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Diabetes and the Gut Microbiome

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Summary: Gut dysbiosis in diabetes mellitus is associated with decreased short-chain fatty acids and epithelial barrier disruption. Microbial-derived toxins move across the "leaky gut" and incur systemic inflammation and insulin resistance. In children, gut dysbiosis has been associated with risk of developing type 1 diabetes mellitus. In animal models, the obesity phenotype is transferable via microbiota transplantation. Plant-based low protein diets and certain anti-diabetic drugs have been associated with positive microbiome effects. Clinical trials with prebiotics and probiotics have yielded mixed results. Further investigations are needed to evaluate the gut microbiome as a potential therapeutic target for diabetes prevention and management.
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Keywords: Diabetes mellitus, gut microbiome, prebiotics, probiotics

Bacterial cells in the healthy adult person outnumber human cells by more than 10-fold, and more than 70% of this microbial population is in the intestinal tract.[1,2] Abundance and diversity of bacteria increases from the stomach (10^2-10^4 cells/mL) to the colon (>10^{12} cells/mL) as oxygen tension decreases, and as the gut lumen becomes enriched with molecules that can be used as microbial nutrients.[1,3] Given the vast number of microorganisms concentrated in the intestinal tract, it is not surprising that products of bacterial metabolism modulate host health. The gut microbiome has been implicated in the pathophysiology of numerous chronic diseases ranging from allergic disorders and chronic kidney disease (CKD), to heart disease and cancer[2,4-6]; this review focuses on the role of the gut microbiome in diabetes mellitus pathophysiology.

In the infant and growing child, the gut microbiome plays a critical role in shaping the immune system.[7] In adults, the microbiome continues to modulate host health via production of beneficial micronutrients (vitamins and short-chain fatty acids [SCFAs]) or harmful gut-derived bacterial toxins. Two metabolic derangements of the gut microbiome are prevalent in chronic disease states including diabetes mellitus and CKD: decreased bacterial SCFAs and increased gut-derived uremic toxins. These pathways are discussed in more detail later.

ALTERATIONS IN GUT MICROBIAL POPULATIONS IN DIABETES MELLITUS

Intestinal microbiota in healthy individuals are mostly from the bacterial phyla Firmicutes and Bacteroidetes (>90%), followed by Actinobacteria and Verrucomicrobia; the proportion of pathogenic and opportunistic species is small (0.1%).[8,9] Under normal homeostasis, the microbiome is predominantly saccharolytic, that is, anaerobic fermentation of complex carbohydrates (particularly dietary fibers) produces methane, hydrogen, and SCFAs. However, there is a shift to a more proteolytic microbiome in certain chronic disease states, and this can be exacerbated by a low-fiber diet. Protein catabolism produces potentially toxic end-products such as ammonia, thiols, and indoles. A well-described example is CKD, in which urea and other waste products accumulate in the blood in the setting of decreased kidney function; these waste products diffuse into the gut lumen and exert a selection pressure for proteolytic bacteria, which generate precursors for indoxyl sulfate, trimethylamine N-oxide (TMAO), p-cresol sulfate, and so forth.[2,10] In phylogenic microarray analysis of stool samples from end-stage kidney disease patients, more than 200 bacterial operational taxonomic units from 23 bacterial families were significantly different in abundance as compared with control subjects.[11] These included increased bacterial counts from the Micrococcaceae, Clostridiaceae, Enterobacteriaceae, Moraxellaceae, Pseudomonadaceae, and Verrucomicrobiaceae families; whereas Prevotellaceae, Lactobacillaceae, and Alcaligenaceae families were reduced markedly.[11] The gut wall

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integrity is compromised as a result of local inflammation; subsequently, bacterial-derived toxins move across the "leaky gut" and promote systemic inflammation and multi-organ dysfunction.[2]

