

The Influence of Specific Microbial Species on Diabetes

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Diabetes mellitus (DM) is a metabolic disorder with an alarming incidence rate and a considerable burden on the patient's life and health care providers. An increase in blood glucose level and insulin resistance characterizes it. Internal and external factors such as urbanization, obesity, and genetic mutations could increase the risk of DM. Microbes in the gut influence overall health through immunity and nutrition. More studies have been conducted to evaluate and estimate the role of the gut microbiome in diabetes development, progression, and management.

Bifidobacterium adolescentis

Bifidobacterium bifidum

diabetes

gut

Lactobacillus rhamnosus

1. Diabetes Management Using Microbial Species

The development of diabetes is associated with profound gut dysbiosis [1]. Restoring the balance of gut microbiome composition by administering probiotics (live non-pathogenic microorganisms) in an adequate concentration has been reported to improve diabetes [2]. Several human and non-human studies reported the influence of using probiotics for diabetes. For example, in diabetic patients given yogurt containing *L. acidophilus* La5 and *B. lactis* Bb12 as probiotics, fasting blood glucose, insulin, insulin resistance, and glycosylated hemoglobin levels were reduced [3]. A meta-analysis of 520 type 2 diabetic patients reported that probiotic administration improved glycemic control and lipid metabolism [4]. Probiotic administration also influences oxidative status and inflammatory parameters in diabetic patients [5]. Seventy participants with diabetes were given probiotics for a month which significantly reduced the levels of IL-6, IL-1, IL-8, and TNF- α compared to the control group [6]. The data showed how probiotic administration influenced the inflammatory response in participants with diabetes. The administration of *Lactobacillus* for two months reduces uric nitrogen in the blood [7]. Additionally, probiotic administration influenced and regulated the level of glycated hemoglobin, total cholesterol, triglycerides, and low-density lipoprotein cholesterol in pre-clinical diabetes [8]. On the other hand, similar results were observed when the probiotic was given to animal models. The administration of *Bifidobacterium* for one month and *Lactobacillus* for three months in a mouse model with type 2 diabetes was reported to normalize glucose metabolism and insulin sensitivity [9][10]. One of the concerns with probiotic treatment is safety and tolerability. All the mentioned studies reported no adverse effects and probiotic usage was safe. Despite that, more efforts are required to standardize the protocol and estimate the proper dosage.

2. *Bifidobacterium adolescentis*

Bifidobacteria are Gram-positive, non-spore-forming, and non-motile bacteria known to be the first colonizer of the infant gut [11]. Their presence in the gut has been linked to several beneficial effects on the host as they prevent intestinal inflammation, colonic adenomas, and cancer [12]. *Bifidobacterium adolescentis* is a vital gut flora in adults [13][14]. In patients with type 2 diabetes, the abundance of *B. adolescentis* in the intestine is significantly reduced [15]. Using *B. adolescentis* (1×10^8 cfu/mL) daily on twenty volunteers aged 50 to 60 for thirty days as a supplementation alleviates gut microbiome disorder and reduces blood glucose [16].

Additionally, administering eight strains of *B. adolescentis* (2×10^8 cfu/mL) for 12 weeks in diabetic mice restored gut microbiome homeostasis, alleviated inflammation, and increased the abundance of short-chain fatty acid-producing microorganisms [17]. Moreover, supplementing *B. adolescentis* (5×10^8 cfu/mL) in mice fed a high-fat diet daily for twelve weeks improved insulin sensitivity and reduced visceral fat accumulation [18]. Unfortunately, the literature lacks more data that support or challenge the observed beneficial effects of *B. adolescentis* administration in diabetes. Furthermore, protocol standardization is required to ensure the safety and efficacy of using such an approach. **Figure 1** highlights the main pathways affected by *B. adolescentis* administration in diabetes.

