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Does Inflammation Affect Outcomes in Dialysis Patients?

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Abstract

Chronic, low-grade inflammation is a common comorbid condition in chronic kidney disease (CKD), and particularly in chronic dialysis patients. In this review, we consider the question of whether inflammation affects outcomes in dialysis patients. Levels of pro-inflammatory cytokines, as well as C-reactive protein, are elevated in chronic dialysis patients. Multiple factors likely contribute to chronic inflammatory activation in kidney disease patients including the uremic milieu, lifestyle and epigenetic influences, infectious and thrombotic events, the dialysis process, and dysbiosis. Increased inflammatory markers in both CKD and chronic dialysis patients are associated with adverse clinical outcomes including all-cause mortality, cardiovascular events, kidney disease progression, protein energy wasting and diminished motor function, cognitive impairment, as well as other adverse consequences including CKD-mineral and bone disorder, anemia, and insulin resistance. Strategies that have been shown to reduce chronic systemic inflammation in CKD and chronic dialysis patients include both pharmacological and non-pharmacological interventions. However, despite evidence that systemic inflammatory markers can be lowered in kidney disease patients treated with various strategies, evidence that this improves clinical outcomes is largely unavailable and represents an important future research direction. Overall, there is strong observational evidence that inflammation is high in chronic dialysis patients and that this is independently associated with numerous adverse clinical outcomes. Targeting inflammation represents a potentially novel and attractive strategy if it can indeed improve adverse outcomes common in this population.

Keywords

chronic dialysis; endpoints; inflammatory; kidney disease; outcomes

Prevalence of end-stage renal disease (ESRD) in the United States is rising and is associated with high morbidity and mortality, as well as healthcare expenditure.[1] Over recent decades, there has been considerable research implicating inflammation in chronic kidney disease (CKD) and ESRD, thus, inflammation could now be considered a well-established rather than a novel risk factor for clinical outcomes. In this review, we will consider the question of whether inflammation affects outcomes in chronic dialysis patients. We will discuss evidence of increased inflammation in CKD and chronic dialysis patients, the

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Disclosures

None.

association of elevated inflammatory markers with adverse clinical outcomes, and both pharmacological and non-pharmacological strategies to reduce inflammation in CKD and chronic dialysis.

Overview of Inflammation in CKD and Chronic Dialysis

It was first proposed in 1983 that inflammation, via monocyte release of interleukin-1 (IL-1), the master cytokine of inflammation, was the basis of numerous complications in chronic dialysis.[2] It is now appreciated that the development of inflammation in CKD begins well before the need for chronic dialysis, and elevated levels of inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) suggest that CKD and chronic dialysis can both be viewed as low-grade inflammatory processes.[3, 4] In CKD, inflammatory macrophages infiltrate the kidney, promoting release of pro-inflammatory cytokines including, IL-1β, tumor necrosis factor-α (TNF-α), IL-6, and interleukin-23 (IL-23).[5] While the release of pro-inflammatory cytokines may have acute beneficial effects, chronic inflammation is recognized to promote adverse consequences.[6] In fact, persistent low-grade inflammation has been recognized as an important contributor to risk of mortality, cardiovascular events, kidney disease progression, and other adverse outcomes in both CKD and chronic dialysis.[7–9]

Evidence of Increased Inflammation in CKD and Chronic Dialysis

Chronic, low-grade inflammation is regarded as a common comorbid condition in CKD, and particularly in chronic dialysis patients.[7] Several circulating markers are commonly assessed as indicators of systemic inflammation. IL-1 is a pro-inflammatory mediator of both acute and chronic inflammation, and induces synthesis and expression of hundreds of secondary inflammatory mediators.[10] IL-1β is the main form of circulating IL-1 and is initially synthesized as a precursor (pro-IL-1β) that becomes activated in the setting of a macromolecular structure known as the inflammasome,[10, 11] which is activated in CKD and perpetuates the inflammatory response.[12, 13] IL-6 is a pro-inflammatory cytokine that promotes inflammatory events through activation and proliferation of lymphocytes, differentiation of B cells, leukocyte recruitment, and induction of the acute-phase protein response in the liver.[14] IL-6 can be induced by IL-1 and by TNF-α, the latter of which is a soluble receptor primarily produced by monocytes and macrophages and elevated in states of chronic inflammation.[15] CRP is an acute phase reactant, downstream from IL-6, and is a more specific marker of plaque vulnerability and risk of cardiovascular events, with data suggesting it may play a direct role in atherogenesis rather than simply acting as a marker, as previously believed.[16]