Alterations in gut microbial diversity are similarly evident in diabetes mellitus. Obesity is a state of chronic low-grade systemic inflammation, and obesity-induced insulin resistance is central to the pathophysiology of type 2 diabetes mellitus.[12] Mouse models of obesity have shown gut dysbiosis including a decrease in the Bacteroidetes/Firmicutes ratio.[13] Furthermore, germ-free mice do not develop obesity when exposed to a Western-style high-fat diet.[14] The obesity phenotype can be transmitted by fecal transplant. Ellekilde et al[15] treated adult mice with ampicillin to eradicate gut flora, and the mice developed metabolic features of obesity including β-cell hyperactivity when inoculated with cecal content from obese mice. In human beings, a population study of obese and nonobese Danish individuals showed that obesity traits (adiposity, insulin resistance, dyslipidemia, low-grade systemic inflammation) were associated with lower gut microbial diversity.[16]

Decreased gut microbial diversity has been shown in adults with type 2 diabetes mellitus, with decreased Bifidobacterium, Firmicutes, and Clostridia, and increased Betaproteobacteria.[17,18] It has been proposed that proliferation of gram-negative bacteria may explain the increase in serum endotoxin and low-grade systemic inflammation that is observed in both obesity and type 2 diabetes mellitus.[17,19,20] This pathologic pathway is amplified further when there is concurrent kidney disease. In a study of 14 patients with biopsy-proven diabetic nephropathy, Tao et al[21] noted increased density of gram-negative *Escherichia−Shigella* and *Prevotella* gut bacteria in diabetic nephropathy patients, compared with diabetic individuals without kidney disease. As further testament to the importance of the gut microbiota in diabetic kidney disease, frequent use of antibiotics (which disrupts the balance of normal intestinal flora) has been associated with more severe diabetic nephropathy in patients with type 1 diabetes mellitus.[22]

DECREASED PRODUCTION OF SCFAS

The major SCFAs produced by the gut microbiota include butyrate, acetate, and propionate. SCFAs are a major nutrient source for the epithelial cells that line the intestinal tract. Gut dysbiosis with deficient production of bacterial SCFAs leads to impairment of the intestinal barrier, promoting translocation of toxins from the gut lumen into the bloodstream. Relevant to the pathogenesis of diabetes mellitus, SCFAs also suppress host appetite by increasing the release of satiety hormones and stimulating vagal afferent chemoreceptors, increase energy expenditure by up-regulating thermogenesis-related proteins in hepatocytes and adipocytes, and increase glucose-stimulated insulin secretion (Fig. 1).[23]

Compelling evidence for a central role of gut microbial SCFAs in the development of type 1 diabetes mellitus came from The Environmental Determinants of Diabetes in the Young (TEDDY) study. This multinational study was a longitudinal analysis of gut metagenomes from 783 children (101 of whom were diagnosed with type 1 diabetes mellitus) in the United States and three European countries, starting at the age of 3 months until 10 years of age.[24] The expression of microbial genes that regulate the biosynthesis of SCFAs was lower in children who developed type 1 diabetes mellitus than in matched controls.[24] These findings were consistent with an earlier study in which children with β-cell autoantibodies were reported to have a low abundance of lactate- and butyrate-producing gut microbiota.[25] Furthermore, in the TEDDY cohort, supplementing infants with probiotics within 27 days of life correlated with a decreased risk of developing type 1 diabetes mellitus.[24] Data from large genome-wide association studies suggest that genetic variants in patients with type 2