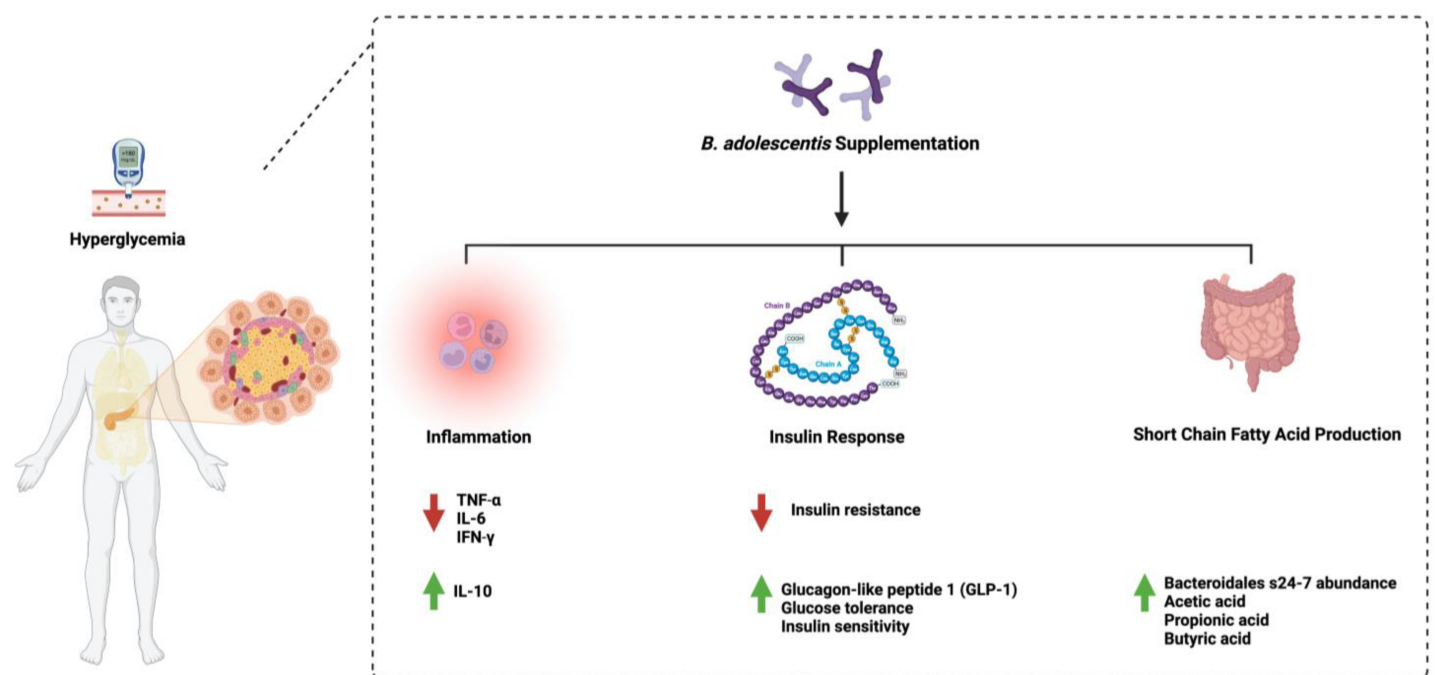


Figure 1. Overview illustration of *Bifidobacterium adolescentis* on diabetes. The figure shows the three main pathways: inflammation, insulin response, and the production of short-chain fatty acids by microorganisms. Created with [BioRender.com](https://www.biorender.com).

3. *Bifidobacterium bifidum*

Bifidobacterium bifidum is one species of naturally occurring microbiota detected in breastfed infants [19]. It is considered a dominant resident of the gut population [20]. *B. bifidum* consists of 3000 genes that encode carbohydrate enzymes such as glycosyl transferases (GTs), glycosyl hydrolases (GHs), and carbohydrate

