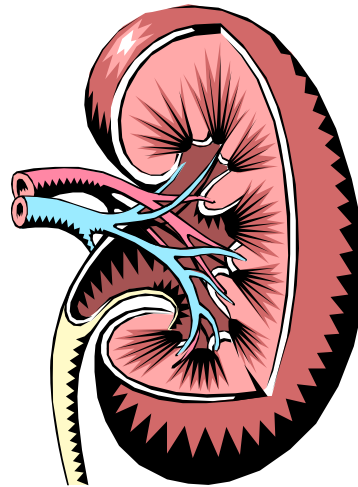


# Inflammation in Chronic Kidney Disease (CKD) Stage 5



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## Disclosure declaration

Accredo Health, Incorporated, provides service discussed in this presentation. We have made every effort to present unbiased and objective information pertaining to Inflammation in Chronic Kidney Disease (CKD) Stage 5.

No grants or honorariums have been received for the development or presentation of this course.

# Course requirements

- Registered Dietitians and Patient Care Technicians must complete the attendance roster. Completion and submission of a course evaluation is encouraged, but not required.
- Nurses must complete the attendance roster, including their license number and signature. Completion and submission of the evaluation is encouraged, but not required.



# Presentation objectives

- Provide an overview of inflammation in CKD Stage 5 patients
- Describe the various inflammatory markers
- Identify possible causes of inflammation in dialysis patients
- Discuss the latest research on inflammation and cardiovascular disease (CVD)
- Define malnutrition-inflammation complex syndrome (MICS)

# Chronic kidney disease

- 500,000 CKD Stage 5 patients 2010<sup>1</sup>
- 785,000 CKD Stage 5 patients by the year 2020<sup>2</sup>
- High mortality rate: 20%-25%<sup>3</sup>
  - 2/3 die within 5 years<sup>4</sup>
  - CVD top cause of death<sup>5</sup>
    - 30 times greater risk vs. general population<sup>6</sup>



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

<sup>2</sup>Gilbertson D, Collins A. Projecting the ESRD population to 2020. USRDS 2007 presentation.

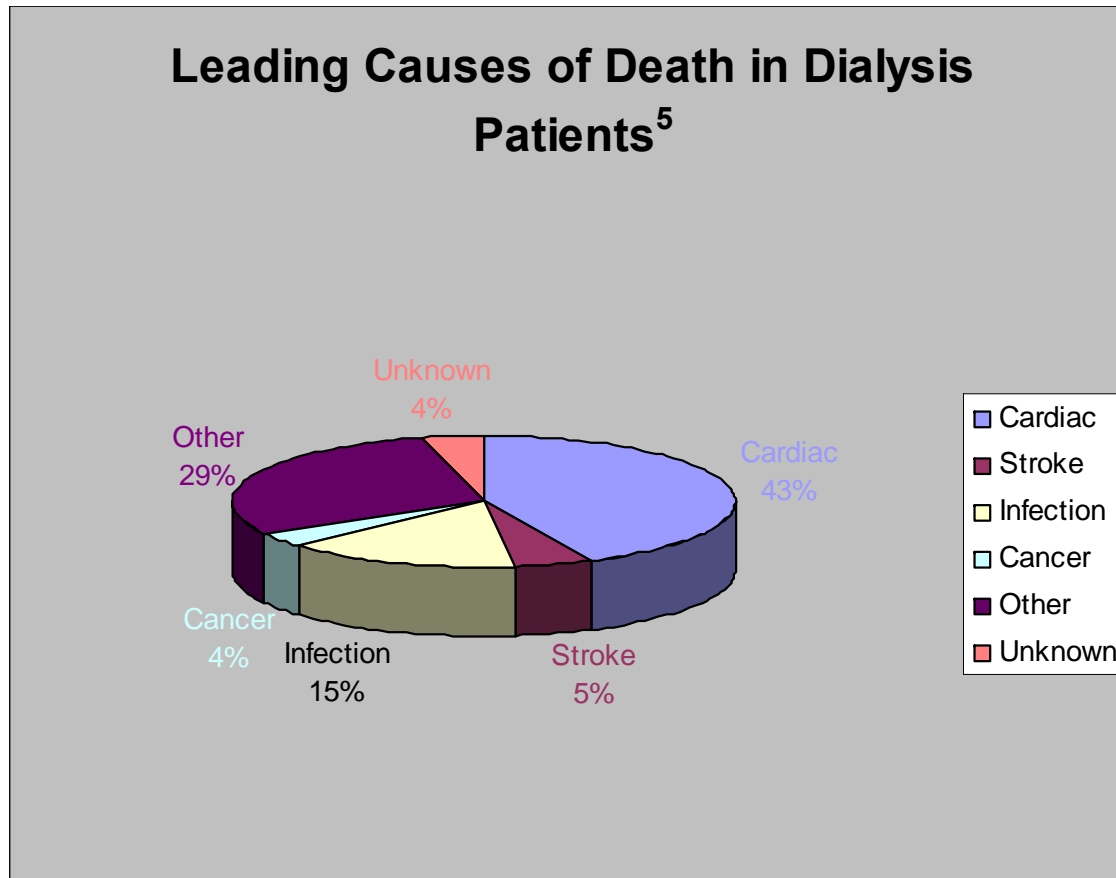
<sup>3</sup>Dezfuli A, et al. J of Renal Nutr. 2009; 19: 291-297.