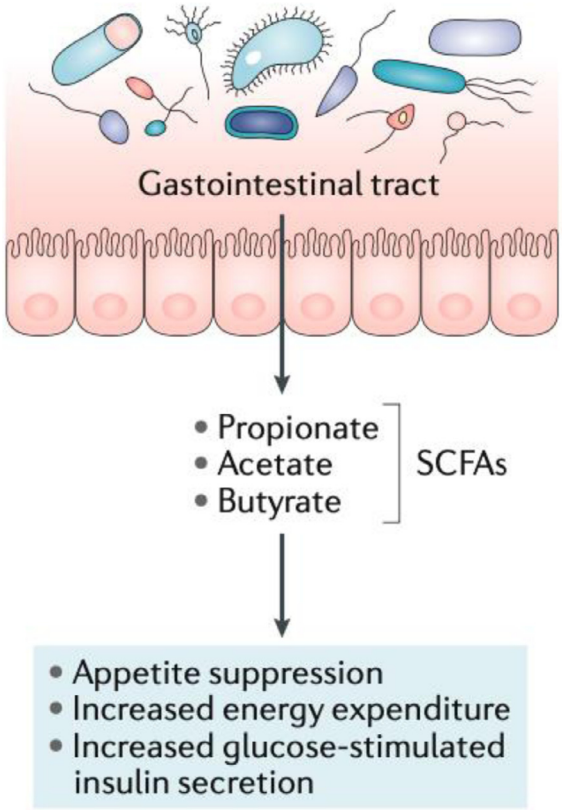

Figure 1. Short-chain fatty acids (SCFAs) generated by the gut microbiota include propionate, acetate, and butyrate, which are essential nutrients for intestinal epithelial cells. SCFAs modulate host energy and glucose metabolism through effects on appetite, energy expenditure, and insulin secretion. Reproduced with permission from Lau and Vaziri.[75]

diabetes mellitus influence gut bacterial production of the SCFAs butyrate and propionate, which in turn modulate host insulin sensitivity.[26]

GUT-DERIVED MICROBIAL TOXINS

Indoxyl sulfate, *p*-cresyl sulfate, TMAO, and other bacterial-derived metabolites traditionally have been labeled as uremic toxins because they were studied initially in the setting of CKD; it may be time to change this terminology because these microbial-derived toxins now have been implicated in nonkidney diseases including diabetes mellitus and coronary artery disease.

Gut dysbiosis is associated with a shift from a saccharolytic to a more proteolytic microbial community; toxins produced from amino acid catabolism lead to injury in multiple organ systems (Fig. 2). Tryptophan is metabolized into indole by intestinal bacteria, which subsequently is sulfated in the liver to form indoxyl sulfate. *P*-cresol sulfate is derived from phenylalanine and tyrosine, and is conjugated by gut microbes to produce the toxin *p*-cresyl sulfate. Bacterial metabolism of quaternary amines (eg, phosphatidylcholine, L-carnitine) yields trimethylamine, which is oxidized rapidly in the liver to produce TMAO.

Blood TMAO levels are associated strongly with type 2 diabetes mellitus, particularly when the estimated glomerular filtration rate is less than 90 mL/min/1.73 m^2.[27] In a randomized controlled trial of four different weight-loss diet interventions in 504 overweight or obese adults, restriction of dietary choline and L-carnitine was associated with decreased blood TMAO and improved insulin sensitivity at 2 years.[28] Higher serum *p*-cresol levels are associated independently with diabetes after adjustment for kidney function,[29] suggesting that this gut-derived microbial toxin may be a common pathologic pathway in both diabetes and CKD. In the Urinary Biomarker for

