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Role of gut–kidney axis in renal diseases and IgA nephropathy

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Purpose of review: Growing evidence show the importance of gut/kidney axis in renal diseases.

Advances in gut microbiome sequencing, associated metabolites, detection of gut permeability and inflammation provide new therapeutic strategies targeting gut for kidney diseases and particularly for Immunoglobulin A (IgA) nephropathy (IgAN).

Recent findings: The diversity and composition of gut flora have been recently deeply explored in kidney diseases. Modulation and depletion of microbiota in animal models allowed the understanding of molecular mechanisms involved in the crosstalk between gut, immune system and kidney. New clinical trials in order to positively modulate microbiota result in improvement of gastrointestinal disorders and inflammation in patients suffering with kidney diseases.

Summary: The investigation of gut alterations in kidney diseases open new therapeutic strategies. In IgAN, targeted treatments for intestinal inflammation and modifications of gut microbiota seem promising.

Keywords

IgA nephropathy, intestinal inflammation, kidney diseases, microbiota

INTRODUCTION

Kidney diseases are various, inducing chronic organ injuries and potentially its loss of function. These diseases represent a major worldwide issue, affecting around 10% of the population. Classical treatments for kidney failure are dialysis and renal transplantation with side effects for patients. Acute kidney injury (AKI) or chronic kidney disease (CKD) both result in the production of circulating uremic toxins due to the diminution of renal filtration, leading to the deterioration of other organs (heart, bones, digestive tract, etc.). Better understanding of pathological mechanisms involved in kidney diseases brings the scientific community to the exploration of other body compartments with a particular interest for the gut. This review will summarize the latest data on interactions between intestinal inflammation, gut microbiota and kidney diseases. A special focus on IgA nephropathy (IgAN) gut/kidney axis will be discussed with common molecular pathological pathways.

INTESTINAL INFLAMMATION AND KIDNEY DISEASES

Gut permeability and inflammation are often described associated with kidney diseases. Indeed, inflammatory bowel diseases (IBD) display a higher risk of gut permeability and are associated with a higher risk for CKD [1,2]. A recent meta-analysis showed among CKD patients recurrent IBD occurs for 27.6% and de novo IBD for 18.8% [3]. In kidney transplanted patients, IBD concomitance was associated with poor outcomes [4]. Another symptom of gastrointestinal disorder in CKD is constipation, often under-recognized, affecting the quality of life of CKD patients [5]. Interestingly, some drugs for constipation exhibit renoprotective effects with potential benefits for CKD patients [5]. In another hand, CKD through the production of uremic toxin and bacterial translocation. Circulating Lipopolysaccharide (LPS) subtypes found in patients with kidney failure differ from healthy individuals [6]. The authors then explored whether End-stage renal diseases (ESRD) chronic inflammation was related to LPS composition by testing cytokine secretion in monocyte cultures. They observed that inflammation in ESRD patients may be not related to higher bacterial translocation, but to reduced LPS neutralization capacity and differences in translocated LPS subtypes. So, the loss of intestinal integrity in CKD patients seems to be associated to an inadequate immune response leading to inflammation. Notably, obesity, diabetes and nonalcoholic fatty liver disease (NAFLD) are also associated to a higher risk of CKD [7–13]. The management of obesity with diet restriction results in amelioration of kidney function in CKD patients [14]. Snelson et al. [15–16] showed that long-term intake of processed foods drives intestinal barrier permeability and inflammation with a higher risk of CKD in rodent models. By contrast, a dietary fiber maintains gut integrity and reduces inflammation [15]. Long term high protein diet is also deleterious for kidney, increasing gut permeability [16]. Modifications of diet to reduce intestinal inflammation appear promising in CKD patients. A pilot study of gluten-free diet in children with kidney diseases positively impact immune responses with anti-inflammatory effects [17]. The main mechanism of these diet interventions is the modulation of gut microbiota.

GUT MICROBIOTA AND KIDNEY DISEASES

Gut microbiota induce immune responses and are powerful modulators of inflammation and intestinal integrity, impacting kidney function. The interplay between gut microbiota and kidney function is bidirectional. Animal studies showed that the absence of microbiota can exacerbate some cases of kidney damage through changes of metabolites [18] or attenuate kidney injury and inflammation [19]. CKD mice exhibit an altered gut flora. Fecal microbiota transplantation from healthy mice improves and increases gut microbiota diversity in CKD mice [20]. Gut microbiota transfer from CKD patients into rats induced disruption of the gut epithelial barrier through the production of phenol [21]. In a model of mouse model of AKI [22], gut microbiota dysbiosis is associated to leaky gut. Fecal transplantation from AKI mice to germ-free mice exacerbated inflammation and AKI. Antibiotic treatment was protective for kidney. The modification of diet with fermented fibers results in microbial production of short-chain fatty acids (SCFA) preventing AKI in mice [23]. In patients, gut microbiota was demonstrated to be impacted both AKI [24] and CKD. Gut microbiota in patients suffering with CKD showed decreased a diversity [25,26] and microbial composition modifications [25,27&,28,29] associated with disease severity [25,30–32]. Moreover, treatment of kidney failure seems to modify gut microbiota. Peritoneal dialysis has also an impact on gut flora in patients with kidney failure [33]. There is a lower bacterial diversity and a higher