Levels of pro-inflammatory cytokines including IL-1β,[17] IL-1 receptor antagonist (IL-1Ra),[5] TNF-α,[15, 17] and IL-6[5, 18], as well as CRP levels,[5, 18] increase with progressively declining renal function. Indeed, in CKD and chronic dialysis, markers of systemic inflammation are notably elevated, including IL-1Ra,[19] IL-1β[17], CRP[3, 4, 18, 20, 21], and IL-6[3, 4, 18]. Albumin and fibrinogen levels, two other acute-phase reactants, are lower and higher in CKD, respectively.[18, 20, 21] Overall level of inflammation appears to be generally lower in chronic peritoneal dialysis compared to hemodialysis patients.[22]

Etiology of Inflammation in CKD and Chronic Dialysis

Multiple factors likely contribute to chronic inflammatory activation in kidney disease patients (Figure 1). With declining renal function, both decreased renal clearance, as well as increased production, contribute to higher levels of circulating cytokines.[6, 23] The uremic milieu also promotes oxidative stress[18] and carbonyl stress[24], both of which are highly pro-inflammatory. Epigenetic influences, resulting from the interaction between genetic background and diet, lifestyle, and environment also contribute to increased inflammation.[7] Frequent infectious and thrombotic events provide additional inflammatory stimulations, particularly in dialysis patients, including catheter-related bloodstream infections, access site infections and thrombosed intravenous fistulas and grafts.[25] The microbiological quality of the dialysate and impurities in dialysis water may also contribute to inflammation.[26, 27] Overall, the acute effect of hemodialysis on cytokine levels is controversial, with inconsistent results regarding changes in IL-1 β, TNF- α, IL-6, and interleukin-18.[28–32] It is possible that changes in plasma cytokine levels lag behind stimulation and that other factors may modify concentrations at later time points.[33] In fact, hemodialysis has been shown to acutely up-regulate transcription of pro-inflammatory cytokines.[33]

Dietary factors common in CKD, such as low dietary potassium and phosphorus, can alter the gut microbiome, leading to dysbiosis (pathogen overgrowth in the gut).[34] Metabolic alterations associated with uremia also favor dysbiosis, which promotes translocation of bacterial DNA and endotoxins to the bloodstream via colon wall inflammation and epithelial tight junction barrier breakdown (i.e., “leaky gut”), thus promoting systemic inflammation.[34, 35] Other commonly proposed mechanisms for chronic inflammation include altered adipose tissue metabolism via pro-inflammatory adipokines[36] and a high prevalence of pro-inflammatory comorbidities, such as diabetes and atherosclerotic disease.[7]

Inflammatory Markers are Predictors of Adverse Clinical Outcomes

Increased inflammatory markers in CKD and chronic dialysis patients are associated with adverse clinical outcomes including all-cause mortality, cardiovascular events, kidney disease progression, protein energy wasting and diminished motor function, cognitive impairment, as well as other adverse consequences including CKD-mineral and bone disorder (CKD-MBD), anemia, and insulin resistance (Figure 2). We will review the epidemiological, as well as pre-clinical evidence, supporting these associations.

All-Cause Mortality

Elevated CRP[9, 37–40] and IL-6[41–44] have been repeatedly shown to independently predict all-cause mortality in chronic hemodialysis patients. In contrast, an early observational study found that albumin but not CRP was independently associated with mortality in this population.[45] IL-1 and TNF-α have additionally been associated with mortality in chronic hemodialysis patients.[43] Elevated inflammatory markers, including CRP and low albumin, also predict all-cause mortality earlier in CKD, in stage 3–4 patients.[46] Of note, evidence of an association of elevated CRP with all-cause mortality in peritoneal dialysis patients has been inconsistent, however, and may be limited by the relatively small sample sizes of the cohorts examined.[47, 48] Serial measurements of CRP

improve prediction of mortality compared to a single value.[40] This is an important consideration, as inflammatory markers are subject to significant variability over time, influenced by factors including the stimulus of dialysis, acute infection, and comorbidities. [49]

