Kidney Res Clin Pract 34 (2015) 191–193

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Editorial

The gut–kidney connection in advanced chronic kidney disease

Recent basic and clinical findings emphasize that chronic kidney disease (CKD) is a common disease of national significance in many developed countries. In Japan, 1 in 8 adults suffers from CKD, although less than 10% of people know the term "CKD". CKD is asymptomatic and leads to development of end-stage renal failure with hemodialysis and increased mortality. The main cause of mortality in patients with end-stage renal failure is cardiovascular events. Although this is at least partly explained by the presence of common factors that lead to the development of cardiovascular disease and aggravation of kidney failure, such as hypertension, dyslipidemia, diabetes, and aging, recently highlighted evidence clearly demonstrates that CKD acts independently as a key risk factor of cardiovascular events and other organ damage, including cognitive disorders [1,2]. This in turn strongly suggests the harmful effect of kidney damage on other organs, such as the heart, brain, and vessels. The remote effects or distant organ effects of the kidney are mediated by humoral factors in the systemic circulation in CKD patients and manifested as various complications and increased mortality. Furthermore, as described previously, the process of aging *per se* significantly accelerates the year-by-year development and progression of CKD. This is particularly so in the superaging society of Japan, where people older than 65 years now account for 26.8% of the total population. Kidney aging results in a decrease in the estimated glomerular filtration rate (eGFR) in association with tubulointerstitial thickening, even in healthy individuals, and CKD shows premature aging phenotypes in the kidney, accelerating kidney aging [3]. These findings emphasize the importance of research into solutions for CKD and the distant organ effects of CKD in an aging society. In particular, prevention of the development and retardation of the progression of CKD, namely the maintenance of kidney homeostasis, is beneficial for the regulation of systemic homeostasis and consequently for the achievement of a long and healthy life span.

CKD results in an increase in the uremic toxin level in plasma as the disease and aging progress. The accumulation of uremic toxins in the body is regulated by the balance between their production and clearance by the kidney. Importantly, a developing consensus states that uremic toxins are a consequence of not only kidney failure but also renal pathogen-induced acceleration of the progression of CKD and kidney aging. For example, uremic toxins derived mainly from carbohydrates, such as glyoxal, methylglyoxal, and 3-deoxyglucosone, cause unfavorable posttranslational modification of proteins or DNA (referred to as glycation or the Maillard reaction) and produce advanced glycation end products. These uremic toxins themselves or the advanced glycation end products induce glycative stress, which causes cellular dysfunction and subsequent damage to many organs, accelerating kidney damage and causing remote organ effects. Glycative stress caused by these uremic toxins in glomerular and tubular cells is a major risk factor in the development of end-stage renal failure in CKD patients both with and without diabetes. Importantly, kidney and vascular aging are positively correlated with increased glycative stress, and the condition is ameliorated by the antiglycative stress enzyme glyoxalase [4]. To support this notion, glyoxalase activity is decreased with aging, and the overexpression of glyoxalase extends life span in wild-type *Caenorhabditis elegans* [5]. Another kind of uremic toxin that is derived from amino acids, such as indoxyl sulfate or p-cresyl sulfate, predominantly induces or alters stress signal responses, which also contribute to the pathophysiology of CKD and kidney aging. These include hypoxic, oxidative stress, and endoplasmic reticulum (ER) stress responses [6,7]. Previous findings demonstrated that indoxyl sulfate exacerbates tubulointerstitial hypoxia *via* (1) demand for oxygen consumption by oxidative stress; (2) derangement of the hypoxia adaptive response pathway, which is mediated by hypoxia-inducible factor; and (3) suppression of erythropoietin production, which leads to renal anemia [6]. Indoxyl sulfate also induces the maladaptive ER stress response, namely the unfolded protein response pathway, which results in tubular cell apoptosis and the impairment of tubular cell proliferation for repair in CKD model rats [7]. Indoxyl sulfate is closely related to not only tubular homeostasis but also tubular aging: It induces tubular senescence, as estimated by senescence-associated beta-galactosidase activity and other senescence markers [8]. Taken together, these findings indicate that various kinds of uremic toxins that accumulate in CKD patients and the aged act as pathogenic factors, which alter protein structure and function, termed defective proteostasis, or which induce maladaptive stress signals. They closely contribute to not only kidney damage but also the defective link between the kidney and distant organs. This evidence emphasizes that therapeutic approaches that target uremic toxins will have beneficial effects on kidney homeostasis and in the prevention of kidney damage and aging.