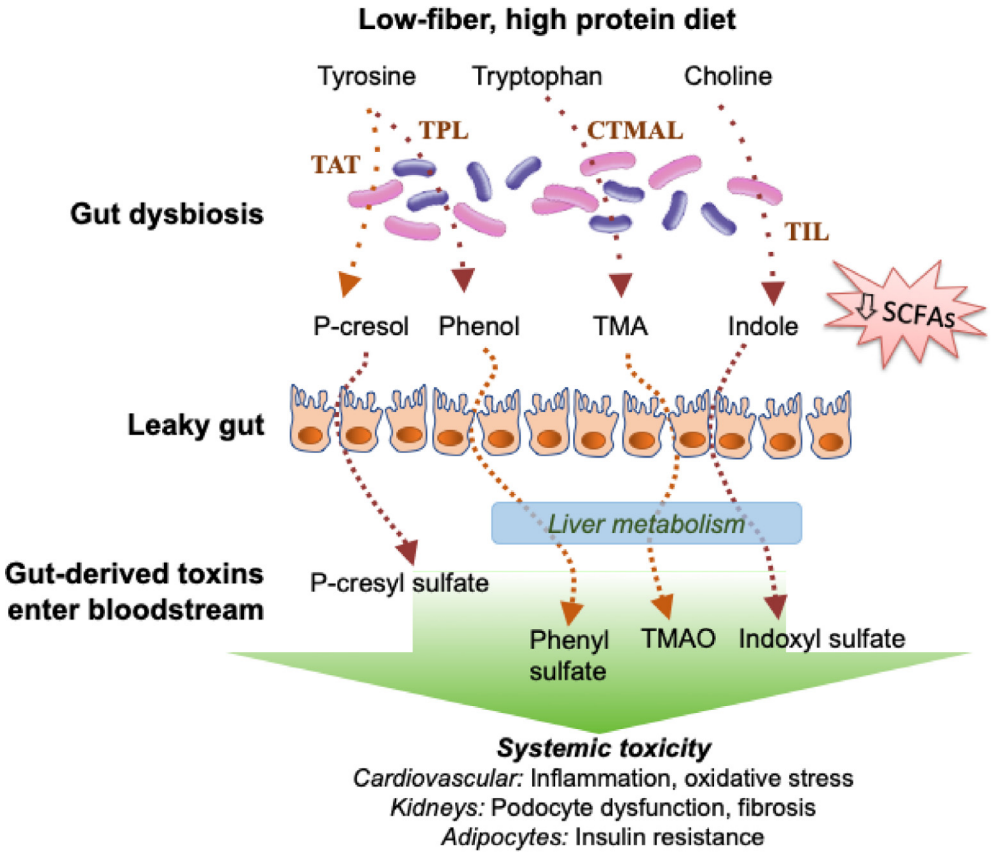

Figure 2. The intestinal microbiome is altered in chronic kidney disease and generates uremic toxins that translocate across the leaky gut barrier into the bloodstream, inducing systemic inflammation and multi-organ dysfunction. Many of these uremic toxins have been implicated in the pathophysiology of nonkidney diseases, including obesity and diabetes mellitus. Key microbial enzymes include tyrosine aminotransferase (TAT) and tyrosine phenol-lyase (TPL), which generate p-cresol and phenol, respectively, from tyrosine; carnitine trimethylamine lyase (CTMAL), which metabolizes trimethylamine (TMA) from choline; and tryptophan indole-lyase (TIL), which generates indole from tryptophan. Subsequent enterocyte or hepatic metabolism leads to production of the major uremic toxins p-cresyl sulfate, phenyl sulfate, indoxyl sulfate, and trimethylamine N-oxide (TMAO). Microbiome dysbiosis also is associated with decreased production of short-chain fatty acids (SCFAs), which deprives host enterocytes of an important nutrient source; SCFA deficiency further aggravates insulin resistance and systemic inflammation.

Continuous and Rapid Progression of Diabetic Nephropathy cohort of 362 Japanese adults with type 1 and 2 diabetes mellitus and preserved estimated glomerular filtration rate, the baseline phenyl sulfate levels predicted a 2-year progression of albuminuria.[30] Furthermore, Kikuchi et al[30] showed that oral administration of phenyl sulfate in non-CKD mouse models of diabetes induced podocyte damage.

PLANT-DOMINANT, LOW-PROTEIN DIET AND THE GUT MICROBIOME

Eating a plant-dominant, fiber-rich diet that is low in animal protein may favorably modulate the gut microbiome by decreasing generation of bacterial-derived toxins such as TMAO, which is associated with cardiovascular disease and insulin resistance.[31-34] The high fiber intake from legumes, grains, vegetables, and fruits can further up-regulate carbohydrate fermentation and down-regulate protein catabolism, and increase generation of beneficial SCFAs. A recent systematic review noted that 19 of 32 studies dealing with type 2 diabetes and/or obesity reported beneficial effects of plant-based dietary interventions (study duration, 3-24 mo) such as more pronounced weight loss, decreasing hemoglobin A1c, and an improved lipid profile.[35] However, these studies did not directly assess changes in the microbiota. One small study in 10 healthy volunteers compared plant-based versus animal-based diet in a cross-over trial design. After only 5 days, there was a shift toward a more carbohydrate-fermenting microbial population.[36]