Cardiovascular Outcomes

The risk of cardiovascular mortality or a cardiovascular event in CKD and chronic dialysis patients is significantly increased compared to patients without CKD, even in the presence of similar cardiovascular risk factors.[50] Evidence supports the belief that increased systemic inflammation is independently associated with cardiovascular endpoints in kidney disease patients. Indeed, high CRP levels independently predict cardiovascular mortality in chronic hemodialysis patients,[9, 37, 38] as well as patients with stage 3–4 CKD.[46] Increased IL-6 levels also predict cardiovascular mortality in chronic hemodialysis patients. [48] Similarly, elevated CRP is an independent predictor of cardiovascular events in peritoneal dialysis patients. [48]

The association of chronic systemic inflammation with cardiovascular mortality may be mediated by increased left ventricular hypertrophy, as elevated CRP levels independently predict left ventricular mass index in chronic hemodialysis patients.[51] Similarly, in pre-dialysis CKD patients, elevated CRP and IL-6 levels are associated with increased left ventricular mass index or left ventricular hypertrophy[52, 53], as well systolic dysfunction. [52] Systemic inflammation may also promote cardiovascular mortality via atherogenesis. Elevated inflammatory markers are associated with increased risk of coronary events in women with reduced estimated glomerular filtration rate (eGFR)[54], as well as carotid intimal medial thickness in pre-dialysis CKD.[8] Increased CD16+ monocytes, which promote inflammation and atherogenesis, are also independently associated with cardiovascular events in chronic dialysis patients,[55] as well as patients with pre-dialysis CKD.[56] Additionally, chronic inflammation can promote vascular calcification, via interplay with several markers of mineral metabolism.[6]

Pre-clinical studies indicate that pro-inflammatory cytokines, including IL-6 and TNF-α, may have direct atherogenic properties.[57] CRP also promotes monocyte adhesion to endothelial cells, leading to vascular smooth muscle cell proliferation and migration, and atherogenesis.[57] Pro-inflammatory cytokines can additionally promote cardiac remodeling and hypertrophy, as well as stimulate apoptosis in cardiomyocytes.[58, 59] While pro-inflammatory cytokines are not constitutively expressed in the myocardium, they are upregulated in response to myocardial injury which may also contribute to their increased circulating levels.[60]

Kidney Disease Progression

Chronic systemic inflammation also appears to be a key mechanism in kidney disease progression. Elevated inflammatory markers predict both decline in kidney function as well as incident CKD in community-based populations,[61–65] as well as decline in eGFR and progression to ESRD in patients with prevalent CKD.[66, 67] However, in the Modification of Diet in Renal Disease (MDRD) study, CRP was not an independent risk factor for

progression of non-diabetic kidney disease, measured as decline in GFR.[68] Inflammatory markers do appear to predict eGFR decline in both microalbuminuric type 1 diabetics,[69] as well as progression to ESRD in type 2 diabetes.[70] Additionally, inflammatory markers associate with residual renal function in patients close to the initiation of dialysis[71] and in peritoneal dialysis patients.[72] The loss of residual renal function in peritoneal dialysis patients is also predicted by increased inflammatory markers.[73]

Mechanistically, pro-inflammatory cytokines may mediate glomerular injury, promoting monocyte and macrophage influx, mesangial cell proliferation, and fibrosis.[74–76] The Nlrp3 inflammasome is also activated during renal injury, and inflammasome-dependent cytokines contribute to kidney disease progression.[13] The activation and subsequent assembly of the inflammasome controls the production of numerous pro-inflammatory cytokines, including IL-1 β and IL-18.[13]

Protein Energy Wasting and Motor Function

Protein energy wasting, a condition characterized by multiple metabolic and nutritional derangements, is present in approximately 20–50% of chronic dialysis patients, and is characterized by loss of lean body mass and decreased visceral protein stores.[77] Cytokine-adipokine signaling plays an important role in protein energy wasting.[78] Protein energy wasting is one of the most important predictors of morbidity and mortality in CKD and ESRD.[78] Elevated inflammatory markers are also associated with reduced physical function, muscle mass, and muscle strength in the general aging population,[79] and impaired physical performance predicts all-cause mortality in patients with CKD.[80]

