Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2025, 15(11), 237-264
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

The Investigation into Correlation between Type 2 Diabetes Mellitus and the Gut Microbiota

Shuran Liu, Alex Zhu*

School of Nursing, Huazhong University of Science and Technology, Wuhan, China
Email: *809983895@qq.com

How to cite this paper: Liu, S.R. and Zhu, A. (2025) The Investigation into Correlation between Type 2 Diabetes Mellitus and the Gut Microbiota. *Open Journal of Endocrine and Metabolic Diseases*, **15**, 237-264.
https://doi.org/10.4236/ojemd.2025.1511022

Received: September 28, 2025
Accepted: November 23, 2025
Published: November 26, 2025

Abstract

This study investigates the complex interactions between gut microbiota and the pathogenesis of type 2 diabetes mellitus (T2DM). T2DM, a prevalent metabolic disorder, is closely linked to both insulin resistance and inflammation, conditions that have been increasingly associated with gut microbial composition. Recent evidence suggests that dysbiosis—the imbalance in gut microbial populations—contributes to T2DM progression by altering short-chain fatty acid (SCFA) production, influencing bile acid metabolism, and increasing systemic inflammation through pathways such as endotoxemia and modulation of immune responses. This review analyzes the critical role of SCFAs, bile acids, and gut-brain axis signaling in metabolic regulation, focusing on their mechanisms of action in glucose homeostasis and insulin sensitivity. Furthermore, the potential of microbiome-targeted therapies, including probiotics, prebiotics, fecal microbiota transplantation (FMT), and innovative engineered bacterial treatments, is evaluated. While therapeutic interventions targeting gut microbiota demonstrate promise in improving T2DM outcomes, gaps remain in understanding optimal microbial compositions and long-term efficacy. This paper underscores the need for further research into the microbial ecology of T2DM and the development of personalized microbial therapies to mitigate the disorder's complications.

Keywords

T2DM, Diabetes, Intestinal Flora, Microbe

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic metabolic disease. Its global

*Corresponding author.

prevalence continues to rise and has become a major public health challenge [1]. The core feature of this disease lies in the progressive decline of the body's ability to maintain blood glucose homeostasis. Its occurrence is due to the combined effect of genetic susceptibility and environmental factors, and it has significant multifactorial characteristics. The incidence of T2DM has been steadily increasing worldwide, both in developed and developing countries, affecting a wide range of people [2]. Although the exact etiology and pathogenesis of this disease have not been fully clarified, the current research consensus holds that insufficient insulin secretion and insulin resistance (IR) are its core pathophysiological basis. It is particularly worth noting that insulin resistance is closely related to obesity status, and obesity itself is the result of the complex interweaving of genetic background, lifestyle, and socio-economic factors [3].

Recent studies have emphasized the key role of the gut microbiota in the occurrence and development of type 2 diabetes mellitus (T2DM), revealing an important interaction between the gut microbiota ecosystem and the metabolic health of the host [4]-[10]. There are approximately 500 to 1,000 types of microorganisms colonizing the human intestinal tract, with a total cell count far exceeding that of the human body's own cells (more than ten times). It is estimated to contain 10 to 14 bacteria and can be regarded as a complex "microbial organ". The collective genetic material carried by these microbial communities, namely the "microbiome", has a total number of genes that is more than 100 times that of the human nuclear genome [11].

Although the number of studies exploring the association between gut microbiota and type 2 diabetes mellitus (T2DM) is increasing, there is still a significant knowledge gap in our understanding of the specific mechanisms by which these microorganisms affect metabolic processes. For instance, although the associations between dietary patterns, gut microbiota composition, and type 2 diabetes mellitus (T2DM) have been well documented, there is still a lack of consensus in the academic community as to which specific microbial species or their metabolites have the greatest influence on the development of insulin resistance. Furthermore, existing studies often fail to fully consider the complex interactions between individual genetic factors and microbial diversity, as well as the influence of social determinants on dietary habits and the health status of the microbiome. Filling these research gaps is crucial for developing targeted intervention measures and individualized treatment strategies aimed at reducing the risk of T2DM and improving metabolic health [12].

2. The Crucial Role of Intestinal Flora in the Progression of T2DM

Intestinal flora, also known as gut microbiota, plays a crucial role in the progression of Type 2 Diabetes Mellitus (T2DM). The gut microbiota is a complex community of microorganisms living in the human digestive tract, and its composition and function are increasingly recognized as important factors in metabolic

health and disease, including T2DM. When interpreting microbiota-diabetes associations, key confounders such as host genetics, dietary composition, and common medications (especially metformin and antibiotics) must be accounted for, as they independently influence both microbial composition and glucose homeostasis, potentially obscuring causal relationships. In this paper, these factors have been considered seriously.

2.1. Common Intestinal Flora and Its Classification

The human gastrointestinal tract harbors a vast microbial ecosystem dominated by bacteria, with biomass reaching 1 - 1.5 kg and cell counts approximating 10^{14}—exceeding human somatic cells by an order of magnitude [6]. Although over 500 species may reside in the gut, only about 100 have been characterized, and more than 99% of total abundance is attributable to just 30 - 40 predominant species [13] (**Figure 1**). The community is dominated by four major phyla—Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%), and Actinobacteria (3%)—which together constitute approximately 98% of the microbiota [12]. Functionally, these bacteria fall into three categories: commensal/protective, pathogenic, and opportunistic pathogens, with Firmicutes and Bacteroidetes hosting most functional groups [14].

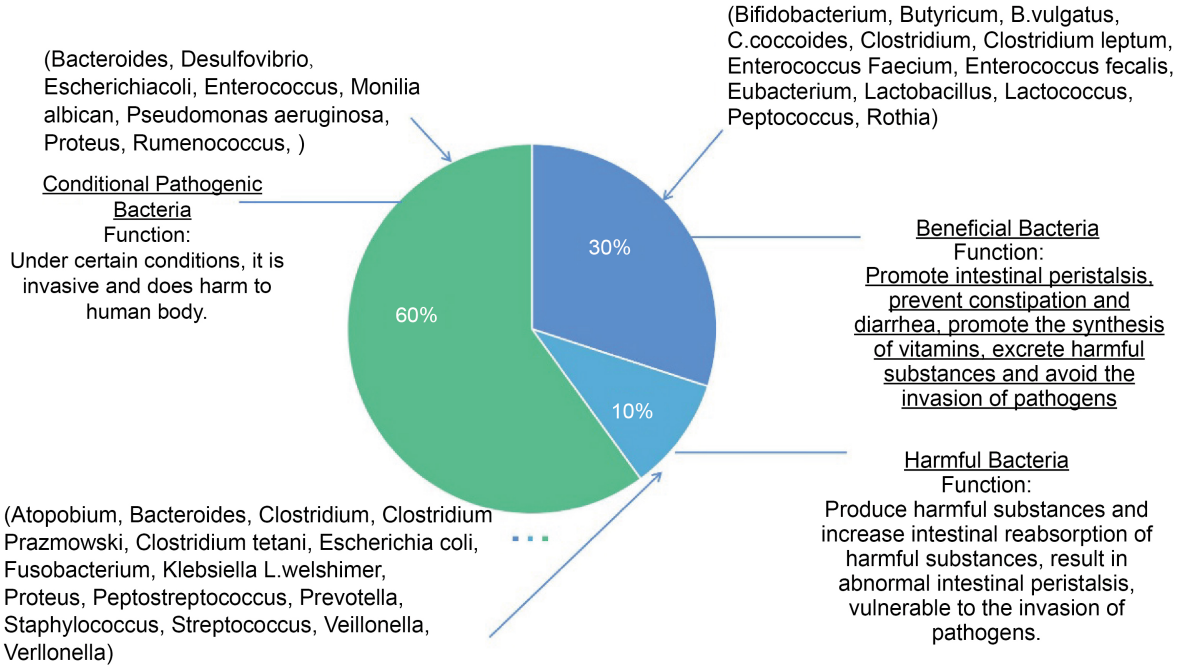

Figure 1. The classification of intestinal flora and their basic function.

2.2. Potential Pathways of Intestinal Flora Effects on T2DM

The gut microbiota affects T2DM through multiple pathways, including inflammation, SCFA production, bile acid metabolism, and the gut-brain axis. Dysbiosis, or an imbalance in gut microbiota, can exacerbate insulin resistance, alter glucose

metabolism, and promote systemic inflammation, all of which are critical factors in the progression of T2DM. Understanding these pathways highlights the potential for therapeutic interventions targeting gut microbiota to manage or prevent T2DM.

Short-Chain Fatty Acid (SCFA) Production

Short-chain fatty acids (SCFAs), alternatively termed volatile fatty acids, are low-molecular-weight carboxylates containing 1 - 6 carbon atoms. These compounds are principally synthesized within the human colon through anaerobic microbial fermentation of indigestible carbohydrates. The predominant SCFAs include acetate, propionate, and butyrate, which collectively represent the most abundant fractions. Key bacterial producers encompass *Bacteroides*, *Clostridium*, *Bifidobacterium*, *Eubacterium*, *Streptococcus*, and *Peptostreptococcus* species.

Growing research implicates SCFAs as significant modulators in type 2 diabetes mellitus (T2DM) pathogenesis (**Figure 2**). Experimental studies report diminished SCFA levels (acetate, propionate, butyrate) in high-fat-diet/streptozotocin-induced diabetic rodents compared to healthy controls [15] [16]. Clinically, fecal propionate and butyrate concentrations are markedly reduced in T2DM patients relative to healthy individuals, with acetate also demonstrating a non-significant decreasing trend [17]. Proposed mechanisms for SCFA-mediated effects on T2DM involve: Enhanced insulin secretion, Improved insulin sensitivity, Activation of intestinal gluconeogenesis, Increased energy expenditure, Attenuation of adiposity, and inflammatory responses.

Short-chain fatty acids (SCFAs) demonstrate modulatory effects on pancreatic insulin secretion, confer protection against dietary insulin resistance, and potentiate insulin sensitivity [18] [19]. Clinical evidence indicates inverse correlations between circulating concentrations of total SCFAs, acetate, and propionate with fasting insulin levels and HOMA-IR indices [20]. Experimental models reveal that SCFAs—notably propionate—enhance glucose-dependent insulin secretion while preserving β-cell integrity through suppression of apoptosis, stimulation of proliferation, and inhibition of trans-differentiation toward α-cell phenotypes [19] [21].

Butyrate administration demonstrates efficacy in improving insulin sensitivity and mitigating insulin resistance across murine models and human cohort studies [22] [23], with proposed mechanisms involving enhanced energy expenditure and mitochondrial biogenesis [22]. Intestinal gluconeogenesis (IGN) is the *de novo* synthesis of glucose from non-carbohydrate precursors within the enterocytes of the small intestinal mucosa. It is an endogenous metabolic process that contributes to systemic glucose homeostasis, independent of the liver and kidneys, the two principal organs traditionally associated with gluconeogenesis. It also contributes significantly to systemic glucose regulation. Butyrate and propionate activate IGN through distinct pathways—cAMP-mediated signaling and gut-brain neural circuits, respectively—leading to suppressed hepatic glucose output and improved glycemic control [24].

