內生性毒素與心血管的糾纏

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Despite sophisticated dialysis machine and membrane and better clearance, the prevalence of cardiovascular disease and mortality remains high in hemodialysis patients. Some uremic toxins, other than hydro-soluble ones may be responsible of the culprit. Protein bound uremic toxins are retained solutes associated with endothelial dysfunction, vascular disease and immune dysregulation in renal patients. Two retained solutes, p-cresyl sulfate (PCS) and indoxyl sulfate (IS), are associated with cardiovascular events and mortality in hemodialysis and chronic kidney disease (CKD) patients. Indoxyl sulfate is eliminated from organic anion transporters 1 and 3 (OAT1/3) of proximal tubules. Consequently, the serum levels of PCS and IS are elevated in renal patients. These solutes are not cleaned sufficiently by conventional hemodialysis because of large albumin binding.

p-Cresyl sulfate is the main metabolite of p-cresol, derivative of tyrosine and also of phenylalanine and plant phenols. Recently, p-cresol was found to be an artifact derived from PCS produced during sample preparation. Recent research has suggested a novel role of PCS as a possible cardiovascular risk factor. P-cresyl sulfate activates leucocyte free radical production and induces a dose-dependent shedding of endothelial microparticles in the absence of overt endothelial damage. Clinically, high serum levels of PCS were associated with coronary atherosclerosis, cardiovascular disease, renal progression and death in CKD patients.

Indoxyl sulfate is derived from dietary indole, a metabolite of tryptophan. The overloading of this solute in CKD rat results in glomerular sclerosis and interstitial fibrosis via aberrant genetic expression of TGF-β1, TIMP-1 and Pro-α1 collagen, and complex redox alteration. Indoxyl sulfate is also associated with vascular dysfunction by promoting vascular smooth muscle cell proliferation via activation of platelet-derived growth factor receptors and mitogen-activated protein kinase pathways, and endothelial dysfunction. Clinically, high serum levels of IS were associated with increased aortic calcification, vascular stiffness, and consequently, cardiovascular mortality in CKD patients.

These protein bound uremic toxins exert cardiovascular toxicities through different mechanisms. These proposed pathways included the induction of endothelial inflammation, increase of oxidative stress, promotion of leukocyte and macrophage activation, proliferation of vascular smooth muscle cells, induction of insulin resistance and dysmetabolism and targeting of EGF receptor leading to tissue remodeling.

In the present review, we introduce the novel role of these protein bound uremic toxins, discuss its relationship with cardiovascular interaction and propose possible therapeutic strategies for its removal.