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Inflammation: Cause of Vascular Disease and Malnutrition in Dialysis Patients

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Inflammation occurs in response to tissue injury or the presence of foreign antigens and is important in the mobilization of specific immunologic and nonimmunologic defenses against injury. The vascular endothelium is altered to allow immune competent cells to access the interstitial space. Muscle and visceral proteins are catabolized and the amino acids are used either to supply energy or as substrates for the production of acute-phase proteins that play a role in defense. Restoration of muscle mass is impaired while inflammation is on going. Lipids are mobilized. Although serving a vital role in allowing host survival from acute injury or infection, if unimpeded, or if triggered inappropriately, the acute-phase response may instead lead to increased vascular injury and progressive loss of muscle and visceral protein pools causing malnutrition. Markers of inflammation (C reactive protein [CRP] or interleukin-6 [IL-6] levels) are associated with cardiovascular risk in the general population and in dialysis patients. Hypoalbuminemia also is associated with cardiovascular risk in dialysis patients. Although albumin is considered a marker of nutrition, changes in albumin levels are associated with increased levels of acute-phase proteins. Persistent changes in albumin levels are caused by reduced albumin synthesis associated with inflammation and not decreased normalized protein catabolic rate. The cause(s) of inflammation must be identified and treated to resolve malnutrition and reduce cardiovascular risk.

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Patients with end-stage renal disease have a marked increase in mortality.[1] Although cardiovascular disease is the most common cause of death, markers normally associated with malnutrition, low serum albumin,[2] prealbumin,[3,4] and creatinine rather than hypercholesterolemia,[5] are most predictive of death. This has been misinterpreted as suggesting that presence of malnutrition, possibly resulting from anorexia in part arising from inadequate dialysis, is what leads to increased mortality risk. Hypoalbuminemia is, however, uncommon in pure protein energy malnutrition[6] and generally requires additional factors, such as inflammation, for albumin concentration to be decreased significantly.[7,8]

Albumin, similar to other nutritional markers, such as prealbumin (transthyretin),[9-12] and transferrin[13] are negative acute-phase proteins.[14] The synthesis of these proteins decreases during inflammation, as does their serum concentration, changes that occur entirely independent of nutritional state.[14] Albumin concentration in dialysis patients is correlated negatively with levels of positive acute-phase proteins. Positive acute-phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA),[15,16] fibrinogen, and ferritin exhibit an increased rate of synthesis and increased plasma level during inflammation under the control of specific cytokines (interleukin-6 [IL-6], tumor necrosis factor α, [TNFα]).[17,18] All of these markers of inflammation are statistically powerful determinants of serum albumin concentration in end-stage renal disease (ESRD) patients.

Other markers that normally are used to diagnose malnutrition are found to be present simultaneously with markers of inflammation. Stenvinkel et al[19] established that patients with pre-ESRD who were judged to be malnourished by mea-

