A review on involvement of gut microbiota in insulin dependent diabetes

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Abstract

Type 1 diabetes, which is insulin-dependent, is the most common autoimmune illness in children. It even can cause mortality in young adults. Genetic, epigenetic, as well as external factors all have the potential to influence this illness. This condition may be brought on by a major alteration in the composition of the intestinal microbiota. Recent study data on those with Type 1 diabetes along with additional animal specimens lends more credence to the idea that variations in the overall makeup of the gut microbiome precede the onset of the condition. In this instance our focus is on the correlation underlying alterations in the makeup of the microbiota in the intestines and the onset of Type 1 diabetes, as well as any potential biological causes of this occurrence and evidence-based measures that might be taken to avoid it.

Keywords: Diet, Autoimmune Illness, GUT Microbiota, Immune System, Type 1 Diabetes.

Introduction

Type 1 diabetes (T1D) or juvenile diabetes also known as insulin-dependent diabetes mellitus (IDDM) is a multifactorial, immune-mediated disease, characterized by the progressive destruction of autologous insulin-producing beta cells (β cells) of islets of Langerhans of pancreas (Fig. 1) (American Diabetes Association, 2020). Insulin is a 51 amino acid containing peptide hormone synthesized by β cells which plays an important role in the regulation of blood sugar levels. Frequent urination, increased thirst, increased hunger, weight loss, and other significant complications like ketoacidosis, coma, or even death are common signs of hyperglycemia. Additional signs include blurred vision, exhaustion and sluggish wound healing. Heart disease, stroke, kidney failure, foot ulcers, and eye damage are examples of long-term consequences of T1D. Diabetes mellitus is diagnosed by measuring fasting (F) & postprandial blood glucose level (PP) or glycated haemoglobin (HbA1C) in the blood. In T1D, autoantibodies are present against insulin or the protein GAD-65(Glutamic acid decarboxylase), IA-2, IA-2β, and/or ZNT8 proteins and declining levels/absence of C-peptide (Zhou et al., 2020; Hasain et al., 2020; Sharma et al., 2019). Variations in the three HLA class II genes i. e HLA-DRB1, HLA-DQA1 and HLA-DQB1 involved in antigen presentation account for around half of the disease's heredity (Sharma et al., 2020). Genetic, epigenetic, and environmental factors are responsible for destruction of beta cells and development of T1D (Altveş et al., 2020). T1D incidence has increased steadily over the past few decades, and this trend cannot be attributed to genetic factors only (Li et al., 2020). Changes in our way of life, such as those in our nutrition, hygiene, and use of antibiotics, have already been proposed as a potential cause of the increased occurrence of T1D. Microbiota, which are impacted by all of these factors, have only recently been acknowledged as important environmental factors affecting the development of T1D (Nyavor et al., 2020).

Insulin-dependent diabetes is an autoimmune condition brought on by inadequate insulin synthesis as a result of the Langerhans beta cells' death. It affects children and young adults at alarming rates. Environmental causes or a hereditary flaw may be to blame. Due to their role in immune system development and upkeep the gut microbiota has been acknowledged as one of the most important aspects of the environment. The four major phyla Firmicutes, Bacteroidetes,
Actinobacteria, and Proteobacteria make up over ninety-five per cent of the microbiota in the intestines. In the mature human gut, Firmicutes and Bacteroidetes are the most widespread (Manchanyake et al., 2019; Hidalgo-Cantabrana et al., 2017). Youngsters who receive breast milk have a predominance of actinobacteria in their intestines. The most prevalent member of the Actinobacteria family along with a probiotic species is Bifidobacterium. These are frequently referred to as the "hidden organ" of the human body because of the wide range of physiologic tasks they perform, including defending against pathogens, generating energy, preserving intestinal epithelial credibility, as well as managing inflammatory processes (Takagi et al., 2018).

According to the existing research, an individual who is genetically predisposed to Insulin dependent diabetes may have an abnormal growth or shift of their beneficial microbiota, which could lead to autoimmune damage of cells (Pasolli et al., 2019; Knip et al., 2017). The evidence that self or non-self immunoregulation is regulated by bacteria found within the gastrointestinal system in a mutually beneficial manner supports the hypothesis that immunological schooling promptly in life is necessary (Mishra et al., 2020). A second modification in the gut microbiota known as "dysbiosis" as an outcome of the gut mucosal barrier's leakiness enhances the risk of illness. Pediatrics immunoregulation maturity has been pushed back as a result of either of factors (Clarke et al., 2019). The impact of gut microbiota on the onset of T1D will be discussed in brief in this review, along with the potential for developing novel microbiota-based therapeutics for the prevention and treatment of T1D.

