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.

KEYWORDS C-reactive protein, serum amyloid A, cytokines, endothelium, HDL

Patients with end-stage renal disease have a marked increase in mortality. Although cardiovascular disease is the most common cause of death, markers normally associated with malnutrition, low serum albumin, prealbumin, and creatinine rather than hypercholesterolemia, 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 and generally requires additional factors, such as inflammation, for albumin concentration to be decreased significantly.

Albumin, similar to other nutritional markers, such as prealbumin (transthyretin) and transferrin, are negative acute-phase proteins. The synthesis of these proteins decreases during inflammation, as does their serum concentration, changes that occur entirely independent of nutritional state. 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), 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 alpha [TNFα]). 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 established that patients with pre-ESRD who were judged to be malnourished by mea-
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 and Yeun et al 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, 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, which should in turn lead to a reduction in creatinine generation. 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).4 In longitudinal studies, 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. 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. In another study, the subpopulations of men who benefited from aspirin were those with increased CRP levels. 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.

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 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. The lipoprotein Lp(a) is another powerful risk factor for vascular disease. 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. 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 and the apolipoprotein A-I (apo A-I) that normally composes about half of the proteins in HDL is replaced by SAA. 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.

**Antioxidant Effect of HDL**

HDL normally suppresses the effects of cytokines on their induction of adhesion molecules by endothelial cells. Inflammation alters HDL structure and function to remove these anti-inflammatory properties by reducing the levels of aryl hydrocarbon hydrodase and paroxynase.

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. 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. Inflammation alters HDL structure and function to remove these anti-inflammatory properties. 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 but other studies found an increase primarily in dialyzed patients. Several factors have been proposed to promote this inflammation, including increased oxidative stress and the accumulation of postsynthetically modified proteins (advanced glycation end products and products of carbonyl stress), 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). 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
Markers of inflammation are present in increased frequency in patients who have not yet undergone dialysis, Patient both on hemodialysis and peritoneal dialysis. In most studies, approximately 30% of these populations have increased levels of either CRP, SAA, or IL-6 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 values varied considerably in individual dialysis patients. The variability in CRP level was approximately 2 orders of magnitude greater than that of albumin, 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.

Currently, we do not know the cause of the inflammatory response. Many candidate causes have been suggested, including dialysis against nonbiocompatible membranes, the use of nonsterile dialysate, and back leak of dialysate across the dialysis membrane. 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, 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. 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

24. Li YP, Lecker SH, Chen Y, et al: TNF-alpha increases ubiquitin-conju-