



[Science Archives \(ISSN:2582-6697\)](https://doi.org/10.47587/SA.2023.4403)

Journal homepage: www.sciencearchives.org



<https://doi.org/10.47587/SA.2023.4403>

Review Article



A review on involvement of gut microbiota in insulin dependent diabetes

Diptendu Sarkar¹✉ and Kamalesh Das²

¹Department of Microbiology, Ramakrishna Mission Vidyamandira, Belur Math, Howrah-711202, West Bengal, India

²Department of Physiology, Uluberia College, Uluberia, Howrah-711315, West Bengal, India

Received: May 26, 2023/ Revised: June 24, 2023/Accepted: June 25, 2023

✉ Corresponding Author: diptendu81@gmail.com

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-2 β , 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 (Manchanayake 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).

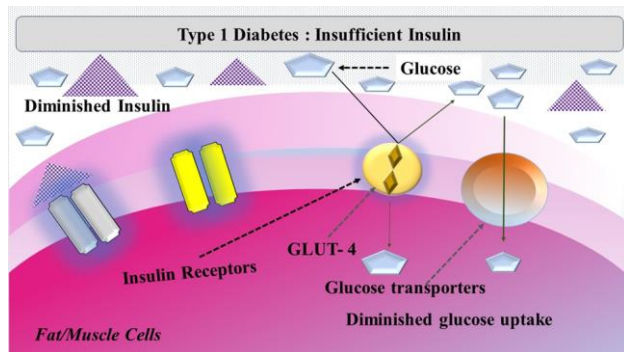


Fig. 1 Type 1 diabetes (T1D)/ juvenile diabetes/Insulin dependent diabetes mellitus (IDDM) is an autoimmune disease

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 proteomic including stool cultures also revealed poor *Bifidobacterium* colonization (Maffei 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. cellulosityticus*, *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).

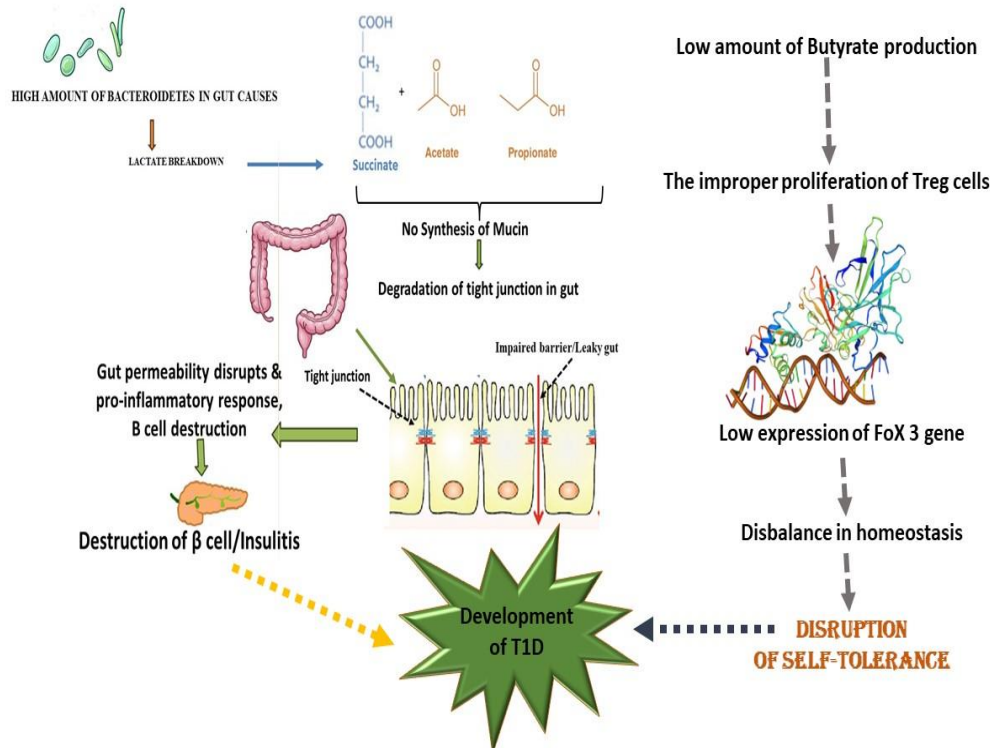


Fig. 2 Possible role of gut microbiota in the pathogenesis of type 1 diabetes

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 feces 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 insulinitis 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).