Materials and Methods

We undertook a thorough investigation into the complex pathways linking GM dysbiosis with the onset of T1DM and accompanying microvascular consequences using literature published over the previous five years, up until August 2023. The electronic databases Scopus, Google Scholar, and the US National Library of Medicine (PubMed) were utilized to find pertinent papers on our topic. To prevent using any dated information, studies published between 1 January 2015 and 1 August 2023 were chosen. The terms gut microbiota, dysbiosis, type 2 diabetes, immunologic pathways, and therapeutic approaches were all used in various combinations. There were several different article categories included, including reviews, guidelines, clinical trials, randomized controlled trials, multicenter studies, and meta-analyses. A brief summary of all the pertinent data that was taken from the chosen publications is provided here.

Gut Microbiota Composition in Type 1 Diabetic Humans

During a new investigation, sixteen healthy individuals and Sixteen folks with insulin dependent diabetes were used from Spain. It came to light that when contrasted to Sixteen healthy kids, those having insulin dependent diabetes had higher concentrations of Bacteroides as well as Veillonella and lower concentrations of Bifidobacterium along with Lactobacillus (Hidalgo-Cantabrana et al., 2017; Komaroff et al., 2017). In people with Insulin dependent diabetes, the Firmicutes/Bacteroides (F/B) ratio is substantially lower (Takahashi et al., 2020). So, Bacteroides are associated positively with insulin dependent diabetes and Firmicutes association is negative. Not only the F/B ratio but also the diversity of the gut microbiota also declines in insulin dependent diabetes patients. The Clostridium clusters IV and XIVa (a type of Firmicutes) butyrate producers were reduced, according to metagenomic information collected in numerous researches (Sanchez-Rodriguez et al., 2020). Because butyrate generators convert lactate in butyrate, that is linked to tight junction development, mucin production, as well as enhances gut epithelial credibility, that they operate as guardians (Galle-Treger et al., 2019). The biosynthesis of the tight junction and the development of mucin are unrelated processes that lactate undergoes when it is fermented to short-chain fatty acids like propionate, acetate, and succinate. Therefore, butyrate producers compared to propionate producers benefit from a healthy gut. Reduced butyrate production has also been observed among kids with pancreatic autoimmune disease including seniors with long-standing insulin dependent diabetes (Cryan et al., 2019).

Diabetes patients with insulin dependent conditions additionally experienced a drop in Bifidobacterium levels. In many instances, 16S rRNA sequencing yields findings that are identical as well. The study of the microbial proteome including stool cultures also revealed poor Bifidobacterium colonization (Maffeis et al., 2016). Varying Bacteroides collected from faces of patients as well as healthy people have a tendency to show that certain species, such as B. graminisolvens, B. cellulosityicus, B. finegoldii, B. stercoris, B. eggerthii, and B. fragilis, each present at 3.45%, have been isolated solely from insulin-dependent patients with diabetes (Knip et al., 2017; Kieser et al., 2017).
Role of GUT Microbiota in the Pathogenesis of Type 1 Diabetes

The two most often utilized animal models for autoimmune diabetes research include non-obese diabetic (NOD) mice and bio-breeding diabetes-prone (BB-DP) mice. Both versions have insulin dependent diabetes and the insulin dependent diabetes susceptibility gene. In BB-DP rats, receiving treatment with antibiotics lowers their likelihood of developing illness; NOD rats also experience this consequence (Galle-Treger et al., 2019; Meroni et al., 2019). Diabetes increases when NOD mice undergo regeneration in a specified pathogen-free (SPF) environment (Rukavina Mikusic et al., 2020).

