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Does Inflammation Fuel the Fire in Chronic Kidney Disease?

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Since the landmark 1961 publication from the Framingham Study identifying smoking as a modifiable cardiac risk factor,[1] the field of preventive cardiology has burgeoned, and the science of risk factor analysis [2] has been applied to other chronic diseases. Of most interest is the identification of risk factors that are not only predictive of disease but are also both modifiable and causal: for the example of cardiovascular disease (CVD), gender is predictive, but non-modifiable; homocysteine levels are predictive, modifiable, but not necessarily causal; and hypertension is predictive, modifiable, and causal, in that treatment reliably reduces the risk of disease.

For chronic kidney disease (CKD), risk factors can be divided into risk of initiation of kidney damage and risk for progression of established kidney damage. Unlike CVD, where identifiable 'events' demarcate the transition from risk and subclinical disease to overt disease, CKD is typically asymptomatic, and markers of damage, such as albuminuria, are few. Thus for most patients, CKD is first diagnosed as an estimated glomerular filtration rate (GFR) less than 60ml/min/1.73 m^2. This diagnosis is a point on a continuous spectrum, so that passing the CKD threshold is more likely a sign of progression rather than initiation. Despite the continuous nature of kidney function loss, passing below an estimated GFR of 60 ml/min/1.73 m^2 – well prior to end-stage renal disease (ESRD) -- has been associated with a myriad of complications, including CVD,[3,4] muscle weakness,[5] cognitive abnormalities,[6] hospitalizations,[3] physical impairment[7] and high cost.[8] Thus, finding new targets for early treatment and prevention of CKD would be a major advance.

On a population basis, a number of predictive, modifiable and causal risk factors have been identified for kidney disease progression: of these, diabetes, hypertension, and vascular disease[9,10] are the most common illnesses, while smoking and non steroidal anti-inflammatory use (NSAID) use[11] are the most common exposures.[12,13] However, these factors do not entirely explain the population prevalence of CKD.[10]

A host of inflammatory peptides, including C-reactive protein, fibrinogen, D-dimer, and many others, have been proposed as risk factors for CVD;[14,15] many of these are not modifiable or causal, although recent data suggest that treatment of inflammation in those with elevated C-reactive protein may in fact lower cardiac risk.[16] Given the many similarities between risk factor profiles for cardiac and kidney diseases, it is reasonable to ask whether inflammation promotes the progression of kidney disease. The similarities between atherosclerosis and glomerulosclerosis have been proposed by various investigators; both atherosclerosis and glomerulosclerosis lead to influx of monocytes, production of lipid-laden macrophages, an increased presence of cholesterol and cholesterol esters, proliferation of contractile cells and

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matrix expansion resulting in fibrosis.[17,18] Biological studies suggest that inflammation plays a key role in both processes,[19,20] and subclinical measures of atherosclerosis have been associated with kidney function decline.[21] Chronic kidney disease and an inflammatory milieu are often found together,[22] with a high prevalence of increased c-reactive protein (CRP), fibrinogen and white blood cell (WBC) count, and low albumin noted in stages 3–5 CKD.[23–26] The causal links between the two have not however been established in epidemiological studies.

Several analyses of large cohort studies have attempted to address these issues by examining inflammation and subsequent kidney disease outcomes. In the National Health And Nutrition Examination Study, low albumin and high white count were associated with future ESRD or death from kidney disease.[27] In the Cardiovascular Health Study (CHS) cohort, older adults with high levels of CRP, factor VII, fibrinogen, WBC count, and hemoglobin or low levels of albumin had a greater risk of progressive loss of kidney function as assessed by a change of more than 3 ml/min/1.73 m^2/year over 7 years.[28] Post-hoc analysis of the Cholesterol and Recurrent Events Trial suggested that, in those with established CKD, high CRP and soluble TNF receptor II levels were associated with faster progression.[29] However, these associations have not been previously been explored in a younger population with normal kidney function at baseline and multiple measures of kidney function over time to define incident CKD.

