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Rucha J. Mehta
Edmo Clinic, Cardiometabolic Department, Apollo CVHF, Ahmedabad, Gujarat, India

The Interplay between Gut Dysbiosis and Diabetic Nephropathy: Implications for Treatment and Management

Introduction

The population of microbes (microbiome) in the intestine is a symbiotic ecosystem conferring trophic and protective function [1]. Gut dysbiosis refers to an imbalance in the composition and function of the gut microbiota, which can disrupt the gut barrier and contribute to systemic inflammation [1]. An altered gut microbiome has been implicated in many conditions such as diabetes [2], obesity [3], inflammatory [4], autoimmune and neurological conditions. Diabetic nephropathy (DN) remains a leading cause of end-stage renal disease (ESRD) worldwide affecting almost a third of patients with diabetes [5]. Although many of the causes and consequences of oxidative stress and inflammation in DN have been extensively explored, little attention had been paid to the intestine and its microbial flora as a potential source of these problems.

This editorial reviews the current understanding of gut dysbiosis in the context of diabetic nephropathy, highlighting the potential mechanisms involved and discussing the implications for future research and clinical practice.

Address for correspondence:
Dr Rucha J. Mehta, MD FACP
Edmo Clinic, Cardiometabolic Department, Apollo CVHF,
Ahmedabad, Gujarat, India
1101, Shapath V SG Hwy, Ahmedabad, 380015, India
Mobile: +91-9979726969
E-mail: ruchamehtamd@gmail.com
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Gut dysbiosis and implications for nephropathy

The gut-kidney axis refers to the bidirectional relationship between gut health and renal function. While a healthy microbiome is defined by the diversity in bacterial species [6], there exists a remarkable commonality among individuals. Over 50% of healthy individuals have the same 75 bacterial species in common and bacteria from only 7–9 phyla (from the 55 known bacterial phyla) are detected in humans. Over 90% of the bacteria identified in the gut microbiome belong to the Bacteroidetes and Firmicutes phyla, which include the bacteria genera of Bactereoides, Alistipes, Prevotella, Porphyromonas, Clostridium, Dorea, Faecalibacterium, Eubacterium, Ruminococcus and Lactobacillus [7].

Recent studies have revealed a significant link between gut dysbiosis and diabetic nephropathy. Vaziri et al. have shown in different models of chronic kidney disease (CKD) in rats a significant disruption of the colonic, ileal, jejunal and gastric epithelial tight junctions [8]. Several mechanisms have been proposed to explain this connection; and determine what precedes the other i.e. is it the gut dysbiosis that triggers the DN or vice versa. Regardless, it makes for interesting rumination; as we continue our search for early markers of DN and earlier interventions to prevent the progression of the same to ESRD.

The structure of the gastrointestinal barrier consists of the apical membrane of the intestinal epithelial cells and the apical junctional complex which seals the gap between the adjacent epithelial cells [8]. The apical junctional complex consists of the tight junction which prevents the influx of microorganisms and

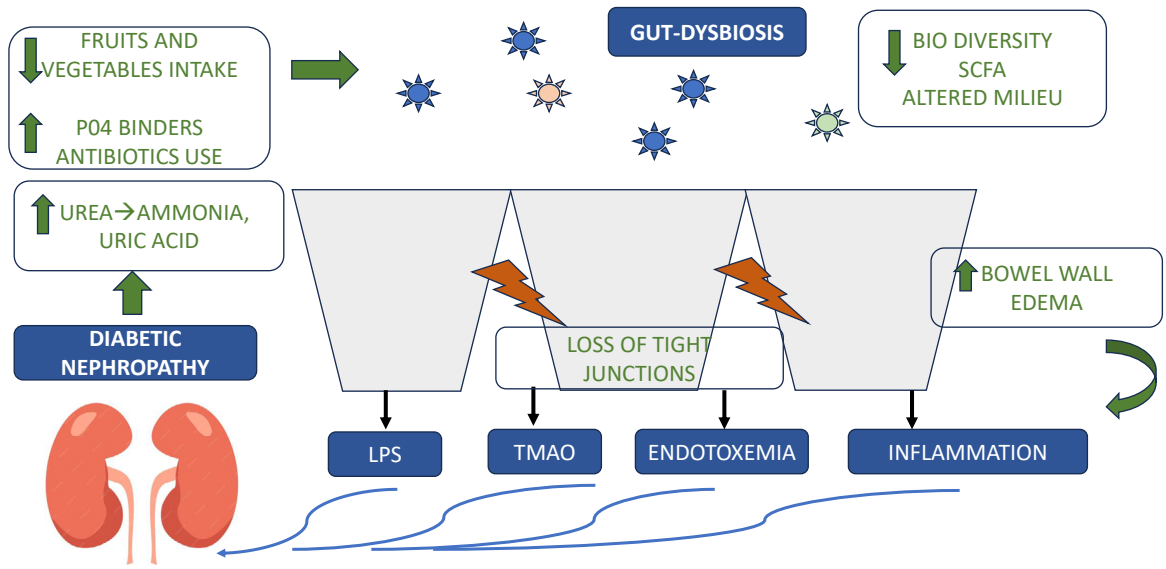

Figure 1. The Gut–Kidney Axis
Increased uremic toxins such as uric acid, lead to increased ammonia production, along with reduced fiber intake and increased use of phosphate binders (PO4) and antibiotics cause a reduced gut biodiversity and dysbiosis and production of short chain fatty acids (SCFA). This along with increased intestinal wall edema and disruption of the tight junctions leads to increased endotoxin production such as lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO) which in turn cause endotoxemia and inflammation worsening the progression of diabetic nephropathy

