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Impact of gut microbiota in immunoglobulin A nephropathy; a letter to the editor to the recent findings

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Letter to Editor

To Editor,

Immunoglobulin Nephropathy is a prevalent type of primary glomerulonephritis and an idiopathic disease (1). Following the first description of IgA nephropathy (IgAN) by Berger and Hinglais in 1968, it has become a major cause of end-stage renal disease (ESRD). Half of IgAN patients progress to ESRD, necessitating dialysis and kidney transplantation. Many individuals worldwide suffer from chronic kidney disease each year, thus IgAN requires further attention (2).

Immunoglobulin A nephropathy represents a significant health burden due to an aging population, the disease itself, and growth in dialysis patients (3). There are estimates of a 5% prevalence of IgAN in the Middle East (4), 10%–35% prevalence in Europe (5), and 50% prevalence in East Asia (mainly Japan (6) and China (7)). Despite several treatments, it can lead to ESRD within 10 years, especially in East Asia, About 20% of all adult patients (8). Previous studies showed that most of the IgA1 antigens found in healthy individuals (into two subclasses of human IgA molecules) are detected in circulating immune complexes and in mesangial areas of cases with IgAN (9). Following IgA1 accumulation in the glomerular mesangium, this disease begins to develop (10). In addition to the role of IgA1 at the beginning of IgAN pathogenesis, there is also a correlation between IgA excess production and renal disease progression (11). The

molecular basis of the disease showed, when abnormal IgA binds to anti-glycan immunoglobulin G, the immune complexes will form (12). These complexes deposit in the glomerular mesangium as a result of antigen stimulation in susceptible hosts, resulting in inflammation and tissue damage. Then, the glomerular mesangial inflammation, mesangial proliferation, and glomerular sclerosis lead to kidney dysfunction (11). In addition to T-cell-dependent mechanisms, IgA production can also be modulated by mechanisms independent of the T-cells (8). Following the infection with some commensal bacteria or overgrowing of harmful bacteria, we will face a cascade of activated T-cell-dependent production of IgA, which in turn stimulates the production of excess IgA without any exogenous invasion. Pathogenic bacteria exposure also triggers the production of galactose-deficient IgA1 in the mucosa-associated lymphoid tissue. Thereby, recurrent or chronic bacterial infections, stimulation of mucosal immune response, and also the production of IgA, cause the extension of IgAN (13).

Health and disease are influenced by the gut microbiome (14). In addition to the digestion of complex polysaccharides (15), regulation of the immune system (16), synthesis of certain endogenic vitamins and amino acids (17), and also the metabolism of bile acids (18), the microbiota plays a significant role in metabolic activities of the host (15). Furthermore, epigenetic modification by

