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Inflammatory Marker Mania in Chronic Kidney Disease: Pentraxins at the Crossroad of Universal Soldiers of Inflammation

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Even though the high prevalence of chronic inflammation and its link to poor outcome in chronic kidney disease (CKD) are not news any more (1,2), many clinicians and investigators remain interested in research about inflammatory markers in kidney disease. There are several reasons: (*a*) Recent studies, both epidemiologic and basic science, have suggested that in the general population, chronic inflammation may have a stronger causal role in engendering atherosclerotic cardiovascular disease than LDL hypercholesterolemia (3,4); this notion may lead to a major shift away from the traditional Framingham paradigm and toward the nontraditional paradigm of inflammation (5); (*b*) inflammation seems to be at least one of the reasons for the high burden of atherosclerotic cardiovascular disease and death in individuals with CKD (6); (*c*) patients with CKD and higher serum levels of inflammatory markers such as C-reactive protein (CRP) and IL-6 have a higher rate of CKD progression (7) and poor clinical outcomes, including higher death rates (8); and (*d*) inflammation may be the missing link between the surrogates of malnutrition-wasting syndrome such as hypoalbuminemia and poor survival in patients with CKD, especially. those who undergo maintenance dialysis treatment (9,10). On the basis of these premises, many nephrologists are interested in relevant information about the inflammatory markers and their associations with both CKD progression and cardiovascular disease and death in this population (Table 1).

CRP is probably the most notorious inflammatory marker in CKD. It was first described in the 1930s for its role in serologic reactions to pneumococcal pneumonia (11). CRP, a pentagon-shaped protein that is produced by the liver, binds to phosphocholine, leading to recognition of foreign pathogens and phospholipid constituents of damaged cells (12). The bound CRP not only activates the complement but also binds to phagocytic cells to initiate elimination of targeted cells, say *Pneumococci*, by interaction with both humoral and cellular effector systems of inflammation, including inflammatory cytokines (12). The *rapidity* of the CRP response, in contrast to the slower adaptive immune response represented by antibody production, makes it one of the fastest soldiers of the "special force" of our immune system known as "acute-phase response." Under such acute conditions, serum CRP level can surpasses the 50-mg/L range but returns to normal (<1 mg/L) once the infection subsides (Table 2) (13). The problem arises, however, when these destined-to-be "acute" soldiers circulate "chronically" in our vessels (14), as though the gone-awry universal soldiers would not want to evacuate the streets after taking over the town with the excuse of national security. The chronically elevated CRP levels, usually between 3 and 10 mg/dl, are associated with subsequent endothelial dysfunction and atherosclerotic cardiovascular disease (15), similar to the gradual devastation that a militarized government can impose on a nation by consuming its vital resources and deteriorating its economy. To that end, it is not surprising to observe such an unacceptably high burden of atherosclerotic cardiovascular disease and death in patients with CKD and dialysis patients, in whom CRP levels not infrequently maintain in ranges between 10 to 50 mg/L (Table 2) as though the nation were engaged in an ongoing and unending war with no exit strategy.

Such metaphoric descriptions of the role of CRP in causing cardiovascular disease, even if they may belittle the sophisticated pathophysiologic mechanisms behind the inflammatory processes, underscore the potential role of the correction of inflammation to improve cardiovascular disease and survival in CKD. CRP is now considered a member of the pentraxins, a family of inflammatory proteins characterized by calcium-dependent ligand binding and a distinctive flattened β-jellyroll structure similar to that of the legume lectins (16). The name "pentraxin" is derived from the Greek word for five (penta) and berries (ragos), relating to the radial symmetry of five monomers forming a pentagon ring. The "short" pentraxins include CRP and serum amyloid P. The "long" pentraxins include pentraxin 3 (PTX3), a cytokine-modulated molecule, and several neuronal pentraxins (Table 1) (17).

In this issue of *CJASN*, Tong *et al.* (18) show that PTX3 concentrations are higher in patients with pre-CKD compared with non-CKD control subjects. PTX3 has significant correlations with estimated creatinine clearance and serum levels of albumin, CRP, IL-6, fibrinogen, and vascular cellular adhesion

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Table 1. Inflammatory markers that have been studied in patients with CKD[a]