In this issue of AJKD, Bash and colleagues [cite] use 14 yr follow up from the Atherosclerosis Risk in Communities (ARIC) study to provide insight into the links between inflammation and incident CKD, as defined by estimated GFR (using the MDRD equation) less than 60 ml/min/1.73 m2 or a ICD-9 code reflective of CKD; albuminuria was not measured in this study, and therefore was not used as part of the definition of CKD. The ARIC cohort included a middle-aged (45–64) group of white and African American men and women, drawn from 4 U.S. cities; those with baseline CKD were excluded, leaving a sample of 14,854 individuals. Six different markers of inflammation and hemostasis (white blood cell count, fibrinogen, von Willebrand factor, factor VIIc, factor VIIIc, and serum albumin) were assessed. The findings were striking: even after adjustment for known risk factors and baseline estimated GFR, five of the six analytes tested had significant associations with incident CKD. Factor VIIc (which was associated with incident CKD in CHS) was not found to have a significant association in ARIC. For the other analytes, the highest quartile of each marker (except for albumin where it was the lowest quartile) was associated with a 20–40% increase in the adjusted risk of incident CKD in comparison with the lowest quartile; graded associations were seen with incident CKD risk across the full measured range.

The large multi-racial cohort, long follow-up, and robust results across different definitions of CKD and across the various inflammatory markers are major strengths of this work. Most studies of incident CKD have had either estimates of GFR[6,9] or diagnostic codes for CKD-related hospitalizations,[27] but not both; this limits the specificity or sensitivity, respectively, of study findings. The results of this study were similar using either definition but were stronger using diagnostic codes, as expected from others' findings that diagnostic codes are more specific and tend to detect more advanced CKD.[30]

A few limitations deserve mention. Although the authors studied multiple different inflammatory markers, they did not include CRP, which is currently the most commonly measured inflammatory marker in clinical practice.[31] It is not clear, outside of the research setting, whether measurement of multiple markers is required to define inflammation or whether one marker would suffice. In this study, for instance, the correlation between factor VIIIC and von Willebrand factor is 0.7, suggesting that only one of these would need to be measured in practice; correlations between the other analytes are weaker and it is not clear which combination of these would be of most value. We would infer that serum albumin would

be the best single analyte to measure, as the associations with increased risk of CKD were significant even with minimally decreased levels of albumin, and given that these risks were minimally attenuated by multivariate adjustment; however, albumin level is less specific for inflammation or thrombosis than some of the other markers, and may be confounded by other illnesses.

An additional question that is not specifically addressed in this manuscript is the fraction of CKD risk attributable to this constellation of inflammatory markers versus other, traditional markers of CVD. This would be important in directing potential therapeutic interventions; for example, if traditional factors account on a population basis for 95% of the risk of incident CKD, or if inflammation proves to be a relatively minor mediator of traditional risk factors[32], then inflammation may only be of academic significance in promoting incident CKD. To move from a study like this one, which assesses the relative risk associated with inflammation, to predictive use of inflammatory markers to identify individuals at risk for CKD, studies of the test characteristics of the markers would be needed including receiver-operator characteristic curves, discrimination, and test calibration, and a substantial addition to known risk factors would be required.[33]

Risk associations such as those found in this work may be confounded by residual disease (e.g. more severe diabetes not adequately characterized by a binary variable might be associated with inflammation and with incident CKD) or by unmeasured disease such as subclinical cardiovascular disease and in particular albuminuria (as acknowledged by the authors). The 'non-CKD' cohort in this study is defined by eGFR > 60 ml/min/1.73 m^2; this cohort includes a subgroup of individuals with albuminuria who may be more likely to progress than those with estimated GFR < 60 ml/min/1.73 m^2 and no albuminuria.[34,35] Furthermore, albuminuria is independently associated with inflammatory markers such as fibrinogen levels.[36] Thus, the association of inflammatory markers with incident CKD may be confounded by unmeasured albuminuria at baseline.

The important findings of this study should be replicated in a population with data on albuminuria, and the comparative importance of inflammation versus other risk factors should be assessed. If a strong and independent association with a high attributable risk due to inflammation is demonstrated, the value of inflammatory markers in predicting CKD should be assessed, and trials using anti-inflammatory therapies to prevent progression or initiation of CKD should be considered. Given what we know about the morbidity and mortality associated with chronic kidney disease, the identification of inflammation as a predictive, modifiable, and treatable risk factor would be welcome news indeed.

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