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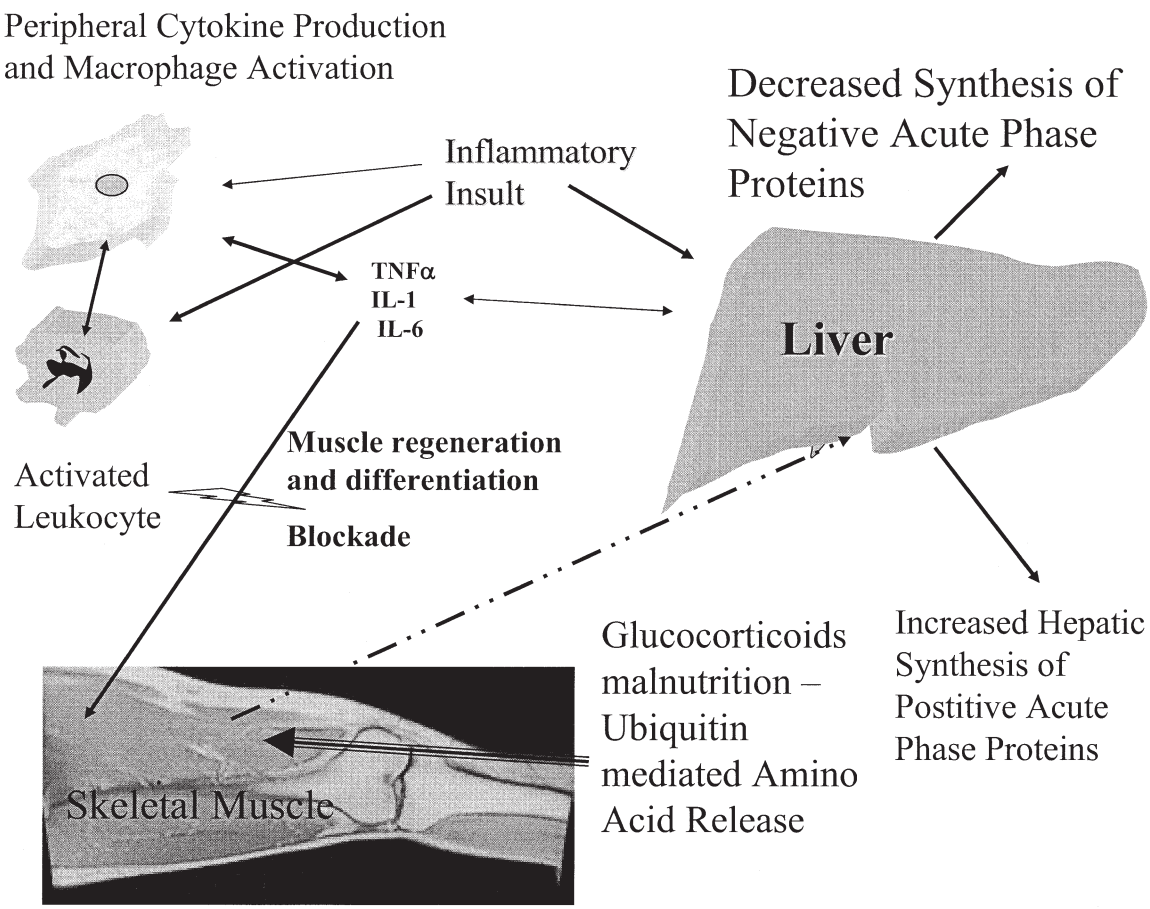

Figure 1 Effect of inflammation on hepatic and muscle protein synthesis and catabolism. Cytokines alter hepatic gene expression to augment synthesis of positive acute-phase proteins and reduce synthesis of negative acute-phase proteins. Muscle protein catabolism is increased through a ubiquitin adenosine triphosphate–dependent process stimulated in part by glucocorticoids. Muscle regeneration is impeded by a nuclear factor κ B–linked process blocking messenger RNA translation.

sures of subjective global assessment also had markers consistent with the presence of inflammation. Both CRP and fibrinogen levels were significantly greater in groups of patients with a subjective global assessment of 2 or greater. Disturbingly, the prevalence of vascular disease, judged by prevalence of carotid plaques and increased calculated intima-media area, also was increased in this cohort. In this context, both Zimmermann et al[20] and Yeun et al[2] found that overall mortality and cardiovascular mortality both were significantly higher in patients with increased CRP or SAA levels. In the study by Yeun et al,[2] the inclusion of CRP in the regression model eliminated albumin as a predictor of risk.[2] These findings are mirrored by a recent series of publications looking at the association between cardiovascular risk and CRP levels in patients without renal disease (discussed later).

In addition to its effect on serum protein, inflammation also mediates changes in muscle mass,[21,22] which should in turn lead to a reduction in creatinine generation.[23] TNFα, in addition to stimulating protein degradation, also decreases protein accrual by muscle in the process of replenishing wasted muscle by decreased expression of MyoD, a transcription factor that may be important for replenishing wasted muscle (Fig 1).[24] In longitudinal studies,[25] the serum creatinine level is observed to decrease over time when the CRP concentration is increased in dialysis patients. Functionally, IL-6 levels also predict future ambulatory disability.[26]

The relationship between markers of inflammation (CRP, SAA, and IL-6) and serum albumin concentration also are found in peritoneal dialysis patients.[27] In this population, transperitoneal albumin losses also contribute importantly to serum albumin concentration, however, transperitoneal albumin loss is entirely independent of markers of inflammation. Although some patients with high losses of albumin across the peritoneal membrane also may experience inflammation, this is only by chance. As in the hemodialysis population, markers of inflammation in peritoneal dialysis patients also predict death.[28]