<sup>4</sup>Kalantar-Zadeh K, et al. Nephrol Dial Transplant. 2005; 1-9.

<sup>5</sup>USRDS 2005 Annual Data Report.

<sup>6</sup>American Heart Association. An overview of the kidney in CVD. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=681>. Accessed on 7/24/2009.

# CVD as top cause of death



<sup>5</sup>USRDS 2005 Annual Data Report.

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# Cardiovascular events in progressing kidney disease

Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated glomerular filtration rate (GFR)<sup>8</sup>

Estimated GFR	Death from any cause	Any CV Event	Any Hospitalization
<i>adjusted hazard ratio</i>			
Greater than 60 mL/min/1.73m <sup>2</sup>	1	1	1
45-59 mL/min/1.73m <sup>2</sup>	1.2	1.4	1.1
30-44 mL/min/1.73m <sup>2</sup>	1.8	2	1.5
15-29 mL/min/1.73m <sup>2</sup>	3.2	2.8	2.1
Less than 15 mL/min/1.73m <sup>2</sup>	5.9	3.4	3.1

<sup>8</sup>Go AS, et al. N Engl J Med. 2004; 351:1296-1305.

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# Hot off the press

Abundant research supporting inflammation and protein-energy malnutrition (PEM) as top potential reasons for the increased risk of CVD and mortality in dialysis patients.<sup>1</sup>



*Journal of Renal Nutrition*

*Kidney International*

*American Society for Parenteral &  
Enteral Nutrition*

*American Journal of Clinical Nutrition*

*Nephrology Dialysis Transplantation*

*American Journal of Kidney Diseases*

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

# What is inflammation?

- “Localized protective response elicited by injury or destruction of tissue that serves to destroy, dilute, or sequester both the injurious agent and injured tissue”<sup>1</sup>
- Body’s reaction to
  - Trauma
  - Infections
  - Toxic injury



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

# What is inflammation?



# Levels of inflammation

- Acute phase



- Positive acute-phase markers

- Cytokines: Interleukin-1 (IL-1), interleukin-6, interleukin-10, tumor necrosis factor- $\alpha$ 
      - C-reactive protein
      - Ferritin

- Negative acute-phase markers

- Albumin

# Inflammatory markers

- C-reactive protein (CRP)
  - Most clinically useful marker of CV inflammation
    - Strong predictor of CV events
    - May have association with increased atherogenesis
  - Acute phase protein produced by the liver
  - More useful when provided in serial vs. single-draw
  - National Kidney Foundation (NKF) references CRP as less than 8 mg/L.<sup>14</sup>
    - Varies from study to study as “high” or “normal”
    - General population 0 mg/L - 5 mg/L<sup>15</sup>

<sup>14</sup>Pocket guide to nutrition assessment of the patient with chronic kidney disease, 4th ed. National Kidney Foundation. 2009

<sup>15</sup>Basic Skills in interpreting laboratory data. April 2004

# Inflammatory markers

- Cytokines

- IL-1, IL-6, IL-10

- IL-6

- Induces fibrinogen

- Possible relationship with progression of carotid atherosclerosis during dialysis