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 (Veprík 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.

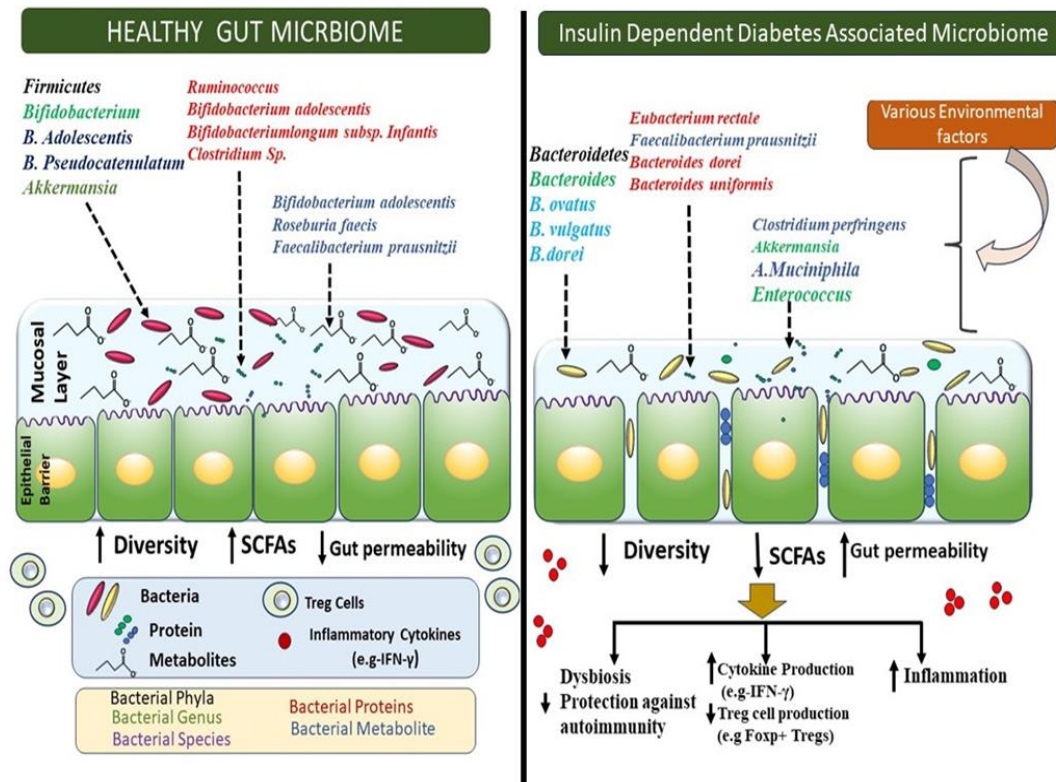


Fig. 3 Possible mechanism to support the gut microbial impact on the development of type 1 diabetes

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 diverged 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 β -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 β -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 β -cells and exerts a trophic impact on them (Marcelino et al., 2019), which reduces inflammatory reactions and β -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 β -cells (Kim et al., 2016).