esterases (CEs) [21]. This showed the ability of *B. bifidum* to metabolize host-derived glycans such as human milk oligosaccharides and mucin [22]. Using *B. bifidum* in diabetes management has started to gain more scientific attention recently. A single administration dosage of 1×10^7 cfu/mL daily for 28 days reduced fasting blood glucose, glycosylated hemoglobin, triglycerides (TG), and total cholesterol in Wistar rats [23]. Additionally, diabetic patients treated with a collection of probiotics, including *B. bifidum* (2×10^9 cfu/mL) daily for 12 weeks, significantly decreased insulin resistance, fasting blood glucose, and increased insulin sensitivity and HDL cholesterol level. It also improved the total antioxidant capacity and reduced the C-reactive protein level [24]. The combination treatment of different *Bifidobacterium* spp., including *B. bifidum* and excluding *B. adolescentis*, ameliorated insulin resistance and reduced blood glucose levels in mice [25]. More studies are needed to evaluate how *B. bifidum* manages diabetes. Additionally, studies that address the influence of *B. bifidum* and *B. adolescentis* may be essential for better treatment outcomes. **Figure 2** highlights the main pathways affected by *B. bifidum* administration in diabetes.

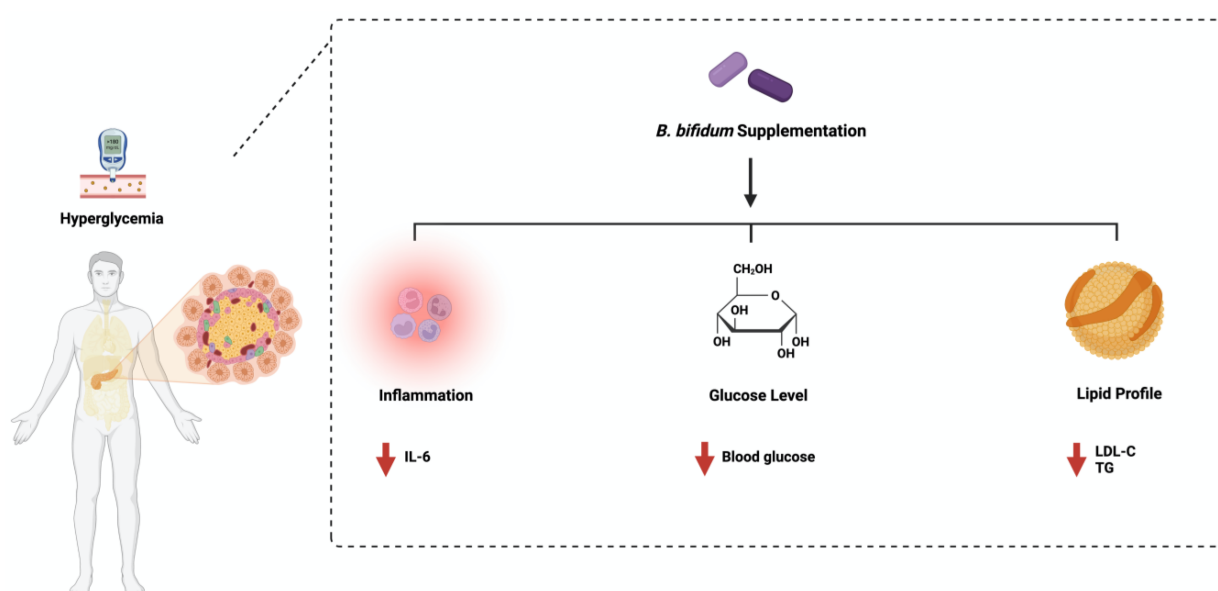


Figure 2. Overview illustration of *Bifidobacterium bifidum* on diabetes. The figure shows the three main pathways: inflammation, insulin response, and lipid profile. Created with [BioRender.com](https://www.biorender.com).

4. *Lactobacillus rhamnosus*

Lactobacillus rhamnosus was first isolated in 1983 and is known for its ability to resist stomach acidity and strong avidity for intestinal cells. It has been widely used in targeting multiple pathological conditions, such as cancer, as an effective probiotic [26]. Administering *L. rhamnosus* daily (1×10^8 cfu/mL) in rodents for four weeks improved glucose tolerance by reducing endoplasmic reticulum stress [27]. Additionally, in mice fed a high-fat diet, treating 10^9 cfu/mL of *L. rhamnosus* daily significantly reduced the insulin level and fasting blood glucose. It also reduced proinflammatory cytokines such as IL-6 and TNF- α [28].