It implies that some particular microbiological invasions offer protection from T1D. Probiotics with *Clostridium butyricum* are used to prevent insulin dependent diabetes from developing in NOD mice, which may not only prevent it from happening but also boost the F/B ratio (Takahashi et al., 2020; Karuranga et al., 2019). Transplanted of faces microbiota (FMT) alters insulin dependent diabetes susceptibility as well (Mariño et al., 2019). When compared with non-obese diabetes-resistant (NOR) mice, NOD animals have higher levels of diabetogenic microorganisms. According to an investigation (Lucier et al., 2022; Valdes et al., 2018), the FMT from NOD to NOR mice begin with insulitis in NOR mice. Whenever the whole microbiota of NOD mice with a low prevalence had been introduced into NOD mice with high prevalence, the rate of disease did not diminish. However, when one particular microbe (such *Akkermansia muciniphila*) has been introduced into high-incidence NOD mice, it slows the progression of diabetes, indicating that a particular microorganism may have a role in the pathogenesis of insulin dependent diabetes (Zhu et al., 2018).

About six months after being born, when insulin dependent diabetes patients had it, 16S genome sequencing of the fecal bacterial population revealed a larger level of *Bacteroidetes* over *Firmicutes*, although the proportion of F/B declines over time in autoimmune instances. However, it decreases in people without autoimmune illness (Zhu et al., 2018). Investigations have shown that compared to non-breastfed newborns, newborns who are breastfed have a stable gut microbiota comprised mainly of *Bifidobacterium* (Yu et al., 2017). According to one study, supplementing with probiotic during the first four weeks of pregnancy lowers the likelihood of cell autoimmunity in newborns who are genetically predisposed to insulin dependent diabetes (Michael et al., 2017; McCoy et al., 2017). A youngster who consumes prebiotics for a period of one year could modify the intestinal permeability as well as the overall makeup of their gut microbiota that will increase the functionality of their cells (Fujio-Vejar et al., 2017).

Fig. 2 Possible role of gut microbiota in the pathogenesis of type 1 diabetes
Possible Mechanism to Support the GUT Microbial Impact on the Development of Type 1 Diabetes

The gut bacteria community fluctuates in accordance with the diet because they are inherently able to digest some particular substrates (Ohira et al., 2017). As shown in Fig. 2, lactate can be transformed into butyrate or short-chain fatty acids like acetate, succinate, propionate, etc. The lactate model postulates that the lactic acid-along with butyrate-producing bacteria Prevotella and Akkermansia contribute to the maintenance of the gut epithelial layer's integrity (Aoki et al., 2017). Because butyrate causes mucin to be produced, which creates tight junctions. However, other bacteria, such Bacteroides and Veillonella, ferment lactate to create succinate, acetate, and propionate, which change the tight junction and enhance the openness of the epithelium (Oliveira et al., 2019). By preventing NK-B activation (signaling via the GPCR) and assisting in the development of the antioxidant defense system and NO generation, butyrate maintains the anti-inflammatory response in the healthy gut (Gomes, et al., 2017). Additionally, it promotes the development of Treg (regulatory T lymphocyte) cells outside of the thymus. Treg cells prevent T-cell proliferation and cytokine production while preserving homeostasis along with self-tolerance, which inhibits the immunological response (Veprik et al., 2016). In the -cells of NOD mice, butyrate also contributes to the expression of cathelicidin-related antimicrobial peptides (CRAMP). According to other researchers, this peptide operates by reducing the inflammatory response in the pancreatic islets (Zhao et al., 2018). Free fatty acid receptor 2 (FFAR2) is a further receptor that butyrate activation. It encourages the intestinal release of GLP-1 (glucagon-like peptide 1) and inhibits the buildup of fat (Ferris et al., 2017). It has been also reported that GLP-1 encourages release of insulin while inhibiting the release of glucagon (Lucier et al., 2022).

Gut microbiota’s effect on the innate immune mechanism

An essential part of the innate immune system is Toll-Like Receptors (TLR). It may trigger the innate immune system by identifying the pathogen-associated molecular pattern (PAMP) of bacteria (Sanna et al., 2019). Myeloid Differentiation Primary Response Gene 88 (MyD88) encodes a single type of the major adaptor proteins of several TLR, has been demonstrated to cause diabetes in NOD mice. According to published research, MyD88-deficient NOD mice are totally resistant from T1D when exposed to a microbial environment that is different from that of wild-type (WT) NOD mice (Louis et al., 2017). Therefore, the Myd88 gene's existence or lack in NOD mice alters the makeup of microorganisms.