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short-chain fatty acids from beneficial bacteria modulates inflammation (19). There has been increasing evidence that changes in the gut microbiota (primarily, changes in the relative proportions of various bacteria) are related to obesity, diabetes, bipolar disorder, and depression (20). Gut microbiota has been shown to affect kidney disease outcomes in recent years. Gut microbiome dysbiosis in the gut-kidney axis is associated with chronic kidney disease (21). In chronic kidney disease, chronic inflammation is believed to originate from the gut. The microbiota has a protective effect against renal damage by modulating the immune response. Microbiota also has a preventable effect on ischemia-reperfusion-induced acute kidney injury. Gut bacteria-derived uremic toxins such as p-cresol sulfate and indoxyl sulfate, indole, and trimethylamine N-oxide, can stimulate the release of pro-inflammatory cytokines, resulting in renal injury. Among them, gut microbiota-derived trimethylamine N-oxide is related to chronic kidney disease progression (8). A variety of pathologies, including endothelial dysfunction, are caused by elevated uremic toxins, which are retained in the blood when the kidneys are not functioning properly (22). On the other hand, the genes associated with susceptibility to IgAN are involved in maintaining the intestinal epithelial barrier, inflaming the gut, and detecting mucosal pathogens, suggesting a kidney-gut link (8). In IgAN, there is dysregulation of the immune system and gut dysbiosis. In this disease, the interaction between the gut-kidney axis and alterations in the gut microbiota may be key factors in the development of IgAN (23). Subsequent to gut dysbiosis, intestinal membrane disruption will proceed, along with bacteria translocation into the blood, which increases intestinal permeability (24). This condition is associated with the activation of innate immune response, and enhancing the systematical inflammatory response, which can lead to aggravation of IgAN, CKD, and finally ESRD (25). The gut microbiota especially specific microbes may serve as the potential IgAN biomarkers and therapeutic targets (23). In the gut microbiota, six bacterial phyla dominate. These include *Fusobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria*, and *Verrucomicrobia*. In fact, over 90% of all bacteria belong to *Firmicutes* and *Bacteroidetes* families (8). The increase in the families of *Polyangiaceae, Moraxellaceae, Nesterenkonia, Thiothrix, Pseudomonadaceae, Megasphaera, Bilophila*, and Bifidobacterium were detected in IgAN too (23). Likewise, recent studies also showed the abundance of the gut microbiota genus and species of *Streptococcaceae, Ruminococcaceae, Lachnospiraceae* families in the IgAN (26). Conversely, immunoglobulin A nephropathy may be facilitated by declines in the abundance of the Prevotella genus, as a protective species in the salivary and gut ecosystems (27). Similarly, IgAN patients showed lower *Synergistetes, Megamonas, Streptococcus, Fusobacteria, Haemophilus, Veillonella,* and *Enterococcus* abundance (23). Intestinal epithelial barrier penetration may be exacerbated by the increase in the *Escherichia-Shigella* population because of decreased butyrate biosynthesis and increased oxidative stress (28). More recent investigations showed, the stool of IgAN patients, had more *Escherichia-Shigella, Legionella, Enhydrobacte,* and *Parabacteroides* genera (29). Patients with IgAN had depleted levels of *Roseburia* and *Faecalibacterium*, which produce butyrate (30). Interestingly, the activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), which is implicated in the pathogenesis of IgAN, was inhibited in vitro by the culture supernatant of *Faecalibacterium* (31). Besides providing energy to the intestinal mucosa, butyrate exerts anti-inflammatory effects, then affects regulatory T (Treg) cells, which contribute to IgAN pathogenesis (32).

References
1. Al Hussain T, Hussein MH, Al Mana H, Akhtar M. Pathophysiology of IgA Nephropathy. Adv Anat Pathol. 2017;24:56-62. doi: 10.1097/PAP.0000000000000134
2. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368:2402-14. doi: 10.1056/NEJMra1206793.
3. Masakane I, Taniguchi M, Nakai S, Tsuchida K, Wada A, Ogata S, et al. Annual Dialysis Data Report 2016, JSDT Renal Data Registry. Renal Replacement Therapy. 2018;4:45. doi: 10.1186/

s41100-018-0183-6.

4. Demircin G, Delibaş A, Bek K, Erdoğan O, Bülbül M, Baysun S, et al. A one-center experience with pediatric percutaneous renal biopsy and histopathology in Ankara, Turkey. Int Urol Nephrol. 2009;41:933-9. doi: 10.1007/s11255-008-9433-9

5. Kurnatowska I, Jędrzejka D, Małyska A, Wągrowska-Danilewicz M, Danilewicz M, Nowicki M. Trends in the incidence of biopsy-proven glomerular diseases in the adult population in central Poland in the years 1990-2010. Kidney Blood Press Res. 2012;35:254-8. doi: 10.1159/000334418.

6. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al; Committee for Standardization of Renal Pathological Diagnosis and Working Group for Renal Biopsy Database, Japanese Society of Nephrology, Tokyo, Japan. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol. 2011;15:493-503. doi: 10.1007/s10157-011-0430-4.

7. Zhou FD, Zhao MH, Zou WZ, Liu G, Wang H. The changing spectrum of primary glomerular diseases within 15 years: a survey of 3331 patients in a single Chinese centre. Nephrol Dial Transplant. 2009;24:870-6. doi: 10.1093/ndt/gfn554.

8. Han L, Fang X, He Y, Ruan XZ. ISN Forefronts Symposium 2015: IgA Nephropathy, the Gut Microbiota, and Gut–Kidney Crosstalk. Kidney International Reports. 2016;1:189-96. doi: 10.1016/j.ekir.2016.08.002.

9. Pabst O. New concepts in the generation and functions of IgA. Nat Rev Immunol. 2012;12:821-32. doi: 10.1038/nri3322.

10. Zhao N, Hou P, Lv J, Moldoveanu Z, Li Y, Kiryluk K, et al. The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. Kidney Int. 2012;82:790-6. doi: 10.1038/ki.2012.197.

11. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46:1187-96. doi: 10.1038/ng.3118.

12. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22:1795-803. doi: 10.1681/ASN.2011050464.

13. Qin W, Zhong X, Fan JM, Zhang YJ, Liu XR, Ma XY. External suppression causes the low expression of the Cosmc gene in IgA nephropathy. Nephrol Dial Transplant. 2008;23:1608-14. doi: 10.1093/ndt/gfm781.

14. Meijers B, Evenepoel P, Anders HJ. Intestinal microbiome and fitness in kidney disease. Nat Rev Nephrol. 2019;15:531-545. doi: 10.1038/s41581-019-0172-1.

15. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005;307:1915-20. doi: 10.1126/science.1104816.

16. Hooper LV. Bacterial contributions to mammalian gut development. Trends Microbiol. 2004;12:129-34. doi: 10.1016/j.tim.2004.01.001.

17. Hill MJ. Intestinal flora and endogenous vitamin synthesis. Eur J Cancer Prev. 1997;6 Suppl 1:S43-5. doi: 10.1097/00008469-199703001-00009

18. Hylemon PB, Harder J. Biotransformation of monoterpenes, bile acids, and other isoprenoids in anaerobic ecosystems. FEMS Microbiol Rev. 1998;22:475-88. doi: 10.1111/j.1574-6976.1998.tb00382.x.

19. Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJ, de Almeida DC, et al. Gut Bacteria Products Prevent AKI Induced by Ischemia-Reperfusion. J Am Soc Nephrol. 2015;26:1877-88. doi: 10.1681/ASN.2014030288.

20. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528:262-266. doi: 10.1038/nature15766.

21. Sugurmar ANK, Mohd R, Shah SA, Neoh HM, Cader RA. Gut microbiota in Immunoglobulin A Nephropathy: a Malaysian Perspective. BMC Nephrol. 2021;22:145. doi: 10.1186/s12882-021-02315-z.

22. Pluznick JL. The gut microbiota in kidney disease. Science. 2020 Sep 18;369:1426-1427. doi: 10.1126/science.abd8344

23. Dong R, Bai M, Zhao J, Wang D, Ning X, Sun S. A Comparative Study of the Gut Microbiota Associated With Immunoglobulin a Nephropathy and Membranous Nephropathy. Front Cell Infect Microbiol.2020;10:557368.doi:10.3389/fcimb.2020.557368.

24. Smerud HK, Fellström B, Hällgren R, Osagie S, Venge P, Kristjánsson G. Gluten sensitivity in patients with IgA nephropathy. Nephrol Dial Transplant. 2009;24:2476-81. doi: 10.1093/ndt/gfp133.

25. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol. 2014;25:657-70. doi: 10.1681/ASN.2013080905

26. De Angelis M, Montemurno E, Piccolo M, Vannini L, Lauriero G, Maranzano V, et al. Microbiota and metabolome associated with immunoglobulin A nephropathy (IgAN). PLoS One. 2014;9:e99006. doi: 10.1371/journal.pone.0099006.

27. Khasnobish A, Takayasu L, Watanabe KI, Nguyen TTT, Arakawa K, Hotta O, et al. Dysbiosis in the Salivary Microbiome Associated with IgA Nephropathy-A Japanese Cohort Study. Microbes Environ. 2021;36:ME21006. doi: 10.1264/jsme2.ME21006.

28. Croxen MA, Law RJ, Scholz R, Keeney KM, Wlodarska M, Finlay BB. Recent advances in understanding enteric pathogenic Escherichia coli. Clin Microbiol Rev. 2013;26:822-80. doi: 10.1128/CMR.00022-13.

29. Shah NB, Nigwekar SU, Kalim S, Lelouvier B, Servant F, Dalal M, et al. The Gut and Blood Microbiome in IgA Nephropathy and Healthy Controls. Kidney360. 2021;2:1261-1274. doi: 10.34067/KID.0000132021.

30. Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut. 2018;67:534-541. doi: 10.1136/gutjnl-2016-313332.

31. Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol Lett. 2009;294:1-8. doi: 10.1111/j.1574-6968.2009.01514.x.

32. Ruszkowski J, Lisowska KA, Pindel M, Heleniak Z, Dębska-Ślizień A, Witkowski JM. T cells in IgA nephropathy: role in pathogenesis, clinical significance and potential therapeutic target. Clin Exp Nephrol. 2019;23:291-303. doi: 10.1007/s10157-018-1665-0.