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Gut Microbial Translocation in the Pathogenesis of Systemic Inflammation in Patients with End-Stage Renal Disease

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Background

Chronic kidney disease (CKD) accelerates cardiovascular disease, increases the incidence and severity of microbial infections, anemia, cachexia and numerous other morbidities that shorten the life span and greatly impair the quality of patients’ lives. These abnormalities are associated with and are largely mediated by systemic inflammation and oxidative stress, common features of CKD [1], which have been attributed to numerous factors [2]. The severity of CKD-associated systemic inflammation correlates directly with the magnitude of endotoxemia in the absence of clinically detectable infection [3]. Although presence of endotoxin in the blood of ESRD patients was attributed to dialysate contamination, its presence in patients who do not receive dialysis treatment and in animals with experimental renal failure supports its endogenous origin, the most likely source being the gastrointestinal tract, home to a huge microbial community. This assumption is supported by several studies which have reported the presence of gut bacterial DNA fragments in the blood of CKD patients maintained on hemodialysis [4] and in CKD patients who did not receive dialysis treatment [5]. Moreover, colonic bacterial DNA has been detected in the mesenteric lymph nodes, blood, liver and spleen of animals with experimental CKD [6].

CKD-Induced Disruption of Intestinal Epithelial Barrier

Since in healthy humans and animals, the epithelial barrier prevents translocation of bacteria and their harmful by-products and components, the presence of endotoxemia and the detection of the gut microbial DNA in the blood of ESRD patients and in the blood and multiple tissues of CKD animals point to impairment of intestinal barrier structure and function.

This barrier consists of the apical membrane of the epithelial cells and the junctional adhesion complex that seals the gap between adjacent cells and includes the tight junction (TJ) and the subjacent adherens junction. There is mounting evidence that advanced CKD impairs intestinal epithelial barrier structure and function, thereby enabling the entry of endotoxin and other bacterial components in the intestinal wall and systemic circulation [7, 8]. In fact, massive depletion of the gastrointestinal epithelial tight junction proteins was reported in CKD animals [9, 10]. Moreover, in vitro studies revealed significant depletion of the tight junction proteins and reduction of trans-epithelial electrical resistance in cultured human colonocytes incubated in media containing human uremic plasma [11]. Subsequent experiments have lead to the identification of ammonia, a product of microbial urease, as the principal mediator of uremia-induced intestinal barrier disruption [12, 13].

Effect of CKD on Intestinal Microbiome

In addition to disrupting the epithelial barrier, advanced CKD alters the composition [4–6, 14] and function [15] of the intestinal microbiome. This phenomenon is driven by the luminal influx of urea, dietary restrictions and
pharmacologic interventions that alter the gut’s biochemical milieu leading to dysbiosis marked by the dominance of urease expressing and indole and p-cresol forming bacteria and the suppression of the short-chain fatty acid-forming bacteria [15]. As noted above, formation of ammonia from urea by the urease producing bacteria is essential for the breakdown of gut epithelial barrier structure and function, leading to local and systemic inflammation. Local inflammation, in turn, further amplifies the associated barrier disruption forming a vicious circuit, compounded by the diminished production of short-chain fatty acids, which are a major source of nutrients for colonocytes and for anti-inflammatory regulatory T lymphocytes. Finally, increased production of the potent pro-inflammatory molecules p-cresol sulfate and indoxyl sulfate by the gut microbial flora combined with their impaired renal clearance contributes to the associated systemic inflammation.

Bacterial Translocation in ESRD Patients

Using bacterial 16S rDNA amplification and DNA pyrosequencing, Kehui Shi and associates in this issue of *Digestive Diseases and Sciences* [16] analyzed blood and feces in a group of Chinese ESRD patients maintained on hemodialysis, a group of ESRD patients who did not receive dialysis treatment, and a group of healthy control individuals. In addition, they tested the dialysis solution for presence of bacterial DNA. Bacterial DNA was present in the plasma of 27% patients receiving and 20% of patients not receiving dialysis treatment. The fecal microbiome was significantly different between the ESRD and healthy control groups, confirming the results of the earlier studies [14, 15]. Moreover, the majority of bacteria detected in the blood of ESRD groups were also present in their feces. Only a few of the dialysate samples contained a low concentration of bacterial DNA from four microbial genera of which three were present in the patients’ blood and one in both blood and stool. Bacterial DNA present in the blood of dialysis patients is greatly different from the DNA fragments detected in the dialysate solution [4]. Taken together, these observations support the gut as the primary source of circulating microbial DNA in the ESRD population. This conclusion is further supported by the presence of microbial DNA in the blood of the subgroup of ESRD patients who did not receive dialysis therapy.

The percentage of patients with detectable circulating bacterial DNA was greater, and plasma concentration of bacterial DNA was significantly higher in the subgroup of the ESRD patients who were maintained on hemodialysis than those who were not, suggesting that the dialysis procedure may intensify the CKD-induced disruption of the intestinal epithelial barrier structure and function. Several factors may account for this phenomenon, including intradialytic and post-dialytic hypotension which can lead to bowel ischemia and inter-dialytic fluid retention which can lead to bowel edema [17], events that can intensify gut epithelial barrier disruption in these patients. In addition, gastrointestinal micro-bleed caused by systemic anticoagulation used with each hemodialysis treatment combined with uremic platelet dysfunction and high incidence of angiodysplasia in this population [18] can affect the integrity of the gut epithelial barrier structure and alter the microbial flora which is highly sensitive to the changes in the available iron pool. In confirmation of previous studies, both ESRD groups studied by Shi et al. [16] had plasma endotoxin concentrations far greater than those in the dialysis solution. This observation refuted the previously held notion that the dialysis solution is the source of the post-dialysis rise in plasma endotoxin, a phenomenon most likely due to the aforementioned transient bowel ischemia.

The Causal Link with Systemic Inflammation

While endotoxemia and systemic inflammation are present in nearly all patients with advanced CKD, measurable bacterial DNA was found in some, but not all ESRD patients employed in the study reported by Shi et al. [16]. The severity of systemic inflammation and the level of pro-inflammatory cytokines and chemokines were significantly greater in the subgroup of patients with detectable circulating bacterial DNA than those without. Moreover, the plasma concentration of pro-inflammatory mediators correlated with the amount of bacterial DNA in this subgroup, supporting the observation that intestinal epithelial barrier disruption positively correlates with detectable circulating bacterial DNA.

Summary and Future Directions

ESRD alters the biochemical milieu of the gastrointestinal tract changing the composition and function of the intestinal microbial flora while disrupting the epithelial barrier. The altered microbiome forms noxious products, which, combined with a leaky barrier facilitates the translocation of bacterial components into the systemic circulation, triggering local and systemic inflammation (Fig. 1). Shi et al. [16] confirmed the presence of bacterial DNA in the blood of ESRD patients and provided convincing evidence for the gut as its primary source. The study further illustrated the link between translocation of bacterial fragments with the severity of the prevailing systemic inflammation in the ESRD population.

Future studies are needed to explore the potential impact of dietary modifications, longer, gentler and more frequent
dialysis treatments, the use of prebiotics, probiotics, and renal transplantation on microbial translocation and the associated systemic inflammation in this vulnerable population.

Conflict of interest  None.

References


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