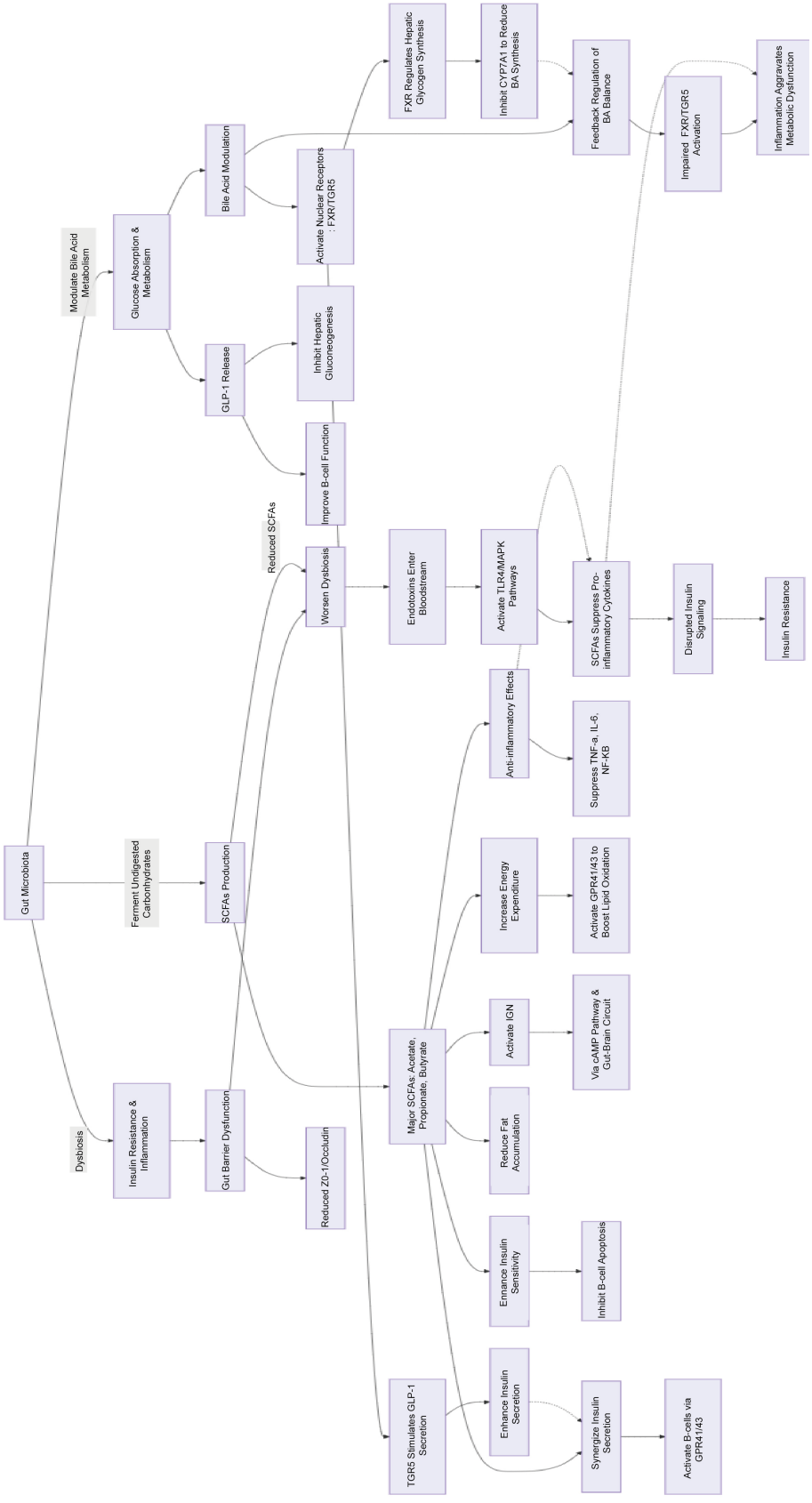

Figure 2. Possible pathways of intestinal flora effects on T2DM.

Six human G protein-coupled receptors (GPCRs, a large superfamily of integral membrane proteins characterized by a common architecture of seven transmembrane α-helices, which transduce extracellular signals into intracellular responses by activating heterotrimeric guanine nucleotide-binding proteins upon agonist binding) interact with SCFAs, including prominently expressed GPR41, GPR43, and GPR109a across immune cells, adipocytes, and neural tissues [25]. Ligand-specific activation occurs at: Propionate/butyrate-bound GPR41/GPR109a reduces cAMP, activating PKA and MAP kinases (ERK/p38); Acetate/butyrate/propionate-activated GPR43 similarly inhibits cAMP while stimulating PLCβ, Ca^{2+} mobilization, and PKC [26].

SCFAs (particularly acetate, propionate, butyrate) stimulate enteroendocrine L-cells to secrete PYY and GLP-1, and promote adipose leptin release via GPR41/43 activation [27]-[30]. Additionally, SCFAs elevate whole-body energy expenditure and lipid oxidation—demonstrated by colonic SCFA infusion increasing fat oxidation, resting energy expenditure, and PYY in overweight humans [31]. Dietary butyrate supplementation similarly enhances energy expenditure and confers resistance to diet-induced obesity in murine models [22].

Insulin Resistance and Inflammation

Perturbations in gut microbiota composition (dysbiosis) correlate with elevated intestinal permeability. This compromised barrier facilitates systemic translocation of bacterial endotoxins like lipopolysaccharides (LPS), triggering chronic low-grade inflammation. Such inflammation impairs insulin signaling cascades, thereby fostering insulin resistance—a central pathophysiological feature of T2DM.

Dysbiosis specifically reduces expression of intestinal tight junction proteins ZO-1 and occludin, which critically maintain barrier integrity by preventing paracellular passage of luminal macromolecules (including microbes and toxins). Additionally, it disrupts the dual-layered intestinal microbial barrier: Mucosa-adherent flora (primarily Bifidobacterium and Lactobacillus), Luminal flora (dominated by Escherichia coli and Enterococcus).

Concurrently, pathogenic bacteria colonize the intestinal mucosa unchecked. This barrier dysfunction may provoke bacterial translocation and endogenous infections, culminating in metabolic endotoxemia.

Endotoxins—notably LPS from Gram-negative bacterial outer membranes—enter circulation via dysbiosis-induced mechanisms: High-fat diets and other stressors alter microbial ecology (diminishing beneficial Bifidobacterium/Lactobacillus while expanding Gram-negative populations), increase intestinal permeability, and compromise barrier function. These shifts collectively enhance LPS production, absorption, and systemic dissemination. Within the circulation, LPS complexes with CD14 (a glycosylphosphatidylinositol-anchored receptor) and engages Toll-like receptor 4 (TLR4) on monocyte-macrophages. This interaction activates TLR4 and MAPK signaling pathways in skeletal muscle and adipose tissue, propagating inflammation and insulin resistance development.

Short-chain fatty acids (SCFAs) contribute to colonic acidification, restrict pro-

liferation of pathogenic bacteria, stabilize water-electrolyte balance, and prevent intestinal dysregulation. Contemporary research confirms SCFAs' capacity to attenuate proinflammatory cytokine production, facilitating mucosal repair and reducing colonic inflammation [32]-[35]. Intestinal dysbiosis diminishes SCFA biosynthesis, impairing anti-inflammatory responses and promoting inflammatory pathogenesis.

Type 2 diabetes mellitus (T2DM) progression is intrinsically linked to chronic low-grade inflammation, making inflammation modulation a therapeutic priority. Butyrate mitigates adipose-macrophage crosstalk-induced inflammation through suppressed lipolysis and inflammatory pathway inhibition [36]. Specifically, it significantly reduces: Tumor necrosis factor-alpha (TNF-α), Monocyte chemoattractant protein-1 (MCP-1), Interleukin-6 (IL-6), while inhibiting nuclear factor kappa-B (NF-κB) activation. Similarly, propionate demonstrates anti-inflammatory efficacy in adipose tissue, significantly downregulating inflammatory mediators including TNF-α and CC chemokine ligand 5 (CCL5) [37].

Modulation of Glucose Absorption and Metabolism

The gut microbiota regulates bile acid (BA, a kind of steroid-derived, amphipathic molecule synthesized in the liver from cholesterol that facilitates the emulsification, digestion, and absorption of dietary lipids and fat-soluble vitamins in the small intestine) profiles, subsequently influencing glucose metabolism through activation of nuclear receptors, including FXR and TGR5. Dysbiosis-induced alterations in BA composition can disrupt glucose homeostasis, contributing to hyperglycemia in T2DM.

Bile acids serve not only as primary biliary components but also as terminal metabolites of hepatic cholesterol catabolism. They facilitate fat and fat-soluble vitamin absorption/transport while functioning as signaling molecules that modulate energy metabolism and restrain bacterial overgrowth. Within the intestine, gut microbes transform conjugated BAs into secondary BAs via enzymatic reactions, yielding deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), and rodent-specific ω-muricholic acid (ωMCA) [38]. Key bacterial genera involved include: *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium*, and *Listeria*: Mediate BA deconjugation via bile salt hydrolases (BSH). Clostridium and Eubacterium: Generate secondary BAs through 7-α-dehydroxylation [39] [40]. *Bacteroides*, *Eubacterium*, *Clostridium*, *Escherichia*, and *Eggerthella*: Facilitate BA epimerization [39].

Most BAs (e.g., cholic acid/CA, chenodeoxycholic acid/CDCA, DCA, UDCA, αMCA, ωMCA) undergo enterohepatic recirculation via ileal reabsorption and portal venous return to the liver [39]. Crucially, gut flora convert primary BAs to secondary BAs, activating BA receptors [41]. This stimulates nuclear receptors (farnesoid X receptor/FXR, Takeda G-protein receptor 5/TGR5) that regulate: Hepatic BA synthesis, Intestinal BA reabsorption, lipid/glucose/energy metabolism [42] [43].

Additionally, BAs preserve intestinal barrier integrity, inhibiting bacterial trans-

location [44]. Consequently, dysbiosis reduces secondary BA production, impairing receptor activation and promoting glucose dysregulation in T2DM pathogenesis (**Figure 2**).

TGR5 represents one of the most critical bile acid receptors, widely expressed in multiple tissues, including intestinal and pancreatic epithelia. Its activation potency by bile acids follows the hierarchy: lithocholic acid (LCA) > deoxycholic acid (DCA) > chenodeoxycholic acid (CDCA) > cholic acid (CA) [45]. TGR5 agonism demonstrates therapeutic potential for type 2 diabetes mellitus (T2DM) management, exemplified by the significant glucose-lowering effects of high-dose TGR5 agonist SB-756050 in clinical trials [46]. The primary established mechanism involves TGR5-mediated potentiation of glucagon-like peptide-1 (GLP-1) secretion from intestinal L-cells [47]. Thomas *et al.* revealed this process involves elevated ATP/ADP ratios triggering subsequent intracellular calcium mobilization [48]. Beyond enteroendocrine cells, TGR5 activation in pancreatic α-cells stimulates proglucagon processing into GLP-1 and promotes its release [49]. The resultant GLP-1 acts on pancreatic β-cells to potentiate insulin secretion—a well-characterized pathway for glucose homeostasis restoration and T2DM amelioration [50].

FXR is another key receptor for bile acids (BAs) and is highly expressed in the liver, intestine, and kidneys. BAs is a natural ligand of FXR. Chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), and cholic acid (CA) all belong to the high-affinity agonist ligands of FXR, among which CDCA has the strongest efficacy in activating FXR [51]. Multiple studies have pointed out that activating FXR is helpful for improving type 2 diabetes mellitus (T2DM). The research by Zhang *et al.* confirmed that FXR activation can enhance glycogen synthesis in the liver of diabetic mice and significantly improve their hyperglycemia and hyperlipidemia conditions [52]. Furthermore, studies have found that an intestinal-limiting FXR agonist (Fexaramine) can promote Browning of adipose tissue in mice, alleviate obesity, inflammation, and insulin resistance [53]. In terms of the mechanism of action, the activation of intestinal FXR can induce the release of fibroblast growth factor 15 (FGF15, which is FGF19 in the human body). This factor reaches hepatocytes through the portal vein and binds to the FGFR4/βKlotho receptor in the liver, thereby inhibiting the expression of CYP7A1. Ultimately, it reduces the synthesis of BAs in the liver [45] [51]. Meanwhile, FGF19 can also stimulate liver glycogen synthesis, but it does not promote adipogenesis [54]. Potthoff *et al.* found that FGF15/19 released from the small intestine inhibits hepatic gluconeogenesis by suppressing the CREB-PGC-1α pathway [55]. The apparent contradiction regarding FXR's metabolic effects may stem from its tissue-specific functions, where intestinal FXR inhibition often improves glucose metabolism while hepatic FXR activation generally exerts beneficial systemic metabolic effects [56]. However, several studies have also shown that inhibiting FXR is beneficial for glucose metabolism, obesity, and diabetes. Intestinal selective inhibition of FXR exacerbates obesity-related metabolic dysfunction, including insulin resistance [57].

