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Review Article

Possible Roles of Gut Microbiota in Maternal Transmission of Type-2 Diabetes Mellitus

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Abstract
Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders, associated with significant mortality and reduced quality of life. The incidence of T2DM has increased rapidly in recent decades, especially in developing countries. T2DM is a multifactorial disease influenced by genetics, epigenetics, and environmental factors. One intriguing feature of T2DM is its familial aggregation and excess maternal transmission of disease from affected mothers to their offspring. However, genetic and epigenetic mechanisms alone do not fully explain this relatively high rate of maternal transmission. The gut microbiome has been shown to exert significant effects on glucose metabolism, body fat content, and insulin resistance. Moreover, the gut flora is partially acquired from the mother, either during pregnancy or after birth. Although the gut flora changes rapidly in response to environmental factors, a signature of the maternal microbiota can be traced in the offspring. Thus, a similar microbiome within a semi-haploidentical genetic context may increase susceptibility to T2DM in offspring. This study discussed current evidence on the importance of gut flora in the pathophysiology of T2DM and explored potential mechanisms of action.
Keywords: Type 2 diabetes mellitus, Glucose metabolism, Gut microbiome, Familial aggregation, Maternal transmission

Introduction

Diabetes mellitus is one of the leading causes of mortality related to non-communicable diseases worldwide.[1] Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diabetes cases.[2,3] The global morbidity of T2DM has doubled over the last decades, and its incidence is estimated to rise to 366-439 million cases by 2030, constituting 7.7% of the world's adult population aged 20–79 years.[2,4,5] Aging, urbanization, and industrial lifestyles are believed to account for the increased incidence of T2DM.[4] Accordingly, developing countries have reported the majority of new T2DM cases in recent years. Asia, as a rapidly developing continent, has emerged as the new epicenter of T2DM due to the fast rate of urbanization and lifestyle transitions over a relatively short period.[4] Given that T2DM could become a serious global health problem in the coming decades, expanding the current knowledge on its pathophysiology could profoundly help its prevention and treatment. T2DM is a multifactorial disease with potential roots in both genetics and environmental factors. Moreover, epigenetics has emerged as one of the key players in the pathophysiology of this disease. For instance, intrauterine malnutrition and low birth weight have been associated with an increased incidence of T2DM.[6-8] Although substantial effort has been made in recent years to clarify the pathophysiology of T2DM, multiple aspects remain poorly understood. In the present review, we discussed the evidence on the familial aggregation of T2DM, with a focus on the possible impact of gut microbiota on the maternal transmission of disease risk.

Familial Aggregation and Maternal Transmission of Type 2 Diabetes Mellitus

Several studies have reported familial aggregation of T2DM across various geographic areas.[9-12] Generally, a common finding of these studies is the higher incidence of T2DM in offspring of mothers suffering from T2DM. Studies conducted on Europid populations have suggested a substantial maternal transmission of T2DM.[13,14] Alcolado and Alcolado[12] reported that among patients with a single affected parent, mothers with T2DM were significantly more prevalent than fathers (207 mothers vs. 82 fathers). They concluded that maternal factors appear to play an important role in the inheritance of T2DM. Young et al[15] found that a maternal history of T2DM was present in 60% of Caucasian and West Indian T2DM patients, while in Asian patients, this percentage was only 34.33%. Familial aggregation and higher maternal transmission were also reported by Arfa et al[16] in a Tunisian T2DM population. Although there are numerous reports supporting the maternal transmission of T2DM, Viswanathan et al[10] did

not observe any significant maternal transmission among the Indian population.