http://dx.doi.org/10.1016/j.krcp.2015.08.007

How are uremic toxins removed from the blood stream to prevent CKD and kidney aging? AST-120, an agent that reduces serum and urinary concentrations of indoxyl sulfate, is commercially available in Japan, Korea, and the Philippines. AST-120 is an orally administered intestinal sorbent that adsorbs uremic toxins and their precursors including indole, which is a precursor of indoxyl sulfate. Theoretically, adsorption of uremic toxins may prolong the time to initiation of hemodialysis and improve uremic symptoms. Recent *in vivo* findings in CKD model animals demonstrated a suppressive effect of AST-120 on the progression of CKD. Two large clinical studies were performed to confirm these effects in humans: the Evaluating Prevention of Progression in Chronic Kidney Disease studies (EPPIC-1 and EPPIC-2), which were conducted as multinational, randomized, double-blind, safety, and efficacy trials. These trials evaluated whether the addition of AST-120 to standard therapy in patients with moderate to severe CKD can slow the progression of renal disease, defined as initiation of dialysis, kidney transplantation, or doubling of the serum creatinine level. Results showed no significant difference in time to occurrence of a primary end point event between the AST-120 and placebo groups in either study. Although change from baseline eGFR in the AST-120 and placebo groups did not significantly differ in EPPIC-1, a significant difference was seen in EPPIC-2 and in the pooled analysis of the two trials [9]. In another randomized crossover study of Stage 5 predialysis CKD patients, add-on AST-120 resulted in a positive change in eGFR [10]. Although AST-120 improves uremic symptoms, the discrepant results for the renoprotective effects of AST-120 in these human trials may be due to poor compliance with AST-120, which requires a relatively large amount of intake of the reagent. Further investigations are required to develop effective therapies targeting uremic toxins in human patients.

A second approach to reducing uremic toxin accumulation in the body is to suppress uremic toxin formation. Importantly, the cutting edge technology of metabolomics has demonstrated that some uremic toxins are metabolites derived from gut microbiota and that the alteration of microbiota profile is closely associated with the level of uremic toxin formation. For example, indole and p-cresol, which are precursors of indoxyl sulfate and p-cresyl sulfate, respectively, are produced by the microbiota as a metabolite of amino acids (indoxyl sulfate from tryptophan and p-cresyl sulfate from tyrosine). It is the consensus that CKD often alters the microbiota profile in association with an increase in indoxyl sulfate or p-cresyl sulfate as disease progresses. This is another representative example of the remote effect of CKD, showing a deleterious effect of kidney disease on the intestinal microbiota with subsequent increases in uremic toxins and aggravation of remote effects on other organs. Our group demonstrated that in 5 of 6 nephrectomy CKD model rats, a prebiotic (galacto-oligosaccharides), which reduces the indoxyl sulfate level by modification of microbiota profile in CKD, ameliorated the progression of kidney damage [11]. Of note, this amelioration of CKD progression by modulation of microbiota was associated with a reduction in tubular damage caused by ER stress. Lubiprostone, commonly used for the treatment of constipation, also ameliorates the progression of CKD and the accumulation of uremic toxins by improving the gut microbiota and intestinal environment [12]. These findings indicate the impact of the microbiota as a culprit in the progression of CKD and raise the possibility of therapeutic approaches that target the microbiota. Meanwhile, from the point of view of uremic toxin formation, a low protein diet may also be beneficial. Although the renoprotective effects of a low protein diet are controversial, some clinical studies failed to show renoprotection with a low protein diet in CKD patients [13]. These findings suggest that the modulation of microbiota may be more effective than a low protein intake in regulating amino acid–derived uremic toxin formation. Taken together, these findings indicate that the suppression of the accumulation of uremic toxins by both absorption and decreased formation may be a beneficial approach to delaying CKD progression and kidney aging.