Pertinent to patients with diabetic kidney disease, an active area of investigation in CKD is the plant-dominant, low-protein (PLADO) diet, which restricts protein intake to 0.6 to 0.8 g/kg body weight per day, whereby more than 50% of protein is from plant-based sources.[37] Aside from the microbiome-targeted benefits of decreased gut-derived uremic toxins and increased SCFAs described earlier, the PLADO diet also minimizes glomerular hyperfiltration from high-protein intake.[33] In a small study that included nine CKD patients per group, a low-protein diet with or without inulin prebiotic supplementation for 6 months was reported to modify the gut microbiome, increase serum bicarbonate, and improve physical function scores.[38] Further studies are needed to examine the role of PLADO regimens in diabetes.

ORAL ANTIDIABETIC MEDICATIONS AND THE GUT MICROBIOME

Metformin, the most frequently prescribed initial oral medication to treat type 2 diabetes, has been reported to increase beneficial gut microbiota that produce the SCFAs butyrate and propionate. Furthermore, metformin increases *Akkermansia muciniphila*, which is a commensal bacteria that stimulates mucin secretion (important for mucosal barrier integrity[39]) and has been associated with adipose tissue metabolism and glucose homeostasis.[40-42]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to alter the gut microbiome in animal studies. In diabetic mice, dapagliflozin therapy was associated with mild changes in the microbiome and decreased vascular stiffness.[43] In nondiabetic CKD mice, canagliflozin increased cecal SCFAs and significantly decreased blood uremic toxins such as indoxyl and p-cresyl sulfates without hypoglycemia.[44] One proposed mechanism is that off-target inhibition of SGLT1 occurs in the small intestine, which results in decreased carbohydrate absorption in the upper gastrointestinal tract; increased delivery of complex carbohydrates to the colon subsequently promotes saccharolytic fermentation and production of beneficial SCFAs.[44]

A small clinical trial from The Netherlands compared dapagliflozin with gliclazide (24 and 17 patients per study arm) and reported no significant change in overall microbial diversity.[45] However, specific bacterial subpopulations involved in SCFA or uremic toxin production were not analyzed separately. There is an ongoing clinical trial in Korea comparing microbiome effects with SGLT2 inhibitors versus metformin (ClinicalTrials.gov ID: NCT03204799). A separate trial in Estonia is investigating the gut microbiome as a secondary end point with SGLT2 inhibitors versus glucagon-like peptide 1−receptor agonists (NCT04151849). More research is needed to fully evaluate the impact of antidiabetic medications on the gut microbiome.

PREBIOTICS AND PROBIOTICS IN DIABETES MELLITUS

Given the accumulating evidence pointing to an integral role for the gut microbiome in diabetes pathophysiology, several studies have investigated microbiota-targeted interventions as a novel strategy to prevent or treat diabetes. Through modulation of inflammatory pathways within the gut microbiome,[46] the overall goal is to reduce gut permeability, decrease systemic inflammation, and improve insulin sensitivity.[47,48] These interventions can be in the form of prebiotics or probiotics. Prebiotics are nondigestible food ingredients, typically plant fibers, that are easily fermentable by beneficial gut bacteria to increase production of SCFAs.[49,50] Common prebiotics include oligosaccharides such as xyloseoligosaccharide, inulin, galacto-oligosaccharides, and fructooligosaccharide.[46] In CKD, high amylose resistant starch has been shown to decrease microbial dysbiosis and oxidative stress in rat models[51,52] and in chronic hemodialysis patients.[53,54] Probiotics are living organisms ingested via supplements or fermented foods (dairy, yogurts) that are believed to improve the health of the host. Commonly

Table 1. Animal Studies and Clinical Trials Investigating the Potential Utility of Prebiotics, Probiotics, and Symbiotics in Diabetes Mellitus