Another study revealed that the increase of taurine binding β-carnocholic acid (TβMCA) in the intestine would inhibit the intestinal FXR signal transduction, thereby reducing the synthesis of ceramides and further weakening liver gluconeogenesis [58]. Trabelsi *et al*. found that the deletion of FXR would increase the gene expression and secretion of glucagon-like peptide-1 (GLP-1), thereby improving glucose metabolism [59]. In addition, the treatment of ob/ob mice with colevilam (a bile acid chelating agent) can inhibit the FXR activity in intestinal L cells, promote the production and secretion of GLP-1, and improve blood glucose levels [56]. Recent studies have identified that the gut microbiota-GUDCA-gut FXR axis mediates the clinical benefits of metformin [59]. Specifically, the use of metformin in the treatment of newly diagnosed patients with type 2 diabetes mellitus (T2DM) leads to a decrease in the abundance of *Bacteroides fragile* and an increase in GUDCA levels. The latter further inhibits intestinal FXR, thereby improving metabolic dysfunction, including hyperglycemia.

A significant limitation in this area is the apparent dual role of FXR signaling in glucose metabolism, necessitating further research to clarify its context-dependent functions and therapeutic targeting potential.

3. The Damage and Associated Disease Induced by Gut Bacteria in T2DM

Diabetes is defined by chronically elevated blood glucose concentrations resulting from either deficient insulin secretion by pancreatic β-cells or reduced peripheral tissue responsiveness to insulin signaling [60]. Inadequately managed diabetes and concomitant metabolic dysfunctions—including dyslipidemia, heightened oxidative stress, and hypertension [61]—contribute to the development of both microvascular and macrovascular pathologies. Microvascular complications, involving damage to small-caliber vessels, manifest as diabetic nephropathy, neuropathy, and retinopathy. Conversely, macrovascular complications affecting large arteries comprise cerebrovascular disease, coronary artery disease, and peripheral vascular disease [62]. Furthermore, poorly regulated diabetes-driven macrovascular damage may precipitate congestive heart failure, dyslipidemia, stroke, systemic inflammation, increased adiposity, peripheral vascular impairment, and disturbances in electrolyte homeostasis [63].

Extensive research confirms a significant correlation between alterations in gut microbial profiles and diabetes pathogenesis. Specifically, dysbiosis—marked by disrupted Bacteroidetes-to-Firmicutes ratios—is associated with heightened intestinal permeability. This compromised barrier facilitates the translocation of bacterial metabolites, eliciting inflammatory cascades characteristic of diabetes. Conversely, several bacterial species demonstrate protective roles against diabetes development through the mitigation of proinflammatory mediators and the preservation of gut barrier function. Notably, *Lactobacillus fermentum*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Roseburia intestinalis*, *Akkermansia muciniphila*, and *Bacteroides fragilis* collectively enhance glucose homeostasis and insulin sensitiv-

ity while suppressing proinflammatory cytokines. Pharmacological agents like metformin, a cornerstone of diabetes therapy, are recognized to alter gut microbiota composition. This suggests metformin's therapeutic actions involve microbiota crosstalk through modulation of inflammatory pathways, glucose regulation, intestinal permeability, and enrichment of short-chain fatty acid (SCFA)-producing bacteria [64]. In diabetic patients with gut dysbiosis, metformin stimulates butyrate and propionate production, thereby promoting amino acid catabolism [65]. These microbial shifts, coupled with increased gastrointestinal *Akkermansia* abundance, potentially mediate metformin's glucoregulatory benefits [66]. Chronic low-grade inflammation and oxidative stress—metabolic features linking gut dysbiosis to type 2 diabetes—also participate in diabetic complication initiation and progression [67] [68]. This interconnection underscores microbiota modulation as a promising therapeutic avenue for diabetes and its sequelae, which will be elaborated in subsequent sections.

3.1. Intestinal Flora and Diabetic Nephropathy

Diabetic nephropathy (DN, a progressive microvascular complication of diabetes mellitus, characterized histopathologically by glomerular basement membrane thickening, mesangial expansion, nodular glomerulosclerosis, and albuminuria, ultimately leading to a decline in glomerular filtration rate and end-stage renal disease) develops in nearly 40% of individuals with suboptimally managed diabetes [69], of whom approximately 20% necessitate hemodialysis intervention [70]. This pathology frequently progresses to end-stage renal disease (ESRD) and concomitant cardiovascular sequelae [71]. The rising incidence of DN and ESRD correlates strongly with modern lifestyle patterns and behavioral factors implicated in diabetes and hypertension pathogenesis [72] [73]. Emerging evidence indicates gut microbial dysbiosis may play a role in chronic kidney disease (CKD) development [74]. Notably, metabolites derived from gut bacteria influence both CKD initiation and advancement [75], while deteriorating renal function conversely worsens microbial imbalance—establishing a pathological feedback loop [76].

3.2. Intestinal Flora and Diabetic Retinopathy

In suboptimally controlled diabetes, elevated intraocular pressure and vascular glucose accumulation compromise visual function [77]. These pathological processes drive ocular microvascular complications, including cataract formation, glaucoma development, and retinopathy progression [78]. Diabetic retinopathy (DR, a progressive microvascular complication of diabetes mellitus characterized by retinal microvascular damage, including microaneurysms, intraretinal hemorrhages, capillary non-perfusion, and pathological neovascularization, which can lead to macular edema, vitreous hemorrhage, and retinal detachment, ultimately causing vision impairment and blindness)—a vision-threatening consequence of inadequate diabetes management—may ultimately progress to blindness [79]. Pathological features of DR include retinal microglial hyperactivation and immune cell in-

filtration into retinal tissues [80]. Moreover, amplified oxidative stress and inflammatory responses impair renin-angiotensin system (RAS) functionality, thereby potentiating metabolic dysregulation underlying conditions like DR [81]-[87]. Notably, gut microbial dysbiosis has been implicated in the pathogenesis of diabetic retinopathy.

Microbial communities exhibit site-specific compositional differences throughout the body, including ocular tissues. Whereas gut microbiota is predominantly colonized by Firmicutes and Bacteroidetes [88], the ocular surface microbiome is chiefly characterized by Proteobacteria and Actinobacteria [89] [90]. Collectively, these three phyla constitute over 87% of ocular microorganisms [91]. Dysbiosis in either intestinal or ocular surface microbiota correlates with various ophthalmic pathologies. Patients with diabetic retinopathy (DR) demonstrate significantly reduced proportions of Bacteroidetes and Actinobacteria relative to healthy controls. Concurrently, *Acidaminococcus*, *Escherichia*, and *Enterobacter* genera are substantially enriched in DR patients [92]. Recent investigations reveal decreased Mucoromycota filamentation in DR subjects compared to non-afflicted individuals. Similarly, among type 2 diabetics with DR, 12 of 18 microbial genera exhibit depletion [93]. Microbiota-derived metabolites—notably trimethylamine N-oxide (TMAO) from dietary choline—associate with DR pathogenesis. DR patients display elevated plasma TMAO and proinflammatory cytokines versus diabetics without retinopathy, with concentrations correlating with disease severity [94]. Microbiome analyses further identify marked Pasteurellaceae reduction in DR [95]. These collective findings implicate distinct compositional shifts in both gut bacterial and fungal microbiota in diabetic retinopathy development.

3.3. Intestinal Flora and Diabetic Neuropathy

Persistently unmanaged diabetes causes diabetic neuropathy—a neurodegenerative condition involving peripheral nerve damage that manifests as pain and sensory loss [96] [97]. Hallmark pathological features include substantially reduced peripheral innervation, heightened neuroinflammation, demyelination, axonal degeneration, and diminished neural regenerative potential [98]. Affecting ~50% of diabetic patients [97], this disorder impacts multiple physiological systems, contributing to cardiovascular dysfunction, gastrointestinal motility impairment (including gastroparesis), dyshidrosis, and endocrine disturbances. The pathogenesis of diabetic peripheral neuropathy involves interconnected mechanisms: oxidative stress, polyol pathway hyperactivation, and inflammatory cascades [99] [100]. Insulin resistance further contributes to peripheral neuropathic development. Despite being a principal complication of diabetes mellitus, the complete pathomechanisms underlying peripheral diabetic neuropathy remain incompletely elucidated.

Diabetic neuropathy correlates with disrupted gut microbial diversity and elevated pathogenic abundance [101]. Comparative assessment of gut microbiota among diabetic neuropathy patients, non-neuropathic diabetics, and healthy controls demonstrated increased Firmicutes and Actinobacteria, coupled with reduced Bacteroide-

tes in neuropathy subjects relative to both comparator cohorts. At genus resolution, *Bacteroides* and *Faecalibacterium* exhibited depletion, while *Escherichia-Shigella*, *Lachnoclostridium*, *Blautia*, *Megasphaera*, and *Ruminococcus torques* demonstrated enrichment. These microbial perturbations may arise from the pathophysiology of insulin resistance. Notably, *Megasphaera* abundance directly associates with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) scores in diabetic neuropathy patients, indicating an insulin resistance-peripheral neuropathy nexus [101].

3.4. Intestinal Flora and Cerebrovascular Disease

Globally, stroke represents a predominant contributor to disability, with diabetes mellitus constituting a significant risk factor [102]. Suboptimal glycemic control exacerbates cerebrovascular disease progression and elevates mortality [103]. Emerging evidence links gut microbial dysbiosis to stroke occurrence [104], potentially mediated through microbiota's endocrine, neural, and immunomodulatory interactions with the central nervous system that directly modulate neurochemistry [105].

Trimethylamine-N-oxide (TMAO), previously referenced, remains extensively investigated in gut microbiota-stroke pathophysiology. This metabolite originates from phosphatidylcholine and L-carnitine conversion to trimethylamine, followed by hepatic oxidation via flavin monooxygenases [106]. Although associations between TMAO, atherosclerosis, and stroke risk are established, the mechanistic underpinnings remain incompletely characterized. TMAO concentrations significantly correlate with proinflammatory intermediate monocytes, potentially promoting monocyte-mediated inflammatory responses [107]. Additional proposed pathways connecting TMAO to cerebrovascular events include: Potentiation of platelet hyperreactivity [108], disruption of cholesterol homeostasis [109], and acceleration of foam cell formation [110]. TMAO further associates with established ischemic stroke risk factors, including atrial fibrillation [111] and diabetes mellitus [112].

3.5. Intestinal Flora and Coronary Heart Disease

Nowadays, coronary artery disease (CAD) represents the primary contributor to disease burden and mortality, while also serving as a crucial prognostic indicator for long-term outcomes in diabetic patients. Individuals with diabetes and concomitant heart disease exhibit a 2- to 4-fold elevated mortality risk [113]. Substantial evidence confirms gut microbiota's pivotal involvement in fundamental metabolic pathways—particularly cholesterol and uric acid homeostasis—while concurrently modulating oxidative stress and inflammatory cascades through bioactive metabolites implicated in atherogenesis and coronary heart disease pathogenesis [114].

Overall, while associations between gut dysbiosis and various T2DM complications are increasingly established, the current evidence is largely correlative, and

definitive causal mechanisms, as well as the therapeutic potential of targeting these microbial pathways, require further rigorous investigation (Figure 3).