Fig. 3 Possible mechanism to support the gut microbial impact on the development of type 1 diabetes

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According to another investigation, NOD mice with the deletion of the Toll/interleukin-1 receptor (TIR)-domain-containing-adaptor-inducing interferon (TRIF) were shielded from the onset of type 1 diabetes (Pingitore et al., 2017). The results of additional study suggested that changed onset of diabetes may be caused by modified gut bacteria (Fig. 3). In addition, germs isolated from WT NOD mice cause more inflammatory reactions in vitro than do TRIF-/- NOD mice. Comparing fecal specimens from TRIF-/- NOD and WT NOD mice, 16S rRNA sequencing was used to determine the diversity of the gut's microbes. This analysis revealed that Sutterella (Proteobacteria) along with Rikenella (Bacteroidetes) were less prevalent in TRIF-/- NOD mice than in WT NOD mice. Additionally, TRIF-/- NOD animals reported an increase in Turicibacter (Firmicutes) in contrast to WT NOD mice (Gomes et al., 2017; Jergens et al., 2019).

### Impact of gut microbiota on the Adaptive Immune system

The adaptive immune system's main building blocks, T helper 1 (Th1) and T helper 2 (Th2) cells, are impacted by the gut microbiota (Wahlström et al., 2016). Disruption to the cells in T1D is caused by a dispersion of the Th1/Th2 responses. The Foxp3 transcription factor, which is essential for the preservation of homeostasis including the onset of tolerance, is expressed during the developmental phase of regulatory T lymphocytes (Tregs). The production of IL-17 by Th17 cells, which have a role in the pathogenesis of T1D, helps to remove pathogens and stimulate inflammation. Depending on the level of TGF-β, Treg and Th17 cells diversified from naive CD4+ T cells. In order to maintain the autoimmunity under control, homeostasis between the Treg cells and the Th17 cell need to be preserved (Gomes et al., 2017; Rajani et al., 2018). In the killing of -cells, CD8+ T lymphocytes are crucial. The antibiotic therapy triggered the insulin-reactive pathogenic CD8+ T cells, hastening the onset of T1D in NOD mice (Nerild et al., 2018).

### Possibilities for Preventing and Controlling Type 1 Diabetes

Thirty percent of infants have a genetic predisposition to T1D, yet the majority never get the condition. It's crucial to fight off this illness. In this scenario, there are three distinct types of avoidance that we can consider: primary prevention, which occurs prior to seroconversion, secondary prevention, which occurs when B cell autoimmunity has already developed but aims to avert or postpone the onset of the disease, and tertiary prevention, which occurs while T1D has become already existing and aims to avoid the adverse effect (Schoeler et al., 2019).

### Primary Prevention of T1D

A newborn baby got the first inoculation from her mother during birth, the development of its gut microbial community starts with that but in the case of caesarean-born children, they got no natural inoculum from their mother (Zhuang et al., 2019). Naturally, a newborn baby got a *Lactobacillus*-dominated vagina inoculum from its healthy mother. So, a *Lactobacillus* inoculum should provide to the caesarean-born baby to mimic the natural phenomena. As the main source of *Bifidobacterium*, breastfeeding needs to be promoted in terms of lactation. It has been demonstrated that toddlers who drink formulated milk containing probiotics as well as prebiotics change their gut microbiota profile similarly compared with babies who breastfeed (Zhao et al., 2019).

### Secondary along with Tertiary Prophylaxis of T1D

After the onset of the autoimmune event, nutrition plays a major role in reducing or delaying the chance of developing T1D. The amount of carbohydrate consumed affects the T1D's advancement (Andraos et al., 2020). Proper probiotics as well as prebiotics need to be used in addition to a healthy diet for preventative purposes, as diet exerts a stronger influence on the metabolic activity of the microorganisms in our gut (Prieto et al., 2018). Fecal microbial transplantation (FMT) and the administration of a mucosa-protective medication are two more potential methods (Marcelino et al., 2019). It must be remembered that fecal transplantation's usefulness would be moderate or transient if it were to occur without any dietary changes. In this regard, mucosa-protective medications like gelatin tannate may be utilized for the purpose of barrier-modulating medication (Tosti et al., 2018). This medication creates links between mucin in order to form a bioprotective layer. In other words, it has a subliminal anti-inflammatory action (Qi et al., 2018).