proinflammatory cytokine production among hemodialysis non survivor patients [34]. In kidney transplanted patients, the diversity of gut microbiota is lower compared to healthy individuals and abundances of bacteria differ [35]. Immunosuppressive treatments also influence gut microbiota of transplanted patients [35]. Among the different CKD, gut microbiota is altered in diabetic nephropathy with a decrease of bacterial richness and diversity [36,37], in idiopathic nephrotic syndrome including membranous nephropathy, minimal change nephrosis and focal segmental glomerulosclerosis [37–40]. In lupus nephritis, the decrease of microbiota diversity is associated to disease activity and immune parameters [41]. Metabolites secreted by the aberrant gut microbiota of CKD seem to exacerbate kidney failure [42]. Toxins produced by gut bacteria can also amplify the deleterious effects of uremic toxins generated by renal failure [43]. Specific metabolites derived from microbiota increased in CKD patients include indole [29], and trimethylamine N-oxide (TMAO) [44]. TMAO concentrations negatively correlated with kidney function. Inhibition of microbiota-dependent, TMAO production attenuates CKD in mice [45]. However, a recent study suggests that gut bacteria are not the main contributors of uremic toxins in blood of CKD patients [46]. Other metabolites from gut microbiota can play a role in kidney diseases. The decrease of gut microbiota-derived SCFA is described in CKD [27], such as butyrate in idiopathic nephrotic syndrome patients [39]. SCFA are known to exert anti-inflammatory properties, enhancing immune regulation.

In order to positively modulate gut flora, various nutritional therapies have been tested in CKD patients. Low protein or Mediterranean diets can alter gut microbiota composition, reduce circulating uremic toxins and improve intestinal epithelial integrity [47,48] with a reduction of inflammation [49]. In a pediatric cohort of CKD patients [50], dietary fiber intake reduced circulating toxins. In adult CKD patients, deterioration of kidney function was reduced by a plant-centered diet [51]. In a randomized controlled trial, the prebiotic fructooligosaccharide intake decreased circulating IL-6 levels and uremic toxins and preserved endothelial function [52]. A symbiotic formulation also resulted in toxin and intestinal permeability decrease in CKD patients with impaired kidney function [53]. Figure 1 summarizes the interactions between gut and kidney and potential therapies based on diets or medications.

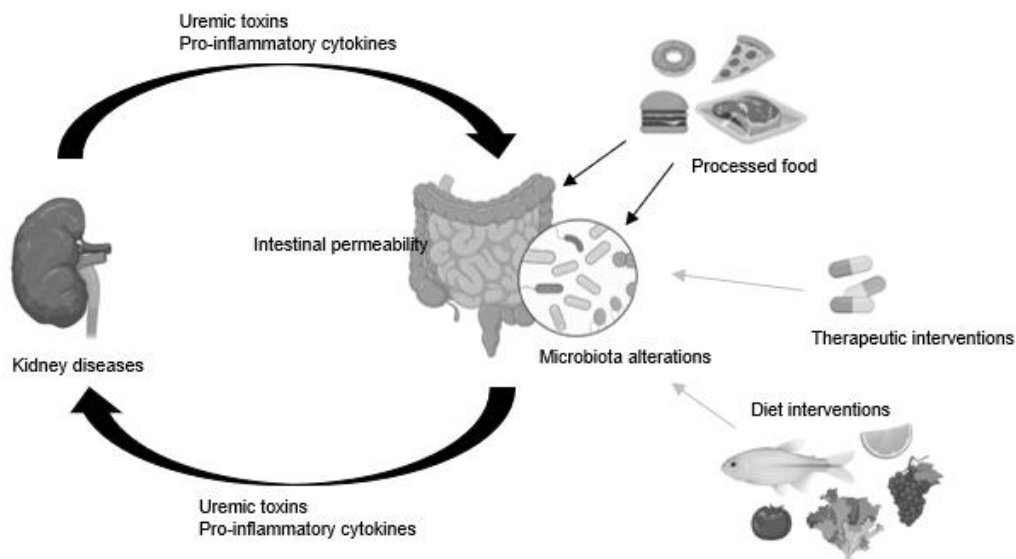


FIGURE 1. Deleterious interactions between gut and kidney and potential interventions targeting gut to treat kidney diseases. In kidney diseases, the injuries lead to the decline of filtration function and accumulation of uremic toxins in blood. Moreover, inflammation is often associated with production of pro-inflammatory cytokines by the kidney. The gut is then damaged, with an increased permeability and microbiota is altered. Microbiota also produce uremic toxins and the dysbiosis induces intestinal immune responses, increasing the body inflammation and exacerbating kidney damage. The effects of processed food are additive to this phenomenon. Protein reduced diets and augmentation of fruit and vegetable consumption show positive effects for patients with kidney diseases, as therapies targeting intestinal dysfunctions.