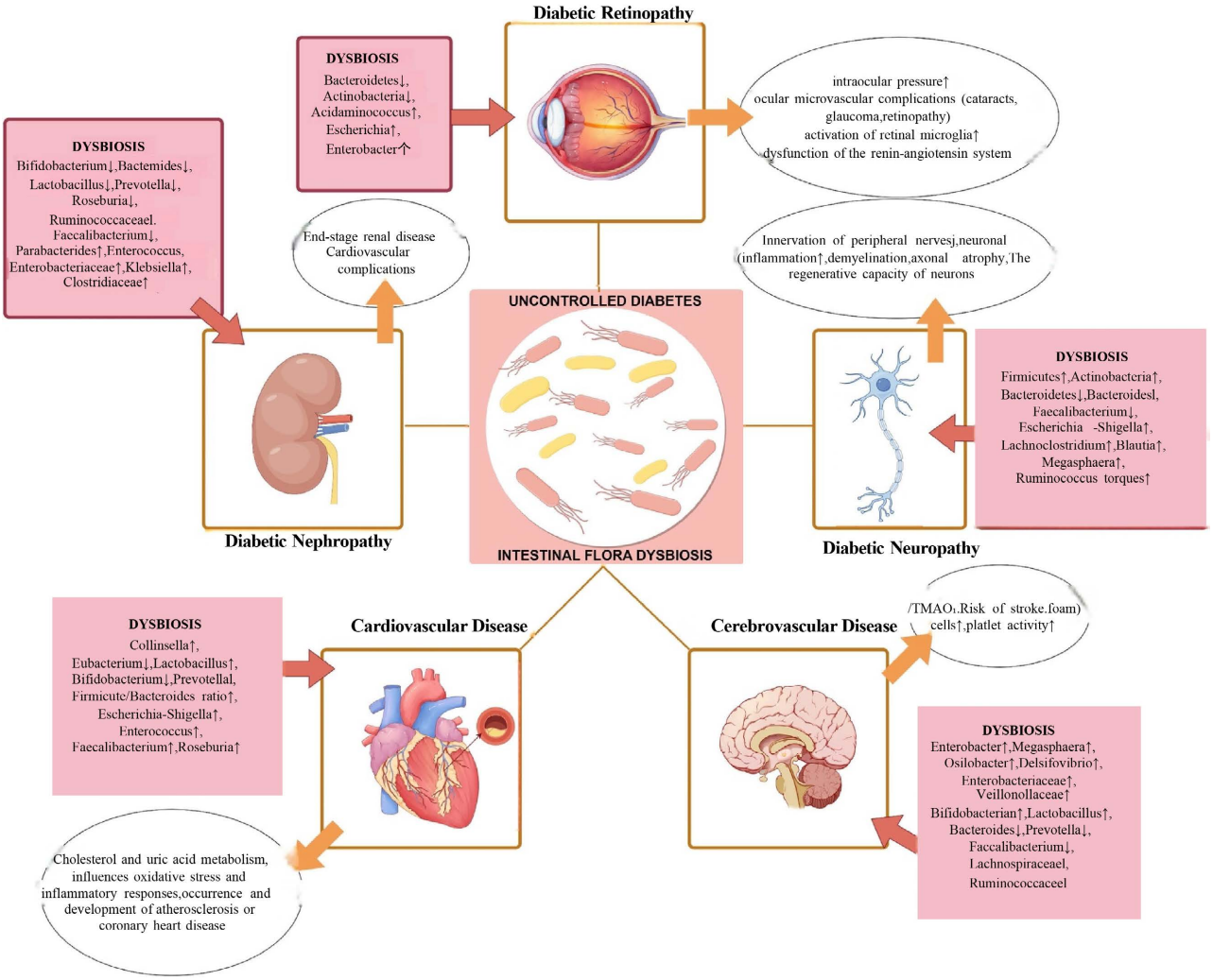

Figure 3. The physiological changes induced by gut bacteria in T2DM are classified by systems.

4. Management and Treatment of Diabetes in Relation to Gut Microbiota

Gut microbiota modulation offers promising therapeutic avenues for diabetes management. Fecal microbiota transplantation (FMT) demonstrates potential for enhancing insulin sensitivity, though outcomes exhibit interstudy variability and long-term efficacy remains undetermined. Metformin's glucose-regulating effects are partially mediated by microbial compositional shifts, while probiotics, prebiotics, and their synergistic combinations (symbiotics) collectively improve glycemic regulation and attenuate inflammatory responses. Dietary interventions like intermittent fasting (IF) and fasting-mimicking diets (FMDs) may ameliorate diabetic parameters through gut microbial restructuring. Novel biotherapeutic approaches—including genetically engineered bacteria and bacteriophage-based

therapies—represent precision-targeted modalities for future diabetes interventions.

4.1. Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) has emerged as a significant investigative modality in gut microbiome research, garnering substantial attention for elucidating microbial roles across disease states. While most clinical trials have prioritized Clostridium difficile infections with favorable outcomes [115] [116], this foundation has prompted exploration of FMT as a therapeutic intervention for type 2 diabetes (T2D) [117]. Rodent studies demonstrate notable metabolic improvements following microbiota transfer: MyD88-deficient NOD mice exhibited enhanced insulin sensitivity [118]; db/db diabetic mice receiving microbiota from healthy Chinese donors showed reduced fasting glycemia [119]; Germ-free murine models transplanted with microbiota from metformin-treated patients developed improved glucose tolerance [120]. Preliminary human studies suggest lean-donor FMT may boost insulin sensitivity, potentially mediated by enrichment of butyrate-producing taxa [117]. In metabolic syndrome patients, lean-donor FMT outperformed autologous transplantation in male recipients, with insulin sensitivity enhancements observed at 6-week follow-up [121]. Contrastingly, FMT from vegan donors—despite distinctive microbial signatures [122]—failed to reduce recipient TMAO levels [123], underscoring outcome variability. The intervention's long-term efficacy, safety profile, and sustained clinical effects remain inadequately characterized, warranting expanded investigation. A study found that repeated FMT treatments, especially when combined with lifestyle intervention, led to a significantly higher proportion of patients acquiring beneficial donor microbiota compared to the control group. This successful engraftment resulted in specific beneficial changes, such as an increase in butyrate-producing bacteria, and was associated with clinical improvements, including reduced cholesterol and liver stiffness.

4.2. Anti-Diabetic Drugs

Metformin represents a cornerstone therapeutic for type 2 diabetes (T2D), with emerging evidence implicating gut microbiota in its antihyperglycemic mechanism. The gut's essential role is highlighted by observations that intravenous metformin administration—unlike oral delivery—fails to reduce hyperglycemia, underscoring enteric microbial involvement in its efficacy [124]. Metformin consistently restructures gut microbial communities in both preclinical models and humans, driving compositional shifts toward healthier profiles [121] [125] [126]. Notably, these alterations occur irrespective of glycemic outcomes, suggesting microbiota remodeling represents a glucose-independent effect. Specific taxonomic changes include: Enriched taxa: *Akkermansia muciniphila*, *Bifidobacterium bifidum*, *Escherichia* spp., *Lactobacillus* spp., *Shigella* spp. Depleted taxa: *Clostridium* spp., *Intestinibacter* spp. [121] [127] [128]. These compositional shifts associate with functional modifications in short-chain fatty acid (SCFA) biosynthetic path-

ways—particularly butyrate and propionate production [129] [130]. Metformin further enhances metabolic function through: Bile acid metabolism regulation, Gut barrier fortification, Endotoxemia reduction, Stimulated GLP-1 and PYY secretion [131]. Additionally, it lowers circulating TMAO by suppressing trimethylamine-producing bacteria [132]. Transfer of metformin-modified microbiota confers metabolic benefits to recipient animals, demonstrating therapeutic transmissibility [121]. Contradictory evidence exists regarding microbiota dependency: microbiota ablation failed to abolish metformin's T2D benefits in some models [133]. While microbial contributions remain subject to ongoing debate, metformin's intrinsic anti-inflammatory properties may independently mediate therapeutic effects.

4.3. Probiotics

Probiotics, live microorganisms that confer health benefits, have attracted attention in T2D management, although clinical studies remain limited. Preliminary findings suggest that altering gut microbiota composition via probiotic supplementation may improve T2D outcomes by reducing inflammation, intestinal permeability, and oxidative stress. Common probiotics include *Bifidobacterium longum* subsp. *infantis*, *Lactobacillus*, *Streptococcus*, *Pediococcus*, and *Lactococcus* species [134]. Several species, such as *L. gasseri*, *Lactobacillus helveticus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*, have been shown to lower fasting blood glucose and HbA1c levels [135]-[137]. Probiotics exhibit antioxidant and immunomodulatory properties by mitigating oxidative stress and inflammatory cytokines, which may help reduce blood glucose levels and T2D risk [138]. A recent meta-analysis revealed that probiotic supplementation significantly improves fasting blood glucose, HbA1c levels, and insulin resistance. Therefore, probiotics may serve as a complementary strategy to pharmacological treatments and lifestyle interventions for managing T2D [139] [140].

4.4. Prebiotics

Prebiotics constitute indigestible dietary substrates that confer host benefits through selective stimulation of beneficial gut microorganisms [141]. Inulin—an extensively researched prebiotic—improves glycemic regulation by stimulating colonic GLP-1 secretion and suppressing plasma ghrelin in preclinical models [142]. Nevertheless, direct effects of inulin supplementation on human type 2 diabetes (T2D) demonstrate inconsistent clinical evidence. Divergent findings exist: certain studies report reductions in fasting glucose, HbA1c, and inflammatory markers among T2D patients, while others show negligible metabolic impact. Beyond glycemic modulation, inulin and similar prebiotics modify gut microbial ecology by enriching beneficial taxa, including Bifidobacterium and *Bacteroides*. Synergistic combinations of prebiotics with probiotics (termed symbiotics) potentiate beneficial effects beyond monotherapeutic approaches. Research indicates specific probiotic-inulin pairings elevate butyrate generation beyond isolated interventions.

Clinically, symbiotic formulations improve fasting glycemia and HbA1c levels, suggesting potential for T2D risk mitigation.

4.5. Intermittent Fasting (IF)

Intermittent fasting (IF), defined by cyclic caloric restriction, extends longevity and attenuates age-related disease risk—including type 2 diabetes (T2D)—in experimental models [143]. Preclinical studies demonstrate enhancements in body composition, glycemic control, and inflammatory markers, with gut microbiota mediating these benefits [144] [145]. Human evidence, however, exhibits limited consensus. Recent murine research demonstrated that IF restructured gut microbial communities in diabetic models, enriching beneficial taxa while depleting pathogenic organisms [146]. This microbial reorganization correlated with enhanced glycemic regulation and insulin sensitivity. Fasting-mimicking diets (FMDs)—designed to pharmacologically emulate IF effects—similarly demonstrated capacity to reconstruct gut microbiota and improve insulin responsiveness. Collectively, these findings propose that IF may ameliorate T2D pathophysiology through microbiota modulation, though longitudinal human trials are required to establish sustained efficacy.

4.6. Engineering Bacteria and Phages

Synthetic biology has enabled the engineering of bacteria for therapeutic purposes. For example, engineered **Lactobacillus reuteri** can produce interleukin-22 (IL-22), enhancing gut defense mechanisms and providing resistance against bacterial infections [147]. Engineered **Lactobacillus gasseri** secreting GLP-1 has shown promise in lowering blood glucose in diabetic rats. Similarly, **Escherichia coli** modified to secrete GLP-1 or PDX-1 can induce insulin secretion in response to glucose [148]. Bacteriophages, which specifically target bacteria, are also being explored as tools to manipulate gut microbiota [149]. Fecal virome transplantation has been shown to alter gut microbiota composition and improve metabolic outcomes, suggesting a potential role for phages in T2D management [150]. These approaches hold promise for the development of targeted microbial therapies for T2D in future clinical applications.

Overall, while these microbiota-targeting interventions show considerable promise, their clinical translation is often constrained by limited large-scale human trials, incomplete understanding of underlying mechanisms, and interindividual variability in treatment responses [151].

Another clinical study shows that Fecal Microbiota Transplantation (FMT) demonstrates a direct and beneficial impact on type 2 diabetes (T2D) by significantly improving insulin resistance (HOMA-IR) and reducing body mass index (BMI) in patients. The engraftment of donor microbiota successfully altered the gut microbial community, increasing its diversity and showing a significant correlation with clinical improvements. Notably, specific bacteria that colonized after FMT were negatively associated with insulin resistance, underscoring a mecha-

nistic link between microbiota changes and T2D metabolic enhancement [152].

5. Conclusion

This study highlights the significant influence of gut microbiota on insulin resistance, glucose metabolism, and inflammation in T2DM, exploring therapies like fecal microbiota transplantation (FMT), probiotics, prebiotics, and metformin. While these approaches show potential for improving insulin sensitivity and managing glycemic levels, inconsistencies in results and long-term effects suggest the need for more comprehensive research. Future research should focus on large-scale, longitudinal human studies to better understand the sustained impacts of gut microbiota interventions, the optimal compositions of beneficial bacteria, and the integration of personalized microbiome-based therapies for diabetes management. Additionally, investigations into the role of engineered bacteria and phages could provide targeted approaches to restoring healthy microbiota and mitigating complications associated with T2DM.

