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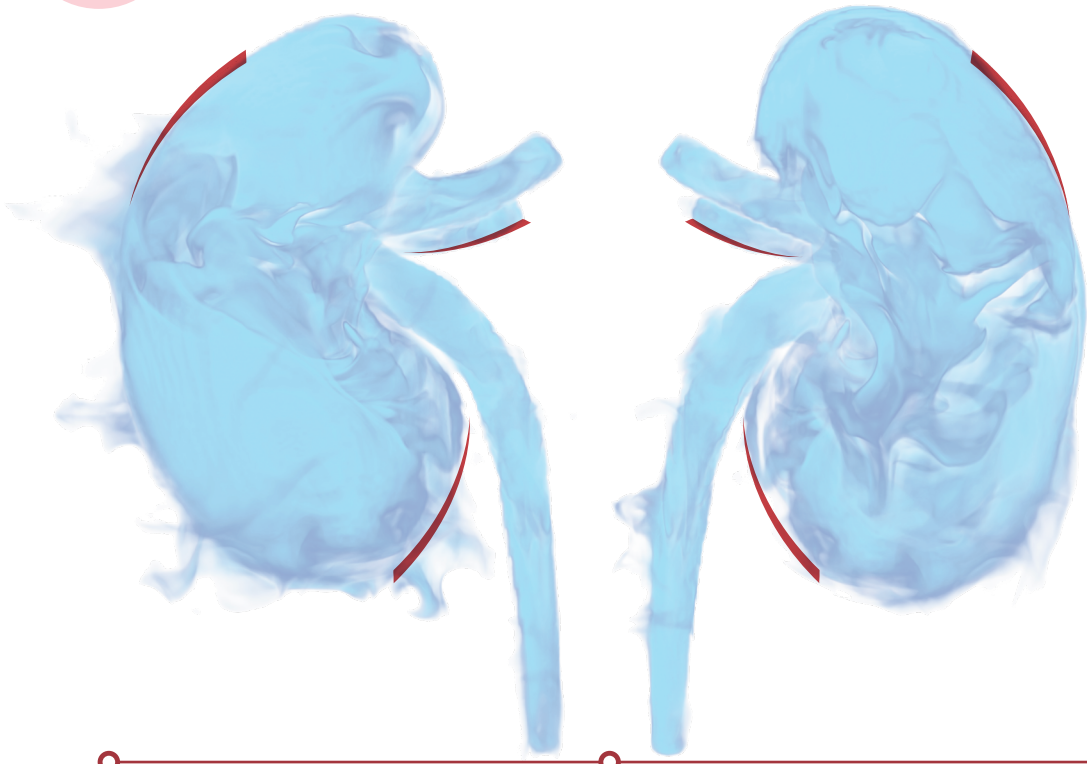
Nephro Update

Effects of probiotics on glycemic regulation



Various studies have shown that probiotics exert their direct or indirect effects on glucose metabolism in almost all tissues and organs of the body.

Probiotic supplementation has demonstrated beneficial effects on glycemic control, uremic toxins, blood urea nitrogen, oxidative stress, and markers of inflammation in patients with kidney disease.

Probiotics could delay the progression of renal function injury and improve glucose and lipid metabolism in patients with DKD.

ISSUE 2

Expert Opinion

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- The gut microbiota plays an important pathogenic role in the progression of diabetes mellitus to diabetic kidney disease, and subsequent end-stage renal disease.
- Gut microbiota dysbiosis may promote the development and progression of DKD.
- Probiotics can improve host metabolism, relieve uremic toxicity, lower pro-inflammatory factor levels, and delay the progression of renal function injury by maintaining intestinal epithelial barrier function, competing with pathogens for nutrients, and regulating the host immune response.
- Probiotics can delay progression of renal function injury and improve glucose metabolism in patients with DKD.
- Studies have also shown the potential use of probiotics in the improvement of glycemic parameters in patients with diabetic nephropathy.

Introduction

Maintaining glucose homeostasis is important for preventing the onset of diseases associated with a disturbance of glucose homeostasis, like insulin resistance, glucose intolerance, and type 2 diabetes. Persistent hyperglycemia is a very dangerous condition that can result in more severe complications associated with heart disease, eye, kidney, nerve damage, and cancer.[1] The prevalence of chronic kidney disease is about 5 times among patients with diabetes as compared to the general population.[2]

Diabetic kidney disease (DKD), or diabetic nephropathy (DN) is a potentially fatal complication of diabetes mellitus and is a significant cause of chronic kidney disease.[3] DKD is one of the most common complications of diabetes and is the primary cause of end-stage kidney disease (ESRD). Important mechanisms for DKD include abnormal glucose and lipid metabolism, renal hemodynamic changes, oxidative stress, and immune-inflammatory responses.[4]

Gut microbiota can promote DKD progression

Bile acid is essential for the function of intestinal barrier, and the intestinal flora is required for its production and metabolism. The activation of Farnesoid X receptor (FXR) and the membrane G protein-coupled bile acid receptor-1 (TGR5) by bile acid signal transduction leads to the activation of various intracellular signal pathways. The bile acid signal is enhanced by intestinal flora. Alteration in the intestinal dominant flora can weaken the activation of FXR and TGR5. This causes metabolic disorders.[5]

The gut microbiota plays its pathogenic roles in the entire DM-DKD-ESRD progression.[6]