IgA NEPHROPATHY: AN EXAMPLE OF TIGHT MOLECULAR LINKS IN GUT/KIDNEY AXIS

IgAN is characterized by the deposition of Galactose deficient IgA1 (Gd-IgA1) complexes in the renal mesangium. Deposition of IgA1 in kidney results from a complex cascade of events involving low glycosylation of IgA1, auto-immune responses against Gd-IgA1 Abs (IgG and IgA), generation of high MW IgA complexes due to binding to soluble CD89 IgA receptor after shedding from monocytes, interaction with other IgA1 receptors on mesangial cells (TfR1, beta1.4galactosyltransferase), activation of mesangial cells, leukocyte-mediated inflammation through the transmembrane CD89 receptor crosslinking by IgA-immune complexes and overexpression of TfR1 and transglutaminase 2 (TG2) increasing IgA deposits [54,55]. As IgA are mainly produced at mucosal surfaces in responses to microorganisms, an evident implication of gut axis occurs in IgAN.

Microbiota modifications and IgA responses in IgA nephropathy

The majority of IgA is produced in the gut in response to microbiota stimulation and gut microbiota dysbiosis are associated to immune-related diseases. The gut microbiota composition in IgAN was recently explored. All studies showed modifications of bacterial abundances in IgAN patients [40,56–59]. Associated to these gut microbiota alterations, the production of metabolites was also modified in blood, urine and feces of IgAN patients [56,58]. Interestingly, SCFA, which exhibit anti-inflammatory properties, are decreased in feces of IgAN patients [60]. Some IgAN markers of disease such as proteinuria and hematuria or Gd-IgA1 correlated positively or negatively with different bacterial abundances [40,57,61]. To assess the effects of gut microbiota on IgAN, the effects of depletion of gut microbiota by antibiotic treatments was assessed in a humanized mouse model of IgAN. It resulted in a reduction of intestinal IgA production, and the prevention of renal IgA deposits and proteinuria [62]. Rifaximin, a nonabsorbable antibiotic often used clinically to modulate the gut microbiota was also tested in this mouse model with the same beneficial effects [63]. A study reported two female IgAN patients with failure of immunosuppression who underwent fecal microbiota transplantation [64]. Partial remission of their clinical symptoms was associated with increased diversity of their gut microbiota. All these modulations of gut microbiota suggest new therapeutic approaches for IgAN.

In another hand, host genetic variants associated to IgAN were linked to particular bacterial modifications [65]. B cell activating factor (BAFF) transgenic mice (overexpressing BAFF, an important cytokine for IgA class switch, which results in an increased production of IgA and IgG) exhibited IgA deposition in their kidneys and gut flora modifications [66]. In IgAN patients, increased BAFF levels are associated to an augmentation of gut-homing memory B cells producing IgA [67&]. So, interplay between host and microbiota is complex and bidirectional in IgAN.

Intestinal barrier and inflammation in IgA nephropathy

IgAN patients seem to exhibit an increased intestinal permeability. Moreover, in a IgAN rat model, Zhou et al. explored intestinal barrier damages and tight junction proteins [68]. They showed that intestinal-barrier damage was associated to decreased expression of ZO-1, OCLN and MUC2 and intestinal-microbiota dysbiosis in IgAN rats. The prevalence of IBD in IgAN patients increased over time in a Finnish cohort [69]. This was confirmed recently in a Swedish study of a large cohort of 3963 biopsy-proven IgAN patients [70]. Moreover, and

importantly, among patients with IgAN, the presence of IBD enhances the risk of progression to ESRD. A case series of IgAN associated with IBD showed that patients exhibit frequent inflammatory lesions [71]. IBD and IgAN share genetic susceptibility loci as CARD9 and HORMAD2 and recently the complement factor B in a Chinese Han population was also described [72], reinforcing the genetic links between these diseases.

To dampen intestinal inflammation, a targeted release formulation of budesonide (TRF-budesonide) designed to deliver the drug to the distal ileum was tested in IgAN patients in a phase 2b trial (NEFIGAN study) and resulted in reduction of proteinuria [73]. In posttransplant IgAN, this therapy was also efficient [74]. The comparison of TRF-budesonide to classical corticoids showed a higher decrease of proteinuria in a small cohort of IgAN patients [75]. Unexpectedly, in two IgAN patients treated for chronic constipation, Lubiprostone ameliorated their clinical symptoms of IgAN [76] indicating that modifications of enteral

environment may result in improvement of kidney function. So targeting intestinal inflammation in IgAN appears to be a promising therapy.