- Strong association with co-morbidity in hemodialysis patients

- Strong predictor of CVD and mortality



# Inflammatory markers

- Tumor necrosis factor (TNF), AKA cachectin<sup>10</sup>
  - TNF- $\alpha$ 
    - Involvement with several other inflammatory markers
    - Promotes catabolism, induces anorexia<sup>1</sup>

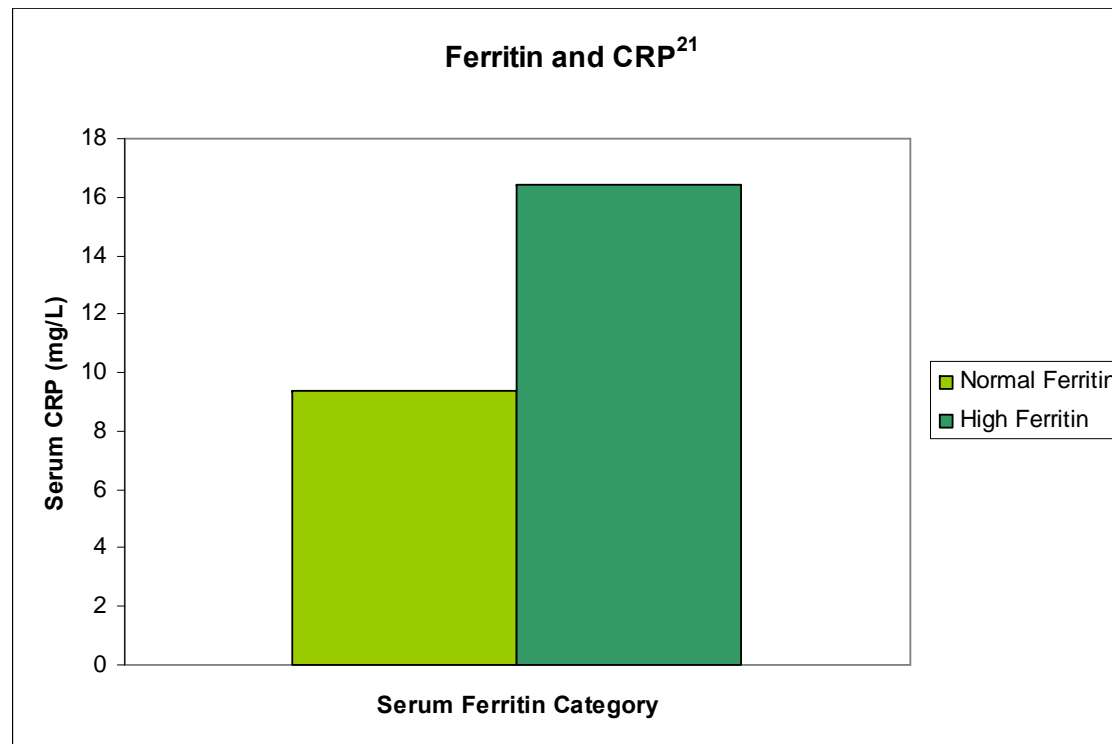


<sup>10</sup>Kalantar-Zadeh K, et al. Am J Clin Nutr. 2004; 80:299-307.

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

# Inflammatory markers

- Ferritin
  - Positive acute phase reactant
  - TNF- $\alpha$  increases ferritin sub-units



<sup>21</sup>Kalantar-Zadeh K, et al. Nephrol Dial Transplant. 2004;19:141-149.

# Inflammatory markers

- Albumin
  - Negative acute-phase reactant
  - Suppressed when CRP is elevated
  - Less than 3.0 gm/dL = inflammation indicator<sup>22</sup>



<sup>22</sup>National Kidney Foundation. Managing Protein Energy Wasting: the role of serum albumin in stratifying risk in dialysis patients. May 2009.

# Inflammation in CKD Stage 5

- 30%-60% of European and Northern American dialysis patients have increased levels of inflammatory markers<sup>1</sup>



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.