Category	Marker (Commonly Used Abbreviation)	Evidence for Outcome Predictability in CKD[b]
Short pentraxins	C-reactive protein (CRP)	+++
	Serum amyloid P (SAP)	+
Long pentraxins	Pentraxin-3 (PTX3)	+
	Neuronal pentraxins	?
Proinflammatory cytokines	Interleukin-6 (IL-6)	+++
	Interleukin-1β (IL-1β)	+
	Tumor necrosis factor α (TNF-α)	+/−
	Interleukin-8 (IL-8)	+
	Interleukin-18 (IL-18)	?
	Interleukin-12 (IL-12)	?
	Interferon gamma (IFN-γ)	+
Anti-inflammatory cytokines	Interleukin-10 (IL-10)	?
	IL-1 receptor antagonist (IL-1ra)	+
	Interleukin-4 (IL-4)	?
	Transforming growth factor β (TGF-β)	?
Adipokines and related compounds	Adiponectin	++
	Visfatin	+
	Resistin	+
	Leptin	+
	CD163	+
Adhesion molecules and endothelial markers	Intercellular adhesion molecule-1 (ICAM-1)	++
	Vascular cellular adhesion molecule-1 (VCAM-1)	++
	E-selectin	+
Coagulation markers	Fibrinogen	+
	Tissue plasminogen activator (t-PA)	+
	Plasminogen activator inhibitor-1 (PAI-1)	+
	von Willebrand factor (vWF) and factor VII	?
	Fibrin D-dimer	?
Inflammatory molecules with negative acute-phase reaction	Albumin (negative)	+++
	Transferrin or TIBC	++
	Iron	++
	Fetuin	+
Inflammatory lipoproteins	HDL inflammatory index (HII)	+
	Oxidized LDL (oxLDL)	+
Inflammatory enzymes	Myeloperoxidase (MPO)	+
	Matrix metalloproteinase-9 (MMP-9)	+
Proinflammatory transcription factors	Activator protein-1 (AP-1)	+
	Nuclear factor-κB (NF-κB)	+
Other inflammatory markers	Serum ferritin	+++
	Serum amyloid A (SAA)	+
	Neopterin (monocyte/macrophage activator)	+
	Platelet count	+
	WBC count	++
	Neutrophil count	+
	Erythrocyte sedimentation rate (ESR)	+

[a]TIBC, total iron-binding capacity; WBC, white blood cell. +/−, mixed data; +, some evidence of association; ++, moderate evidence; +++, strong and consistent evidence; ?, no data available.
[b]Evidence for chronic kidney disease (CKD) outcome predictability pertains to CKD progression or patient survival.

molecule-1. Patients with a history of cardiovascular disease or kidney disease wasting (KDW), as assessed by subjective global assessment, have higher PTX3 levels. Tong *et al.* also found that the highest PTX3 tertile was associated with an almost two-fold increase in death risk after adjusting for age, gender, history of cardiovascular disease, and serum CRP. Of note, CRP, the short

Table 2. Interpretations of serum CRP levels and atherosclerotic cardiovascular disease

Serum CRP Levels (mg/L)	Interpretation
<1	Normal
1 to 3	Possibly increased cardiovascular risk (grey zone)
3 to 10	Highly likely increased cardiovascular risk, common in moderate CKD
10 to 50	Common in maintenance dialysis patients
>50	Acute infection/inflammation (usually temporary)

pentraxin, loses its mortality predictability when adjusted for PTX3, the long pentraxin (18). On the basis of these data, the investigators advance the hypothesis that PTX3 might more acutely and rapidly reflect the risk for cardiovascular disease in CKD than CRP. Does it mean that among the exceptionally fast soldiers of the acute-phase response, some soldiers are even faster than the others and take the lead in sustaining the damage? Does it mean that the long and short pentraxins have differential roles at the crossroad of universal soldiers of inflammation in CKD?

The analyses of marker–outcome associations are usually subject to inherent limitations. First, there are collineralities among many of these markers and conditions. For instance, hypoalbuminemia, a KDW marker, is also an acute-phase reactant (19). In the study by Tong *et al.* (18), serum albumin had a strong correlation with PTX3 ($r = -0.42$), yet apparently albumin was not included in the survival models as a covariate to be adjusted for. One might argue against the inclusion of collinear covariates, which could lead to overadjustment bias, especially when KDW is in the causal pathway of the inflammation–outcome association (10,19). Conversely, one might also argue against this notion by maintaining that KDW is a possible cause of inflammation, as recently shown in animal models, in which induction of protein malnutrition led to activation of inflammatory cascade (20). Multivariate statistics can, therefore, be a significant source of errors and bias either way, and the association found after multivariate adjustment should be interpreted with great caution.

The field of inflammation in CKD is an ever-evolving field. Almost every month, a new inflammatory marker is introduced, and at a similar rate, a new study showing some "association" between the new marker and clinical outcomes is published. Whether the PTX3, as the prototype of long pentraxins, can offer more than what the short pentraxin CRP has offered thus far remains to be seen. As Tong *et al.* (18) appropriately alluded to, further studies are needed to determine whether PTX3 is merely yet another marker of inflammation in CKD with adding little new to the big pile of "associations" in inflammatory marker mania of CKD or whether the found associations suggest a pathogenic role in atherosclerotic cardiovascular disease in CKD distinct from that of CRP. It is believed—or at least hoped—that anti-inflammatory therapy such as IL-1 receptor antagonist (21) or nutritional interventions with anti-inflammatory and antioxidative properties (22) may be the key to improving longevity in CKD. Anti-inflammatory treatments may be our last best hope, because decades of treating such conventional risk factors as hypercholesterolemia and hypertension have not improved survival in dialysis patients (23); neither have the randomized, controlled trials such as the Die Deutsche Diabetes-Dialyse (4D) Study shown any promise (24). Treating inflammation in patients with CKD will hopefully bring the peaceful and civil conditions back to the war-torn CKD populations.

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Disclosures

None.

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See the related article, "Plasma Pentraxin 3 in Patients with Chronic Kidney Disease: Associations with Renal Function, Protein-Energy Wasting, Cardiovascular Disease, and Mortality," on pages 889–897.