Authors' Contributions

Shuran Liu contributed mostly to this work; Shuran Liu conceptualized and designed the study, created the artwork, supervised, and made critical revisions, conducted the literature review, did the analysis, interpretation of data, and drafted the original manuscript; Alex Zhu finished the total abstract of the paper. All authors prepared and approved the submitted version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Song, S. and Lee, J.E. (2018) Dietary Patterns Related to Triglyceride and High-Density Lipoprotein Cholesterol and the Incidence of Type 2 Diabetes in Korean Men and Women. *Nutrients*, **11**, Article No. 8. https://doi.org/10.3390/nu11010008

[2] Jeon, J., Jang, J. and Park, K. (2018) Effects of Consuming Calcium-Rich Foods on the Incidence of Type 2 Diabetes Mellitus. *Nutrients*, **11**, Article No. 31. https://doi.org/10.3390/nu11010031

[3] Qin, J.J., Li, Y.R., Cai, Z.M., Li, S.H., Zhu, J.F., Zhang, F., *et al.* (2012) A Metagenome-Wide Association Study of Gut Microbiota in Type 2 Diabetes. *Nature*, **490**, 55-60. https://www.nature.com/articles/nature11450

[4] Cox, L.M. and Blaser, M.J. (2014) Antibiotics in Early Life and Obesity. *Nature Reviews Endocrinology*, **11**, 182-190. https://doi.org/10.1038/nrendo.2014.210

[5] Gilbert, J.A., Blaser, M.J., Caporaso, J.G., Jansson, J., Lynch, S.V. and Knight, R. (2018) Current Understanding of the Human Microbiome. *Nature Medicine*, **24**, 392-400. https://www.nature.com/articles/nm.4517

[6] Manrique, P., Bolduc, B., Walk, S.T., van der Oost, J., de Vos, W.M. and Young, M.J. (2016) Healthy Human Gut Phageome. *Proceedings of the National Academy of Sciences*, **113**, 10400-10405. https://doi.org/10.1073/pnas.1601060113

[7] Bajzer, M. and Seeley, R.J. (2006) Obesity and Gut Flora. *Nature*, **444**, 1009-1010. https://www.nature.com/articles/4441009a

[8] Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R. and Gordon, J.I. (2006) An Obesity-Associated Gut Microbiome with Increased Capacity for Energy Harvest. *Nature*, **444**, 1027-1031. https://doi.org/10.1038/nature05414

[9] Yano, J.M., Yu, K., Donaldson, G.P., Shastri, G.G., Ann, P., Ma, L., *et al.* (2015) Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. *Cell*, **161**, 264-276. https://doi.org/10.1016/j.cell.2015.02.047

[10] Zhang, C., Zhang, M., Wang, S., Han, R., Cao, Y., Hua, W., *et al.* (2009) Interactions between Gut Microbiota, Host Genetics and Diet Relevant to Development of Metabolic Syndromes in Mice. *The ISME Journal*, **4**, 232-241. https://doi.org/10.1038/ismej.2009.112

[11] Ma, Q., Li, Y., Li, P., Wang, M., Wang, J., Tang, Z., *et al.* (2019) Research Progress in the Relationship between Type 2 Diabetes Mellitus and Intestinal Flora. *Biomedicine & Pharmacotherapy*, **117**, Article ID: 109138. https://doi.org/10.1016/j.biopha.2019.109138

[12] Tremaroli, V. and Bäckhed, F. (2012) Functional Interactions between the Gut Microbiota and Host Metabolism. *Nature*, **489**, 242-249. https://www.nature.com/articles/nature11552

[13] Furet, J., Firmesse, O., Gourmelon, M., Bridonneau, C., Tap, J., Mondot, S., *et al.* (2009) Comparative Assessment of Human and Farm Animal Faecal Microbiota Using Real-Time Quantitative PCR. *FEMS Microbiology Ecology*, **68**, 351-362. https://doi.org/10.1111/j.1574-6941.2009.00671.x

[14] Adak, A. and Khan, M.R. (2019) An Insight into Gut Microbiota and Its Functionalities. *Cellular and Molecular Life Sciences*, **76**, 473-493. https://doi.org/10.1007/s00018-018-2943-4

[15] Li, L.Y., Pan, M., Pan, S.J., Li, W., Zhong, Y.D., Hu, J.L. and Nie, S.P. (2020) Effects of Insoluble and Soluble Fibers Isolated from Barley on Blood Glucose, Serum Lipids, Liver Function and Caecal Short-Chain Fatty Acids in Type 2 Diabetic and Normal Rats. *Food and Chemical Toxicology*, **135**, Article ID: 110937. https://www.sciencedirect.com/science/article/abs/pii/S0278691519307276?via%3Dihub

[16] Cao, Y., Yao, G., Sheng, Y., Yang, L., Wang, Z., Yang, Z., *et al.* (2019) JinQi Jiangtang Tablet Regulates Gut Microbiota and Improve Insulin Sensitivity in Type 2 Diabetes Mice. *Journal of Diabetes Research*, **2019**, Article ID: 1872134. https://doi.org/10.1155/2019/1872134

[17] Adachi, K., Sugiyama, T., Yamaguchi, Y., Tamura, Y., Izawa, S., Hijikata, Y., *et al.* (2019) Gut Microbiota Disorders Cause Type 2 Diabetes Mellitus and Homeostatic Disturbances in Gut-Related Metabolism in Japanese Subjects. *Journal of Clinical Biochemistry and Nutrition*, **64**, 231-238. https://doi.org/10.3164/jcbn.18-101

[18] Canfora, E.E., Jocken, J.W. and Blaak. E.E. (2015) Short-Chain Fatty Acids in Control of Body Weight and Insulin Sensitivity. *Nature Reviews Endocrinology*, **11**, 577-591. https://www.nature.com/articles/nrendo.2015.128

[19] Mandaliya, D.K. and Seshadri, S. (2019) Short Chain Fatty Acids, Pancreatic Dysfunction and Type 2 Diabetes. *Pancreatology*, **19**, 280-284. https://doi.org/10.1016/j.pan.2019.01.021

[20] Yamaguchi, Y., Adachi, K., Sugiyama, T., Shimozato, A., Ebi, M., Ogasawara, N., *et al.* (2016) Association of Intestinal Microbiota with Metabolic Markers and Dietary Habits in Patients with Type 2 Diabetes. *Digestion*, **94**, 66-72.

https://doi.org/10.1159/000447690

[21] Pingitore, A., Chambers, E.S., Hill, T., Maldonado, I.R., Liu, B., Bewick, G., *et al.* (2016) The Diet-Derived Short Chain Fatty Acid Propionate Improves Beta-Cell Function in Humans and Stimulates Insulin Secretion from Human Islets *in Vitro*. *Diabetes, Obesity and Metabolism*, **19**, 257-265. https://doi.org/10.1111/dom.12811

[22] Gao, Z., Yin, J., Zhang, J., Ward, R.E., Martin, R.J., Lefevre, M., *et al.* (2009) Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. *Diabetes*, **58**, 1509-1517. https://doi.org/10.2337/db08-1637

[23] Sanna, S., van Zuydam, N.R., Mahajan, A., Kurilshikov, A., Vich Vila, A., Võsa, U., *et al.* (2019) Causal Relationships among the Gut Microbiome, Short-Chain Fatty Acids and Metabolic Diseases. *Nature Genetics*, **51**, 600-605. https://doi.org/10.1038/s41588-019-0350-x

[24] De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchampt, A., *et al.* (2014) Microbiota-Generated Metabolites Promote Metabolic Benefits via Gut-Brain Neural Circuits. *Cell*, **156**, 84-96. https://doi.org/10.1016/j.cell.2013.12.016

[25] Dalile, B., Van Oudenhove, L., Vervliet, B. and Verbeke, K. (2019) The Role of Short-Chain Fatty Acids in Microbiota-Gut-Brain Communication. *Nature Reviews Gastroenterology & Hepatology*, **16**, 461-478. https://doi.org/10.1038/s41575-019-0157-3

[26] Dorsam, R.T. and Gutkind, J.S. (2007) G-Protein-Coupled Receptors and Cancer. *Nature Reviews Cancer*, **7**, 79-94. https://doi.org/10.1038/nrc2069

[27] Tolhurst, G., Heffron, H., Lam, Y.S., Parker, H.E., Habib, A.M., Diakogiannaki, E., *et al.* (2012) Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein-Coupled Receptor FFAR2. *Diabetes*, **61**, 364-371. https://doi.org/10.2337/db11-1019

[28] Larraufie, P., Martin-Gallausiaux, C., Lapaque, N., Dore, J., Gribble, F.M., Reimann, F., *et al.* (2018) SCFAs Strongly Stimulate PYY Production in Human Enteroendocrine Cells. *Scientific Reports*, **8**, Article No. 74. https://doi.org/10.1038/s41598-017-18259-0

[29] Xiong, Y., Miyamoto, N., Shibata, K., Valasek, M.A., Motoike, T., Kedzierski, R.M., *et al.* (2004) Short-Chain Fatty Acids Stimulate Leptin Production in Adipocytes through the G Protein-Coupled Receptor Gpr41. *Proceedings of the National Academy of Sciences*, **101**, 1045-1050. https://doi.org/10.1073/pnas.2637002100

[30] Al-Lahham, S.H., Roelofsen, H., Priebe, M., Weening, D., Dijkstra, M., Hoek, A., *et al.* (2010) Regulation of Adipokine Production in Human Adipose Tissue by Propionic Acid. *European Journal of Clinical Investigation*, **40**, 401-407. https://doi.org/10.1111/j.1365-2362.2010.02278.x

[31] Canfora, E.E., van der Beek, C.M., Jocken, J.W.E., Goossens, G.H., Holst, J.J., Olde Damink, S.W.M., *et al.* (2017) Colonic Infusions of Short-Chain Fatty Acid Mixtures Promote Energy Metabolism in Overweight/Obese Men: A Randomized Crossover Trial. *Scientific Reports*, **7**, Article No. 2360. https://doi.org/10.1038/s41598-017-02546-x

[32] Sorbara, M.T., Dubin, K., Littmann, E.R., Moody, T.U., Fontana, E., Seok, R., *et al.* (2018) Inhibiting Antibiotic-Resistant Enterobacteriaceae by Microbiota-Mediated Intracellular Acidification. *Journal of Experimental Medicine*, **216**, 84-98. https://doi.org/10.1084/jem.20181639

[33] Koh, A., De Vadder, F., Kovatcheva-Datchary, P. and Bäckhed, F. (2016) From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites.

Cell, **165**, 1332-1345. https://doi.org/10.1016/j.cell.2016.05.041

[34] Sawicki, C., Livingston, K., Obin, M., Roberts, S., Chung, M. and McKeown, N. (2017) Dietary Fiber and the Human Gut Microbiota: Application of Evidence Mapping Methodology. *Nutrients*, **9**, 125-145. https://doi.org/10.3390/nu9020125

[35] Chambers, E.S., Viardot, A., Psichas, A., Morrison, D.J., Murphy, K.G., Zac-Varghese, S.E.K., *et al.* (2014) Effects of Targeted Delivery of Propionate to the Human Colon on Appetite Regulation, Body Weight Maintenance and Adiposity in Overweight Adults. *Gut*, **64**, 1744-1754. https://doi.org/10.1136/gutjnl-2014-307913

[36] Ohira, H., Fujioka, Y., Katagiri, C., Mamoto, R., Aoyama-Ishikawa, M., Amako, K., *et al.* (2013) Butyrate Attenuates Inflammation and Lipolysis Generated by the Interaction of Adipocytes and Macrophages. *Journal of Atherosclerosis and Thrombosis*, **20**, 425-442. https://doi.org/10.5551/jat.15065

[37] Al-Lahham, S., Roelofsen, H., Rezaee, F., Weening, D., Hoek, A., Vonk, R., *et al.* (2011) Propionic Acid Affects Immune Status and Metabolism in Adipose Tissue from Overweight Subjects. *European Journal of Clinical Investigation*, **42**, 357-364. https://doi.org/10.1111/j.1365-2362.2011.02590.x

[38] de Aguiar Vallim, T.Q., Tarling, E.J. and Edwards, P.A. (2013) Pleiotropic Roles of Bile Acids in Metabolism. *Cell Metabolism*, **17**, 657-669. https://doi.org/10.1016/j.cmet.2013.03.013