Genetic Explanations for the Familial Aggregation of Type 2 Diabetes Mellitus

When discussing the familial aggregation and maternal transmission of a disease, the first factor that comes to mind is genetics. It has been reported that siblings of patients with T2DM have a 2-3-fold higher risk of developing the disease compared with the general population. Having one parent with T2DM increases the offspring's risk by 30-40%, while having T2DM in both parents increases the risk by 70%.[17-19] Genome-wide association studies identified *HHEX/IDE* and *SLC30A8* as novel T2DM-associated loci.[20-22] Over the past decade, advances in genetic association studies have enabled the identification of at least 75 independent genetic loci related to T2DM, thus providing a better understanding of its genetic basis.[19] However, defining heritability-linked genes and alleles responsible for the maternal transmission of T2DM remains controversial. A large-scale genetic study on T2DM failed to demonstrate a strong correlation between T2DM and genetic background. This survey revealed that common alleles with relatively low effect size (odds ratio 1.10-1.40) could account for only 10–15% of T2DM heritability.[23] Furthermore, most introduced variants are located in intergenic and non-coding regions, making it difficult to explain their mechanistic association with disease pathophysiology. Asamoah et al[24] demonstrated that the rs7903146 allele of *TCF7L2* is associated with the incidence of T2DM in the sub-Saharan African population. Epigenetics has also been recognized as another determining factor in the pathogenesis and familial aggregation of T2DM. Environmental factors may induce epigenetic modifications that can have functional effects and, in some cases, be inherited without affecting the DNA sequence.[6,25-29] Intrauterine exposure to hyperglycemia can also lead to diabetes and obesity in offspring. It is important to note that epigenetic changes are generally reversible, which makes them potential targets for therapeutic purposes.[30,31] One of the first epigenome-wide association studies on T2DM was carried out by Orrhage and Nord,[32] who identified a CpG DNA methylation signature associated with T2DM in non-promoter sites. They concluded that these methylations can alter the DNA binding sites of T2DM-related transcription factors through cis-acting regulatory elements. Subsequent studies independently reported differential methylation at a CpG site (cg19693031) within the *TXNIP* gene, which was significantly associated with T2DM morbidity.[33-35] Although paternal or maternal epigenetic changes have been confirmed in the physiopathology of some diseases,[36] there is currently no similar evidence explaining the maternal transmission of T2DM through epigenetic mechanisms.[9,37,38]

Type 2 Diabetes Mellitus and Gut Flora

The human gut is densely populated with commensal and symbiotic bacteria.[39] The gut microbiota plays a crucial role in shaping the host's defense against pathogens, establishing mucosal immunity, promoting intestinal microvilli, and degrading non-digestible carbohydrates.[40] Increasing evidence suggests that intestinal bacterial species significantly influence glucose metabolism, diet-induced obesity, obesity-associated inflammation, and insulin resistance.[40] Notably, a higher body fat content correlates with elevated fasting glucose and insulin levels.[25]

The first evidence linking gut microbiota to altered glucose metabolism was reported in 2004.[25,41] It was found that the conventionalization of adult germ-free C57BL/6 mice with microbiota harvested from the cecum of normal mice resulted in a 60% increase in body fat and the development of insulin resistance within 2 weeks, despite a reduction of food intake.[25] Moreover, germ-free mice fed a high-fat diet exhibited lower insulin resistance compared to conventionally raised mice.[42] Human newborns receiving an antibiotic regimen are more prone to obesity in later childhood, likely due to alterations in the gut microbiome.[43]

The balance between *Bacteroides* and *Firmicutes*, the two main phyla of gut microbiota, is critically important in the development of T2DM. Additionally, the association between Proteobacteria such as *Escherichia coli* and lipopolysaccharide (LPS)-induced inflammation leading to insulin resistance has been well documented.[44,45] Bacterial components such as LPS can trigger innate immune responses in the gut mucosal immune system, resulting in the secretion of interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6, which collectively promote insulin resistance (Figure 1). The gut microbiome can also affect glucose metabolism by converting the primary bile acids into secondary bile acids (Figure 2). While primary bile acids can contribute to insulin resistance,[46] the secondary acids can protect against obesity and insulin resistance.[47-49] Treatment with vancomycin has been shown to decrease the levels of secondary bile acids in the intestinal lumen by changing the gut flora.[50] Moreover, gut microbiota can metabolize non-digestible carbohydrates into short-chain fatty acids (SCFAs). SCFAs are highly important modulators of immune responses, especially in the gut (Figure 3). Butyrate, as a principal SCFA, contributes to GLP1 secretion from epithelial cells, thereby providing protection against obesity and insulin resistance.[51] In addition, butyrate promotes the differentiation of regulatory T cells (Tregs) in Peyer's patches of the gut.[52] These Tregs can inhibit insulin resistance by suppressing the release of pro-inflammatory cytokines.[53] Other SCFAs, such as propionate and acetate, can trigger intestinal gluconeogenesis and lipogenesis that are protective against diabetes and obesity.[51,54] Conversely, a decrease in butyrate-producing bacteria populations contributes to insulin resistance.[26]