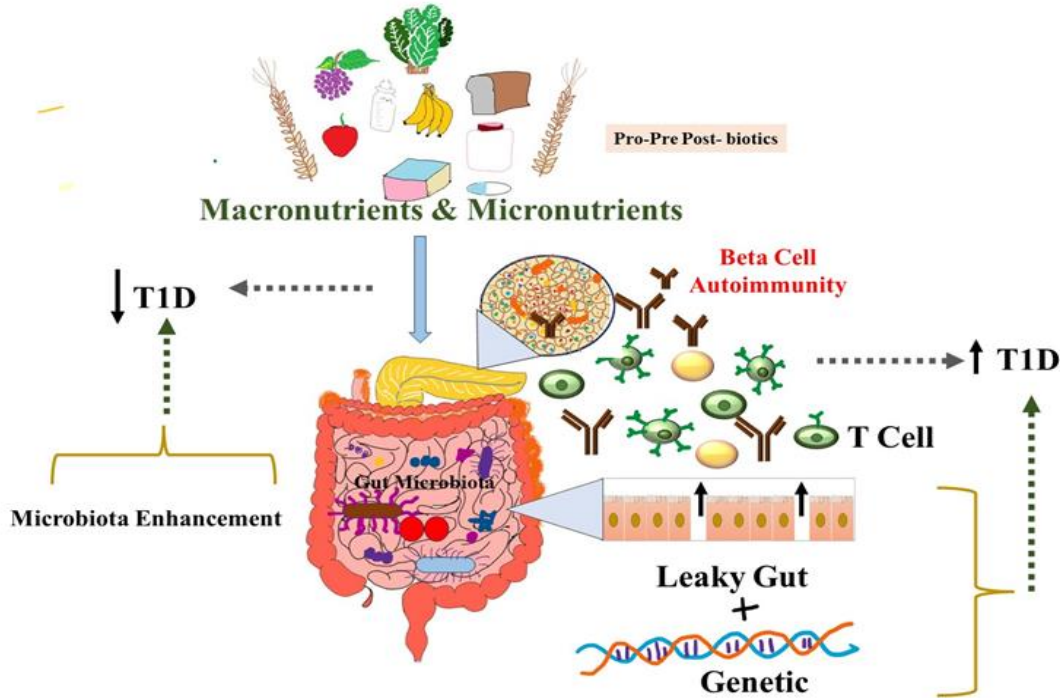


Fig. 4 The impact of the mediterranean diet on gut flora to manage type 1 diabetes

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.

Consent for publication

The author declares that the work has consent for publication.

Conflict of Interest

The author hereby declares no conflict of interest.

Funding support

The author declares that they have no funding support for this study.