[39] Jia, W., Xie, G. and Jia, W. (2017) Bile Acid-Microbiota Crosstalk in Gastrointestinal Inflammation and Carcinogenesis. *Nature Reviews Gastroenterology & Hepatology*, **15**, 111-128. https://doi.org/10.1038/nrgastro.2017.119

[40] Wahlström, A., Sayin, S.I., Marschall, H. and Bäckhed, F. (2016) Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. *Cell Metabolism*, **24**, 41-50. https://doi.org/10.1016/j.cmet.2016.05.005

[41] Xu, J., Wang, N., Yang, L., Zhong, J. and Chen, M. (2024) Intestinal Flora and Bile Acid Interactions Impact the Progression of Diabetic Kidney Disease. *Frontiers in Endocrinology*, **15**, Article ID: 1441415. https://doi.org/10.3389/fendo.2024.1441415

[42] Gérard, P. (2013) Metabolism of Cholesterol and Bile Acids by the Gut Microbiota. *Pathogens*, **3**, 14-24. https://doi.org/10.3390/pathogens3010014

[43] Lefebvre, P., Cariou, B., Lien, F., Kuipers, F. and Staels, B. (2009) Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation. *Physiological Reviews*, **89**, 147-191. https://doi.org/10.1152/physrev.00010.2008

[44] Guarner, F. and Malagelada, J. (2003) Gut Flora in Health and Disease. *The Lancet*, **361**, 512-519. https://doi.org/10.1016/s0140-6736(03)12489-0

[45] Fiorucci, S. and Distrutti, E. (2015) Bile Acid-Activated Receptors, Intestinal Microbiota, and the Treatment of Metabolic Disorders. *Trends in Molecular Medicine*, **21**, 702-714. https://doi.org/10.1016/j.molmed.2015.09.001

[46] Hodge, R.J. and Nunez, D.J. (2016) Therapeutic Potential of Takeda-G-Protein-Receptor-5 (TGR5) Agonists. Hope or Hype? *Diabetes, Obesity and Metabolism*, **18**, 439-443. https://doi.org/10.1111/dom.12636

[47] Shapiro, H., Kolodziejczyk, A.A., Halstuch, D. and Elinav, E. (2018) Bile Acids in Glucose Metabolism in Health and Disease. *Journal of Experimental Medicine*, **215**, 383-396. https://doi.org/10.1084/jem.20171965

[48] Thomas, C., Gioiello, A., Noriega, L., Strehle, A., Oury, J., Rizzo, G., *et al.* (2009) TGR5-Mediated Bile Acid Sensing Controls Glucose Homeostasis. *Cell Metabolism*, **10**, 167-177. https://doi.org/10.1016/j.cmet.2009.08.001

[49] Kumar, D.P., Asgharpour, A., Mirshahi, F., Park, S.H., Liu, S., Imai, Y., *et al.* (2016)

Activation of Transmembrane Bile Acid Receptor TGR5 Modulates Pancreatic Islet α Cells to Promote Glucose Homeostasis. *Journal of Biological Chemistry*, **291**, 6626-6640. https://doi.org/10.1074/jbc.m115.699504

[50] Holst, J.J. (2007) The Physiology of Glucagon-Like Peptide 1. *Physiological Reviews*, **87**, 1409-1439. https://doi.org/10.1152/physrev.00034.2006

[51] Prawitt, J., Abdelkarim, M., Stroeve, J.H.M., Popescu, I., Duez, H., Velagapudi, V.R., *et al.* (2011) Farnesoid X Receptor Deficiency Improves Glucose Homeostasis in Mouse Models of Obesity. *Diabetes*, **60**, 1861-1871. https://doi.org/10.2337/db11-0030

[52] Zhang, Y., Lee, F.Y., Barrera, G., Lee, H., Vales, C., Gonzalez, F.J., *et al.* (2006) Activation of the Nuclear Receptor FXR Improves Hyperglycemia and Hyperlipidemia in Diabetic Mice. *Proceedings of the National Academy of Sciences*, **103**, 1006-1011. https://doi.org/10.1073/pnas.0506982103

[53] Fang, S., Suh, J.M., Reilly, S.M., Yu, E., Osborn, O., Lackey, D., *et al.* (2015) Intestinal FXR Agonism Promotes Adipose Tissue Browning and Reduces Obesity and Insulin Resistance. *Nature Medicine*, **21**, 159-165. https://doi.org/10.1038/nm.3760

[54] Kir, S., Beddow, S.A., Samuel, V.T., Miller, P., Previs, S.F., Suino-Powell, K., *et al.* (2011) FGF19 as a Postprandial, Insulin-Independent Activator of Hepatic Protein and Glycogen Synthesis. *Science*, **331**, 1621-1624. https://doi.org/10.1126/science.1198363

[55] Potthoff, M.J., Boney-Montoya, J., Choi, M., He, T., Sunny, N.E., Satapati, S., *et al.* (2011) FGF15/19 Regulates Hepatic Glucose Metabolism by Inhibiting the CREB-PGC-1α Pathway. *Cell Metabolism*, **13**, 729-738. https://doi.org/10.1016/j.cmet.2011.03.019

[56] Sun, L., Xie, C., Wang, G., Wu, Y., Wu, Q., Wang, X., *et al.* (2018) Gut Microbiota and Intestinal FXR Mediate the Clinical Benefits of Metformin. *Nature Medicine*, **24**, 1919-1929. https://doi.org/10.1038/s41591-018-0222-4

[57] Jiang, C., Xie, C., Lv, Y., Li, J., Krausz, K.W., Shi, J., *et al.* (2015) Intestine-Selective Farnesoid X Receptor Inhibition Improves Obesity-Related Metabolic Dysfunction. *Nature Communications*, **6**, Article No. 10166. https://doi.org/10.1038/ncomms10166

[58] Xie, C., Jiang, C., Shi, J., Gao, X., Sun, D., Sun, L., *et al.* (2016) An Intestinal Farnesoid X Receptor-Ceramide Signaling Axis Modulates Hepatic Gluconeogenesis in Mice. *Diabetes*, **66**, 613-626. https://doi.org/10.2337/db16-0663

[59] Trabelsi, M., Daoudi, M., Prawitt, J., Ducastel, S., Touche, V., Sayin, S.I., *et al.* (2015) Farnesoid X Receptor Inhibits Glucagon-Like Peptide-1 Production by Enteroendocrine L Cells. *Nature Communications*, **6**, Article No. 7629. https://doi.org/10.1038/ncomms8629

[60] DeFronzo, R.A. (2010) Overview of Newer Agents: Where Treatment Is Going. *The American Journal of Medicine*, **123**, S38-S48. https://doi.org/10.1016/j.amjmed.2009.12.008

[61] Bekyarova, G.Y., Ivanova, D.G. and Madjova, V.H. (2007) Molecular Mechanisms Associating Oxidative Stress with Endothelial Dysfunction in the Development of Various Vascular Complications in Diabetes Mellitus. *Folia Medica*, **49**, 13-19.

[62] Baig, M.A. and Panchal, S.S. (2019) Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into Its Applications to Induce Diabetic Complications. *Current Diabetes Reviews*, **16**, 26-39. https://doi.org/10.2174/1573399815666190411115829

[63] Gourgari, E., Dabelea, D. and Rother, K. (2017) Modifiable Risk Factors for Cardiovascular Disease in Children with Type 1 Diabetes: Can Early Intervention Prevent

Future Cardiovascular Events? *Current Diabetes Reports*, **17**, Article No. 134. https://doi.org/10.1007/s11892-017-0968-y

[64] Lee, C.B., Chae, S.U., Jo, S.J., Jerng, U.M. and Bae, S.K. (2021) The Relationship between the Gut Microbiome and Metformin as a Key for Treating Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, **22**, Article No. 3566. https://doi.org/10.3390/ijms22073566

[65] Mardinoglu, A., Boren, J. and Smith, U. (2016) Confounding Effects of Metformin on the Human Gut Microbiome in Type 2 Diabetes. *Cell Metabolism*, **23**, 10-12. https://doi.org/10.1016/j.cmet.2015.12.012

[66] Wu, H., Esteve, E., Tremaroli, V., Khan, M.T., Caesar, R., Mannerås-Holm, L., *et al.* (2017) Metformin Alters the Gut Microbiome of Individuals with Treatment-Naive Type 2 Diabetes, Contributing to the Therapeutic Effects of the Drug. *Nature Medicine*, **23**, 850-858. https://doi.org/10.1038/nm.4345

[67] Fernandes, R., Viana, S.D., Nunes, S. and Reis, F. (2019) Diabetic Gut Microbiota Dysbiosis as an Inflammaging and Immunosenescence Condition That Fosters Progression of Retinopathy and Nephropathy. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1865**, 1876-1897. https://doi.org/10.1016/j.bbadis.2018.09.032

[68] Chen, W., Zhang, M., Guo, Y., Wang, Z., Liu, Q., Yan, R., *et al.* (2021) The Profile and Function of Gut Microbiota in Diabetic Nephropathy. *Diabetes, Metabolic Syndrome and Obesity*: *Targets and Therapy*, **14**, 4283-4296. https://doi.org/10.2147/dmso.s320169

[69] Gross, J.L., de Azevedo, M.J., Silveiro, S.P., Canani, L.H., Caramori, M.L. and Zelmanovitz, T. (2005) Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. *Diabetes Care*, **28**, 164-176. https://doi.org/10.2337/diacare.28.1.164

[70] Gupta, A., Gupta, P. and Biyani, M. (2011) Targeted Therapies in Diabetic Nephropathy: An Update. *Journal of Nephrology*, **24**, 686-695. https://doi.org/10.5301/jn.5000041

[71] Ritz, E. (1999) Nephropathy in Type 2 Diabetes. *Journal of Internal Medicine*, **245**, 111-126. https://doi.org/10.1046/j.1365-2796.1999.00411.x

[72] Sabatino, A., Regolisti, G., Cosola, C., Gesualdo, L. and Fiaccadori, E. (2017) Intestinal Microbiota in Type 2 Diabetes and Chronic Kidney Disease. *Current Diabetes Reports*, **17**, Article No. 16. https://doi.org/10.1007/s11892-017-0841-z

[73] Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., *et al.* (2013) Chronic Kidney Disease: Global Dimension and Perspectives. *The Lancet*, **382**, 260-272. https://doi.org/10.1016/s0140-6736(13)60687-x

[74] Ramezani, A., Massy, Z.A., Meijers, B., Evenepoel, P., Vanholder, R. and Raj, D.S. (2016) Role of the Gut Microbiome in Uremia: A Potential Therapeutic Target. *American Journal of Kidney Diseases*, **67**, 483-498. https://doi.org/10.1053/j.ajkd.2015.09.027

[75] Mahmoodpoor, F., Rahbar Saadat, Y., Barzegari, A., Ardalan, M. and Zununi Vahed, S. (2017) The Impact of Gut Microbiota on Kidney Function and Pathogenesis. *Biomedicine & Pharmacotherapy*, **93**, 412-419. https://doi.org/10.1016/j.biopha.2017.06.066

[76] Vaziri, N.D., Yuan, J., Nazertehrani, S., Ni, Z. and Liu, S. (2013) Chronic Kidney Disease Causes Disruption of Gastric and Small Intestinal Epithelial Tight Junction. *American Journal of Nephrology*, **38**, 99-103. https://doi.org/10.1159/000353764

[77] Lin, K., Hsih, W., Lin, Y., Wen, C. and Chang, T. (2021) Update in the Epidemiology, Risk Factors, Screening, and Treatment of Diabetic Retinopathy. *Journal of Diabetes*

Investigation, **12**, 1322-1325. https://doi.org/10.1111/jdi.13480

[78] Papatheodorou, K., Papanas, N., Banach, M., Papazoglou, D. and Edmonds, M. (2016) Complications of Diabetes 2016. *Journal of Diabetes Research*, **2016**, Article ID: 6989453. https://doi.org/10.1155/2016/6989453

[79] Lee, R., Wong, T.Y. and Sabanayagam, C. (2015) Epidemiology of Diabetic Retinopathy, Diabetic Macular Edema and Related Vision Loss. *Eye and Vision*, **2**, Article No. 17. https://doi.org/10.1186/s40662-015-0026-2