Physical performance, particularly lower extremity performance, is worse across the spectrum of CKD.[81] In chronic hemodialysis patients, levels of inflammatory markers are inversely related to thigh muscle area, an index of muscle wasting.[82] Additionally, higher baseline IL-1β levels are associated with an accelerated decline in an index of muscle mass over a one year follow-up period in chronic hemodialysis patients.[83] Similarly, higher baseline CRP level is associated with greater loss of lean body mass after one year of peritoneal dialysis.[84]

The association between CKD and reduced physical function may be mediated by the effects of inflammation on musculoskeletal function.[80] These changes include stimulation of protein degradation/muscle catabolism and skeletal muscle wasting,[78, 85] suppressed appetite,[86, 87], enhanced resting energy expenditure,[88] and suppression of anabolic hormones such as growth hormone.[89] Uremia may further impair muscle metabolism by augmenting CKD-associated inflammation, oxidative stress, and insulin resistance.[81, 85] Of note, results of a small, randomized, placebo-controlled trial suggest that inhibiting inflammation via an IL-1 trap may improve endurance in stage 3–4 CKD.[90]

Cognitive Function

Cognitive impairment is also common in kidney disease patients. The prevalence of cognitive impairment in ESRD patients is at least twice that of age-matched adults in the general population, and cognitive impairment is already evident in early stages of CKD.[91] CKD is recognized as an independent risk factor for incident cognitive impairment[92, 93]

and cognitive decline.[94, 95] Cognitive impairment is also associated with severity of CKD, with increased impairment on tests including the modified mini-mental state examination and trail making test part B with decreasing kidney function.[96] Importantly, cognitive impairment and dementia are associated with increased risk of death in chronic dialysis patients[97, 98], as well as decreased quality of life.[99]

Elevated systemic markers of inflammation are independently associated with cognitive decline in the general population;[100–102] however, results are not consistent across all studies.[103, 104] Limited available evidence also suggests an association of inflammation with diminished cognitive function in CKD and chronic dialysis patients.[105–107] In chronic hemodialysis patients, IL-6 and TNF-α inversely correlate with the cognitive function subscale of the Kidney Disease Quality of Life questionnaire, suggesting a link between inflammation and cognitive impairment.[105] CRP levels are also independently associated with cognitive performance on the mini-mental state examination before and after a hemodialysis session.[106] Recently, in the Chronic Renal Insufficiency Cohort (CRIC) study, higher CRP, IL-1β, and fibrinogen levels were associated with increased risk of impaired attention during the approximately 6 year follow-up period in individuals with baseline CKD.[107]

Mechanistically, the association of systemic inflammation with cognitive impairment may be mediated by a high prevalence of cardiovascular risk factors known to associate with cognitive impairment, such as diabetes, hypertension, and hypercholesterolemia, as well as depression and medication use.[91] Anemia is an additional risk factor for cognitive impairment that may play a role in this association.[108] The dialysis process may also promote cognitive impairment, due to hemodialysis-related hypotension, microembolization, and cerebral edema.[91] However, acutely, a single dialysis session has been shown to improve neuropsychological testing, including logical and visual memory, psychomotor speed, executive function, and concentration, suggesting a reversible component of cognitive impairment in chronic dialysis patients.[109]

Other Adverse Consequences

Low-grade systemic inflammation has also been shown to associate with other adverse clinical parameters in chronic hemodialysis patients. Numerous epidemiological studies have demonstrated an independent association between inflammation and disturbed markers of mineral metabolism.[110–113] Additionally, in vitro and in vivo studies suggest direct regulation of fibroblast growth factor 23[114–117] and 1,25-dihydroxyvitamin D[118] production by inflammation. However, directly inhibiting inflammation with an IL-1 trap does not change markers of CKD-MBD in patients with stage 3–4 CKD.[90] Inflammation also contributes to anemia and erythropoietin resistance,[119] mediated by decreased erythropoietin production[120], decreased stimulatory activity of erythropoietin [121], and increased production of hepcidin.[122] Inflammation may additionally play a pathogenic role in the development of insulin resistance,[123] as pro-inflammatory cytokines promote decreased skeletal muscle insulin-stimulated glucose uptake.[124]

Strategies to Reduce Chronic Inflammation

Strategies that have been shown to reduce chronic systemic inflammation in CKD and chronic dialysis patients include both pharmacological and non-pharmacological interventions (Figure 3). We will review briefly clinical trials that have evaluated strategies to reduce systemic inflammation in kidney disease patients.