Study Model	Study Population (n per Group)	Intervention	Outcomes	Reference
Animal studies				
Impact of prebiotics on gut microbiota and barrier function in NOD mice (prebiotic study)	NOD/MrkTac mice (n = 34) CTL (n = 20)	Diet supplemented with XOS versus standard chow	XOS is associated with delayed diabetes; fewer cellular infiltrations in pancreatic islets and salivary glands Decreased gut permeability, shift toward more anti-inflammatory macrophage and T-cell profiles	Hansen et al, 2019[57]
Effects of probiotic VSL#3 on the prevention of T1DM in NOD mice (probiotic study)	VSL#3 (n = 10) VSL#3 + RA (n = 17) CTL (n = 19)	VSL#3 group: Oral gavage 3 times/wk starting at 4 weeks until 20 weeks of age VSL#3 + RA: also received 50 ug of all-trans RA by intraperitoneal injection	VSL#3 with/without RA showed reduced insulitis with increased abundance of Clostridia and decreased Bacteroidaceae species; decreased IL1β expression NOD mice receiving VSL#3 alone had reduced intestinal inflammasome activity, and were significantly protected from T1DM	Dolpady et al, 2016[56]
Symbiotic supplementation during pregnancy and HFD-induced metabolic disorders in rats (symbiotic study)	n = 30 (female Wistar rats) Separated into CTL, HFD, and HFD + symbiotic	Symbiotic group gavaged with symbiotics (fructooligosaccharide 10%, and 10^8 CFU/mL of *L rhamnosus* and *Bacillus coagulans*)	HFD + symbiotic group had decreased serum chemerin, insulin, insulin resistance, triglycerides, LDL, and HOMA index	Amirpour et al, 2020[59]
Supplementation effects on metabolic and left ventricular dysfunction in obese insulin-resistant rats (prebiotic, probiotic, and symbiotic study)	HFD (n = 24) Normal chow diet (n = 24)	Rats fed HFD versus normal chow for 12 weeks Further randomized to vehicle, prebiotic, probiotic, or symbiotic	Prebiotic, probiotic, and symbiotic reduced insulin resistance and LV dysfunction in rats on HFD There was improvement in lipid profile and left ventricular function	Tunapong et al, 2018[58]
Clinical studies (randomized controlled trials)				
Studies in children				
Effect of prebiotics on microbiota, intestinal permeability, and glycemic control in T1DM children ages 8-17 y (prebiotic study)	n = 17 Placebo (n = 21)	Oligofructose-enriched inulin supplement versus placebo (maltodextrin) daily for 12 wk	Prebiotics were associated with increased C-peptide and abundance of gut Bifidobacterium; modest decrease in intestinal permeability (did not reach significant difference)	Ho et al, 2019[67] Canada
Cohort from TEDDY study: Effects of early exposure to probiotics on islet autoimmunity in children with increased genetic risk of T1DM (high-risk HLA-DR, HLA-DQ genotypes) (probiotic study)	n = 7,473 (ages, 4-10 y)	Early probiotic exposure during first year of life Study conducted from 2004 to 2010	Early probiotic supplementation during the first 27 days of life significantly decreased risk of islet cell autoimmunity in children with the highest risk of T1DM (children with the HLA-DR3/4 genotype)	Uusitalo et al, 2016[66] United States, Finland, Germany, and Sweden
Studies in pregnant women				
Probiotic effect on glycemic control and lipid profiles in pregnant women with gestational diabetes mellitus (probiotic study)	n = 30 Placebo (n = 30)	Daily capsule containing *L acidophilus* (2×10^9 CFU/g), *L casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g) over 6 wk Placebo = cellulose	Significant decrease in fasting plasma glucose, serum insulin levels, HOMA for insulin resistance, serum triglycerides, and VLDL cholesterol	Karamali et al, 2016[71] Iran
Probiotic effect on insulin resistance in pregnant women	n = 28 Placebo (n = 29)	Daily tablet containing 10^9 CFU of *B bifidum* and 10^9 CFU of *L*	Probiotics lowered fasting glucose and HOMA for insulin resistance; increased insulin	Kijmanawat et al, 2019[70] Thailand

