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Review Article

Targeting gut microbiota as a possible therapy for diabetes

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ABSTRACT

The incidence of diabetes has increased rapidly across the entire world in the last 2 decades. Accumulating evidence suggests that gut microbiota contribute to the pathogenesis of diabetes. Several studies have demonstrated that patients with diabetes are characterized by a moderate degree of gut microbial dysbiosis. However, there are still substantial controversies regarding altered composition of the gut microbiota and the underlying mechanisms by which gut microbiota interact with the body's metabolism. The purpose of this review is to define the association between gut microbiota and diabetes. In doing so an electronic search of studies published in English from January 2004 to the November 2014 in the National Library of Medicine, including the original studies that addressed the effects of gut microbiota on diabetes, energy metabolism, inflammation, the immune system, gut permeability and insulin resistance, was performed. Herein, we discuss the possible mechanisms by which the gut microbiota are involved in the development of diabetes, including energy metabolism, inflammation, the innate immune system, and the bowel function of the intestinal barrier. The compositional changes in the gut microbiota in type 2 and type 1 diabetes are also discussed. Moreover, we introduce the new findings of fecal transplantation, and use of probiotics and prebiotics as new treatment strategies for diabetes. Future research should be focused on defining the primary species of the gut microbiota and their exact roles in diabetes, potentially increasing the possibility of fecal transplants as a therapeutic strategy for diabetes.

1. Introduction

Diabetes mellitus (DM) is becoming a common problem across the entire world. According to the latest information from the International Diabetes Federation in 2013, there are 382 million people now living with diabetes. And this number will rocket to 592 million by 2035 [1]. DM had caused 5.1 million deaths and cost 548 billion USD in healthcare expenses at the end of 2013 [1]. In 2008, a national survey in China revealed that 92.4 million adults had DM, and 148.2 million adults had pre-diabetes [2]. This high prevalence of DM in China might cause more serious diabetes-related burdens than in any other country. (See Table.)

It is known that both genetic and environmental factors contribute to the pathogenesis of DM, particularly type 2

Abbreviations: Acc, acetyl-CoA carboxylase; AMPK, adenosine 5′-monophosphate (AMP)–activated protein kinase; GF, germ-free; GLP, glucagon-like peptide; GPR, G-protein coupled receptor; HbA_{1c}, hemoglobin A_{1c}; IL, interleukin; NOD, non-obese diabetic; SCFA, short chain fatty acid; SREBP-1c, sterol response element binding protein 1c; TLR, Toll-like receptor.

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Table – Changes in the gut microbiota associated with diabetes

Disease	Models	Implicated microbiota	Function changes with DM	Reference
T2D	18 Male patients and 18 controls	*Firmicutes*↓ *Clostridia*↓	Associated with plasma glucose positively and significantly.	12
T2D	345 Chinese patients and controls	*Clostridiales sp. SS3/4*↓ *Eubacterium rectale*↓ *Faecalibacterum prausnitzii*↓ *Roseburia intestinalis*↓ *Roseburia inulinivorans*↓ *Bacteroides caccae*↑ *Clostridium*↑ *Akkermansia muciniphila*↑ *Desulfovibrio sp. 3_1_syn3*↑	Associated with membrane transport of sugars, branched-chain amino acid transport, methane metabolism, xenobiotics degradation and metabolism, sulphate reduction.	13
T2D	145 European women	*Lactobacillus*↑ *Clostridium*↓	Associated with fasting glucose and HbA_{1c},insulin, plasma triglycerides, adiponectin and HDL.	14
T2D	50 Japanese	*Clostridium coccoides*↓ *Atopobium*↓ *Prevotella*↓ *Lactobacillus*↑		15
T1D	4 Matched case–control in Finland	*Firmicutes*↓ *Bacteroidetes*↑		16
T1D	16 White children	*Clostridium*↑ *Bacteroides*↑ *Veillonella*↑ *Lactobacillus*↓ *Bifidobacterium*↓ *Blautia coccoides/Eubacterium rectale*↓ *Prevotella*↓	Associated with the plasma glucose level and HbA_{1c} level.	17

