Topic	My Gut Feeling about PEW in CKD
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Protein-energy wasting (PEW) is prevalent and associated with adverse outcomes in patients with CKD. However, the pathogenesis of PEW in CKD has not been fully identified. The gut microbiota has been implicated in the regulation of host metabolism and energy balance. CKD markedly alters the composition of the gut microbiota. Therefore, gut dysbiosis may play an important role in the development of PEW in CKD. Dietary changes, azotemia, slow colonic transit, and frequent use of antibiotics in CKD patients modulate the gut microenvironment that favors the overgrowth of potentially pathogenic bacteria, which in turn generate a myriad of toxic metabolites including indoxyl sulfate (IS) from protein fermentation. Uremia and fluid retention with bowel edema increase intestinal permeability, resulting in so-called leaky gut. The disruption of the intestinal barrier integrity allows for the penetration of bacterial components and metabolites into systemic circulation, which triggers inflammation that may negatively impact nutritional status. In addition, accumulating data suggest that the uremic milieu itself plays a critical role in the initiation and progression of CVD in CKD. The majority of studies have assessed IS toxicity in cultured cells and animal models. However, human data have been conflicting and the benefit of using orally administered adsorbents to reduce IS levels in unselected CKD patients was not supported by the results from recent large randomized controlled trials. We hypothesized that a postprandial IS concentration may more reflect its toxicity. We established an oral tryptophan challenge test (OTCT) by using a fixed oral loading dose of tryptophan to simulate the postprandial increase of plasma IS, thus identifying the high and low IS producers. The results of the OTCT are integrated with analyses of whole metagenome sequencing of fecal microbiota and genetic polymorphism of CYP2E1 and SULT1A1 to explore the mechanisms of the IS production. A prediction model is constructed based on the individual IS producing capacity as contributed by the gut microbiota and liver enzymes. The IS producer phenotype revealed by the OTCT may serve as a personalized dietary guidance for patients with CKD. To decrease the CVD risk, high IS producers should avoid consuming foods that contain high levels of tryptophan. This will be a major breakthrough in the field of precision medicine for the nutritional management in CKD.