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Chronic Systemic Inflammation in Uremia: Potential Therapeutic Approaches

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Systemic inflammation characterizes several chronic diseases including uremia. Inflammation may contribute to morbidity and mortality by enhancing protein-calorie malnutrition, infectious complications, and atherosclerosis and cardiovascular disease. Although inflammation in renal disease can be caused, at least in part, by reduced renal clearance of proinflammatory mediators (tumor necrosis factor [TNF]-α, interleukin [IL]-6), several pathogenetic mechanisms are likely to contribute to direct activation of the inflammatory process under these conditions. These mechanisms include accumulation of advance glycoxidation end products, production of reactive oxygen species and oxidative damage, and chronic infection. Support for direct activation of systemic inflammation provides a strong rationale for use of anti-inflammatory treatments in uremia. The current article describes the association between uremia and inflammation, provides evidence for activation of inflammatory process, and provides potential therapeutic approaches.
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Inflammation results from an imbalance between effects of proinflammatory and anti-inflammatory cytokines synthesized and secreted by circulating monocytes, tissue macrophages, Kupffer cells, and endothelial cells.[1,2] Tumor necrosis factor (TNF)-α and interleukin (IL)-1 represent major proinflammatory cytokines, whereas IL-6 appears to be the major mediator of acute phase reactants synthesis (Fig. 1).[1,2] Plasma concentrations of acute phase proteins (C reactive protein [CRP], fibrinogen, serum amyloid A, and others) are clinical indicators of systemic inflammation.[1-4] Newer data indicate that systemic chronic inflammatory response occurs and may contribute to both protein-calorie malnutrition and rapid progression of atherosclerotic lesions often observed in patients with end-stage chronic renal failure.[3,4] Chronic inflammation, therefore, may explain the positive correlation between markers of malnutrition (such as hypoalbuminemia and reduced body mass index)[5-7] and excess mortality for cardiovascular disease[8,9] often observed in these patients. In agreement with this view, protective genotypes linked with increased anti-inflammatory cytokine IL-10 are associated with reduced cardiovascular risk in uremic patients.[10] The potential impact of TNF-α polymorphism remains in turn to be determined. TNF-α and other proinflammatory cytokines also may play an important direct role in the onset of the metabolic alterations of chronic renal failure patients, including increased skeletal muscle protein degradation rate, reduced synthesis rates of skeletal muscle protein[11] and liver-synthesized albumin,[5-7] and insulin resistance.[12]

Plasma concentrations of proinflammatory cytokines and of their soluble receptors are increased proportionally with reduced renal function in chronic renal failure on conservative therapy, suggesting that accumulation of these circulating mediators is at least partially caused by their reduced renal clearance.[3-5] It is, however, possible that systemic inflammatory response may be activated directly by uremia-associated factors or by dialysis techniques. Direct contact between blood cells and dialysis membrane, lipopolysaccharides on the dialysate side of the membrane, or chronic subclinical inflammation at the vascular access site represent potential mechanisms leading to inflammatory states in dialysis patients.[13,14] Advanced glycoxidation end products may play a causal role in oxidative stress and inflammation in hemodialysis patients, and increased intracellular advanced glycoxidation end products cause increased mitochondrial production of reactive oxygen species.[15] Oxidative stress characterizes uremia and may contribute to activate chronic inflammation.[16,17] Accumulation of reactive oxygen species may promote activation of nuclear factor κ B, a transcrip-

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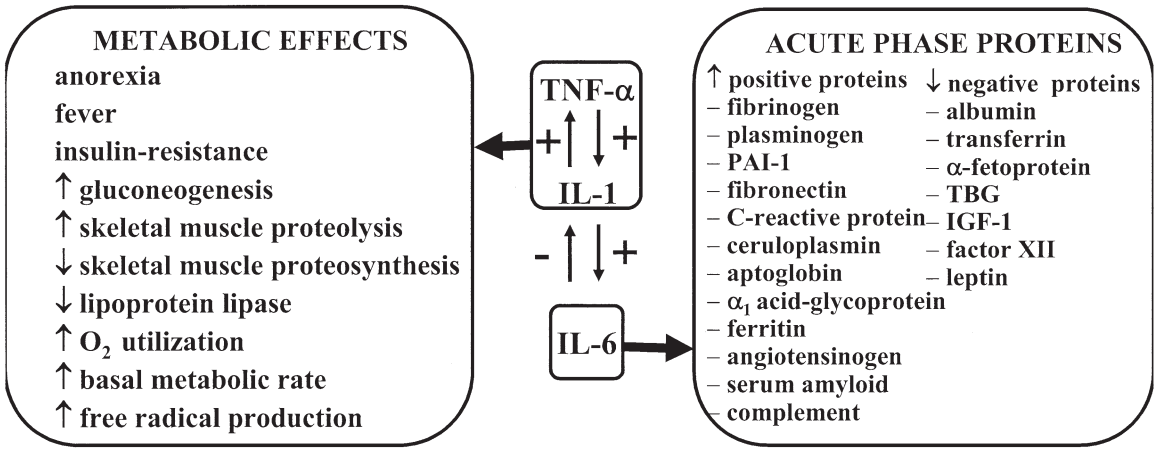

