【Invited Lecture III】

Uremic toxins in CKD/DKD and its remedies

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It is known that a variety of uremic toxins derived from intestinal bacteria exist. We have previously reported that indoxyl sulfate (IS), p-cresyl sulfate (PCS), phenyl sulfate (PS), and trimethylamine N-oxide (TMAO) are 100% derived from intestinal bacteria.

Elevated blood levels of these uremic toxins are associated with increased mortality.

This led us to hypothesize that altering the gut environment to suppress the production of uremic toxins could be a potential treatment for renal failure, and we have been advancing our research using various drugs. Diabetic kidney disease (DKD) represents a major cause of end-stage renal disease. However, it is difficult to identify patients who are at risk of progression. We have reported that Phenyl sulfate (PS) is a modifiable cause and therefore a target for the treatment of DKD. We confirmed that in a diabetic patient cohort (U-CARE study, n=362), serum PS levels significantly related with the basal urinary albumin level. In addition, logistic regression analysis showed that among known ACR predictive factors (age, gender, BMI, SBP, HbA1c, eGFR and suPAR), PS was the only factor which significantly related 2-year progression of albuminuria especially in patients with microalbuminuria. In the microalbuminuria group, ROC curve analysis showed that the c-statistics value using combination of PS with known factors further increased. These data strongly suggested that PS may have a potential as important predictive marker of DKD.

In addition, we have previously report ed that new laxatives, including lubiprostone and linaclotide can reduce gut-derived uremic toxins such as indoxyl sulfate (IS), p-cresyl sulfate (PCS), trimethylamine N-oxide (TMAO) and phenyl sulfate (PS) and confer reno-protective effects in animal models. However, owing to the lack of randomized studies, the effect of such laxatives on CKD patients remains unclear. Furthermore, dehydration following laxative-induced diarrhea is a concern among CKD patients. Therefore, we conducted a randomized, double-blind study to validate the renoprotective effects of lubiprostone in CKD patients and determine safe dosage that did not cause adverse effects . Therefore, we conducted a randomized clinical trial and found that lubiprostone is a novel therapeutic agent for CKD that improves renal function.

References

1, Kikuchi K. Nature Commun 10, 1835, 2019. 2, Mishima E. JASN 26: 1787, 2015 3. Nanto F. NDT 35: 250, 2020, 4. Ho J-J. Physiol Rep.9: e15092, 2021.