noxious substances to the sub-mucosal tissue and the internal milieu. Gut dysbiosis can lead to increased intestinal permeability, allowing endotoxins such as lipopolysaccharides (LPS) to enter the bloodstream [9]. These endotoxins can trigger systemic inflammation, endothelial dysfunction, and fibrosis; which is a key factor in the progression of DN [3, 4]. Dysbiosis can affect renal function through several pathways, including the modulation of gut-derived uremic toxins, such as indoxyl sulfate and trimethylamine-N-oxide (TMAO) [10]. Additionally, the dysbiosis also leads to reduction in normally useful products; such as short-chain fatty acids which are essential for the integrity of colonocytes and the growth of anti-inflammatory regulatory T lymphocytes [4]. The combination of uremic milieu and dietary restrictions work in concert to transform the gut microbiome from the normal symbiotic to a dysbiotic state.

Renal failure results in profound changes in the biochemical milieu of the alimentary tract [11, 12] (Fig. 1). First, the rise in urea concentration in the body fluids leads to its massive influx into the gastrointestinal tract. Within the intestinal tract, urea is hydrolyzed by microbial urease leading to formation of ammonia [$CO(NH2)2 + H2O \rightarrow CO2 + 2NH3$]. Large amounts of urea and uric acid released in the intestine serve as alternative substrates for the microbial flora which normally utilize indigestible complex carbohydrates. Third, dietary restrictions, chief among them is restricted consumption of fruits and vegetables; significantly alter the biochemical milieu of the gastrointestinal tract in the CKD population. Since fruits and vegetables are the main source of dietary fiber, their limited consumption has a deep impact on the composition, function and metabolism of the gut microbiome. Fourth, use of various phosphate binding products, i.e. anion-exchange resins, iron-based products, calcium acetate, calcium carbonate and aluminium hydroxide which are commonly prescribed for patients with advanced CKD, must have as yet unrecognized effects on the gut microbiome. Finally, frequent use of antibiotics to treat vascular access and other infections can significantly affect microbiomes in patients with advanced CKD.

In the current study of Rabea et al. [13], the investigators attempt to study the difference in fecal microbiota of healthy participants and compare it to that of matched individuals with diabetes with and without nephropathy. They demonstrated that fecal samples from DN patients exhibit an imbalance in the gut microbiota, with an increase in Erysipelatoclostridium, Prevotella_9, and Escherichia shigella and a decrease in Roseburia intestinalis. An imbalance in the gut microbiota was significantly correlated with clinical indicators of renal function, cholesterol, blood albumin, and urine albumin creatinine ratio. The findings make

for an interesting conclusion that in early DN (urinary albumin creatinine ratio ≥ 30 mg/g) presence of certain gut microbiota may herald the onset of DN. However, at this point it would be speculative as in their study, as fecal samples were collected only at a single time point and it remains to be seen if this cause or effect or merely serendipity.

Other studies have shown similar indications; microbial DNA [14] when isolated from the stool samples of a group of patients with ESRD maintained on hemodialysis and a group of age-, sex- and ethnicity-matched healthy individuals; showed highly significant differences in the abundance of over 200 bacterial operational taxonomic units (OTUs) belonging to 23 bacterial families between the ESRD and the healthy control groups. Identifying the microbiome shift early in the stage of DN may help us to intervene in a novel way.

Given the emerging evidence linking gut dysbiosis with diabetic nephropathy, it is crucial to consider the potential for microbiota-targeted therapies. Diets rich in fiber [15–17], polyphenols, and other prebiotic compounds can enhance microbial diversity and function. strategies aimed at lowering urea levels may prove useful in improving systemic inflammation in patients with advanced CKD. This supposition is supported by the previously documented salutary effect of urea-lowering strategies such as the use of keto analogs of amino acids [15], low protein diet and possibly longer, more frequent and less aggressive dialysis regimens in CKD patients. Another strategy that can be used to increase delivery of carbohydrates to colon is administration of an inhibitor of small intestinal alpha-glycosidase such as acarbose [16].

Probiotics, which are live microorganisms that confer health benefits to the host, and prebiotics, which are compounds that promote the growth of beneficial gut bacteria, have shown promise in improving gut health and reducing systemic inflammation. Clinical trials are exploring their efficacy in managing diabetic nephropathy by modulating gut microbiota and decreasing systemic inflammation [17].

Fecal Microbiota Transplantation (FMT) [18] involves the transfer of fecal matter from a healthy donor to a recipient to restore a healthy microbiota. While still experimental, FMT has shown potential in treating various diseases associated with dysbiosis, including metabolic disorders. Several pharmacological agents that target gut microbiota or its metabolites are being explored. For instance, inhibitors of gut-derived uremic toxins or agents that reduce intestinal permeability may offer novel therapeutic options for managing diabetic nephropathy [19–20].

Conclusions

We agree with the findings of Rabea et al; that the relationship between gut dysbiosis and diabetic nephropathy underscores the importance of considering the gut microbiota as a critical factor in the management of diabetes-related complications. Understanding "the gut-kidney axis"(fig.1) opens new avenues for therapeutic intervention and highlights the need for continued research in this evolving field. By integrating microbiota-based strategies into clinical practice, we may improve outcomes for patients with diabetic nephropathy and potentially revolutionize the management of this challenging condition.

Despite this, more research is needed to better understand the specific microbial changes associated with DN and to identify biomarkers that can predict disease progression. Additionally, large-scale clinical trials are required to validate the efficacy of microbiota-targeted therapies and to establish optimal treatment protocols.

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