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► **To cite this version:**

Renato C Monteiro, Laureline Berthelot. Role of gut–kidney axis in renal diseases and IgA nephropathy. *Current Opinion in Gastroenterology*, 2021, 37 (6), pp.565-571. 10.1097/MOG.0000000000000789 . hal-04536993

HAL Id: hal-04536993

<https://hal.science/hal-04536993>

Submitted on 8 Apr 2024

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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]. Snellson 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.

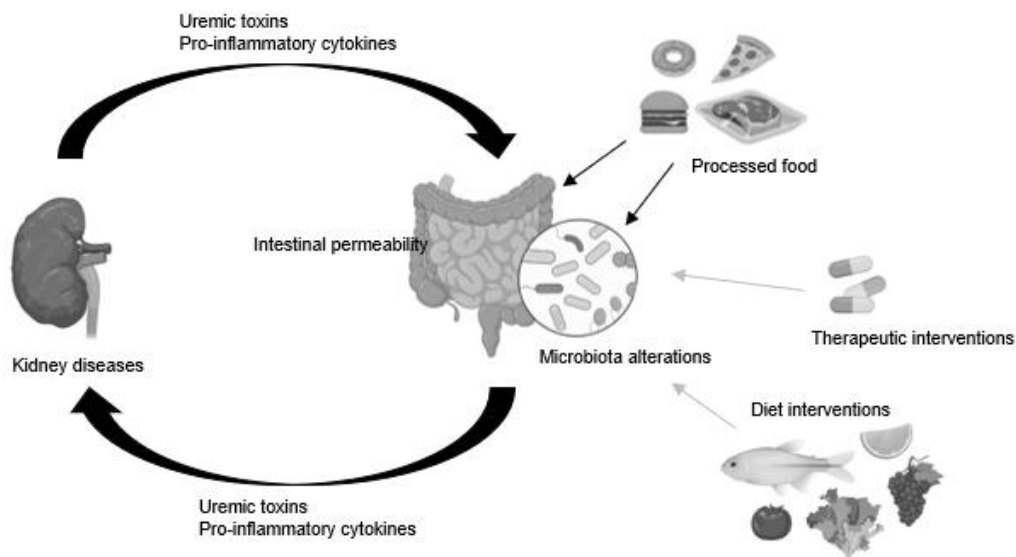


FIGURE 1. Deleterious interactions between gut and kidney and potential interventions targeting gut to treat kidney diseases. In kidney diseases, the injuries lead to the decline of filtration function and accumulation of uremic toxins in blood. Moreover, inflammation is often associated with production 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

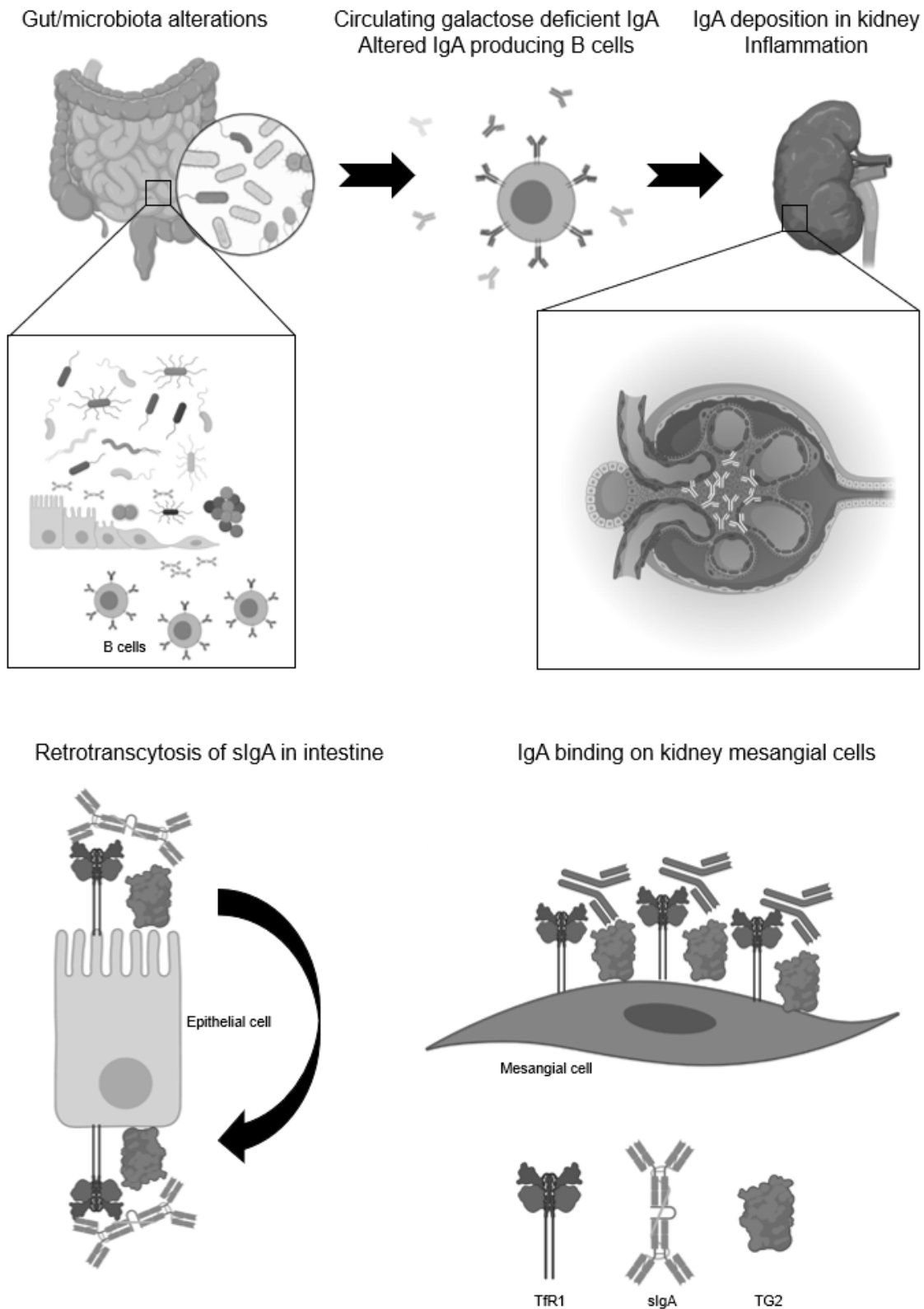


FIGURE 2. Gut/kidney axis in IgA nephropathy. As IgA are mainly produced in the intestinal mucosa, gut alterations seem to induce aberrant glycosylated IgA1 production which deposit in the renal mesangium. The resulting kidney inflammation is highly deleterious. At the intestinal epithelial surface and 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.

Financial support and sponsorship

R.C.M. is supported by AP-HP, Inserm, Paris University, Inflammex laboratory of excellence and Fondation pour la Recherche Me´dicale. L.B. is supported by Inserm and Nantes University.

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