It is a difficult task to distinguish patients who have pure protein calorie malnutrition from patients with either an admixture of inflammation and malnutrition or those who indeed are consuming what normally would be accepted to be adequate calorie and protein intake, yet still appear by standard assessment to be malnourished. It is critical to evaluate these patients for the presence of inflammation and their actual nutritional intake separately. Part of the assessment of malnutrition, including hypoalbuminemia, should be evalu-

ated for the presence of inflammation. The most convenient assay is measurement of the CRP level.

If one assumes that the normalized protein catabolic rate is a reflection of dietary protein intake, then there is a population of dialysis patients who have low albumin levels caused by inadequate dietary protein intake who have no evidence of inflammation. Similarly, there is a group that shows no evidence of reduced nitrogen catabolism, low albumin levels, and have evidence of inflammation. Most patients probably have both to varying degrees. The processes are independent. Nutritional requirements also may be increased for patients facing the challenge of systemic inflammation.

Relationship Between Inflammation and Vascular Disease

Several large cross-sectional studies have identified CRP level as an independent risk factor for cardiac disease in both men and women.[29-31] In the Monitoring Trends and Determinants in Cardiovascular Disease study, CRP level predicted future risk for coronary heart disease in initially healthy middle-aged men.[32] In another study, the subpopulations of men who benefited from aspirin were those with increased CRP levels.[33] Thus, serum CRP level recently has been identified as a powerful predictor of cardiovascular risk, both in the nondialysis patient population and in dialysis patients as well.[2,20,29,31]

One important unresolved question is whether inflammation is the cause of cardiovascular disease or instead a marker of existing disease, or both. Intrinsic to that argument is the question of identification of the source of inflammation. Some argue that vascular disease is itself an inflammatory process[30,31] and that the markers of inflammation measure existing vascular disease. This would suggest that inflammation is a reflection of, rather than a cause of, vascular injury. Inflammation, however, affects plasma protein and lipoprotein composition in ways that suggest it may indeed promote vascular injury. Inflammation also causes changes in vascular endothelial structure (induction of specific adhesion molecules) and in lipoprotein structure and function that favor adhesion of mononuclear molecules to the vascular endothelium and should promote atherogenesis.

Potential Injurious Effects of Inflammation

Fibrinogen is a positive acute-phase protein and correlates with CRP level. Fibrinogen is also an independent cardiovascular risk factor.[34] The lipoprotein Lp(a) is another powerful risk factor for vascular disease.[35] Normally, its plasma level is regulated in response to the size of isoform inherited; those with low molecular weight isoforms have high plasma levels and an increased risk for vascular disease, and those with high molecular weight isoforms have low plasma levels and no increased risk for vascular disease. Inflammation causes increased levels of Lp(a) independent of isoform.[36] Thus, individuals with the high molecular weight isoform may have increased plasma levels of this atherogenic lipoprotein (Fig 2).

In individuals with inflammation, high-density lipoprotein (HDL) levels decrease[37] and the apolipoprotein A-I (apo A-I) that normally composes about half of the proteins in HDL is replaced by SAA.[37-39] This form of HDL is chemoattractive to macrophages as well as the vascular endothelium and has a reduced capacity to reduce oxidized low-density lipoprotein.[37-39]

Antioxidant Effect of HDL

HDL normally suppresses the effects of cytokines on their induction of adhesion molecules by endothelial cells.[40,41] Inflammation alters HDL structure and function to remove these anti-inflammatory properties by reducing the levels of aryl hydrocarbon hydrolase and paroxynase.[38,39,42]

Low-density lipoprotein is therefore more likely to be oxidized because of a decreased ability of HDL to protect it and the increased action of myeloperoxidase, a product of activated neutrophils that chlorinates a tyrosine residue on apo B100.[37] Ceruloplasmin is another acute-phase protein and, thus, its serum concentration also is increased during the acute-phase response. HDL also normally suppresses the effects of cytokines on their induction of adhesion molecules by endothelial cells.[43] Inflammation alters HDL structure and function to remove these anti-inflammatory properties.[44,45] Thus, inflammation is poised to promote vascular injury, as shown in Figure 1.

