Gut Endothelial Leakage of Endotoxin May Be the Source of Vascular Inflammation and Injury in CKD. How Can This Be Targeted?

Related Articles, p. 13 and p. 28

THE RISK OF cardiovascular events increases as glomerular filtration rate declines increasing as much as 35 fold in patients with Stage 5 chronic kidney disease (CKD).[1] Despite the vast increase in risk in this population, biomarkers associated with risk in the general population, such as cholesterol level contribute little risk,[2] while the primary biomarkers associated with increased risk are those linked to inflammation.[3,4] One open question is identifying the causal pathway between inflammatory biomarkers, which themselves may simply provide evidence of inflammation and vascular injury. The risk of adverse cardiovascular outcomes is significantly increased even among individuals with normal renal function after an infectious event.[5] Acute infectious events are followed by changes in vascular structure, specifically an increase in carotid intima-media thickening, even among children after an infection[6] suggesting that inflammation, rather than being a consequence of vascular injury, is on the causal pathway. Inflammation, as measured by C-reactive protein (CRP), by other acute phase proteins or by cytokine levels, is increased well above the general population,[7] even in the absence of obvious prior infectious event among patients with CKD.[8] CRP has been previously reported to be increased in patients with kidney transplants and to be associated with cardiovascular outcomes.[9] The question addressed in this issue of the Journal by Chan et al[10] is identification of endotoxin absorbed through the gut mucosa as 1 potential sources of inflammation in this population as well as linking this to vascular injury and cardiovascular events by its association with sE-selectin, a marker of endothelial cell activation. Ideally, this would suggest that alteration in gut wall permeability to endotoxin or its precursor, lipopolysaccharide (LPS) would provide a therapeutic target, presuming a cause and effect relationship between the biomarkers studies and the causal pathway to injury. Of note, while CRP is indeed highly associated with vascular risk, this acute phase protein may well not be on the causal pathway, but instead reflect an inflammatory response[11] in which cytokines or the inciting inflammatory event, such as LPS or endotoxin causes vascular injury. Chan et al.[10] identify a number of factors, including circulating endotoxin as well as factors associated with body composition and nutrition that were associated both with CRP as well as the endothelial marker sE-selectin, a biomarker associated with endothelial health and vascular injury in other populations.[12] Adiposity, another source of pro-inflammatory cytokines[13] was also associated with sE-selectin, as was 25 OH vitamin D, noted to be associated both with LPS level and the composition of gut bacterial composition.[14] One important target identified[10] that could possibly be altered is the source of endotoxin—a lipid of bacterial origin that itself induces endothelial damage.[15] Endotoxin was identified both as a close correlate to CRP, but also to sE-selectin levels, a marker of endothelial injury, and adverse outcome. Alteration in gut wall permeability is an obvious target and the observation that increased fructose intake and decreased fibrin intake were also associated with inflammation, suggest that affecting gut wall permeability by dietary modification or some other process may be effective in reducing cardiovascular events by reducing exposure to endotoxins. Since changes in dietary patterns and changes within individuals or populations have been associated with changes in the gut microbiome,[16,17] dietary changes designed to effect a change in the microbiome could prove effective in altering gut permeability to toxins. CKD results in profound changes in the composition of the gut microbiome and in disruption of the intestinal epithelial barrier structure and function.[18,19] Two strategies may be used to accomplish change in the microbiome. One is a change in diet and the other is the administration of probiotic bacteria[20,21] although affecting a change in gut flora by administration of probiotics may be challenging.[21] The recommended diet for patients with CKD is low in potassium, phosphorous, and as a consequence, low in plant fiber and symbiotic organisms altering the normal gut microbiome resulting in higher number of pathogens like clostridia, enterobacteria, pseudomonas, and a lower number of beneficial microbes like lactobacilli and bifidobacteria.[19,22-24] The alteration in the gut microbiome results in the production of uremic toxins like advanced glycation products, phenols, and indoles which are then converted to indole-3 acetic acid,