# Mortality

- 30% of heart disease (HD) patients have an abnormal IL-6 or CRP level.<sup>19</sup>
  - 80% of patients with elevated CRP levels were dead within 28 months.<sup>12</sup>
- Greater than 60% mortality in HD patients with IL-6 in upper tertile within 26 months.<sup>23</sup>

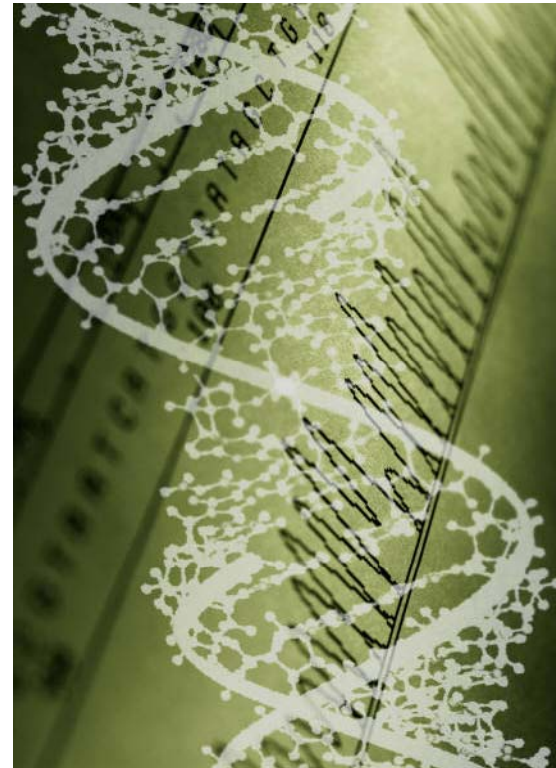
<sup>19</sup>Kaysen GA. Blood Purif. 2002;20:70-80.

<sup>12</sup>Yeun JY, et al. Am J Kidney Dis. 2000; 35:469-476.

<sup>23</sup>Bologa RM, et al. Am J Kidney Dis. 1998;32:107-114.

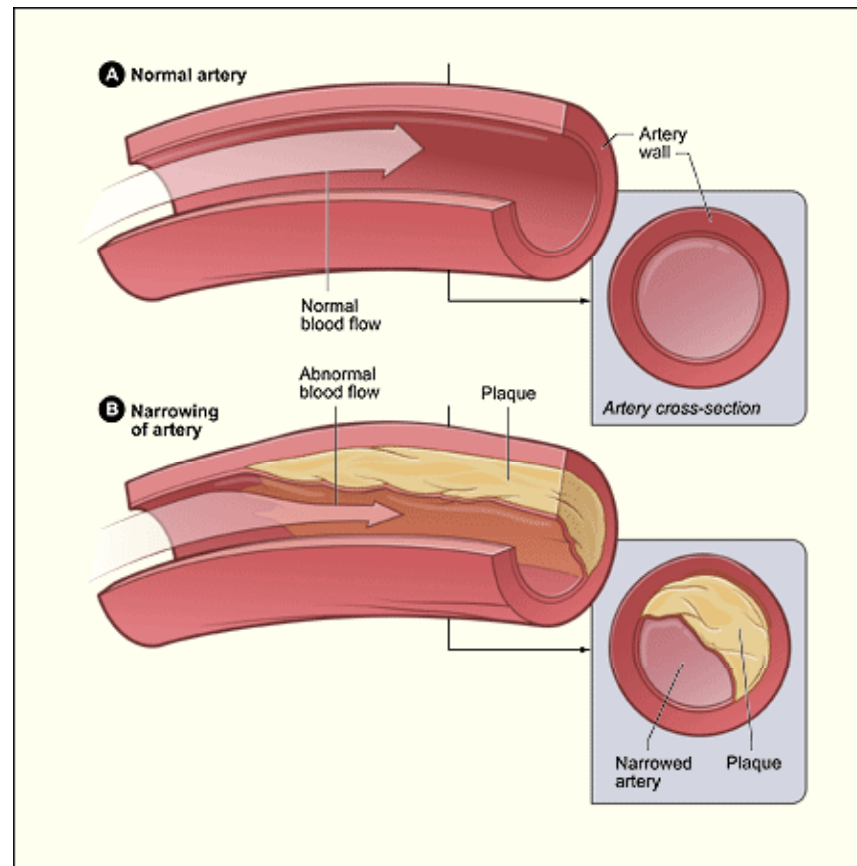
# Levels of inflammation

- Chronic phase
  - Persistent and prolonged
    - Decrease in appetite, anorexia
    - Damage to endothelial cells
    - Fat and muscle wasting
    - Atherosclerosis



# Atherosclerosis

- Series of events following inflammatory response to injury



<sup>32</sup>Image taken from National Heart, Lung and Blood Institute. Available at: [http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis\\_WhatIs.html](http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html). Accessed on 10/23/2009.