Inflammation in the Renal Patient

Is it possible that renal failure per se may contribute to the inflammatory response? In some studies, serum levels of IL-6, IL-1, and TNFα were increased significantly in patients with renal failure, and no difference was observed between long-term and not yet dialyzed patients,[45,46] but other studies found an increase primarily in dialyzed patients.[47] Several factors have been proposed to promote this inflammation, including increased oxidative stress[48,49] and the accumulation of postsynthetically modified proteins (advanced glycation end products[50] and products of carbonyl stress),[51] all promoted by failure of renal clearance. Nevertheless, most pre-ESRD patients do not show evidence of inflammation. A unifying hypothesis still is needed. However, inflammation is found in many pre-ESRD patients, especially in those patients with markers normally used to access nutrition (decreased albumin levels, increased subjective global assessment).[2,3,15,16,19,20,25,27] These tend to be older patients and patients with vascular disease.

The levels of cytokines and acute-phase proteins, however, are significantly greater in dialysis patients when compared with pre-ESRD patients. SAA and IL-6 levels are increased significantly in dialysis patients compared with pre-ESRD or control patients. At any given time, 30% of hemodialysis patients have CRP or SAA levels greater than the normal

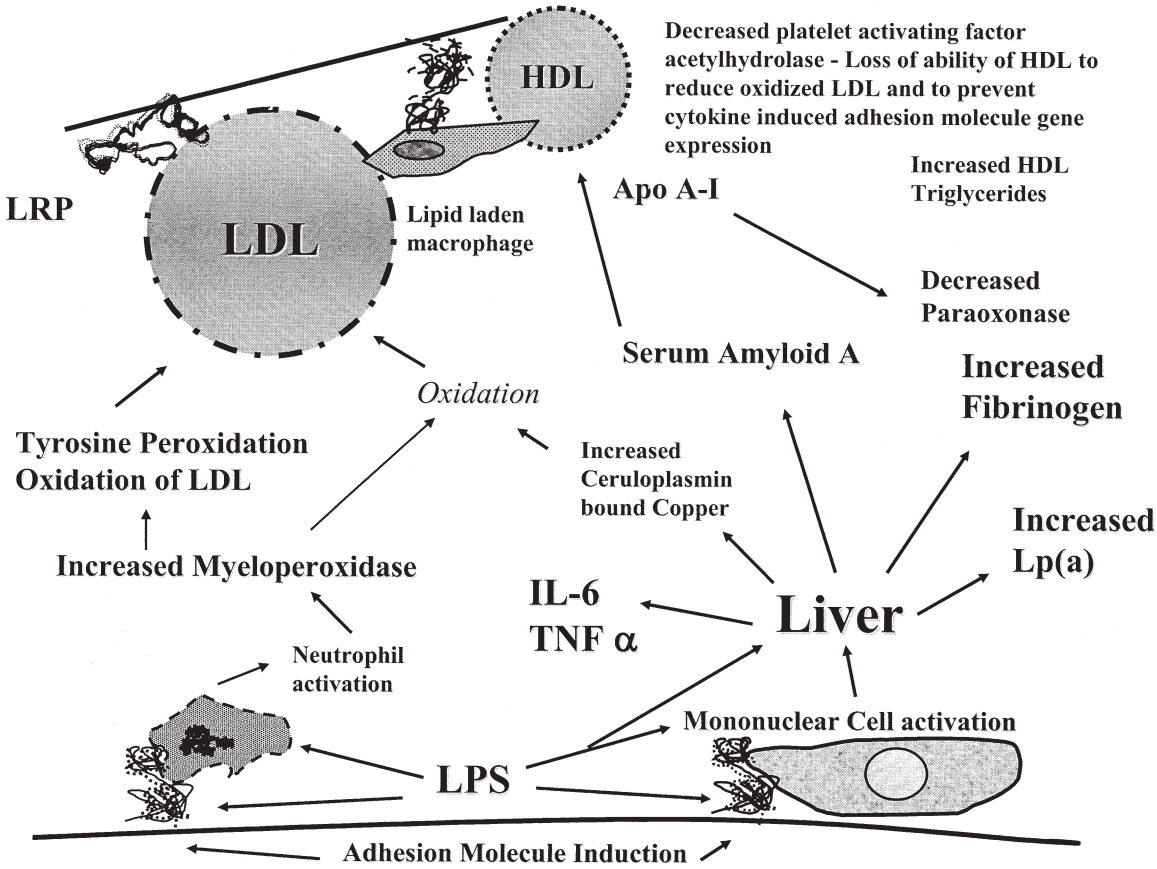

Figure 2 The effect of inflammation on lipoprotein structure and function and on the expression of endothelial cell adhesion molecules. TNFα, IL-1, and other TH1 cytokines increase hepatic synthesis of fibrinogen and SAA. Leukocyte degranulation activates myeloperoxidase, oxidizing low-density lipoprotein, and reducing availability of nitric oxide. HDL no longer serves its role as an antioxidant and fails to inhibit cytokine-mediated changes in endothelial cell structure.

range. This is of concern because increased risk for death occurs with CRP levels within the high normal range. Zimmermann et al[20] found that both CRP and albumin levels were independent predictors of all causes of mortality in hemodialysis patients. Bologa et al[52] reported greater than 60% mortality in hemodialysis patients having IL-6 levels in the upper tertile within 26 months.

