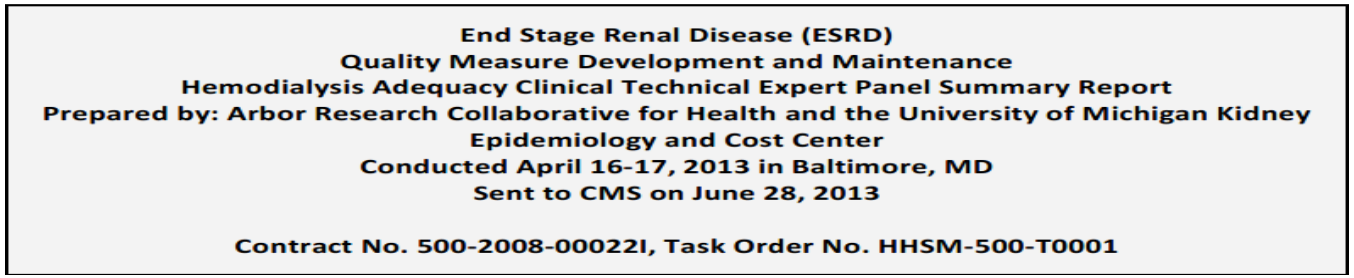
- Counsel patient to consume 1.2-1.5g protein/Kg, ideally 50% High Biologic Value Protein
- If protein needs cannot be met by diet alone, recommend enteral nutrition supplements to meet protein needs.
- Nutrition counseling in earlier stages of CKD, stages 3 and 4 could mitigate the degree of malnutrition patients present with when initiating dialysis
- Utilize Subjective Global Assessment (SGA) to screen patients
- Evaluate barriers to optimal protein intake:
  - Appetite
  - Dialysis Schedule (meals and shopping)
  - Ability of patient or support partners to prepare meals
  - Chewing or swallowing issues
  - Finances
  - QOL

Interventions for Prevention for Inflammation

- Statins: ↓ CRP
- ACE: Anti-inflammatory, delayed progression of CKD
- L-carnitine: Protect against endotoxin ↓TNF-α
- Arginine & Glutamine: ↑enhanced the immume response
- Vitamin C: ↓Vit C ↑ Oxidative stress
- Vitamin E : Vitamin E coated dialyzer
- Active life styles—Aerobic exercise or resistance training
- Diet

Kalantar-Zadeh et al; AJKD, Vol 42, #5 (November) 2003

QIP and Albumin—Current Ruling


End Stage Renal Disease (ESRD)
Quality Measure Development and Maintenance
Hemodialysis Adequacy Clinical Technical Expert Panel Summary Report
Prepared by: Arbor Research Collaborative for Health and the University of Michigan Kidney Epidemiology and Cost Center
Conducted April 16-17, 2013 in Baltimore, MD
Sent to CMS on June 28, 2013

Contract No. 500-2008-00022I, Task Order No. HHSM-500-T0001

- **Measures Pertaining to Achievement of Key Nutritional Parameters**

- Two measures (serum albumin and nPCR) were discussed at the in-person Technical Expert Panel (TEP) meeting in Baltimore, MD as potential quality measures that could indicate achievement of 'nutritional adequacy' among dialysis patients. Due to the extended discussion regarding treatment time and UFR measures, and the need for the TEP to arrive at final recommendations, it was decided that it would not be possible to develop the evidence base or the specifications for these potential nutrition measures at this time and that this exercise was best deferred to a future TEP for consideration.

QUESTIONS?
THANK YOU!

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