The constituents of the intestinal microbiota vary in patients with DKD as compared to the healthy population.[7] Numerous metabolites produced by the gut microbiota can have an impact on the host. By inducing or exacerbating inflammation, the gut microbiota can promote the occurrence of DKD.[3]

Increasing evidence has demonstrated that, during DM and DKD, the intestinal mucosal barrier becomes more permeable due to structural and functional abnormalities, resulting in elevated levels of bacterial endotoxins in the blood, which can trigger inflammation. Persistent inflammation may eventually result in pathological metabolic conditions like obesity, insulin resistance, metabolic syndrome, and hyperglycemia. Intestinal bacteria may pass through the leaky intestinal barrier, which can act as dietary pathogens, or antigens, to trigger an immune response.[3]

Dysbiosis of the gut microbiota in DKD can accelerate the disease by mechanisms like metabolite changes, inflammatory responses, and immune activation.[3]

Effect of probiotics on glucose metabolism

Probiotic supplementation has demonstrated some beneficial effects on glycemic control, uremic toxins, blood urea nitrogen, oxidative stress, and markers of inflammation in patients with kidney disease.[2]

Probiotics are thought to possess anti-inflammatory, antioxidant, and various other favorable gut-modulating properties. *Bifidobacterium* and *Lactobacillus* species in particular support the humoral immune responses against environmental toxins and antigens.[2]

Experimental studies and many randomized trials have demonstrated that the administration of *Lactobacillus acidophilus* as well as *Streptococcus thermophilus* exert antidiabetic effects. Additionally, the use of *Bifidobacterium longum* can alleviate glucose intolerance.[8]

A systematic review by Vlachou E *et al*., demonstrated that probiotics in patients with DKD had significant alterations in biomarkers of inflammation and renal function and in other biomarkers such as fasting plasma glucose (FPG), homeostasis model of assessment-estimated insulin resistance (HOMA-IR), increased quantitative insulin sensitivity check index (QUICKI), insulin, triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-c) and high-density lipoprotein cholesterol (HDL-c) levels.[4]

Dai Y *et al*., conducted a systematic review and meta-analysis to evaluate the impact of probiotics on patients with DKD. The analysis revealed that probiotics enhanced glycemic control as demonstrated by a reduction in levels of FPG, hemoglobin A1c (HbA1c), HOMA-IR, and QUICKI. The study concluded that probiotics could delay the progression of renal function injury, improve glucose and lipid metabolism, and decrease inflammation and oxidative stress in patients with DKD.[4]

The possible mechanism of the hypoglycemic effect is that probiotics may alter intestinal flora to insulinotropic polypeptides and glucagon-like peptide-l (GLP-1), which induce glucose uptake by muscle. Probiotics may improve the parameters of glucose homeostasis by reducing cytokines and suppressing the nuclear factor κ-light chain enhancer of the activated B-cells pathway. Additionally, probiotics interact with gut flora and consequently produce metabolites like short-chain fatty acids (SCFA) and bile acids, which may enhance glycemic control and insulin sensitivity. Probiotics also improve glucose metabolism by regulating the secretion of proinflammatory mediators like tumor necrosis factor-α, interleukin-6, and intestinal GLP-1. Tarrahi MJ *et al*., showed that probiotics significantly reduced FPG and HOMA-IR in patients with DKD.[4]

Mazruei Arani N *et al*., conducted a study to evaluate the effects of probiotic honey containing a viable and heat-resistant probiotic *Bacillus coagulans* on glycemic control, lipid profiles, biomarkers of inflammation, and oxidative stress in patients with diabetic nephropathy. The study demonstrated that after 12 weeks of intervention, patients with diabetic nephropathy who received probiotic honey showed

a significant decrease in insulin levels, HOMA-IR, and a significant increase in QUCIKI as compared to controls (Table 1). Owing to the beneficial effects on markers of insulin metabolism, *Bacillus coagulans* may be useful to decrease diabetes-associated complications. The study concluded that probiotic honey consumption containing *B. coagulans* for 12 weeks among patients with diabetic nephropathy had beneficial effects on insulin metabolism.[9]

Table 1: Effects of probiotic or control honey at study baseline and after 3 months intervention in patients with diabetic nephropathy

Parameters	Control honey (N = 30)			Probiotic honey (N = 30)			*p* value
	Week 0	Week 12	Change	Week 0	Week 12	Change	
Insulin (µIU/ml)	16.1 ± 4.5	16.0 ± 4.6	-0.1 ± 1.3	16.7 ± 5.9	15.5 ± 6.0	-1.2 ± 1.8	0.004
HOMA-IR	4.9 ± 2.1	4.9 ± 2.2	0.003 ± 0.4	5.5 ± 2.2	5.0 ± 2.2	-0.5 ± 0.6	0.002
QUICKI	0.30 ± 0.01	0.30 ± 0.01	-0.0007 ± 0.005	0.30 ± 0.02	0.30 ± 0.02	0.005 ± 0.009	0.004

HOMA-IR: Homeostasis model of assessment-estimated insulin resistance; **QUICKI:** Quantitative insulin sensitivity check index

Furthermore, the administration of probiotic formula containing *Bifidobacterium* species as well as *L. acidophilus, and S. thermophilus* for 12 weeks has shown to ameliorate glycemic control in patients with diabetic nephropathy. Significant reductions were observed in FBG and HbA1c at 12 weeks.[10]

In conclusion, modification of the gut microbiota with probiotic supplementation may be a beneficial method to prevent and control hyperglycemia in clinical practice.[11]

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