Figure 1 Schematic representation of major metabolic effects of proinflammatory cytokines TNF-α, IL-1, and IL-6. As indicated by arrows, TNF-α and IL-1 exert reciprocal stimulation and stimulate IL-6 production, although IL-6 has inhibitory effects on TNF-α and IL-1.

tional factor regulating inflammatory and immune responses, proinflammatory cytokine production, and cell growth.[1,2] Chronic infection by *Chlamydia pneumoniae* also has been proposed recently as a potential cause of chronic systemic inflammation and cardiovascular morbidity in chronic renal failure patients.[18] Systemic inflammatory response also may be activated by as yet unidentified additional factors such as uremic toxins. In agreement with the concept that systemic inflammatory response also is at least in part an active process in uremia, we have observed an increase in transcription levels of TNF-α, a key proinflammatory mediator, in blood cells from uremic patients compared with age- and weight-matched healthy control subjects (Biolo et al, unpublished observation). The activation of inflammatory response in turn provides a strong rationale for anti-inflammatory therapy aimed at reducing systemic inflammation in patients with renal failure.

Potential Approaches to Reduce Chronic Systemic Inflammation in Uremia

Potential approaches for treatment of systemic inflammation have been identified in recent years (Table 1). Evidence for their efficacy in renal disease remains scarce owing to a lack of large, controlled, population studies, but evidence from other chronic inflammatory conditions as well as from preliminary studies in uremia indicate potential for beneficial effects.

Pharmacologic Approaches

Statins

Statins have protective roles on cardiovascular risk in patients without increased plasma lipid concentrations,[19] indicating their pleiotropic effects, which include reduction of plasma markers of systemic inflammation. In experimental settings, statins reduce monocyte production of TNF-α[20] and nuclear factor κ B,[21] before or after addition of oxidized low-density lipoproteins. Simvastatin reduces plasma CRP in patients with hyperlipidemia and coronary artery disease.[22,23] In patients on hemodialysis treatment, treatment with statins was associated with reduction of high-sensitive CRP in a recent study.[24] In another report in similar patients, plasma high-sensitive CRP levels were not reduced significantly during statin treatment, although small group size could have influenced the result.[25]

Angiotensin-Converting Enzyme Inhibitors

Angiotensin II induces proinflammatory cytokines including nuclear factor κ B and TNF-α both in cultured human monocytes[26] and in kidney tissue.[27] Different angiotensin-converting enzyme inhibitors decreased plasma TNF-α, IL-6, and CRP concentrations in patients with chronic heart failure or atherosclerosis,[28,29] both associated with chronic inflammation. In a cross-sectional study, angiotensin-converting enzyme inhibitors have been shown to decrease plasma TNF-α concentration in patients with advanced renal failure on con-

Table 1 Potential Therapeutic Approaches for Systemic Inflammation.

Drugs
Statins[19-25]
ACE-inhibitors[26-30]
Pentoxifylline[31-33]
Thalidomide, β-blockers[34,35]
Antioxidants
Infliximab (TNF-α-neutralizing antibody)
Recombinant human IL-10, and so forth
Nutrients
PUFA[36-40]
L-arginine[41-50]
L-glycine[51-53]
Carnitine[54-57]
Glutamine, and so forth
Physical Exercise[58-60]

Abbreviations: ACE, angiotensin converting enzyme; TNF, tumor necrosis factor; PUFA, polyunsaturated fatty acids.

servative treatment compared with both patients without treatment and those on other antihypertensive drugs,[30] suggesting a protective anti-inflammatory role of angiotensin-converting enzyme inhibitors in this setting.

Pentoxifylline

The inhibitory effects of pentoxifylline on TNF-α production have been shown, making it a potential modulator of systemic inflammation with anti-inflammatory potential.[31] Although decreasing TNF-α levels, pentoxifylline was shown to inhibit sepsis-associated protein wasting, resulting in reduced catabolism through a TNF-mediated pathway.[32] This effect was confirmed recently in chronically uremic patients on conservative treatment in whom pentoxifylline infusion acutely reduced protein catabolism,[33] a characteristic of systemic inflammation activation.