(*continued on next page*)

Table 1 (*Continued*)

Study Model	Study Population (n per Group)	Intervention	Outcomes	Reference
(24-28 wk) with diet-controlled gestational diabetes mellitus (probiotic study)		*acidophilus* over 4 weeks Placebo = gelatin	sensitivity No significant difference in weight gain	
Probiotic effect on gestational diabetes in at-risk overweight or obese women (probiotic study)	n = 439 Fish oil ± probiotics, or placebo	2 fish oil capsules with/without probiotic capsule (10^{10} CFU of *L rhamnosus* and *B lactis*) during pregnancy Placebo = microcrystalline cellulose	No significant difference between intervention groups in terms of glucose, insulin, HOMA2-IR, or onset of gestational diabetes	Pellonpera et al, 2019[69] Finland
Effect of probiotics during the second trimester (~15 weeks into pregnancy) for prevention of gestational diabetes mellitus (probiotic study)	n = 207 Placebo (n = 204)	Daily doses of 10^9 CFU probiotic combination (*L rhamnosus* and *B lactis*) per day from enrollment until birth of infant Placebo = microcrystalline cellulose and dextrose anhydrate capsules	Probiotics did not prevent gestational diabetes in overweight or obese pregnant women	Callaway et al, 2019[68] Australia
Studies in nonpregnant adults				
Effect on glycemic control and other diabetes-related outcomes in T2DM (probiotic study)	n = 68 Placebo (n = 68)	Daily doses of 10^{10} CFU each of *L acidophilus, L casei, Lactobacillus lactis, B bifidum, Bifidobacterium longum*, and *Bifidobacterium infantis* over 12 wk	Probiotics were associated with modest improvement in hemoglobin A1c and fasting insulin levels (not statistically different)	Firouzi et al, 2017[65] Malaysia
Probiotic effect on glycemic control and lipid profile in T2DM patients (probiotic study)	n = 30 Placebo (n = 30)	Daily probiotic capsule containing 7 strains (including *Lactobacillus, Bifidobacterium, Streptococcus*) over 6 wk Placebo	Probiotic group had significant decrease in fasting blood glucose and significant increase in HDL-C levels No significant effect on insulin, triglycerides, total cholesterol, insulin resistance, BMI, or weight fluctuations	Razmpoosh et al, 2018[63] Iran
L casei effect on glycemic response, serum sirtuin 1, and fetuin-A levels in T2DM (probiotic study)	n = 20 Placebo (n = 20)	Daily capsule of 10^8 CFU of *L casei* over 8 wk Placebo = maltodextrin	Probiotic group had significant decrease in fasting blood sugar, insulin concentration, insulin resistance, and fetuin-A levels Significant increase in sirtuin 1 Reduction in hemoglobin A1c level was not significant	Khalili et al, 2019[62] Iran
Probiotic effects on blood endotoxin, inflammatory, and cardiometabolic sta'tus in T2DM patients (probiotics study)	n = 31 Placebo (n = 30)	2 daily capsules of 2.5×10^9 CFU/g Ecologic barrier vs placebo (2.4 g freeze-dried maize starch and maltodextrins) over 6 mo	Probiotics were associated with significant decrease in HOMA-IR, and trend for decreased levels (not statistically significant) in circulating endotoxin (70%), glucose (38%), insulin (38%), triglycerides (48%), total cholesterol (19%), TNF-α (67%), Il6 (77%), CRP (53%), resistin (53%)	Sabico et al, 2019[60] Saudi Arabia
Symbiotic effects on glycemic control, lipid profiles, and microalbuminuria in patients with T2DM (symbiotic study)	n = 35 Placebo (n = 35)	Daily doses of 500 mg of prebiotic (*fructo-oligosaccharide*), probiotics (*Lactobacillus* family, *Bifidobacterium* family, *Streptococcus thermophilus*), B group vitamins (1 mg), lactose (0.5 mg), maltdextrin, magnesium saturate, and talc for 9 weeks Placebo = all of the above except for raw starch replacing the prebiotic and probiotics	Symbiotic group had significant decrease in hemoglobin A1c level by 0.3% and microalbuminuria by 10 mg/g No effect on fasting blood glucose, urea, creatinine, or lipid profile	Ebrahimi et al, 2017[61] Iran