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# Inflammation in ESRD

## Possible causes:

- Decreased clearance of cytokines
  - Oxidative stress\*<sup>24, 25, 13</sup>
- Weakening protein-energy state\*
  - Infections<sup>19</sup>
  - Comorbid conditions\*<sup>1, 19</sup>
    - Hemodialysis<sup>1, 19</sup>
      - Catabolic process

\*May also be related to PEM

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

<sup>13</sup>Stenvinkel P, et al. Kidney Int. 1999; 55: 1899-1911.

<sup>19</sup>Kaysen GA. Blood Purif. 2002;20:70-80.

<sup>24</sup>Pecoits-Filho R, et al. Am J Kidney Dis. 2003;41.

<sup>25</sup>Schettler V, et al. Nephrol Dial Transplant. 1998; 13:2588-2593.

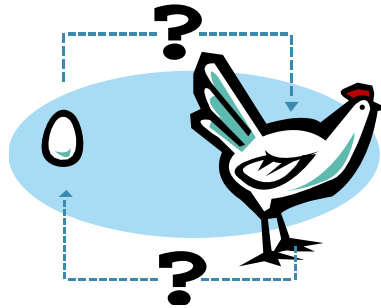
# Inflammation and PEM

- Coexist in CKD Stage 5 patients
  - More common than in general population<sup>1</sup>
- Similarities
  - Anorexia<sup>1</sup>
  - Laboratory measurements
    - Visceral protein status (negative acute phase markers)
  - Overlapping causes
  - CVD and mortality



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

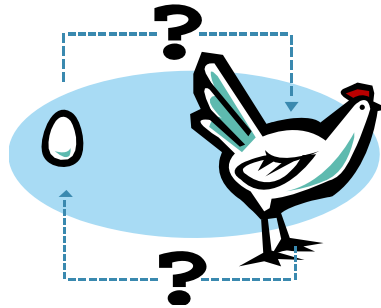
# Inflammation → PEM?



- Proinflammatory cytokines
- Weight loss and negative protein balance with appetite
- Albumin and CRP link
- Hypercholesterolemia link<sup>1</sup>

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

## PEM → Inflammation?<sup>22</sup>



- PEM status markers are used irrespective of inflammation.
- Inflammatory markers vary month to month.
- Malnourished patients are likely deficient in antioxidants.
- Increased serum albumin levels improve survival rate.

<sup>22</sup>National Kidney Foundation. Managing Protein Energy Wasting: the role of serum albumin in stratifying risk in dialysis patients. May 2009.

# Reverse epidemiology

- “Typical” CVD risk factors seem to offer protection.<sup>1,3</sup>
  - Hypercholesterolemia
  - Hypertension
    - No association with death risk
    - Greater survival
  - High body mass index<sup>16</sup>
    - Improved survival
    - Reduced CVD morbidity



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

<sup>3</sup>Dezfuli A, et al. J of Renal Nutr. 2009; 19: 291-297.

<sup>16</sup>Beberashvili I, et al. J of Renal Nutr. 2009; 19:238-247.

# Malnutrition-inflammation complex syndrome<sup>1</sup>

Termed to combine the two conditions in dialysis patients



Malnutrition and inflammation have been associated with CVD and atherosclerosis in CKD Stage 5 patients.

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

# Malnutrition-Inflammation Score (MIS)

- MIS
  - Based on Subjective Global Assessment and Dialysis Malnutrition Score<sup>1,21</sup>
    - BMI
    - Albumin
    - Transferrin
- 0 (normal) – 3 (severe)<sup>21</sup>



<sup>33</sup>Permission to use image obtained from Major League Baseball.

- Superior to SGA and lab values to indicate MICS

<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

<sup>21</sup>Kalantar-Zadeh K, et al. Nephrol Dial Transplant. 2004;19:141-149.