Pharmacological Strategies

Despite scientific interest in trials targeting inflammation in patients with kidney disease for decades, direct anti-cytokine therapies have only been tested very recently in this population. In 2011, four weeks of IL-1β antagonism with anakinra was shown to be efficacious to reduce systemic inflammation, as evidenced by reduced CRP levels[125], and also improved adiponectin levels,[126] in a small study of chronic hemodialysis patients. More recently, in a randomized, double-blind trial in stage 3–4 CKD patients, twelve weeks of treatment with the IL-1 trap rilonacept also reduced CRP levels as compared to placebo[127]. Notably, IL-1 inhibition also improved brachial artery flow-mediated dilation, an index of vascular endothelial function and independent predictor of incident cardiovascular events and mortality.[128] Furthermore, this improvement was associated with reduced vascular oxidative stress, and the drug was well-tolerated. These studies support the need for future trials evaluating the safety and efficacy of direct anti-cytokine therapies for reducing renal and cardiovascular morbidity and mortality in patients with kidney disease. Of note, phase 1 studies of an IL-6 monoclonal antibody in CKD and chronic dialysis patients with chronic inflammation are also currently underway (NCT03126318 and NCT02868229).

Other trials have demonstrated reduced inflammatory markers in CKD and chronic dialysis patients treated with non-specific therapies with anti-inflammatory properties, including statins,[129] cholecalciferol,[130] ACEi/ARB,[131] sevelamer,[132] and peroxisome proliferator-activated receptor-gamma agonists[133]. Growth hormone supplementation also decreases CRP levels in chronic hemodialysis patients.[134] However, despite multiple observations that systemic inflammatory markers can be lowered in kidney disease patients treated with various pharmacological strategies, evidence that this improves clinical outcomes is largely unavailable. In addition to reducing CRP levels, one year of cholecalciferol treatment reduced left ventricular mass index in chronic hemodialysis patients; however, no placebo group was included in this study.[130] Short-term treatment with sevelamer, a non-calcium-based phosphate binder, improved vascular endothelial function measured by brachial artery flow-mediated dilation, in addition to lowering CRP levels, in stage 4 CKD patients.[130]

Notably, in the very recently completed Canakimumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), which enrolled over 10,000 patients with stable coronary artery disease and elevated CRP levels, the IL-1β inhibitor canakinumab significantly reduced the risk of major cardiovascular events by 15%.[135] However, patients with severe CKD (eGFR<30 ml/min/1.73m^2) were excluded from enrollment, thus results are not applicable to patients with advanced CKD or requiring chronic dialysis, who are at high risk for poor cardiovascular outcomes.

Non-Pharmacological Strategies

Several non-pharmacological strategies have also shown efficacy in reducing systemic inflammation in CKD and chronic dialysis patients. These include dietary factors such as catechins (green tea extract),[136] omega-3 fatty acids,[137] soy isoflavones,[138] low dietary fructose,[139] and pomegranate juice.[140] Increased physical activity can also reduce markers of chronic inflammation in patients with CKD.[141] Changes in the delivery of dialysis in chronic hemodialysis patients, including the use of ultrapure dialysate[142] and short daily dialysis[143] also reduce inflammatory markers. However, in general, data supporting the idea that reducing inflammation through non-pharmacological approaches improves clinical endpoints are lacking. One year of pomegranate juice did reduce second hospitalization due to infectious cause as compared to placebo in chronic hemodialysis patients.[140] Additionally, short daily dialysis reduces left ventricular mass index compared to conventional hemodialysis; however, these improvements may be due to decreases in volume and pressure loading, as well as reduced serum phosphorus, rather than reductions in systemic inflammation.[143]