Conflicts of interest

The author has no conflicts of interest to declare.

References

[1] Gajjala PR, Sanati M, Jankowski J: Cellular and molecular mechanisms of chronic kidney disease with diabetes mellitus and cardiovascular diseases as its comorbidities. *Front Immunol* 6:340, 2015

[2] Watanabe K, Watanabe T, Nakayama M: Cerebro-renal interactions: impact of uremic toxins on cognitive function. *Neurotoxicology* 44:184–193, 2014

[3] Kooman JP, Kotanko P, Schols AM, Shiels PG, Stenvinkel P: Chronic kidney disease and premature ageing. *Nat Rev Nephrol* 10: 732–742, 2014

[4] Jo-Watanabe A, Ohse T, Nishimatsu H, Takahashi M, Ikeda Y, Wada T, Shirakawa J, Nagai R, Miyata T, Nagano T, Hirata Y, Inagi R, Nangaku M: Glyoxalase I reduces glycative and oxidative stress and prevents age-related endothelial dysfunction through modulation of endothelial nitric oxide synthase phosphorylation. *Aging Cell* 13:519–528, 2014

[5] Xue M, Rabbani N, Thornalley PJ: Glyoxalase in ageing. *Semin Cell Dev Biol* 22:293–301, 2011

[6] Nangaku M, Mimura I, Yamaguchi J, Higashijima Y, Wada T, Tanaka T: Role of uremic toxins in erythropoiesis-stimulating agent resistance in chronic kidney disease and dialysis patients. *J Ren Nutr* 25: 160–163, 2015

[7] Inagi R, Ishimoto Y, Nangaku M: Proteostasis in endoplasmic reticulum—new mechanisms in kidney disease. *Nat Rev Nephrol* 10: 369–378, 2014

[8] Shimizu H, Yisireyili M, Nishijima F, Niwa T: Stat3 contributes to indoxyl sulfate-induced inflammatory and fibrotic gene expression and cellular senescence. *Am J Nephrol* 36:184–189, 2012

[9] Schulman G, Berl T, Beck GJ, Remuzzi G, Ritz E, Arita K, Kato A, Shimizu M: Randomized placebo-controlled EPPIC trials of AST-120 in CKD. *J Am Soc Nephrol* 26:1732–1746, 2015

[10] Wu IW, Hsu KH, Sun CY, Tsai CJ, Wu MS, Lee CC: Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on stage 5 chronic kidney disease patients: a randomized crossover study. *Nephrol Dial Transplant* 29:1719–1727, 2014

[11] Furuse SU, Ohse T, Jo-Watanabe A, Shigehisa A, Kawakami K, Matsuki T, Chonan O, Nangaku M: Galacto-oligosaccharides attenuate renal injury with microbiota modification. *Physiol Rep* 2. pii: e12029, 2014.

[12] Mishima E, Fukuda S, Shima H, Hirayama A, Akiyama Y, Takeuchi Y, Fukuda NN, Suzuki T, Suzuki C, Yuri A, Kikuchi K, Tomioka Y, Ito S, Soga T, Abe T: Alteration of the intestinal environment by lubiprostone is associated with amelioration of adenine-induced CKD. *J Am Soc Nephrol* 26:1787–1794, 2015

[13] Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, Greene T, Levey AS, Sarnak MJ: Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 53:208–217, 2009

Reiko Inagi
Division of Chronic Kidney Disease Pathophysiology, The University of Tokyo Graduate School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
E-mail address: inagi-npr@umin.ac.jp.

Available online 25 November 2015