# Treatment

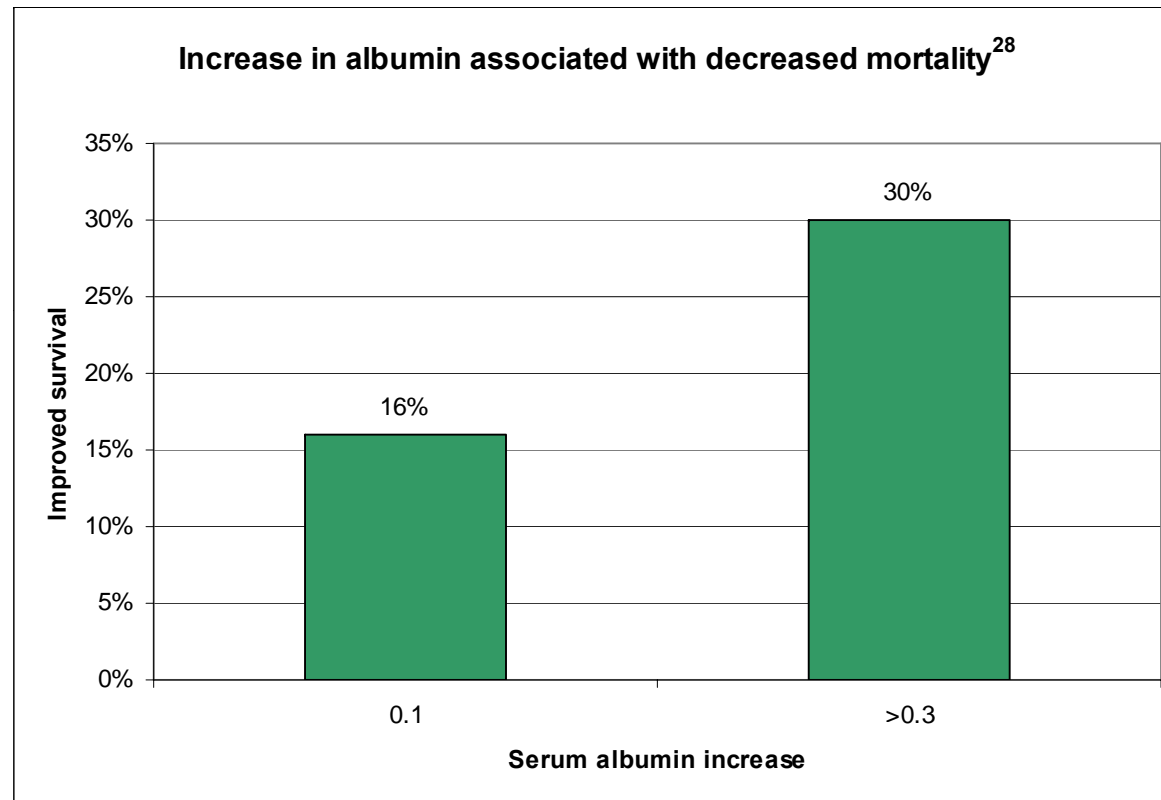
- Improving serum albumin<sup>22,28</sup>
  - Oral supplements
  - Tube feedings
- Intradialytic parenteral nutrition (IDPN)



<sup>22</sup>National Kidney Foundation. Managing Protein Energy Wasting: the role of serum albumin in stratifying risk in dialysis patients. May 2009.

<sup>28</sup>Lacson E, et al. J Ren Nutr. 2007;17:363-371.