References

- Altveş, S., Yildiz, H. K., & Vural, H. C. (2020). Interaction of the microbiota with the human body in health and diseases. *Bioscience of Microbiota, Food and Health*, 39(2), 23–32. <https://doi.org/10.12938/bmfh.19-023>
- American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes – (2020). *Diabetes Care*, 43(Suppl. 1): S14–31. <https://doi.org/10.2337/dc20-S002>.
- Andraos, S., Lange, K., Clifford, S. A., Jones, B., Thorstensen, E. B., Kerr, J. A., O’Sullivan, J. M. (2020). Plasma Trimethylamine N-Oxide and Its Precursors: Population Epidemiology, Parent–Child Concordance, and Associations with Reported Dietary Intake in 11- to 12-Year-Old Children and Their Parents. *Current Developments in Nutrition*, 4(7), nzaa103. <https://doi.org/10.1093/cdn/nzaa103>
- Aoki, R., Kamikado, K., Suda, W., Takii, H., Mikami, Y., Suganuma, N., . . . Koga, Y. (2017). A proliferative probiotic Bifidobacterium strain in the gut ameliorates progression of metabolic disorders via microbiota modulation and acetate elevation. *Scientific Reports*, 7(1). <https://doi.org/10.1038/srep43522>
- Clarke, G., Sandhu, K. V., Griffin, B. T., Dinan, T. G., Cryan, J. F., & Hyland, N. P. (2019). Gut Reactions: Breaking Down Xenobiotic–Microbiome Interactions. *Pharmacological Reviews*, 71(2), 198–224. <https://doi.org/10.1124/pr.118.015768>
- Cryan, J. F., O’Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., . . . Dinan, T. G. (2019). The Microbiota-Gut-Brain Axis. *Physiological Reviews*, 99(4), 1877–2013. <https://doi.org/10.1152/physrev.00018.2018>
- Ferris, S. T., Zakharov, P. N., Wan, X., Calderon, B., Artyomov, M. N., Unanue, E. R., & Carrero, J. A. (2017). The islet-resident macrophage is in an inflammatory state and senses microbial products in blood. *Journal of Experimental Medicine*, 214(8), 2369–2385. <https://doi.org/10.1084/jem.20170074>
- Fujio-Vejar, S., Vasquez, Y., Morales, P., Magne, F., Vera-Wolf, P., Ugalde, J. A., Gotteland, M. (2017). The Gut Microbiota of Healthy Chilean Subjects Reveals a High Abundance of the Phylum Verrucomicrobia. *Frontiers in Microbiology*, 8. <https://doi.org/10.3389/fmicb.2017.01221>
- Galle-Treger, L., Sankaranarayanan, I., Hurrell, B. P., Howard, E., Lo, R., Maazi, H., Akbari, O. (2019). Costimulation of type-2 innate lymphoid cells by G1TR promotes effector function and ameliorates type 2 diabetes. *Nature Communications*, 10(1). <https://doi.org/10.1038/s41467-019-08449-x>
- Gomes, J. M. G., Costa, J. D. A., & Alfenas, R. D. C. G. (2017). Metabolic endotoxemia and diabetes mellitus: A systematic review. *Metabolism*, 68, 133–144. <https://doi.org/10.1016/j.metabol.2016.12.009>
- Hasain, Z., Mokhtar, N. M., Kamaruddin, N. A., Mohamed Ismail, N. A., Razalli, N. H., Gnanou, J. V., & Raja Ali, R. A. (2020). Gut Microbiota and Gestational Diabetes Mellitus: A Review of Host-Gut Microbiota Interactions and Their Therapeutic Potential. *Frontiers in Cellular and Infection Microbiology*, 10. <https://doi.org/10.3389/fcimb.2020.00188>
- Hidalgo-Cantabrana, C., Delgado, S., Ruiz, L., Ruas-Madiedo, P., Sánchez, B., & Margolles, A. (2017). Bifidobacteria and Their Health-Promoting Effects. *Microbiology Spectrum*, 5(3). <https://doi.org/10.1128/microbiolspec.bad-0010-2016>