[80] Beli, E., Yan, Y., Moldovan, L., Vieira, C.P., Gao, R., Duan, Y., *et al.* (2018) Restructuring of the Gut Microbiome by Intermittent Fasting Prevents Retinopathy and Prolongs Survival in *db*/*db* Mice. *Diabetes*, **67**, 1867-1879. https://doi.org/10.2337/db18-0158

[81] Bader, M. (2010) Tissue Renin-Angiotensin-Aldosterone Systems: Targets for Pharmacological Therapy. *Annual Review of Pharmacology and Toxicology*, **50**, 439-465. https://doi.org/10.1146/annurev.pharmtox.010909.105610

[82] Das, A. (2016) Diabetic Retinopathy: Battling the Global Epidemic. *Investigative Opthalmology & Visual Science*, **57**, 6669-6682. https://doi.org/10.1167/iovs.16-21031

[83] Dominguez, J.M., Hu, P., Caballero, S., Moldovan, L., Verma, A., Oudit, G.Y., *et al.* (2016) Adeno-Associated Virus Overexpression of Angiotensin-Converting Enzyme-2 Reverses Diabetic Retinopathy in Type 1 Diabetes in Mice. *The American Journal of Pathology*, **186**, 1688-1700. https://doi.org/10.1016/j.ajpath.2016.01.023

[84] Swetha, E. and Jeganathan, V. (2011) The Therapeutic Implications of Renin-Angiotensin System Blockade in Diabetic Retinopathy. *Current Pharmaceutical Biotechnology*, **12**, 392-395. https://doi.org/10.2174/138920111794480615

[85] Perkins, B.A., Aiello, L.P. and Krolewski, A.S. (2009) Diabetes Complications and the Renin-Angiotensin System. *New England Journal of Medicine*, **361**, 83-85. https://doi.org/10.1056/nejme0904293

[86] Sjølie, A.K., Dodson, P. and Hobbs, F.R.R. (2011) Does Renin-Angiotensin System Blockade Have a Role in Preventing Diabetic Retinopathy? A Clinical Review. *International Journal of Clinical Practice*, **65**, 148-153. https://doi.org/10.1111/j.1742-1241.2010.02552.x

[87] Verma, A., Shan, Z., Lei, B., Yuan, L., Liu, X., Nakagawa, T., *et al.* (2012) ACE2 and Ang-(1-7) Confer Protection against Development of Diabetic Retinopathy. *Molecular Therapy*, **20**, 28-36. https://doi.org/10.1038/mt.2011.155

[88] Tap, J., Mondot, S., Levenez, F., Pelletier, E., Caron, C., Furet, J., *et al.* (2009) Towards the Human Intestinal Microbiota Phylogenetic Core. *Environmental Microbiology*, **11**, 2574-2584. https://doi.org/10.1111/j.1462-2920.2009.01982.x

[89] Huang, Y., Yang, B. and Li, W. (2016) Defining the Normal Core Microbiome of Conjunctival Microbial Communities. *Clinical Microbiology and Infection*, **22**, 643.e7-643.e12. https://doi.org/10.1016/j.cmi.2016.04.008

[90] Ozkan, J., Willcox, M., Wemheuer, B., Wilcsek, G., Coroneo, M. and Thomas, T. (2019) Biogeography of the Human Ocular Microbiota. *The Ocular Surface*, **17**, 111-118. https://doi.org/10.1016/j.jtos.2018.11.005

[91] Lu, L.J. and Liu, J. (2016) Human Microbiota and Ophthalmic Disease. *Yale Journal of Biology and Medicine*, **89**, 325-330.

[92] Das, T., Jayasudha, R., Chakravarthy, S., Prashanthi, G.S., Bhargava, A., Tyagi, M., *et al.* (2021) Alterations in the Gut Bacterial Microbiome in People with Type 2 Diabetes Mellitus and Diabetic Retinopathy. *Scientific Reports*, **11**, Article No. 2738. https://doi.org/10.1038/s41598-021-82538-0

[93] Jayasudha, R., Das, T., Kalyana Chakravarthy, S., Sai Prashanthi, G., Bhargava, A., Tyagi, M., *et al.* (2020) Gut Mycobiomes Are Altered in People with Type 2 Diabetes Mellitus and Diabetic Retinopathy. *PLOS ONE*, **15**, e0243077. https://doi.org/10.1371/journal.pone.0243077

[94] Liu, W., Wang, C., Xia, Y., Xia, W., Liu, G., Ren, C., *et al.* (2020) Elevated Plasma Trimethylamine-N-Oxide Levels Are Associated with Diabetic Retinopathy. *Acta Diabetologica*, **58**, 221-229. https://doi.org/10.1007/s00592-020-01610-9

[95] Huang, Y., Wang, Z., Ma, H., Ji, S., Chen, Z., Cui, Z., *et al.* (2021) Dysbiosis and Implication of the Gut Microbiota in Diabetic Retinopathy. *Frontiers in Cellular and Infection Microbiology*, **11**, Article ID: 646348. https://doi.org/10.3389/fcimb.2021.646348

[96] Feldman, E.L., Callaghan, B.C., Pop-Busui, R., Zochodne, D.W., Wright, D.E., Bennett, D.L., *et al.* (2019) Diabetic Neuropathy. *Nature Reviews Disease Primers*, **5**, Article No. 42. https://doi.org/10.1038/s41572-019-0092-1

[97] Vinik, A.I., Nevoret, M., Casellini, C. and Parson, H. (2013) Diabetic Neuropathy. *Endocrinology and Metabolism Clinics of North America*, **42**, 747-787. https://doi.org/10.1016/j.ecl.2013.06.001

[98] Grasset, E. and Burcelin, R. (2019) The Gut Microbiota to the Brain Axis in the Metabolic Control. *Reviews in Endocrine and Metabolic Disorders*, **20**, 427-438. https://doi.org/10.1007/s11154-019-09511-1

[99] Yagihashi, S., Mizukami, H. and Sugimoto, K. (2010) Mechanism of Diabetic Neuropathy: Where Are We Now and Where to Go? *Journal of Diabetes Investigation*, **2**, 18-32. https://doi.org/10.1111/j.2040-1124.2010.00070.x

[100] Rolim, L.C., da Silva, E.M., Flumignan, R.L., Abreu, M.M. and Dib, S.A. (2019) Acetyl-l-Carnitine for the Treatment of Diabetic Peripheral Neuropathy. *Cochrane Database of Systematic Reviews*, **2019**, CD011265. https://doi.org/10.1002/14651858.cd011265.pub2

[101] Wang, Y., Ye, X., Ding, D. and Lu, Y. (2020) Characteristics of the Intestinal Flora in Patients with Peripheral Neuropathy Associated with Type 2 Diabetes. *Journal of International Medical Research*, **48**, 300060520936806. https://doi.org/10.1177/0300060520936806

[102] Feigin, V.L., Forouzanfar, M.H., Krishnamurthi, R., Mensah, G.A., Connor, M., Bennett, D.A., *et al.* (2014) Global and Regional Burden of Stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *The Lancet*, **383**, 245-255. https://doi.org/10.1016/s0140-6736(13)61953-4

[103] Stevens, R.J., Coleman, R.L., Adler, A.I., Stratton, I.M., Matthews, D.R. and Holman, R.R. (2004) Risk Factors for Myocardial Infarction Case Fatality and Stroke Case Fatality in Type 2 Diabetes. *Diabetes Care*, **27**, 201-207. https://doi.org/10.2337/diacare.27.1.201

[104] Clemente, J.C., Ursell, L.K., Parfrey, L.W. and Knight, R. (2012) The Impact of the Gut Microbiota on Human Health: An Integrative View. *Cell*, **148**, 1258-1270. https://doi.org/10.1016/j.cell.2012.01.035

[105] Carabotti, M., Scirocco, A., Maselli, M.A. and Severi, C. (2015) The Gut-Brain Axis: Interactions between Enteric Microbiota, Central and Enteric Nervous Systems. *Annals of Gastroenterology*, **28**, 203-209.

[106] Tang, W.H.W., Wang, Z., Levison, B.S., Koeth, R.A., Britt, E.B., Fu, X., *et al.* (2013) Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk. *New England Journal of Medicine*, **368**, 1575-1584. https://doi.org/10.1056/nejmoa1109400

[107] Haghikia, A., Li, X.S., Liman, T.G., Bledau, N., Schmidt, D., Zimmermann, F., *et al.* (2018) Gut Microbiota-Dependent Trimethylamine *N*-Oxide Predicts Risk of Cardiovascular Events in Patients with Stroke and Is Related to Proinflammatory Monocytes. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **38**, 2225-2235. https://doi.org/10.1161/atvbaha.118.311023

[108] Zhu, W., Gregory, J.C., Org, E., Buffa, J.A., Gupta, N., Wang, Z., *et al.* (2016) Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell*, **165**, 111-124. https://doi.org/10.1016/j.cell.2016.02.011

[109] Koeth, R.A., Wang, Z., Levison, B.S., Buffa, J.A., Org, E., Sheehy, B.T., *et al.* (2013) Intestinal Microbiota Metabolism of L-Carnitine, a Nutrient in Red Meat, Promotes Atherosclerosis. *Nature Medicine*, **19**, 576-585. https://doi.org/10.1038/nm.3145

[110] Wang, Z., Klipfell, E., Bennett, B.J., Koeth, R., Levison, B.S., DuGar, B., *et al.* (2011) Gut Flora Metabolism of Phosphatidylcholine Promotes Cardiovascular Disease. *Nature*, **472**, 57-63. https://doi.org/10.1038/nature09922

[111] Svingen, G.F.T., Zuo, H., Ueland, P.M., Seifert, R., Løland, K.H., Pedersen, E.R., *et al.* (2018) Increased Plasma Trimethylamine-N-Oxide Is Associated with Incident Atrial Fibrillation. *International Journal of Cardiology*, **267**, 100-106. https://doi.org/10.1016/j.ijcard.2018.04.128

[112] Tang, W.H.W., Wang, Z., Li, X.S., Fan, Y., Li, D.S., Wu, Y., *et al.* (2017) Increased Trimethylamine N-Oxide Portends High Mortality Risk Independent of Glycemic Control in Patients with Type 2 Diabetes Mellitus. *Clinical Chemistry*, **63**, 297-306. https://doi.org/10.1373/clinchem.2016.263640

[113] Aronson, D. and Edelman, E.R. (2014) Coronary Artery Disease and Diabetes Mellitus. *Cardiology Clinics*, **32**, 439-455. https://doi.org/10.1016/j.ccl.2014.04.001

[114] Yissachar, N., Zhou, Y., Ung, L., Lai, N.Y., Mohan, J.F., Ehrlicher, A., *et al.* (2017) An Intestinal Organ Culture System Uncovers a Role for the Nervous System in Microbe-Immune Crosstalk. *Cell*, **168**, 1135-1148.e12. https://doi.org/10.1016/j.cell.2017.02.009

[115] Kassam, Z., Lee, C.H., Yuan, Y. and Hunt, R.H. (2013) Fecal Microbiota Transplantation for Clostridium Difficile Infection: Systematic Review and Meta-Analysis. *American Journal of Gastroenterology*, **108**, 500-508. https://doi.org/10.1038/ajg.2013.59

[116] Spinner, J.A., Bocchini, C.E., Luna, R.A., Thapa, S., Balderas, M.A., Denfield, S.W., *et al.* (2019) Fecal Microbiota Transplantation in a Toddler after Heart Transplant Was a Safe and Effective Treatment for Recurrent *Clostridiodes difficile* Infection: A Case Report. *Pediatric Transplantation*, **24**, e13598. https://doi.org/10.1111/petr.13598

[117] Khoruts, A. and Sadowsky, M.J. (2016) Understanding the Mechanisms of Faecal Microbiota Transplantation. *Nature Reviews Gastroenterology & Hepatology*, **13**, 508-516. https://doi.org/10.1038/nrgastro.2016.98

[118] Peng, J., Narasimhan, S., Marchesi, J.R., Benson, A., Wong, F.S. and Wen, L. (2014) Long Term Effect of Gut Microbiota Transfer on Diabetes Development. *Journal of Autoimmunity*, **53**, 85-94. https://doi.org/10.1016/j.jaut.2014.03.005