diabetes (T2D) [3–5]. Recently, studies revealed that the gut microbiota function as an important environmental factor in the development of DM [6,7]. The human gut hosts trillions of microorganisms, including more than 10^{14} bacteria belonging to 1000 species [8]. The genome size of this microbial organ, collectively termed the microbiome, exceeds the size of the human nuclear genome by 100-fold and provides humans with additional biological and metabolic functions for maintaining homeostasis in the body [9]. Numerous studies have shown that the composition of the gut microbiota is altered in diabetic groups. However, there are no consistent results regarding which species are altered in diabetic patients. Moreover, the detailed mechanisms linking the gut microbiota to diabetes have not been well described. Therefore, we conducted an electronic search of English articles from 2004 to 2014 in Medline to clarify the possible relationship between gut microbiota and diabetes. The MeSH search terms used were gut microbiota, diabetes, metabolic diseases, energy metabolism, immune system, inflammation, gut permeability, and fecal transplant.

In this review, we present data on the changes of the gut microbiota both in type 1 diabetes (T1D) and in T2D, and summarized the possible mechanisms through which the gut microbiota interact with diabetes. Finally, we discussed the very recent research regarding the effects of dietary modulation and fecal transplantation of intestinal microbiota as treatment strategies for diabetes. All of these compelling lines of evidence strongly suggest that gut microbiota might play a significant role in the development and treatment for diabetes.

2. Gut microorganisms and DM

The gut microbiota in our body is part of a dynamic ecosystem, and its composition is altered at the phylum and class levels by environmental and host factors which jointly influence the gut and far removed organs. Thus, the gut microbiota is linked to several human diseases, such as obesity and diabetes [10,11]. Recently, numerous studies indicated a relationship between the gut microbiota and T2D. In 2010, Larsen et al reported that the ratios of *Firmicutes* to *Clostridia* species were attenuated in T2D patients [12]. The ratio of *Bacteroidetes* to *Firmicutes* and the ratio of the *Bacteroides-Prevotella* group to the *C coccoides-E. rectale* group were positively and significantly correlated with plasma glucose concentrations [12]. Qin et al found that Chinese T2D patients exhibited a decline in butyrate-producing bacteria (eg, *Clostridiales sp. SS3/4*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *etc.*) and an increase in several opportunistic pathogens (eg, *Bacteroides caccae*, *Clostridium hathewayi*, *C ramosum*, *C symbiosum* and others) [13]. Moreover, the mucin-degrading species *Akkermansia muciniphila* and sulfate-reducing species *Desulfovibrio sp. 3_1_syn3* were more abundant in T2D samples [13]. Although it is important to characterize the link between gut microbiota and T2D, there are still some shortcomings that should be noted. For example, the entire gut bacteria population was not classified by age, gender, or drug treatment of subjects to minimize the sources of variation. Research was completed in Europe that examined the composition and function of gut microbiota in a well-characterized population of 70-year-old women [14]. In this T2D group, the abundances of 4 *Lactobacillus* species were increased, whereas the abundances of 5 *Clostridium* species were decreased compared to individuals without diabetes. *Lactobacillus* species were positively correlated with fasting glucose and glycosylated hemoglobin A1c (HbA_{1c}). However, *Clostridium* species were negatively correlated to fasting glucose, HbA_{1c}, insulin and plasma triglycerides [14]. In an cohort of Japanese T2D patients, the numbers of *Clostridium coccoides*, *Atopobium*, and *Prevotella* were decreased, while the quantities of total *Lactobacillus* were increased compared to those that were not diabetic [15]. This high *Lactobacillus* level might reflect the original numbers of bacteria in T2D patients because no significant differences were found between the participants who consumed yogurt and those who did not. Currently, the reason for the high counts of *Lactobacillus* in T2D patients remains unclear. Although these independent studies revealed an association between T2D and the gut microbiota, some other discrepancies should not be ignored. For example, neither