- Jergens, A. E., Guard, B. C., Redfern, A., Rossi, G., Mochel, J. P., Pilla, R., Suchodolski, J. (2019). Microbiota-Related Changes in Unconjugated Fecal Bile Acids Are Associated With Naturally Occurring, Insulin-Dependent Diabetes Mellitus in Dogs. *Frontiers in Veterinary Science*, 6. <https://doi.org/10.3389/fvets.2019.00199>
- Karuranga, S., Malanda, B., Saeedi, P. and Salpea, P. (2019). (Eds.) IDF Diabetes Atlas, 9th Edition Committee IDF DIABETES ATLAS: Brussels, Belgium, 2019; ISBN. <https://978-2-930229-87-4>.
- Kieser, K. J., & Kagan, J. C. (2017). Multi-receptor detection of individual bacterial products by the innate immune system. *Nature Reviews Immunology*, 17(6), 376–390. <https://doi.org/10.1038/nri.2017.25>
- Kim, C. (2016). B cell-helping functions of gut microbial metabolites. *Microbial Cell*, 3(10), 529–531. <https://doi.org/10.15698/mic2016.10.536>
- Kim, M., Qie, Y., Park, J., & Kim, C. (2016). Gut Microbial Metabolites Fuel Host Antibody Responses. *Cell Host & Microbe*, 20(2), 202–214. <https://doi.org/10.1016/j.chom.2016.07.001>
- Knip, M., & Honkanen, J. (2017). Modulation of Type 1 Diabetes Risk by the Intestinal Microbiome. *Current Diabetes Reports*, 17(11). <https://doi.org/10.1007/s11892-017-0933-9>
- Komaroff, A. L. (2017). The Microbiome and Risk for Obesity and Diabetes. *JAMA*, 317(4), 355. <https://doi.org/10.1001/jama.2016.20099>
- Li, W. Z., Stirling, K., Yang, J. J., & Zhang, L. (2020). Gut microbiota and diabetes: From correlation to causality and mechanism. *World Journal of Diabetes*, 11(7), 293–308. <https://doi.org/10.4239/wjd.v11.i7.293>
- Louis, P., & Flint, H. J. (2016). Formation of propionate and butyrate by the human colonic microbiota. *Environmental Microbiology*, 19(1), 29–41. <https://doi.org/10.1111/1462-2920.13589>
- Lucier, J. and Weinstock, R. S. (2022). Diabetes Mellitus Type 1. In Stat Pearls; StatPearls Publishing: Treasure Island, FL, USA.
- Maffei, C., Martina, A., Corradi, M., Quarella, S., Nori, N., Torriani, S., Felis, G. E. (2016). Association between intestinal permeability and faecal microbiota composition in Italian children with beta cell autoimmunity at risk for type 1 diabetes. *Diabetes/Metabolism Research and Reviews*, 32(7), 700–709. <https://doi.org/10.1002/dmrr.2790>
- Manchanayake, L. N. (2019). The Impact of Gut Microbiota on Host Obesity. *Journal of Gastrointestinal & Digestive System*, 09(01). <https://doi.org/10.4172/2161-069x.1000591>
- Marcelino, G., Hiane, P. A., Freitas, K. C., Santana, L. F., Pott, A. and Donadon, J. R. (2019). Effects of olive oil and its minor components on cardiovascular diseases, inflammation, and gut microbiota. *Nutrients*, 11:1826. <https://doi.org/10.3390/nu11081826>.
- Mariño, E., Richards, J. L., McLeod, K. H., Stanley, D., Yap, Y. A., Knight, J., Mackay, C. R. (2017). Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. *Nature Immunology*, 18(5), 552–562. <https://doi.org/10.1038/ni.3713>
- McCoy, K. D., Ronchi, F., & Geuking, M. B. (2017). Host-microbiota interactions and adaptive immunity. *Immunological Reviews*, 279(1), 63–69. <https://doi.org/10.1111/imr.12575>
- Meroni, M., Longo, M., & Dongiovanni, P. (2019). Alcohol or Gut Microbiota: Who Is the Guilty? *International Journal of Molecular Sciences*, 20(18), 4568. <https://doi.org/10.3390/ijms20184568>