Markers of inflammation are present in increased frequency in patients who have not yet undergone dialysis, patient both on hemodialysis and peritoneal dialysis.[16] In most studies, approximately 30% of these populations have increased levels of either CRP, SAA,[53] or IL-6[52] in cross-sectional studies. The statistical distribution of these measurements exists in a highly nonnormal manner, with a skew to higher values. This distribution suggests a discontinuous process that is responsible for the event being measured. This hypothesis is supported by recent observations that we have made in a longitudinal study showing that CRP as well as cytokine levels increase in discrete episodes in dialysis patients, suggesting that acute processes strongly contribute to the inflammatory response. Even a single measurement of a marginally increased level of CRP strongly predicts death as well as cardiovascular death in dialysis patients.[2,20] Thus, once patients start dialysis, their risk for both inflammation and subsequent cardiovascular death increases.

Currently, we do not know the cause of the inflammatory response. Many candidate causes have been suggested, including dialysis against nonbiocompatible membranes,[54] the use of nonsterile dialysate,[55] and back leak of dialysate across the dialysis membrane.[56] We have recently found in a longitudinal study in which CRP and other proteins were measured periodically (at least once a month) that CRP values varied considerably in individual dialysis patients. The variability in CRP level was approximately 2 orders of magnitude greater than that of albumin,[57] suggesting that discontinuous processes may play an important role in causing inflammation in this patient population. Cross-sectional studies may therefore miss a portion of dialysis patients who may develop inflammation.

Clearly, the presence of clinically unrecognized infection must be excluded. Furthermore, CRP level is clearly a more sensitive marker of the presence of the acute-phase response than is albumin by orders of magnitude. Malnutrition alone does not cause serum albumin concentration to decrease to much less than 3.5 g/dL.[6,58] Serum albumin concentration less than 3.0 nearly always is accompanied by the presence of

the acute-phase response. Thus, the index of suspicion of underlying inflammatory processes always should be great in the presence of severe hypoalbuminemia. The evaluation of a patient with an increased CRP level should include a careful interval history and physical examination, including a careful assessment of the vascular access.