For tertiary prevention, as the disease is already developed there are a few ways to prevent it such as pancreas transplant, pancreatic islets transplant, stem cell therapy, etc (Kim et al., 2016). Stem cell therapy has the advantage of regenerating capacity. But, none of those techniques are effective in the long term. Only fecal transplantation and a calorie-controlled diet can alter the microbes in the gut, increasing the efficiency of those treatments (Zhao et al., 2019).

### The Impact of the Mediterranean Diet on GUT Flora to Manage Type 1 Diabetes

A chronic autoimmune condition known as type 1 diabetes mellitus (T1DM) is brought on by a complicated interplay between genetic predisposition and environmental variables (Fig. 4) (Schoeler et al., 2019). Regarding the latter, it has been shown in multiple prior studies that the gut microbiota plays a crucial role in the pathogenesis of T1DM by influencing intestinal permeability, molecular mimicry, and modifying the innate and adaptive immune system (Andraos et al., 2020). However, it has recently been hypothesized that the gut microbiota and pancreatic -cells interact directly. This hypothesis is supported by the finding that the exocrine pancreas secretes both digestive enzymes and antimicrobial peptides (AMPs) (Prieto et al., 2018), including cathelicidins and defensins, into the intestinal tract. These AMPs play a crucial role in not only preventing infections but also in
controlling the gut microbiota (Additionally, as previously mentioned, cathelicidin modulates the functions of pancreatic -cells and exerts a trophic impact on them (Marcelino et al., 2019), which reduces inflammatory reactions and -cell death in diabetic people (Tosti et al., 2018). According to some researchers, the gut microbiota produces AMPs through SCFAs (Qi et al., 2018). As a result, gut dysbiosis may result in reduced levels of AMPs, especially of cathelicidin and beta-defensin-1 (Kim et al., 2016), which can cause the onset of autoimmune diabetes (Zheng et al., 2016). However, more research is required to better understand the precise mechanism by which the gut microbiota interacts with the immune system and pancreatic beta-cells (Kim et al., 2016).

![Diagram of the impact of the Mediterranean diet on gut flora to manage type 1 diabetes](image)

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**Fig. 4 The impact of the Mediterranean diet on gut flora to manage type 1 diabetes**

Diet has a significant impact on the gut microbiota's makeup. Numerous inflammatory and immune-mediated disorders have been linked to decreased fibre consumption, according to several observational studies (Zhao et al., 2018). The Mediterranean diet (MD), which emphasizes a high intake of grains (ideally whole grains), legumes, nuts, fruits, vegetables, and seafood, may offer some protection in this situation. The functional qualities of many of the MD's defining traits have favourable effects on health and well-being (Veprik et al., 2016). The primary significant factors of the microbial diversity of the intestine are eating habits, and food components have an impact on both microbial populations and their metabolic processes from an early age (Rajani et al., 2018). Additionally, dietary metabolites affect how the immune system reacts. Epithelial integrity or mucosal immunity are two mechanisms by which food metabolites are thought to primarily exert their effects in the intestine (Zhuang et al., 2019). Due to the compromised epithelial integrity, bacteria and/or their products, such as food antigens and lipopolysaccharides, can diffuse from the intestinal lumen to the tissues and stimulate immune cells more effectively, which may contribute to the pathogenesis of autoimmune diseases like T1DM (Ferris et al., 2017). With MD, consuming a lot of fibre and, consequently, prebiotics, enables the microbiota to have a healthy microbial balance (Prieto et al., 2018). Additionally, as dietary fiber intake increases, the anaerobic gut microbiota produces more short-chain fatty acids (SCFAs), which support gut homeostasis and are also a source of tryptophan metabolites and omega-3 fatty acids (Rajani et al., 2018). Additionally, a better metabolic management is facilitated by a higher consumption of polyunsaturated fatty acids and omega-3 fatty acids (Veprik et al., 2016).

**Conclusion**

The individual's diet determines how the gut microbiota is made up. Consequently, a balanced diet can encourage immune system development. T1D may manifest as the result of dysbiosis. A dietary supplement generated from gut microbiota may cause or stop the development of T1D by fostering or suppressing a state of inflammation. Dysbiosis linked with T1D is primarily caused by members of the genus Bacteroides. Regulated nutrition therapy is the most potential strategy for avoiding T1D in kids with autoimmunity out of all the strategies mentioned herein.
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The author declares that the work has consent for publication.

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