Furthermore, oral administration of *L. rhamnosus* improved glucose tolerance in diabetic rats by downregulating the expression of glucose 6 phosphatase [29]. The administration of *L. rhamnosus* to diabetic mice reduced insulin, glycosylated hemoglobin, and fasting blood glucose levels and increased glucagon-like peptide 1 levels in serum [30]. Similar results were obtained when 3 month old male Zebrafish were used [31]. These observations show the urgent need for protocol standardization and model specification to estimate the beneficial effect of *L. rhamnosus* in diabetes. **Figure 3** highlights the main pathways affected by *L. rhamnosus* administration in diabetes.

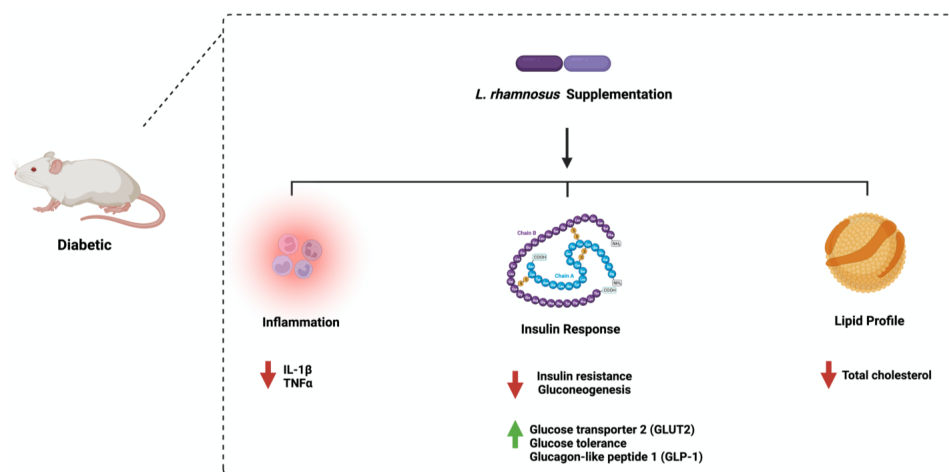


Figure 4. Overview illustration of *Lactobacillus rhamnosus* on diabetes. The figure shows the three main pathways: inflammation, insulin response, and lipid profile. Created with [BioRender.com](https://www.biorender.com/).

5. The Influence of Gut Microbial Species on Diabetes Mellitus

Diabetes is a global metabolic condition with a high incidence rate worldwide. Developing new and improved therapeutic approaches to target the disease and its complications is necessary. The gut microbiota has been linked recently to diabetes. Here, the researchers searched the literature and reported the role played by the three commonly addressed microbial species on diabetes: *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and *Lactobacillus rhamnosus*. Both animal and human studies reported the influence of *Bifidobacterium adolescentis* administration on blood glucose level, an abundance of short-chain fatty acids, and inflammatory response in a dose dependent manner that ranges from 1×10^8 to 5×10^8 CFU/mL. Moreover, administering *Bifidobacterium bifidum* (1×10^7 – 2×10^9 CFU/mL) reduced fasting blood glucose, insulin resistance, and improved sensitivity in human participants with diabetes and animal models. Unfortunately, this is not the case with *Lactobacillus rhamnosus* as most of the available studies reported the role of this species on diabetes in animal models only. Despite that, the data support the positive influence of this species on insulin resistance and lipid profile.

Throughout the literature, the researchers observed the lack of standardization regarding the protocol followed, the model used, the diet used to induce diabetes in animal models, and the mode of administration, as most studies followed oral or intraperitoneal administration. Establishing standardized protocols that specify specific guidelines will help further advance the field. Additionally, the literature shows that many studies investigate a single microbial

species. The gut microbiome is a community of microorganisms interacting with each other and the host. Isolating and investigating a single organism only might not be of great interest. As a starting point, a study may investigate the influence of the three bacterial species mentioned here on diabetes in human and animal models and report the challenges and limitations. By doing so, the researchers can then, step by step, look at the gut microbiome as a community in the context of health and diseases. The following sections highlight some essential topics that need further discussion and research for better treatment outcomes.

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