IgA-transglutaminase 2-TfR1 molecular axis

In IgAN patients, celiac disease risk is increased [77]. As well, patients suffering with celiac disease exhibit more IgAN than control population [78]. In celiac disease, abnormal reactivity against gluten leads to intestinal inflammation and damage. Pathological mechanisms involve TG2 activity and its recognition by auto-antibodies (IgG and IgA). Moreover, TfR1 and TG2 act together to induce retrotranscytosis of IgA-gliadin peptide complexes from the lumen into the lamina propria of the intestine of celiac disease patients [79]. In a humanized IgAN mouse model, TG2 and IgA present in kidney deposits are also dysregulated in intestine [54,80]. Food antigens and gliadin from gluten, have been described to form IgA complexes in IgAN which in some cases can be deposited in the mesangium of IgAN patients. A gluten-free diet in the humanized mouse model of IgAN resulted in a massive decrease of IgA1 deposits in kidney associated with decreased inflammation and less hematuria [80]. This decrease was gluten specific, as re-introduction of gluten in the diet was followed by the re-appearance of mesangial IgA1. The diminution of IgA1 deposits with gluten-free diet was associated with down-regulation of mesangial TG2 and TfR1 expression in mouse kidneys. Moreover, when IgA1 deposits are cleared using anti-IgA1 protease, TG2 and TfR1 expression are no longer detectable [81]. TG2 is also expressed on other kidney cell types, such as tubular cells [82], which could also impact IgA-N progression. Moreover, TG2 concentration in urine from IgAN patients correlated with proteinuria and distinguished active and nonactive patients [83]. So, the same molecules: IgA, TfR and TG2 are involved in pathological mechanisms in gut and kidney inducing inflammation and organ damage (Fig. 2).