Our Opinion

In our opinion, there is strong evidence that inflammation is high in chronic dialysis patients and that this independently predicts numerous adverse clinical outcomes. However, the evidence for a role of inflammation in affecting outcomes is limited by the fact that most of the available evidence is epidemiological in nature, with some additional support provided by mechanistic animal studies. There is also evidence that various interventions, ranging from specific anti-cytokine therapies to non-pharmacological strategies, can reduce circulating inflammatory markers in CKD and chronic dialysis patients. However, data that reducing systemic inflammation improves clinical outcomes are currently lacking; this area represents an important future research direction. Data from the CANTOS trial suggests that reducing inflammation may indeed reduce adverse outcomes in kidney disease patients, but prospective trials in populations of individuals with reduced eGFR, and particularly chronic dialysis patients, are needed. Given the high morbidity and mortality in these patients, targeting inflammation represents a potentially novel and attractive strategy if it can indeed be shown to improve their adverse outcomes.

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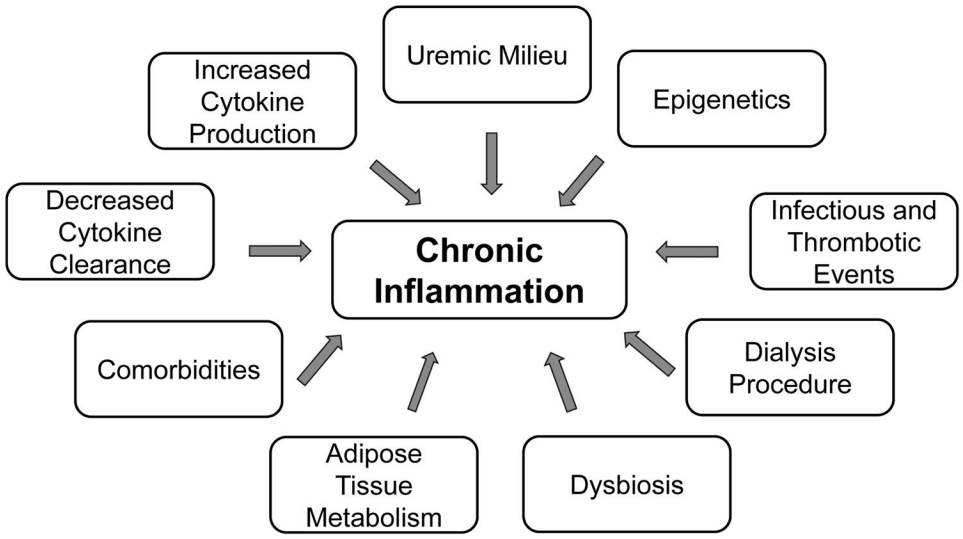

Figure 1. Factors Contributing to Increased Inflammation in Chronic Dialysis Patients

Contributing factors include decreased cytokine clearance and increased production, the uremic milieu, epigenetic influences, infectious and thrombotic events, the dialysis procedure, dybiosis, adipose tissue metabolism, and prevalent comorbid conditions.