- Silverman, M., Kua, L., Tanca, A., Pala, M., Palomba, A., Tanes, C., Mathis, D. (2017). Protective major histocompatibility complex allele prevents type 1 diabetes by shaping the intestinal microbiota early in ontogeny. *Proceedings of the National Academy of Sciences*, 114(36), 9671–9676. <https://doi.org/10.1073/pnas.1712280114>
- Mishra, S. P., Karunakar, P., Taraphder, S., & Yadav, H. (2020). Free Fatty Acid Receptors 2 and 3 as Microbial Metabolite Sensors to Shape Host Health: Pharmacophysiological View. *Biomedicines*, 8(6), 154. <https://doi.org/10.3390/biomedicines8060154>
- Nerild, H. H., Christensen, M. B., Knop, F. K., & Brønden, A. (2018). Preclinical discovery and development of colesevelam for the treatment of type 2 diabetes. *Expert Opinion on Drug Discovery*, 13(12), 1161–1167. <https://doi.org/10.1080/17460441.2018.1538206>
- Nyavoy, Y., Brands, C. R., May, G., Kuther, S., Nicholson, J., Tiger, K., . . . Balemba, O. B. (2020). High-fat diet–induced alterations to gut microbiota and gut-derived lipoteichoic acid contributes to the development of enteric neuropathy. *Neurogastroenterology & Motility*, 32(7). <https://doi.org/10.1111/nmo.13838>
- Ohira, H., Tsutsui, W., & Fujioka, Y. (2017). Are Short Chain Fatty Acids in Gut Microbiota Defensive Players for Inflammation and Atherosclerosis? *Journal of Atherosclerosis and Thrombosis*, 24(7), 660–672. <https://doi.org/10.5551/jat.rv17006>
- Oliveira, R., Canuto, L., & Collares-Buzato, C. (2019). Intestinal luminal content from high-fat-fed prediabetic mice changes epithelial barrier function in vitro. *Life Sciences*, 216, 10–21. <https://doi.org/10.1016/j.lfs.2018.11.012>
- Pasolli, E., Asnicar, F., Manara, S., Zolfo, M., Karcher, N., Armanini, F., Segata, N. (2019). Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle. *Cell*, 176(3), 649–662.e20. <https://doi.org/10.1016/j.cell.2019.01.001>
- Pingitore, A., Chambers, E. S., Hill, T., Maldonado, I. R., Liu, B., Bewick, G., Persaud, S. J. (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(2), 257–265. <https://doi.org/10.1111/dom.12811>
- Prieto, I., Hidalgo, M., Segarra, A. B., Martínez-Rodríguez, A. M., Cobo, A. and Ramírez, M. (2018). Influence of a diet enriched with virgin olive oil or butter on mouse gut microbiota and its correlation to physiological and biochemical parameters related to metabolic syndrome. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0190368>
- Qi, J., You, T., Li, J., Pan, T., Xiang, L., Han, Y., & Zhu, L. (2017). Circulating trimethylamine N-oxide and the risk of cardiovascular diseases: a systematic review and meta-analysis of 11 prospective cohort studies. *Journal of Cellular and Molecular Medicine*, 22(1), 185–194. <https://doi.org/10.1111/jcmm.13307>
- Rajani, C., & Jia, W. (2018). Bile acids and their effects on diabetes. *Frontiers of Medicine*, 12(6), 608–623. <https://doi.org/10.1007/s11684-018-0644-x>
- Rukavina Mikusic, N. L., Kouyoumdzian, N. M., & Choi, M. R. (2020). Gut microbiota and chronic kidney disease: evidences and mechanisms that mediate a new communication in the gastrointestinal-renal axis. *Pflügers Archiv - European Journal of Physiology*, 472(3), 303–320. <https://doi.org/10.1007/s00424-020-02352-x>
- Sanchez-Rodriguez, E., Egea-Zorrilla, A., Plaza-Díaz, J., Aragón-Vela, J., Muñoz-Quezada, S., Tercedor-Sánchez, L., & Abadía-Molina, F. (2020). The Gut Microbiota and Its Implication in the Development of Atherosclerosis and Related Cardiovascular Diseases. *Nutrients*, 12(3), 605. <https://doi.org/10.3390/nu12030605>
- Sanna, S., van Zuydam, N. R., Mahajan, A., Kurilshikov, A., Vich Vila, A., Vösa, U., McCarthy, M. I. (2019). Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nature Genetics*, 51(4), 600–605. <https://doi.org/10.1038/s41588-019-0350-x>
- Schoeler, M., & Caesar, R. (2019). Dietary lipids, gut microbiota and lipid metabolism. *Reviews in Endocrine and Metabolic Disorders*, 20(4), 461–472. <https://doi.org/10.1007/s11154-019-09512-0>
