Progressive Inflammation and Wasting in Patients with ESRD

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Body mass and, more importantly, body cell mass decline in patients with increasing time on RRT (1–3). Malnutrition, defined by low levels of albumin, low levels of prealbumin, low body mass index, and reduced physical function, is predictive of mortality (4). Although albumin concentration may increase in the first year after hemodialysis initiation, as a consequence of either nutritional improvement or the reduction in proteinuria that accompanies loss of residual renal function (5), after that year, the trajectory for albumin and prealbumin is a decrease with vintage (1,3). Albumin concentration as well as creatinine, which is a surrogate for muscle mass, are determined by several factors, but inflammation and nutrition are major determinants (6), with inflammation having greater predictive power (7). Importantly, inflammation is also strongly associated with mortality, and therefore, recognition, prevention, or reversal of it has potential to improve outcomes.

Dialysis patients are inflamed compared with the healthy population, which is assessed by C-reactive protein (CRP) or IL-6. The median value of CRP in most dialysis populations is considerably above the upper tertile in the general population (8). There is an incremental increase in inflammation among patients with CKD stage 5 after initiation of dialysis (9). The average already increased levels of acute phase proteins found in dialysis patients are interrupted by episodes of increased inflammation, which are accompanied by decreases in negative acute phase proteins albumin, prealbumin, and transferrin (5,7,10) (also nutritional surrogate biomarkers) and decreases in creatinine (7), suggesting decline in muscle mass (11). It is unclear whether effects on muscle mass reverse when acute inflammatory insults remit. Over the short term, however, albumin values return to baseline after inflammatory events (5,7), which does not explain the downward trajectory for both postdialysis weight and serum albumin concentration that was observed (3). Decreases in nutritional intake over time have been documented (3), providing one potential target for therapeutic intervention and one mechanism for nutritional decline. den Hoedt *et al.* (12) report a longitudinal decline in albumin similar to the decline reported in the Hemodialysis (HEMO) study (3), but in contrast to previous reports, den Hoedt *et al.* (12) describe a time-dependent increase in inflammation in patients in both treatment arms of the Convective Transport Study (CONTRAST). The greater than 80% prevalence of arteriovenous fistulas at baseline was substantially greater than in the HEMO study (27%), and CRP levels were significantly less than in the HEMO study as well as incident and prevalent hemodialysis patients in the United States (5,7). Serum albumin concentration reflects both inflammation, which is measured as CRP, and nutrition, which is estimated as normalized protein catabolic rate (7) and health-related quality of life (13). However, the dominant driver for albumin concentration as well as creatinine, which is associated with muscle mass (7), is inflammation. Muscle mass has been observed to decrease with years on dialysis (14).

It is rational to associate inflammatory processes with a dialysis population acquiring vascular access other than arteriovenous fistulas. It is unclear within the CONTRAST population whether vascular access changed significantly over time. If there was a significant increase in the prevalence of arteriovenous fistulas, it would offer a potential explanation for the increased inflammatory status described. Nevertheless, the basis for increased inflammation in CKD and dialysis patients overall is not well understood. Alterations in enzyme function, oxidative stress, lipoprotein structure, and function may all play a role, and how these processes progress over time as well as the underlying mechanisms for their derangement may also affect alterations. Improving outcomes in dialysis patients will require more in-depth understanding of these processes. Although it is useful to target vascular access as a driver of inflammation in dialysis patients, underlying processes, such as alterations in the microbiome (15,16), gut permeability to endotoxin (17), and gene expression, also occur with aging (also associated with loss of muscle mass and increased prevalence of inflammation) and in CKD by mechanisms, such as the reduction in nuclear factor erythroid 2–related factor 2 (18,19), and increase in myostatin expression (20). The relative abundance of patients having arteriovenous fistulas likely provides the relatively low level of inflammation in this population, allowing for appreciation that inflammation is a progressive process in dialysis patients. Nutritional deterioration accompanied by increased inflammation over time may indicate intermediate outcomes that require resolution as well as act as canaries in the coal mine, marking processes that increase disability

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and the risk of death in dialysis patients. Recognition that inflammation, like the nutritional variables with which it is associated, progressively changes over time offers a potential area for basic scientific exploration to clarify underlying mechanisms and serves as a potential target for therapeutic intervention.

Disclosures

G.A.K. is a consultant for the Renal Research Institute and has been a speaker for Merck. G.A.K. is also a member of a data safety monitoring board providing oversight for the National Institutes of Health on clinical trials exploring treatment of inflammation, alteration in the gut microbiome, and other interventions.

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See related article, "Clinical Predictors of Decline in Nutritional Parameters over Time in ESRD," on pages 318–325.