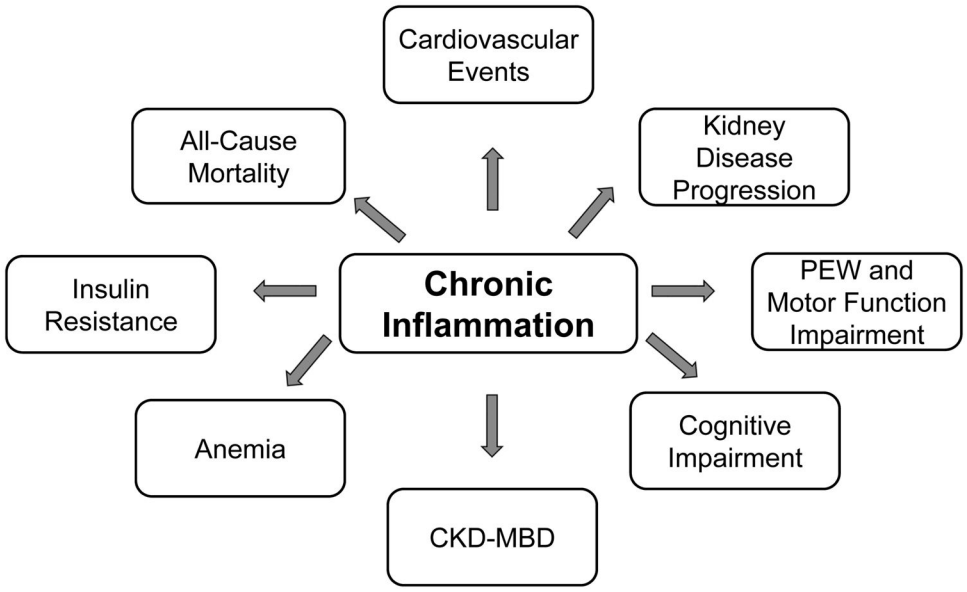

Figure 2. Adverse Clinical Outcomes Associated with Increased Inflammation in Chronic Dialysis

Adverse clinical outcomes that have been associated with elevated systemic inflammatory markers in chronic kidney disease (CKD) and/or chronic dialysis patients include all-cause mortality, cardiovascular events, kidney disease progression, protein energy wasting (PEW) and motor function impairment, cognitive impairment, CKD-mineral bone disorder (CKD-MBD), anemia, and insulin resistance.

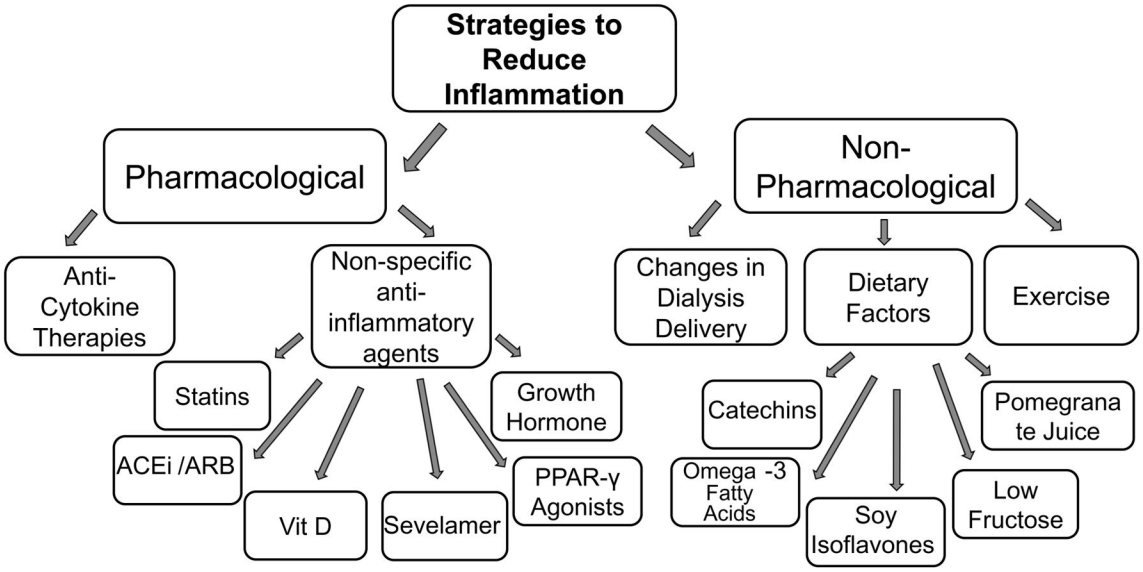

Figure 3. Pharmacological and Non-Pharmacological Strategies to Reduce Inflammation in Chronic Dialysis

Strategies shown to reduce systemic inflammatory markers in chronic kidney disease and/or chronic dialysis patients include pharmacological and non-pharmacological strategies. Pharmacological strategies that have been evaluated are specific anti-cytokine therapies, as well as non-specific agents with anti-inflammatory properties, including statins, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), cholecalciferol (vit D), sevelamer, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, and growth hormone. Non-pharmacological strategies that have been shown to lower systemic inflammatory markers include changes in dialysis delivery, dietary factors (catechins [green tea extract], omega-3 fatty acids, soy isoflavones, low fructose, and pomegranate juice), and exercise.