Figure 2: Gut/kidney axis in IgA nephropathy

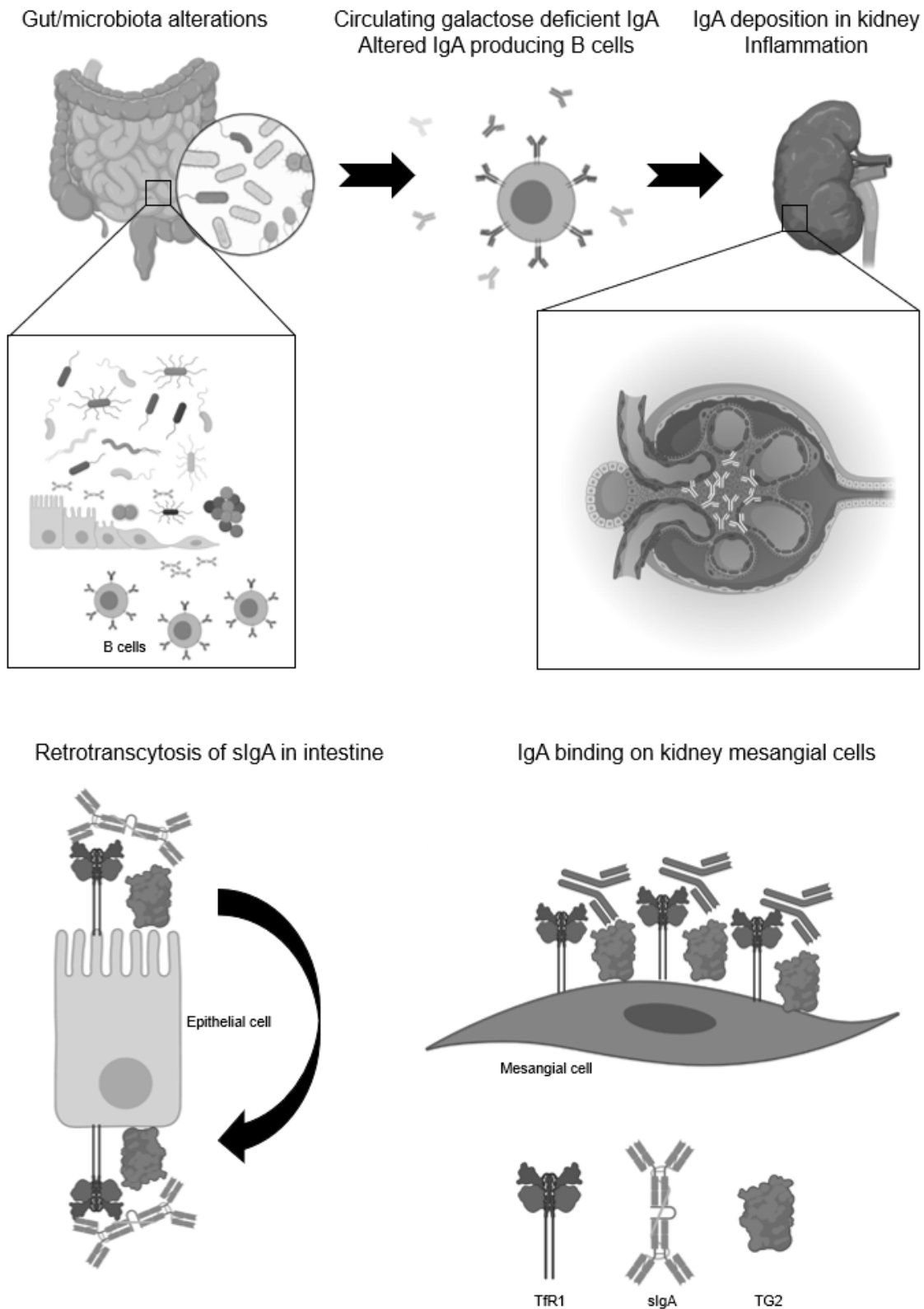


FIGURE 2. Gut/kidney axis in IgA nephropathy. As IgA are mainly produced in the intestinal mucosa, gut alterations seem to induce aberrant glycosylated IgA1 production which deposit in the renal mesangium. The resulting kidney inflammation is highly deleterious. At the intestinal epithelial surface and in the renal mesangium, the same molecular partners are involved: the transferrin receptor (TfR1) and the transglutaminase (TG2), both molecules interact with IgA1 in the pathological mechanisms in the gut and the kidney.

CONCLUSION

Leaky gut, alterations of gut microbiota are associated with kidney diseases deleterious bidirectional effects. Modulation of gut microbiota using diverse therapies could improve clinical outcomes in kidney diseases such as IgAN.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: & of special interest, && of outstanding interest

1. Vajravelu RK, Copelovitch L, Osterman MT, et al. Inflammatory bowel diseases are associated with an increased risk for chronic kidney disease, which decreases with age. *Clin Gastroenterol Hepatol* 2020; 18: 2262–2268.
2. Park S, Chun J, Han KD, et al. Increased end-stage renal disease risk in patients with inflammatory bowel disease: a nationwide population-based study. *World J Gastroenterol* 2018; 24:4798–4808.
3. Hansrivijit P, Puthenpura MM, Thongprayoon C, et al. Incidence and impacts of inflammatory bowel diseases among kidney transplant recipients: a metaanalysis. *Med Sci* 2020; 8:39.
4. Grupper A, Schwartz D, Baruch R, et al. Kidney transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity. *Transpl Int* 2019; 32:730–738.
5. Sumida K, Yamagata K, Kovesdy CP. Constipation in CKD. *Kidney Int Rep* 2020; 5:121–134.
6. Adda-Rezig H, Carron C, Pais de Barros JP, et al. New insights on end-stage renal disease and healthy individual gut bacterial translocation: different carbon composition of lipopolysaccharides and different impact on monocyte inflammatory response. *Front Immunol* 2021; 12:658404.
7. Bae EH, Lim SY, Jung JH, et al. Obesity, abdominal obesity and chronic kidney disease in young adults: a nationwide population-based cohort study. *J Clin Med* 2021; 10:1065.
8. Adair KE, von Waaden N, Rafalski M, et al. Metabolic phenotypes and chronic kidney disease: a cross-sectional assessment of patients from a Large Federally Qualified Health Center. *Life* 2021; 11:175.
9. Pinto KR, Feckingham CM, Hirakata VN. Obesity as a predictive factor for chronic kidney disease in adults: systematic review and meta-analysis. *Braz J Med Biol Res* 2021; 54:e10022.
10. Wang J, Niratharakumar K, Gokhale K, et al. Obesity without metabolic abnormality and incident CKD: a Population-Based British Cohort Study. *Am J Kidney Dis* 2021. S0272-6386:00636-3.
11. Wu H, Lau ESH, Yang A, et al. Young age at diabetes diagnosis amplifies the effect of diabetes duration on risk of chronic kidney disease: a prospective cohort study. *Diabetologia* 2021; 64:1990-2000.
12. Aubert L, Sandino J, Gutierrez-Solis E, et al. Role of nonalcoholic fatty liver disease in the evolution of renal function in patients with diabetes mellitus. *Nephrol Dial Transplant* 2021. May 13;gfab176.
13. Zuo G, Xuan L, Xin Z, et al. New nonalcoholic fatty liver disease and fibrosis progression associate with the risk of incident chronic kidney disease. *J Clin Endocrinol Metab* 2021. Jun 14;dgab425.
14. Wendt R, Oberander N, Weimann A, Beige J. Weight-reduction and changes in renal function in CKD patients participating in a conservative multimodal obesity program. *Clin Nephrol* 2021. May 17. CN110108.
15. Snelson M, Tan SM, Clarke RE, et al. Processed foods drive intestinal barrier permeability and microvascular diseases. *Sci Adv* 2021; 7:eabe4841.
- && Snelson M et al., showed that intake of processed foods drive intestinal barrier permeability with a higher risk of CKD. This diet activates complement and innate immunity in kidney. Interestingly, the kidney injury can be reversed by inhibition of the advanced glycation pathway. A modification of diet with high resistant starch fiber resulted in gut barrier integrity and decreased severity of kidney injury via suppression of complement.**
16. Snelson M, Clarke RE, Nguyen TV, et al. Long term high protein diet feeding alters the microbiome and increases intestinal permeability, systemic inflammation and kidney injury in mice. *Mol Nutr Food Res* 2021; 65:e2000851.
17. Perez-Saez MJ, Uffing A, Leon J, et al. Immunological impact of a gluten-free dairy-free diet in children with kidney disease: a feasibility study. *Front Immunol* 2021; 12:624821.
18. Mishima E, Ichijo M, Kawabe T, et al. Germ-free conditions modulate host purine metabolism, exacerbating adenine-induced kidney damage. *Toxins* 2020; 12:547.
19. Watanabe IKM, Andrade-Silva M, Foresto-Neto O, et al. Gut microbiota and intestinal epithelial Myd88 signaling are crucial for renal injury in UO Mice. *Front Immunol* 2020; 11:578623.
20. Barba C, Soulage CO, Caggiano G, et al. Effects of fecal microbiota transplantation on composition in mice with CKD. *Toxins* 2020; 12:741.
21. Wang X, Hao Y, Liu X, et al. Gut microbiota from end-stage renal disease patients disrupt gut barrier function by excessive production of phenol. *J Genet Genom* 2019; 46:409–412.