# Improvements in serum albumin

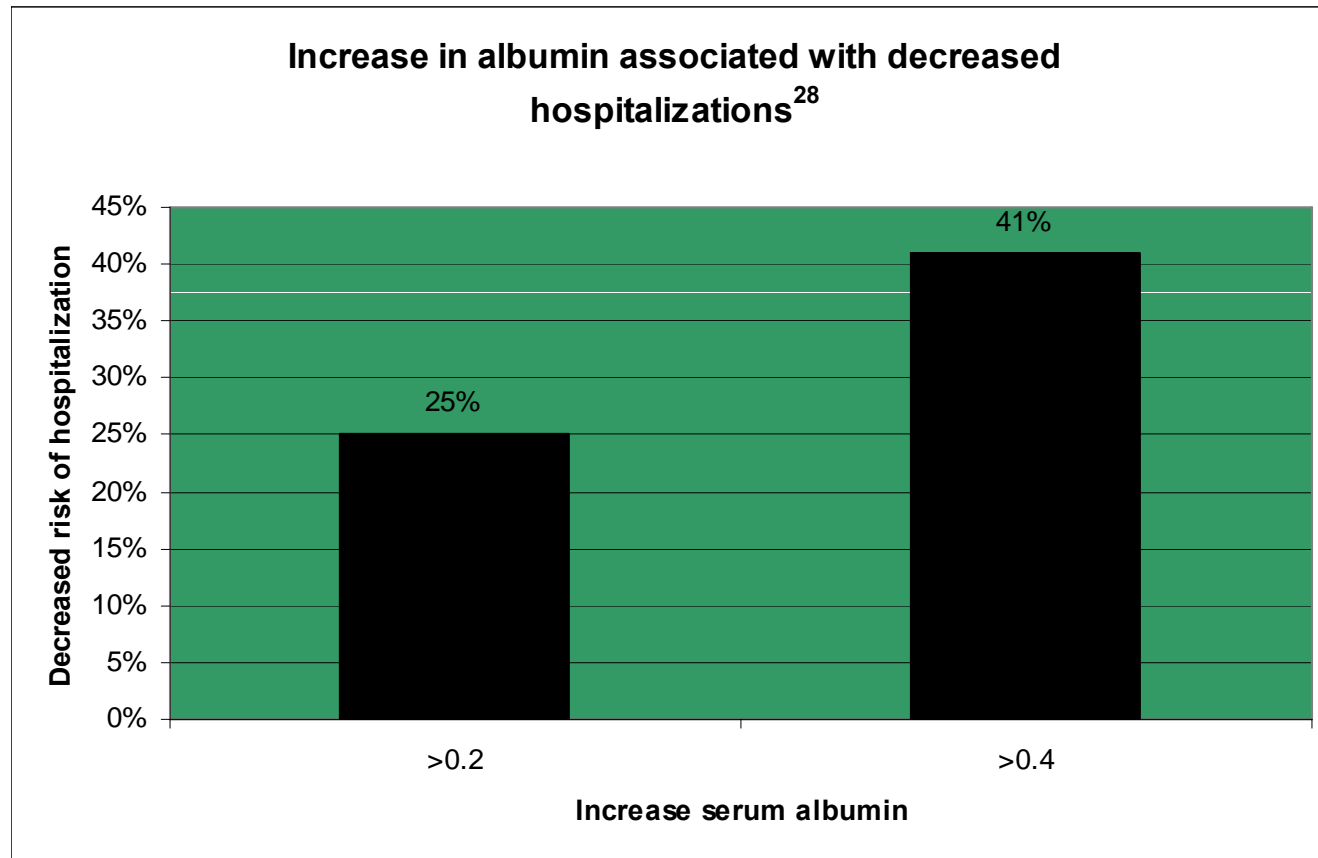


<sup>28</sup>Lacson E, et al. J Ren Nutr. 2007;17:363-371.

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# Improvements in serum albumin



<sup>28</sup> Lacson E, et al. J Ren Nutr. 2007;17:363-371.

# Treatment - Antioxidants

- Deficiency in antioxidants
  - Vitamin C<sup>27,1</sup>
  - Vitamin E<sup>13,30</sup>



<sup>1</sup>Kalantar-Zadeh K, et al. Am J Kid Disease. 2003; 42: 864-881.

<sup>13</sup>Stenvinkel P, et al. Kidney Int. 1999; 55: 1899-1911.

<sup>27</sup>Williamson BC, et al. Renal Nutrition Forum. 2009;28:1-7.

<sup>30</sup>Wang W, et al. Am J of Phys – Ren Phys. 2007; 293: F1123-F1130.

## Others

- Vitamin D<sup>27</sup>
- Potassium<sup>30</sup>
- Fish oil<sup>31</sup>



<sup>27</sup>Williamson BC, et al. Renal Nutrition Forum. 2009;28:1-7.

<sup>30</sup>Wang W, et al. Am J Phys – Ren Phys. 2007; 293: F1123-F1130.

<sup>31</sup>Waitzberg DL, et al. Nutr Clin Pract. 2009; 24: 487-499.

**We CAN help...**



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