References

1. United States Renal Data System: 1995 Annual Data Report. Am J Kidney Dis 26:509-594, 1995
2. Yeun JY, Levine RA, Mantadilok V, et al: C-reactive protein predicts all cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 35:469-476, 2000
3. Avram MM, Goldwasser P, Erroa M, et al: Predictors of survival in continuous ambulatory peritoneal dialysis patients: The importance of prealbumin and other nutritional and metabolic markers. Am J Kidney Dis 23:91-98, 1994
4. Sreedhara R, Avram MM, Blanco M, et al: Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. Am J Kidney Dis 28:937-942, 1996
5. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 15:458-482, 1990
6. Rigaud D, Hassid J, Meulemans A, et al: A paradoxical increase in resting energy expenditure in malnourished patients near death: The king penguin syndrome. Am J Clin Nutr 72:355-360, 2000
7. Moldawer LL, Copeland EM 3rd: Proinflammatory cytokines, nutritional support, and the cachexia syndrome: Interactions and therapeutic options. Cancer 79:1828-1839, 1997
8. Michie HR: Metabolism of sepsis and multiple organ failure. World J Surg 20:460-464, 1996
9. Fung WP, Thomas T, Dickson PW, et al: Structure and expression of the rat transthyretin (prealbumin) gene. J Biol Chem 263:480-488, 1988
10. Samadani U, Qian X, Costa RH: Identification of a transthyretin enhancer site that selectively binds the hepatocyte nuclear factor-3 beta isoform. Gene Expr 6:23-33, 1996
11. Banks RE, Forbes MA, Storr M, et al: The acute phase protein response in patients receiving subcutaneous IL-6. Clin Exp Immunol 102:217-223, 1995
12. Clark GH, Fraser CG: Biological variation of acute phase proteins. Ann Clin Biochem 30:373-376, 1993
13. Milland J, Tsykin A, Thomas T, et al: Gene expression in regenerating and acute-phase rat liver. Am J Physiol 259:G340-G347, 1990
14. Moshage HJ, Janssen JAM, Franssen JH, et al: Study of the molecular mechanisms of decreased liver synthesis of albumin in inflammation. J Clin Invest 79:1635-1641, 1987
15. Kaysen GA, Rathore V, Shearer GC, et al: Mechanisms of hypoalbuminemia in hemodialysis patients. Kidney Int 48:510-516, 1995
16. Yeun JY, Kaysen GA: Acute phase proteins and peritoneal dialysate albumin loss are the main determinants of serum albumin in peritoneal dialysis patients. Am J Kidney Dis 30:923-927, 1997
17. Jensen LE, Whitehead AS: Regulation of serum amyloid A protein expression during the acute-phase response. Biochem J 334:489-503, 1998
18. Wang Y, Ripperger J, Fey GH, et al: Modulation of hepatic acute phase gene expression by epidermal growth factor and Src protein tyrosine kinases in murine and human hepatic cells. Hepatology 30:682-697, 1999
19. Stenvinkel P, Heimburger O, Paultre F, et al: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 55:1899-1911, 1999
20. Zimmermann J, Herrlinger S, Pruy A, et al: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 55:648-658, 1999
21. Li YP, Lecker SH, Chen Y, et al: TNF-alpha increases ubiquitin-conjugating activity in skeletal muscle by up-regulating UbcH2/E220k. FASEB J 17:1048-1057, 2003
22. Guttridge DC, Mayo MW, Madrid LV, et al: NF-kappaB-induced loss of MyoD messenger RNA: Possible role in muscle decay and cachexia. Science 289:2363-2366, 2000
23. Wang ZM, Sun YG, Heymsfield SB: Urinary creatinine-skeletal muscle mass method: A prediction equation based on computerized axial tomography. Biomed Environ Sci 9:185-190, 1996
24. Michael J: Tisdale protein loss in cancer cachexia. Science 29:2293-2294, 2000
25. Kaysen GA, Chertow GM, Adhikarla R, et al: Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. Kidney Int 60:333-340, 2001
26. Ferrucci L, Penninx BW, Volpato S, et al: Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc 50:1947-1954, 2002
27. Yeun JY, Kaysen GA: Acute phase proteins and peritoneal dialysate albumin loss are the main determinants of serum albumin in peritoneal dialysis patients. Am J Kidney Dis 30:923-927, 1997
28. Kim H, Bologa R, Parker T, et al: Serum IL-6 level as an indicator of survival outcome in CAPD patients. J Am Soc Nephrol 10:246A, 1999 (abstr)
29. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 97:2007-2011, 1998
30. Danesh J, Collins R, Appleby P, et al: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: Meta-analyses of prospective studies. JAMA 279:1477-1482, 1998
31. Ridker PM, Buring JE, Shih J, et al: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 98:731-733, 1998
32. Koenig W, Sund M, Frohlich M, et al: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: Results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 99:237-242, 1999
33. Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 336:973-979, 1997
34. Danesh J, Collins R, Appleby P, et al: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: Meta-analyses of prospective studies. JAMA 279:1477-1482, 1998
35. Suzuki K, Kuriyama M, Saito T, et al: Plasma lipoprotein(a) levels and expression of the apolipoprotein(a) gene are dependent on the nucleotide polymorphisms in its 5′-flanking region. J Clin Invest 15:1361-1366, 1997
36. Dieplinger H, Lackner C, Kronenberg F, et al: Elevated plasma concentrations of lipoprotein(a) in patients with end-stage renal disease are not related to the size polymorphism of apolipoprotein(a). J Clin Invest 91:397-401, 1993
37. Van Lenten BJ, Hama SY, de Beer FC, et al: Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 96:2758-2767, 1995
38. Pruzanski W, Stefanski E, de Beer FC et al: Comparative analysis of lipid composition of normal and acute-phase high density lipoproteins. J Lipid Res 41:1035-1047, 2000
39. De Beer FC, Fagan EA, Hughes GRV, et al: Serum amyloid-A protein concentration in inflammatory diseases and its relationship to the incidence of reactive systemic amyloidosis. Lancet 2:231-234, 1982
40. Cockerill GW, Huehns TY, Weerasinghe A, et al: Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. Circulation 103:108-112, 2001
41. Cockerill GW, Saklatvala J, Ridley SH, et al: High-density lipoproteins differentially modulate cytokine-induced expression of E-selectin and cyclooxygenase-2. Arterioscler Thromb Vasc Biol 19:910-917, 1999