22. Yang J, Kim CJ, Go YS, et al. Intestinal microbiota control acute kidney injury severity by immune modulation. *Kidney Int* 2020; 98:932–946.

& Yang J et al., using gut microbiota depletion and fecal microbiota transplantation elucidated mechanisms of bidirectional talk between kidney and gut in mouse model of AKI.

23. Liu Y, Li YJ, Loh YW, et al. Fiber derived microbial metabolites prevent acute kidney injury through g-protein coupled receptors and HDAC inhibition. *Front Cell Dev Biol* 2021; 9:648639.

24. Rydzewska-Rosolowska A, Sroka N, Kakareko K, et al. The links between microbiome and uremic toxins in acute kidney injury: beyond gut feeling—a systematic review. *Toxins* 2020; 12:788.

25. Hu X, Ouyang S, Xie Y, et al. Characterizing the gut microbiota in patients with chronic kidney disease. *Postgrad Med* 2020; 132:495–505.

26. Liu F, Xu X, Chao L, et al. Alteration of the gut microbiome in chronic kidney disease patients and its association with serum free immunoglobulin light chains. *Front Immunol* 2021; 12:609700.

27. Sato N, Kakuta M, Hasegawa T, et al. Metagenomic profiling of gut microbiome in early chronic kidney disease. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association -European Renal Association* 2020. Sep 1;gfaa172.

& Sato N et al. explored the early CKD patients showing that in beginning kidney diseases, gut microbiota is already altered.

28. Hu Q, Wu K, Pan W, et al. Intestinal flora alterations in patients with early chronic kidney disease: a case-control study among the Han population in southwestern China. *J Int Med Res* 2020; 48:300060520926033.

29. Yang CY, Chen TW, Lu WL, et al. Synbiotics alleviate the gut indole load and dysbiosis in chronic kidney disease. *Cells* 2021; 10:114.

30. Ren Z, Fan Y, Li A, et al. Alterations of the human gut microbiome in chronic kidney disease. *Adv Sci* 2020; 7:2001936.

31. Wu W, Lin CY, Chang LC, et al. Gut Microbiota as diagnostic tools for mirroring disease progression and circulating nephrotoxin levels in chronic kidney disease: discovery and validation study. *Int J Biol Sci* 2020; 16:420–434.

32. Wu IW, Gao SS, Chou HC, et al. Integrative metagenomic and metabolomic analyses reveal severity-specific signatures of gut microbiota in chronic kidney disease. *Theranostics* 2020; 10:5398–5411.

33. Hu J, Zhong X, Yan J, et al. High-throughput sequencing analysis of intestinal flora changes in ESRD and CKD patients. *BMC Nephrol* 2020; 21:12.

34. Lin TY, Wu PH, et al. Gut dysbiosis and mortality in hemodialysis patients. *NPJ Biofilms Microbiomes* 2021; 7:20.

35. Swarte JC, Douwes RM, Hu S, et al. Characteristics and dysbiosis of the gut microbiome in renal transplant recipients. *J Clin Med* 2020; 9:386.

36. Du X, Liu J, Xue Y, et al. Alteration of gut microbial profile in patients with diabetic nephropathy. *Endocrine* 2021; 73:71–84.

37. Yu W, Shang J, Guo R, et al. The gut microbiome in differential diagnosis of diabetic kidney disease and membranous nephropathy. *Renal Fail* 2020; 42:1100–1110.

