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-away 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 metaphorical 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...
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
vascular 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.

References

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

<table>
<thead>
<tr>
<th>Serum CRP Levels (mg/L)</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>Normal</td>
</tr>
<tr>
<td>1 to 3</td>
<td>Possibly increased cardiovascular risk (grey zone)</td>
</tr>
<tr>
<td>3 to 10</td>
<td>Highly likely increased cardiovascular risk, common in moderate CKD</td>
</tr>
<tr>
<td>10 to 50</td>
<td>Common in maintenance dialysis patients</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Acute infection/inflammation (usually temporary)</td>
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</tbody>
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17. Shrive AK, Metcalfe AM, Cartwright JR, Greenough TJ: C-reactive protein and SAP-like pentraxin are both present in Limulus polyphemus haemolymph: Crystal structure of Limulus SAP. J Mol Biol 290: 997–1008, 1999


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.