42. Pruzanski W, Stefanski E, Kopilov J, et al: Mitogenic effect of lipoproteins on human vascular smooth muscle cells: The impact of hydrolysis by gr II A phospholipase A(2). Lab Invest 81:757-765, 2001
43. Cockerill GW, Huehns TY, Weerasinghe A, et al: Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. Circulation 103:108-112, 2001
44. Pruzanski W, Stefanski E, de Beer FC, et al: Comparative analysis of lipid composition of normal and acute-phase high density lipoproteins. J Lipid Res 41:1035-1047, 2000
45. Herbelin A, Urena P, Nguyen AT, et al: Elevated circulating levels of interleukin-6 in patients with chronic renal failure. Kidney Int 39:954-960, 1991
46. Pereira BJ, Shapiro L, King AJ, et al: Plasma levels of IL-1 beta, TNF alpha and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. Kidney Int 45:890-896, 1994
47. Cavaillon JM, Poignet JL, Fitting C, et al: Serum interleukin-6 in long-term hemodialyzed patients. Nephron 60:307-313, 1992
48. Ceballos-Picot I, Witko-Sarsat V, Merad-Boudia M, et al: Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure. Free Radic Biol Med 21:845-853, 1996
49. Loughrey CM, Young IS, Lightbody JH, et al: Oxidative stress in haemodialysis. QJM 87:679-683, 1994
50. Odetti P, Cosso L, Pronzato MA, et al: Plasma advanced glycosylation end-products in maintenance haemodialysis patients. Nephrol Dial Transplant 10:2110-2113, 1995
51. Miyata T, van Ypersele de Strihou C, Kurokawa K, et al: Alterations in nonenzymatic biochemistry in uremia: Origin and significance of "carbonyl stress" in long-term uremic complications. Kidney Int 55:389-399, 1999
52. Bologa RM, Levine DM, Parker TS, et al: Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis 32:107-114, 1998
53. Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. Am J Kidney Dis 29:658-668, 1997
54. Parker TF3rd, Wingard RL, Husni L, et al: Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients. Kidney Int 49:551-556, 1996
55. Tielemans C, Husson C, Schurmans T, et al: Effects of ultrapure and non-sterile dialysate on the inflammatory response during in vitro hemodialysis. Kidney Int 49:236-243, 1996
56. David S, Tetta C, Canino F, et al: Production of platelet activating factor by human neutrophils after backfiltration of endotoxin contaminated dialysate. ASAIO J 39:M773-M777, 1993
57. Kaysen GA, Dubin JA, Müller HG, et al: and the HEMO Group. The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients. Kidney Int 58:346-352, 2000
58. Keys A, Brozek J, Henschel A, et al: The Biology of Human Starvation. Minneapolis: University of Minnesota Press, 1950