(*continued on next page*)

Table 1 (*Continued*)

Study Model	Study Population (n per Group)	Intervention	Outcomes	Reference
Symbiotic effect on CIMT, biomarkers of inflammation, and oxidative stress in overweight, T2DM, coronary heart disease patients ages 50-85 y (symbiotic study)	n = 30 Placebo (n = 30)	Daily capsule of *L acidophilus* strain T16 (2×10^9 CFU/g), *L casei* strain T2 (2×10^9 CFU/g), and *B bifidum* strain T1 (2×10^9 CFU/g), and 800 mg of inulin over 12 wk Placebo = 800 mg inulin and starch	Significant decrease in serum hs-CRP and plasma malondialdehyde Significant increase in nitric oxide Overall, no conclusive effect on biomarkers of oxidative stress or CIMT	Farrokhian et al, 2019[64] Iran

Abbreviations: BMI, body mass index; CIMT, carotid intima-media thickness; CRP, C-reactive protein; CTL, controls; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IR, insulin resistance; LDL, low-density lipoprotein; LV, left ventricular; MrkTac; NOD inbred mouse strain by Taconic; NOD, nonobese diabetic mice; RA, retinoic acid; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TEDDY, The Environmental Determinants of Diabetes in the Young; TNF, tumor necrosis factor; VLDL, very-low-density lipoprotein; VSL#3, probiotic formulation by VSL Pharmaceuticals; XOS, xylooligosaccharide.

researched probiotics include strains of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Bifidobacterium lactis, Streptococcus*, and the yeast *Saccharomyces boulardii.*[55] Symbiotics combine both prebiotics and probiotics.

Animal studies[56-59] and clinical trials[60-72] examining prebiotics, probiotics, and symbiotics in diabetes mellitus are summarized in Table 1. Results have been mixed, and most studies were limited by a small sample size. The most encouraging results were from the TEDDY cohort of more than 7,000 children, which showed an effect of early probiotic supplementation during the first 27 days of life in terms of decreasing the risk of developing type 1 diabetes mellitus in the high-risk HLA-DR3/4 genotype.[66] Probiotic trials involving several hundred pregnant women did not show a benefit for preventing gestational diabetes.[68,69] Other small studies of probiotics in adults with type 2 diabetes mellitus have not shown consistent benefit in terms of improving glycemic or lipid profiles. The largest trial (n = 68 per study arm) was performed in Malaysian patients with non−insulin-dependent type 2 diabetes; their baseline hemoglobin A1c was 7.6% and probiotic therapy decreased the A1c by 0.14% (not statistically different from placebo).[65] Challenges faced by prebiotic/probiotic trials include the following: (1) uncertainty about the appropriate composition of bacteria that will promote health, (2) targeting high-risk individuals for study participation so as to detect meaningful changes in clinical outcomes, and (3) adequate study duration to detect differences between the treatment and placebo groups. Rare cases of sepsis associated with probiotic use have been described in the literature,[73] including a case in a diabetic woman,[74] therefore safety outcomes are an important aspect of clinical trials.

CONCLUSIONS

The gut microbiome modulates host metabolic pathways and the risk for developing diabetes mellitus. Gut dysbiosis leads to decreased production of beneficial SCFA translocation of bacterial-derived toxins into the systemic circulation. Gut-derived bacterial toxins induce insulin resistance, vascular injury, and podocyte damage. More studies are needed to better understand how to invoke a less-pathogenic gut microbiome, whether via plant-dominant, low-protein diets or utilization of prebiotics and probiotics, as a potential therapeutic target within diabetes management.

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