

**Title**  
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**Permalink**  
[https://escholarship.org/uc/item/1jq2z47d](https://escholarship.org/uc/item/1jq2z47d)

**Journal**  
Digestive diseases and sciences, 59(9)

**ISSN**  
0163-2116

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**Publication Date**  
2014-09-01

**DOI**  
10.1007/s10620-014-3287-z

Peer reviewed
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 biochemi-

cal 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 inflam-
mation, 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 con-
ducts to the associated systemic inflammation.

Bacterial Translocation in ESRD Patients

Using bacterial 16S rDNA amplification and DNA py-
rosequencing, 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 con-
centration 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
diasis patients is greatly different from the DNA frag-
ments detected in the dialysate solution [4]. Taken toge-
er, these observations support the gut as the primary
source of circulating microbital DNA in the ESRD popu-
lation. 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 pro-
cedure may intensify the CKD-induced disruption of the
intestinal epithelial barrier structure and function. Several
factors may account for this phenomenon, including intra-
dialytic 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 anticoag-
ulation 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 circu-
lating bacterial DNA than those without. Moreover, the
plasma concentration of pro-inflammatory mediators cor-
related 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 intes-
tinal microbital 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 il-
lustrated 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

18. Gerson LB. The presence of hemodialysis has been associated with GI hemorrhage, likely owing to intermittent usage of heparin for dialysis treatments and the presence of uremia-induced platelet dysfunction. Am J Med. 1985;79:552–559.