Other pharmacologic approaches shown to reduce in vivo markers of chronic systemic inflammation, such as plasma TNF-α and CRP levels, include β-blockers[34] and thalidomide.[35] No controlled studies are available for these agents in renal failure patients.

Nutritional Interventions

Unsaturated Fatty Acids (n-3)

Dietary intake of fish oil with unsaturated n-3 fatty acids has been long recognized to reduce production of systemic inflammation markers and their plasma concentration in humans.[36] Fish oil has been shown to reduce plasma inflammation markers in chronic inflammatory diseases,[37] and it has been used for treatment of immunoglobulin A nephropathy, in which it reduces the rate of loss of renal function.[38] Eicosapentanoic acid administration reduces in vivo low-density lipoprotein peroxidation in dialysis patients,[39] in turn a marker of oxidative damage that can contribute to systemic inflammation activation. In patients with renal failure, 12 months of n-3 supplementation resulted in reduced ex vivo monocyte production of TNF-α and IL-1β,[40] indicating anti-inflammatory effects in the setting of uremia.

L-Arginine

L-arginine is the N donor for nitric oxide (NO) synthesis by NO synthase (NOS), and therefore is an important regulator of hemodynamics and blood flow favoring vasodilatation. L-arginine effects have been associated with reduced tissue inflammation markers in experimental models including stent injury[41] and renal transplantation[42] in the rat. L-arginine supplementation also has been linked with improved renal function or reduced loss of function in streptozotocin-induced diabetes[43] and aging in rats,[44] as well as in human kidney transplant recipients.[45] These effects could be caused in part by restoration of NO availability that is reported to be decreased by the majority of studies in animal and human models of end-stage renal disease.[46] It is possible that renal effects of L-arginine are at least in part dependent on reduction of organ and/or systemic inflammation that also can be mediated by arginine-induced increased NO availability.[47] Asymmetric dimethyl arginine (ADMA) is an endogenous inhibitor of NOS, reducing NO availability, whose plasma concentration is associated directly with cardiovascular risk in the general population.[48] The plasma ADMA level is increased in patients with end-stage renal disease as well as with incipient renal failure.[49] Plasma ADMA levels are associated positively with inflammatory markers, plasma fibrinogen, and CRP in patients with end-stage renal disease, and ADMA is an independent predictor of mortality and cardiovascular outcome in patients on hemodialysis.[50] Intervention to increase NO availability and reduce inflammation by increasing the L-arginine/ADMA ratio potentially could be beneficial in uremic patients. No controlled studies of effects of L-arginine supplementation on chronic inflammation markers have been completed in patients with uremia.

L-Glycine

L-glycine exerts direct and indirect anti-inflammatory effects in vitro and in vivo in several models including sepsis, shock, and ischemia reperfusion, decreasing oxidative stress and levels of proinflammatory mediators nuclear factor κ B, TNF-α, and IL-1β.[51] In experimental models, L-glycine administration increased renal blood flow and glomerular filtration rates in normal rats with a potential NO-mediated mechanism blocked by NOS inhibitors.[52] Reduced free radical formation mediated protective effects of L-glycine from ischemia-reperfusion renal damage.[53] Both effects could contribute directly to reduce organ and systemic inflammation. No controlled trials are available on potential anti-inflammatory effects of L-glycine in uremic patients.

L-Carnitine

L-carnitine reduces tissue and plasma expression levels of proinflammatory cytokines including TNF-α and IL-1β in several rodent models including sepsis[54] and heart failure.[55] Carnitine is depleted during dialysis and carnitine supplementation to dialysis patients has been reported to improve lipid metabolism as well as the incidence of intradialytic muscle cramps, hypotension, asthenia, and muscle weakness.[56] Six months of L-carnitine supplementation increased the total plasma antioxidant capacity in dialysis patients, potentially reducing a potent proinflammatory stimulus.[57]

Physical Exercise

Recent data suggest that mid- and long-term muscle training programs may reduce systemic inflammatory response in several physiologic and pathologic conditions including aging[58] and obesity.[59] Training reduced TNF-α gene expression in skeletal muscle in the elderly.[60] It is possible that modulation of the systemic inflammatory response may partially mediate the effects of exercise on muscle anabolism and strength, as well as bone density and insulin resistance.

Conclusions

Several interventions have been successful in reducing markers of inflammation and the inflammatory process in chronic diseases and experimental models. Despite the importance of chronic systemic inflammation in contributing to morbidity and mortality in uremia, little information is available on the efficacy of pharmacologic and nutritional anti-inflammatory

treatments in renal failure patients. Future studies should be designed to test these treatments under controlled conditions.

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