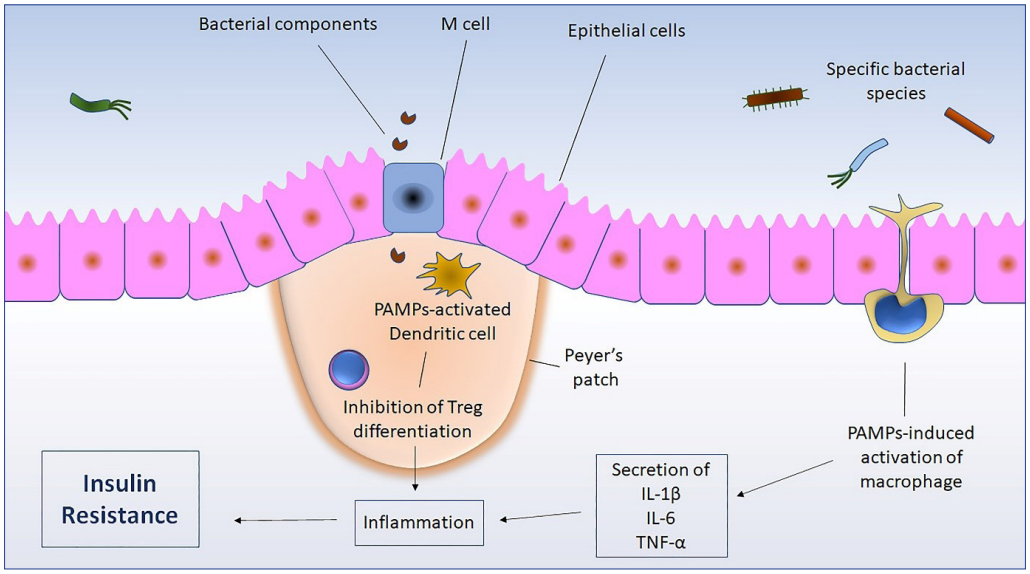

Figure 1. Involvement of Some Gut Bacteria in the Development of Insulin Resistance Through PAMPs- Mediated Inflammation in the Gut. *Note.* PAMPs: Pathogen-associated molecular patterns

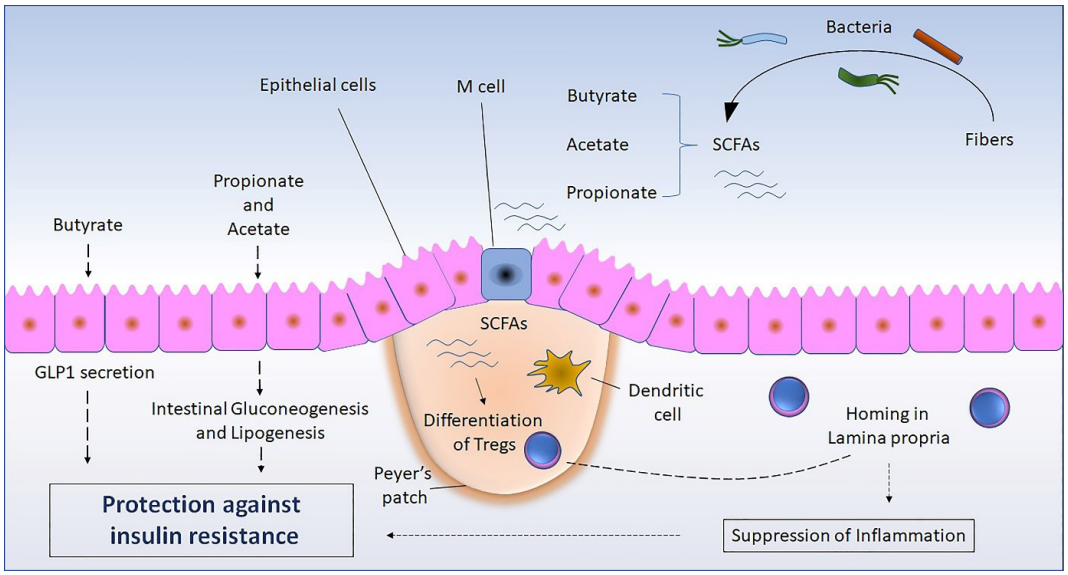

Figure 2. The Impact of the Gut Microbiome on Bile Acid Metabolism and Its Effect on Insulin Resistance

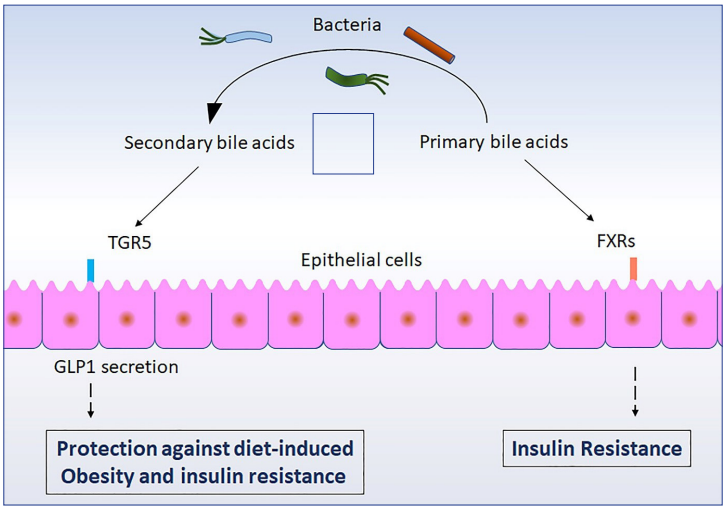

Figure 3. Schematic Illustration of the Gut Microbiome's Role in the Production of SCFAs and Their Impact on Glucose Tolerance. *Note.* SCFA: Short-Chain fatty chains