- Sharma, M., Li, Y., Stoll, M. L., & Tollefsbol, T. O. (2020). The Epigenetic Connection Between the Gut Microbiome in Obesity and Diabetes. *Frontiers in Genetics*, 10. <https://doi.org/10.3389/fgene.2019.01329>
- Sharma, S., & Tripathi, P. (2019). Gut microbiome and type 2 diabetes: where we are and where to go? *The Journal of Nutritional Biochemistry*, 63, 101–108. <https://doi.org/10.1016/j.jnutbio.2018.10.003>
- Takagi, T., Naito, Y., Inoue, R., Kashiwagi, S., Uchiyama, K., Mizushima, K., . . . Itoh, Y. (2018). Differences in gut microbiota associated with age, sex, and stool consistency in healthy Japanese subjects. *Journal of Gastroenterology*, 54(1), 53–63. <https://doi.org/10.1007/s00535-018-1488-5>
- Takahashi, D., Hoshina, N., Kabumoto, Y., Maeda, Y., Suzuki, A., Tanabe, H., . . . Hase, K. (2020). Microbiota-derived butyrate limits the autoimmune response by promoting the differentiation of follicular regulatory T cells. *EBioMedicine*, 58, 102913. <https://doi.org/10.1016/j.ebiom.2020.102913>
- Tosti, V., Bertozzi, B. and Fontana, L. (2018). Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 73:318–26. <https://doi.org/10.1093/gerona/glx227>
- Valdes, A. M., Walter, J., Segal, E., & Spector, T. D. (2018). Role of the gut microbiota in nutrition and health. *BMJ*, k2179. <https://doi.org/10.1136/bmj.k2179>
- Veprík, A., Laufer, D., Weiss, S., Rubins, N., & Walker, M. D. (2016). GPR41 modulates insulin secretion and gene expression in pancreatic β-cells and modifies metabolic homeostasis in fed and fasting states. *The FASEB Journal*, 30(11), 3860–3869. <https://doi.org/10.1096/fj.201500030r>
- Wahlström, A., Sayin, S., Marschall, H. U., & Bäckhed, F. (2016). Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. *Cell Metabolism*, 24(1), 41–50. <https://doi.org/10.1016/j.cmet.2016.05.005>
- Yu, H., Gagliani, N., Ishigame, H., Huber, S., Zhu, S., Esplugues, E., Flavell, R. A. (2017). Intestinal type 1 regulatory T cells migrate to periphery to suppress diabetogenic T cells and prevent diabetes development. *Proceedings of the National Academy of Sciences*, 114(39), 10443–10448. <https://doi.org/10.1073/pnas.1705599114>
- Zhao, L., Zhang, F., Ding, X., Wu, G., Lam, Y. Y., Wang, X., Zhang, C. (2018). Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science*, 359(6380), 1151–1156. <https://doi.org/10.1126/science.aao5774>
- Zhao, Z., Shi, A., Wang, Q., & Zhou, J. (2019). High Oleic Acid Peanut Oil and Extra Virgin Olive Oil Supplementation Attenuate Metabolic Syndrome in Rats by Modulating the Gut Microbiota. *Nutrients*, 11(12), 3005. <https://doi.org/10.3390/nu11123005>
- Zheng, S., Zhao, M., Wu, Y., Wang, Z., & Ren, Y. (2015). Suppression of pancreatic beta cell apoptosis by Danzhi Jiangtang capsule contributes to the attenuation of type 1 diabetes in rats. *BMC Complementary and Alternative Medicine*, 16(1). <https://doi.org/10.1186/s12906-016-0993-4>
- Zhou, H., Sun, L., Zhang, S., Zhao, X., Gang, X., & Wang, G. (2020). Evaluating the Causal Role of Gut Microbiota in Type 1 Diabetes and Its Possible Pathogenic Mechanisms. *Frontiers in Endocrinology*, 11. <https://doi.org/10.3389/fendo.2020.00125>
- Zhu, W., Winter, M. G., Byndloss, M. X., Spiga, L., Duerkop, B. A., Hughes, E. R., . . . Winter, S. E. (2018). Precision editing of the gut microbiota ameliorates colitis. *Nature*, 553(7687), 208–211. <https://doi.org/10.1038/nature25172>

Zhuang, R., Ge, X., Han, L., Yu, P., Gong, X., Meng, Q., Zhou, X. (2019). Gut microbe-generated metabolite trimethylamine N-oxide and the risk of diabetes: A systematic review and dose-response

meta-analysis. *Obesity Reviews*, 20(6), 883–894.
<https://doi.org/10.1111/obr.12843>

How to cite this article

Sarkar, D. and Das, K. (2023). A review on involvement of gut microbiota in insulin dependent diabetes. *Science Archives*, Vol. 4(4), 255-263
<https://doi.org/10.47587/SA.2023.4403>

This work is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/)



Publisher's Note: The Journal stays neutral about jurisdictional claims in published maps and institutional affiliations.