[119] Zhang, P.P., Li, L.L., Han, X., Li, Q.W., Zhang, X.H., Liu, J.J., *et al.* (2020) Fecal Microbiota Transplantation Improves Metabolism and Gut Microbiome Composition in Db/Db Mice. *Acta Pharmacologica Sinica*, **41**, 678-685. https://doi.org/10.1038/s41401-019-0330-9

[120] La Sala, L., Carlini, V., Macas-Granizo, M.B., Trabucchi, E., Pontiroli, A.E., Berra, C., *et al.* (2025) The Eternal Struggle between Titans: Fecal Microbiota Transplant (FMT) versus Metformin in Type 2 Diabetes (T2D) Gut Dysmotility. *Journal of Advanced*

Research. https://doi.org/10.1016/j.jare.2025.09.021

[121] Kootte, R.S., Levin, E., Salojärvi, J., Smits, L.P., Hartstra, A.V., Udayappan, S.D., *et al.* (2017) Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. *Cell Metabolism*, **26**, 611-619.e6. https://doi.org/10.1016/j.cmet.2017.09.008

[122] Wu, G.D., Compher, C., Chen, E.Z., Smith, S.A., Shah, R.D., Bittinger, K., *et al.* (2014) Comparative Metabolomics in Vegans and Omnivores Reveal Constraints on Diet-Dependent Gut Microbiota Metabolite Production. *Gut*, **65**, 63-72. https://doi.org/10.1136/gutjnl-2014-308209

[123] Wang, J., Gao, Y., Ren, S., Li, J., Chen, S., Feng, J., *et al.* (2024) Gut Microbiota-Derived Trimethylamine N-Oxide: A Novel Target for the Treatment of Preeclampsia. *Gut Microbes*, **16**, Article ID: 2311888. https://doi.org/10.1080/19490976.2024.2311888

[124] Bonora, E., Cigolini, M., Bosello, O., Zancanaro, C., Capretti, L., Zavaroni, I., *et al.* (1984) Lack of Effect of Intravenous Metformin on Plasma Concentrations of Glucose, Insulin, C-Peptide, Glucagon and Growth Hormone in Non-Diabetic Subjects. *Current Medical Research and Opinion*, **9**, 47-51. https://doi.org/10.1185/03007998409109558

[125] Forslund, K., Hildebrand, F., Nielsen, T., Falony, G., Le Chatelier, E., Sunagawa, S., *et al.* (2015) Disentangling Type 2 Diabetes and Metformin Treatment Signatures in the Human Gut Microbiota. *Nature*, **528**, 262-266. https://doi.org/10.1038/nature15766

[126] Ejtahed, H., Tito, R.Y., Siadat, S., Hasani-Ranjbar, S., Hoseini-Tavassol, Z., Rymenans, L., *et al.* (2019) Metformin Induces Weight Loss Associated with Gut Microbiota Alteration in Non-Diabetic Obese Women: A Randomized Double-Blind Clinical Trial. *European Journal of Endocrinology*, **180**, 165-176. https://doi.org/10.1530/eje-18-0826

[127] Rosario, D., Benfeitas, R., Bidkhori, G., Zhang, C., Uhlen, M., Shoaie, S., *et al.* (2018) Understanding the Representative Gut Microbiota Dysbiosis in Metformin-Treated Type 2 Diabetes Patients Using Genome-Scale Metabolic Modeling. *Frontiers in Physiology*, **9**, Article No. 775. https://doi.org/10.3389/fphys.2018.00775

[128] Malik, F., Mehdi, S.F., Ali, H., Patel, P., Basharat, A., Kumar, A., *et al.* (2018) Is Metformin Poised for a Second Career as an Antimicrobial? *Diabetes/Metabolism Research and Reviews*, **34**, e2975. https://doi.org/10.1002/dmrr.2975

[129] Lee, H. and Ko, G. (2014) Effect of Metformin on Metabolic Improvement and Gut Microbiota. *Applied and Environmental Microbiology*, **80**, 5935-5943. https://doi.org/10.1128/aem.01357-14

[130] de la Cuesta-Zuluaga, J., Mueller, N.T., Corrales-Agudelo, V., Velásquez-Mejía, E.P., Carmona, J.A., Abad, J.M., *et al.* (2016) Metformin Is Associated with Higher Relative Abundance of Mucin-Degrading *Akkermansia muciniphila* and Several Short-Chain Fatty Acid-Producing Microbiota in the Gut. *Diabetes Care*, **40**, 54-62. https://doi.org/10.2337/dc16-1324

[131] Rodriguez, J., Hiel, S. and Delzenne, N.M. (2018) Metformin: Old Friend, New Ways of Action-Implication of the Gut Microbiome? *Current Opinion in Clinical Nutrition & Metabolic Care*, **21**, 294-301. https://doi.org/10.1097/mco.0000000000000468

[132] Kuka, J., Videja, M., Makrecka-Kuka, M., Liepins, J., Grinberga, S., Sevostjanovs, E., *et al.* (2020) Metformin Decreases Bacterial Trimethylamine Production and Trimethylamine N-Oxide Levels in Db/Db Mice. *Scientific Reports*, **10**, Article No. 14555. https://doi.org/10.1038/s41598-020-71470-4

[133] Adeshirlarijaney, A., Zou, J., Tran, H.Q., Chassaing, B. and Gewirtz, A.T. (2019) Amelioration of Metabolic Syndrome by Metformin Associates with Reduced Indices of Low-Grade Inflammation Independently of the Gut Microbiota. *American Journal of Physiology-Endocrinology and Metabolism*, **317**, E1121-E1130. https://doi.org/10.1152/ajpendo.00245.2019

[134] Kechagia, M., Basoulis, D., Konstantopoulou, S., Dimitriadi, D., Gyftopoulou, K., Skarmoutsou, N., *et al.* (2013) Health Benefits of Probiotics: A Review. *ISRN Nutrition*, **2013**, Article ID: 481651. https://doi.org/10.5402/2013/481651

[135] Yun, S.I., Park, H.O. and Kang, J.H. (2009) Effect of *Lactobacillus gasseri* bnr17 on Blood Glucose Levels and Body Weight in a Mouse Model of Type 2 Diabetes. *Journal of Applied Microbiology*, **107**, 1681-1686. https://doi.org/10.1111/j.1365-2672.2009.04350.x

[136] Hove, K.D., Brøns, C., Færch, K., Lund, S.S., Rossing, P. and Vaag, A. (2015) Effects of 12 Weeks of Treatment with Fermented Milk on Blood Pressure, Glucose Metabolism and Markers of Cardiovascular Risk in Patients with Type 2 Diabetes: A Randomised Double-Blind Placebo-Controlled Study. *European Journal of Endocrinology*, **172**, 11-20. https://doi.org/10.1530/eje-14-0554

[137] Singh, R., Sharma, P. and Bhardwaj, P. (2016) Administration of *Lactobacillus casei* and *Bifidobacterium bifidum* Ameliorated Hyperglycemia, Dyslipidemia, and Oxidative Stress in Diabetic Rats. *International Journal of Preventive Medicine*, **7**, Article No. 102. https://doi.org/10.4103/2008-7802.188870

[138] Kleniewska, P. and Pawliczak, R. (2024) The Link between Dysbiosis, Inflammation, Oxidative Stress, and Asthma—The Role of Probiotics, Prebiotics, and Antioxidants. *Nutrients*, **17**, Article No. 16. https://doi.org/10.3390/nu17010016

[139] Bock, P.M., Telo, G.H., Ramalho, R., Sbaraini, M., Leivas, G., Martins, A.F., *et al.* (2020) The Effect of Probiotics, Prebiotics or Synbiotics on Metabolic Outcomes in Individuals with Diabetes: A Systematic Review and Meta-Analysis. *Diabetologia*, **64**, 26-41. https://doi.org/10.1007/s00125-020-05295-1

[140] Kasińska, M.A. and Drzewoski, J. (2015) Effectiveness of Probiotics in Type 2 Diabetes: A Meta-Analysis. *Polish Archives of Internal Medicine*, **125**, 803-813. https://doi.org/10.20452/pamw.3156

[141] Gibson, G.R. and Roberfroid, M.B. (1995) Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics. *The Journal of Nutrition*, **125**, 1401-1412. https://doi.org/10.1093/jn/125.6.1401

[142] Cani, P.D., Dewever, C. and Delzenne, N.M. (2004) Inulin-Type Fructans Modulate Gastrointestinal Peptides Involved in Appetite Regulation (Glucagon-Like Peptide-1 and Ghrelin) in Rats. *British Journal of Nutrition*, **92**, 521-526. https://doi.org/10.1079/bjn20041225

[143] Anson, R.M., Guo, Z., de Cabo, R., Iyun, T., Rios, M., Hagepanos, A., *et al.* (2003) Intermittent Fasting Dissociates Beneficial Effects of Dietary Restriction on Glucose Metabolism and Neuronal Resistance to Injury from Calorie Intake. *Proceedings of the National Academy of Sciences*, **100**, 6216-6220. https://doi.org/10.1073/pnas.1035720100

[144] Zhang, C., Li, S., Yang, L., Huang, P., Li, W., Wang, S., *et al.* (2013) Structural Modulation of Gut Microbiota in Life-Long Calorie-Restricted Mice. *Nature Communications*, **4**, Article No. 2163. https://doi.org/10.1038/ncomms3163

[145] Zarrinpar, A., Chaix, A., Yooseph, S. and Panda, S. (2014) Diet and Feeding Pattern Affect the Diurnal Dynamics of the Gut Microbiome. *Cell Metabolism*, **20**, 1006-1017. https://doi.org/10.1016/j.cmet.2014.11.008

[146] Liu, Z., Dai, X., Zhang, H., Shi, R., Hui, Y., Jin, X., *et al.* (2020) Gut Microbiota Mediates Intermittent-Fasting Alleviation of Diabetes-Induced Cognitive Impairment. *Nature Communications*, **11**, Article No. 855. https://doi.org/10.1038/s41467-020-14676-4

[147] Hendrikx, T., Duan, Y., Wang, Y., Oh, J., Alexander, L.M., Huang, W., *et al.* (2018) Bacteria Engineered to Produce IL-22 in Intestine Induce Expression of REG3G to Reduce Ethanol-Induced Liver Disease in Mice. *Gut*, **68**, 1504-1515. https://doi.org/10.1136/gutjnl-2018-317232

[148] Duan, F., Curtis, K.L. and March, J.C. (2008) Secretion of Insulinotropic Proteins by Commensal Bacteria: Rewiring the Gut to Treat Diabetes. *Applied and Environmental Microbiology*, **74**, 7437-7438. https://doi.org/10.1128/aem.01019-08

[149] Hsu, B.B., Gibson, T.E., Yeliseyev, V., Liu, Q., Lyon, L., Bry, L., *et al.* (2019) Dynamic Modulation of the Gut Microbiota and Metabolome by Bacteriophages in a Mouse Model. *Cell Host & Microbe*, **25**, 803-814.e5. https://doi.org/10.1016/j.chom.2019.05.001

[150] Rasmussen, T.S., Mentzel, C.M.J., Kot, W., Castro-Mejía, J.L., Zuffa, S., Swann, J.R., *et al.* (2020) Faecal Virome Transplantation Decreases Symptoms of Type 2 Diabetes and Obesity in a Murine Model. *Gut*, **69**, 2122-2130. https://doi.org/10.1136/gutjnl-2019-320005

[151] Ng, S.C., Xu, Z., Mak, J.W.Y., Yang, K., Liu, Q., Zuo, T., *et al.* (2021) Microbiota Engraftment after Faecal Microbiota Transplantation in Obese Subjects with Type 2 Diabetes: A 24-Week, Double-Blind, Randomised Controlled Trial. *Gut*, **71**, 716-723. https://doi.org/10.1136/gutjnl-2020-323617

[152] Wu, Z., Zhang, B., Chen, F., Xia, R., Zhu, D., Chen, B., *et al.* (2023) Fecal Microbiota Transplantation Reverses Insulin Resistance in Type 2 Diabetes: A Randomized, Controlled, Prospective Study. *Frontiers in Cellular and Infection Microbiology*, **12**, Article ID: 1089991. https://doi.org/10.3389/fcimb.2022.1089991