Maternal Transmission of the Intestinal Flora to Offspring

Studies on identical twins demonstrated that the gut microbiome is relatively heritable. Moreover, some species are more heritable, while others are more responsive to environmental conditions. The most heritable species is C*hristensenellaceae*, which is mainly assumed to be associated with health and glucose tolerance.[41,55] Although rapid changes take place in the gut microbiome in response to different nutritional regimens and environmental conditions, a signature of the microbiome is attributable to each person, provided there is no history of aggressive antibiotic therapy.[56,57] The gastrointestinal tract of normal newborn infants is sterile but becomes colonized immediately after birth by environmental organisms.[28] However, in the last decade, investigators suggested that pregnancy may be the initial time of bacterial exposure for the developing fetus.[6,7,29] Some studies have shown that high counts of coagulase-negative enterococci, staphylococci, and enterobacteria colonize the intestine of vaginally and cesarean-delivered term and preterm infants, even from the first day of life. Other studies have suggested that low levels of bacteria in umbilical cord blood, amniotic fluid, placenta, and fetal membrane may contribute to the development of the fetal immune system prior to birth.[6-8] However, the vaginal and intestinal flora of the mother are the primary sources of the infant's intestinal flora. It has been proposed that the composition of the initial gut flora exerts a long-lasting effect on the human microbiome.[32,33] Therefore, the initial development and maturation of the neonatal microbiome are largely determined by maternal microbiota, and any disruption in mother-to-newborn bacterial transmission may increase the risk of autoimmune and metabolic disorders, including diabetes, in the offspring.[34,35,37,38] This topic becomes particularly interesting when considering the semi-haploidentical relationship of mother to offspring, especially regarding HLA molecules, which are key immunologic determinants in the incidence of T2DM.[58] Thus, the transmitted flora will encounter an immune system that is somewhat similar to the maternal immune system.

Effects of Probiotics on Type 2 Diabetes Mellitus

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a beneficial health effect on the host".[59] Prebiotics and probiotics are conventional tools for dietary-mediated modulation of the intestinal microbial community.[59-61] The beneficial effects of these modulators could be summarized as: shaping the intestinal immune system, increasing mineral bioavailability, preventing gastrointestinal infections, ameliorating inflammatory bowel disease, and reducing the risk of malignancies and metabolic disorders.[62-70] Dehghan et al[71] reported that prebiotic supplementation can ameliorate inflammation and metabolic endotoxemia in women with T2DM. Probiotics and prebiotics can also reduce levels of waste products such as urea, creatinine, and uric acid.[72-74] In another study, patients receiving lactulose prebiotic showed higher colony counts of bifidobacteria and lactobacilli,[71,75] bacteria with verified benefits on glucose metabolism and general health.[72-74] Some studies showed that certain probiotics can secrete molecules analogous to insulin with similar biological activity in animals and humans.[76,77] In a randomized trial, Tonucci et al[78] showed that probiotic consumption improves glycemic control in T2DM patients. Several meta-analyses have also verified the beneficial impact of probiotics in the management of T2DM.[79-81]

Conclusion

Regarding the relative heritability of the gut microbiome and the prominent role of gut flora in the initiation and progression of T2DM, mother-to-offspring transmission of gut microbiome appears to contribute to the incidence of T2DM along with previously defined factors such as genetics, epigenetics, and lifestyle. We propose this as a potential explanation for the high prevalence of familial aggregation of T2DM and the excess maternal transmission. In this regard, bacteria with properties such as inability to metabolize bile acids, inability to produce SCFAs, and heightened activation of innate immune responses may be considered diabetogenic. However, T2DM is a multifactorial condition, influenced by a myriad of environmental and genetic factors. Based on accumulating evidence, the maternal microbiome could be regarded as a novel contributor in the pathogenesis of T2DM.

Authors' Contribution

Conceptualization: Hamid Tayebi Khosroshahi.
Funding acquisition: Alireza Mardomi.
Investigation: Hamid Tayebi Khosroshahi.
Visualization: Alireza Mardomi.
Writing-original draft: Hamid Tayebi Khosroshahi.
Writing-review & editing: Alireza Mardomi.

Competing Interests

The authors declare no competing interests.

Ethical Approval

Not Applicable.

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