38. He H, Lin M, You L, et al. Gut Microbiota profile in adult patients with idiopathic nephrotic syndrome. *Biomed Res Int* 2021; 2021:8854969.

39. Zhang J, Luo D, Lin Z, et al. Dysbiosis of gut microbiota in adult idiopathic membranous nephropathy with nephrotic syndrome. *Microb Pathog* 2020; 147:104359.

40. Dong R, Bai M, Zhao J, et al. A comparative study of the gut microbiota associated with immunoglobulin a nephropathy and membranous nephropathy. *Front Cell Infect Microbiol* 2020; 10:557368.

41. Azzouz D, Omarbekova A, Heguy A, et al. Lupus nephritis is linked to disease activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis* 2019; 78:947–956.

42. Wang X, Yang S, Li S, et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. *Gut* 2020; 69:2131–2142.

43. Gryp T, Huys GRB, Joossens M, et al. Isolation and quantification of uremic toxin precursor-generating gut bacteria in chronic kidney disease patients. *Int J Mol Sci* 2020; 21:1986.

44. Zeng Y, Guo M, Fang X, et al. Gut microbiota-derived trimethylamine N-oxide and kidney function: a systematic review and meta-analysis. *Adv Nutr* 2021; 12:1286–1304.

45. Zhang W, Miikeda A, Zuckerman J, et al. Inhibition of microbiota-dependent TMAO production attenuates chronic kidney disease in mice. *Sci Rep* 2021; 11:518.

46. Gryp T, De Paepe K, Vanholder R, et al. Gut microbiota generation of protein bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease. *Kidney Int* 2020; 97:1230–1242.

&& Gryp T et al. showed that gut microbiota is not the main provider of circulating uremic toxins in CKD.

47. Rocchetti MT, Di Iorio BR, Vacca M, et al. Ketoanalogs' effects on intestinal microbiota modulation and uremic toxins serum levels in chronic kidney disease (Medika2 Study). *J Clin Med* 2021; 10:840.

48. Wu IW, Lee CC, Hsu HJ, et al. Compositional and functional adaptations of intestinal microbiota and related metabolites in CKD patients receiving dietary protein restriction. *Nutrients* 2020; 12:2799.