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indoxyl sulfate (IS), and p-cresyl sulfates, glucuronides,[25,26] which are associated with the levels of inflammatory biomarkers.[27] This leads to generation and absorption trimethylamine (TMA), which is converted to potentially harmful TMA oxide (TMAO) by the liver. While TMAO is associated with vascular injury in non-CKD patient populations[28] and while levels are greatly elevated among dialysis patients, there does not appear to be an association between TMAO levels and cardiovascular outcome or inflammation in dialysis patients,[29] similar to what is observed for low-density lipoprotein cholesterol levels.[2,30] If the pathway to vascular injury is mediated by endotoxin directly and can be altered by changing gut wall permeability, alteration in gut flora may provide a therapeutic target.

Also in this issue of the Journal, Borges et al[26] used probiotic supplementation to alter the gut flora in dialysis patients. They found that uremic toxins, inflammatory markers, and gut profile were not altered. In addition, serum potassium, urea, and IS were increased. This was a double-blind, randomized, placebo-controlled trial enrolling 46 hemodialysis patients of whom 23 received probiotics (Streptococcus thermophilus, Lactobacillus acidophilus, and Bifidobacteria longum) daily for 3 months and 23 received placebo. No change was observed in gut microbiota profile after probiotic or placebo supplementation. Studies in the past have shown benefits of probiotics in CKD population,[31,32] and at same time, some studies have shown negative results.[33-35] One explanation for negative results may be that high urea levels in the colon lumen promote biochemical alterations in the colonic environment.[33,34,36] These alterations may alter enzymatic activity of bacteria including probiotics providing a greater urea hydrolysis rate and large amounts of ammonia. Part of the ammonia may be absorbed reaching the intrahepatic portal circulation and enter the urea cycle, thereby increasing ureagenesis. In addition, ammonia may be converted to ammonium hydroxide, increasing intestinal permeability. Damage to the intestinal barrier could affect the gastrointestinal excretion of potassium and increase membrane permeability to the diffusion of substances (such as IS) from the intestinal lumen into the blood. This may result in worsening of systemic inflammation. In the study of Borget et al., IS levels were increased but other toxins (p-cresyl sulfate and indole-3 acetic acid) showed no significant change.

Prebiotics may contribute to modulation of the gut microbiota and to improve integrity of intestinal epithelial barrier thus promoting more favorable scenario for the introduction of probiotic microorganisms.[37] Besides prebiotics, other strategies like physical activity and oral adsorbents may improve the gut imbalance in CKD. Alteration of the gut bacterial composition may require more intensive intervention than was applied or a change in diet.[21,38,39] However, the study by Borges et al.[26] has a small sample size, inflammatory markers could be influenced by other factors, and food intake was not monitored. A larger study is needed before this approach can be excluded. We need to remember that complexities of the gut microbiota in CKD patients should be taken into the account when probiotics are given to these patients to re-establish the gut microbiota. There are 3 theoretical safety concerns with use of probiotics: (1) occurrence of bacteremia, sepsis, or endocarditis; (2) toxic physiological or metabolic effects on the gastrointestinal tract[40-42] and; (3) transfer of antibiotic resistance in the gastrointestinal flora from commensal or probiotic bacteria to other bacteria or potential pathogens.[41,43] There is theoretical risk of adverse metabolic effects from manipulation of the microbiota with the use of probiotics, even if such manipulation is temporary. The use of probiotics in clinical trials should be accompanied by data safety monitoring and knowledge of antimicrobial susceptibilities of the organism used. Other probiotic organisms, such as Enterococcus, Bacillus, and other spore-forming bacteria, streptococci, are not regarded as safe and have been used as probiotics. The most physiological path to alter the gut microbiota is a change in diet, which may be challenging to implement in this population. Nevertheless, identification of gut bacteria as the source of endotoxin, a likely source of endothelial injury, provides a convenient target for reducing the greatly increased cardiovascular risk in kidney transplant and all CKD patients. Establishing a safe, effective, and convenient therapeutic pathway to achieving this end requires further investigation.

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