49. Lai S, Molfino A, Testorio M, et al. Effect of low-protein diet and inulin on microbiota and clinical parameters in patients with chronic kidney disease. *Nutrients* 2019; 11:3006.
50. El Amouri A, Snauwaert E, Foulon A, et al. Dietary fibre intake is associated with serum levels of uraemic toxins in children with chronic kidney disease. *Toxins* 2021; 13:225.
51. Choi Y, Steffen LM, Chu H, et al. A Plant-centered diet and markers of early chronic kidney disease during young to middle adulthood: findings from the coronary artery risk development in young adults (CARDIA) cohort. *J Nutr* 2021. Jun 4;nxab155.
52. Armani RG, Carvalho AB, Ramos CI, et al. Effect of fructooligosaccharide on endothelial function in CKD patients: a randomized controlled trial. *Nephrol Dial Transplant* 2021. Jan 7;gfaa335.
53. Cosola C, Rocchetti MT, di Bari I, et al. An innovative synbiotic formulation decreases free serum indoxyl sulfate, small intestine permeability and ameliorates gastrointestinal symptoms in a randomized pilot trial in Stage IIIb-IV CKD Patients. *Toxins* 2021; 13:334.
54. Abbad L, Monteiro RC, Berthelot L. Food antigens and transglutaminase 2 in IgA nephropathy: molecular links between gut and kidney. *Mol Immunol* 2020; 121:1–6.
55. Berthelot L, Papista C, Maciel TT, et al. Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J Exp Med* 2012; 209:793–806.
56. De Angelis M, Montemurno E, Piccolo M, et al. Microbiota and metabolome associated with immunoglobulin A nephropathy (IgAN). *PLoS one* 2014; 9:e99006.
57. Hu X, Du J, Xie Y, et al. Fecal microbiota characteristics of Chinese patients with primary IgA nephropathy: a cross-sectional study. *BMC Nephrol* 2020; 21:97.
58. Wu H, Tang D, Zheng F, et al. Identification of a novel interplay between intestinal bacteria and metabolites in Chinese patients with IgA nephropathy via integrated microbiome and metabolome approaches. *Ann Transl Med* 2021; 9:32.
59. Sugumar ANK, Mohd R, Shah SA, et al. Gut microbiota in immunoglobulin a nephropathy: a malaysian perspective. *BMC Nephrol* 2021; 22:145.
60. Chai L, Luo Q, Cai K, et al. Reduced fecal short-chain fatty acids levels and the relationship with gutmicrobiota in IgA nephropathy. *BMCNephrol* 2021; 22:209.
61. Zhong Z, Tan J, Tan L, et al. Modifications of gut microbiota are associated with the severity of IgA nephropathy in the Chinese population. *Int Immunopharmacol* 2020; 89(Pt B):107085.
62. Chemouny JM, Gleeson PJ, Abbad L, et al. Modulation of the microbiota by oral antibiotics treats immunoglobulin A nephropathy in humanized mice. *Nephrol Dial Transplant* 2019; 34:1135–1144.
63. Di Leo V, Gleeson PJ, Sallustio F, et al. Rifaximin as a potential treatment for IgA nephropathy in a humanized mice model. *J Pers Med* 2021; 11:309.
64. Zhao J, Bai M, Yang X, et al. Alleviation of refractory IgA nephropathy by intensive fecal microbiota transplantation: the first case reports. *Ren Fail* 2021; 43:928–933.
65. He JW, Zhou XJ, Li YF, et al. Associations of genetic variants contributing to gut microbiota composition in immunoglobulin A nephropathy. *mSystems* 2021; 6:e00819–e00820.
66. McCarthy DD, Kujawa J, Wilson C, et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. *J Clin Invest* 2011; 121:3991–4002.
67. Sallustio F, Curci C, Chaoul N, et al. High levels of gut-homing immunoglobulin A B lymphocytes support the pathogenic role of intestinal mucosal hyperresponsiveness in immunoglobulin A nephropathy patients. *Nephrol Dial Transplant* 2021; 36:452–464.
- & Sallustio F et al. showed for the first time that gut associated B cell which produced IgA are modified in IgAN patients, associated to elevated BAFF circulating levels.**
68. Zhou N, Shen Y, Fan L, et al. The characteristics of intestinal-barrier damage in rats with IgA nephropathy. *Am J Med Sci* 2020; 359:168–176.
69. Nurmi R, Pohjonen J, Metso M, et al. Prevalence of inflammatory bowel disease and celiac disease in patients with IgA nephropathy over time. *Nephron* 2021; 145:78–84.
70. Rehnberg J, Symreng A, Ludvigsson JF, Emilsson L. Inflammatory bowel disease is more common in patients with IgA nephropathy and predicts progression of ESKD: A Swedish Population-Based Cohort Study. *J Am Soc Nephrol* 2021; 32:411–423.
71. Joher N, Gosset C, Guerrot D, et al. IgA nephropathy in association with inflammatory bowel diseases: results from a national study and systematic literature review. *Nephrol Dial Transplant* 2021. Jan 8;gfaa378.
72. Shi D, Zhong Z, Wang M, et al. Identification of susceptibility locus shared by IgA nephropathy and inflammatory bowel disease in a Chinese Han population. *J Hum Genet* 2020; 65:241–249.
73. Fellstrom BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet* 2017; 389:2117–2127.
74. Lingaraj U, Aralapuram K, Chikkanayakanhalli S, et al. Successful treatment of a patient with posttransplant IgA nephropathy with targeted release formulation of budesonide. *Saudi J Kidney Dis Transpl* 2020; 31:521–523.
75. Ismail G, Obrisca B, Jurubita R, et al. Budesonide versus systemic corticosteroids in IgA Nephropathy: a retrospective, propensity-matched comparison. *Medicine* 2020; 99:e21000.

76. Takeshita M, Tanaka A, Nakamura T, et al. Effect of lubiprostone on urinary protein excretion: a report of two iga nephropathy patients with chronic constipation. *Intern Med* 2019; 58:3255–3259.
77. Nurmi R, Metso M, Porsti I, et al. Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies. *Dig Liver Dis* 2018; 50:27–31.
78. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, et al. Celiac disease and the risk of kidney diseases: a systematic review and meta-analysis. *Dig Liver Dis* 2016; 48:1418–1424.
79. Lebreton C, Menard S, Abed J, et al. Interactions among secretory immunoglobulin A, CD71, and transglutaminase-2 affect permeability of intestinal epithelial cells to gliadin peptides. *Gastroenterology* 2012; 143:698–707. e1-4.
80. Papista C, Lechner S, Ben Mkaddem S, et al. Gluten exacerbates IgA nephropathy in humanized mice through gliadin-CD89 interaction. *Kidney Int* 2015; 88:276–285.
81. Lechner SM, Abbad L, Boedec E, et al. IgA1 protease treatment reverses mesangial deposits and hematuria in a model of IgA nephropathy. *J Am Soc Nephrol* 2016; 27:2622–2629.
82. Ito Y, Tatsukawa H, Yamaguchi H. Detection and identification of potential transglutaminase 2 substrates in the mouse renal glomeruli. *Arch Biochem Biophys* 2018; 660:11–19.
83. Moresco RN, Speeckaert MM, Zmonarski SC, et al. Urinary myeloid IgA Fc alpha receptor (CD89) and transglutaminase-2 as new biomarkers for active IgA nephropathy and henoch-Schonlein purpura nephritis. *BBA Clin* 2016; 5:79–84.