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Review

The Gut–Immune Axis in Type 1 Diabetes: Microbial Dysbiosis and Autoimmune β-Cell Destruction

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Abstract

Type 1 diabetes (T1D) is a chronic autoimmune condition primarily caused by the immune-mediated destruction of pancreatic β-cells, leading to absolute insulin deficiency. While genetic predisposition, particularly within the HLA region, plays a major role in T1D susceptibility, recent research highlights the significance of environmental factors especially gut microbiota in disease onset and progression. The gastrointestinal (GI) tract harbors a diverse microbial ecosystem that influences immune regulation, metabolic processes, and epithelial integrity. Alterations in gut microbiota, or dysbiosis, have been associated with increased intestinal permeability and systemic immune activation, contributing to insulitis and β-cell autoimmunity. Emerging studies, including findings from The Environmental Determinants of Diabetes in the Young (TEDDY) cohort, reveal distinct microbial signatures in children at risk for T1D, often years before clinical diagnosis. These changes are influenced by factors such as diet, antibiotic exposure, infections, and mode of birth. Moreover, interventions like prebiotics, probiotics, and dietary modulation have shown potential in restoring microbial balance and delaying autoimmune onset. Despite growing evidence linking gut health to T1D, challenges remain in distinguishing causal relationships from mere associations. Current and future research is focused on elucidating microbial mechanisms, identifying protective and pathogenic taxa, and designing early-life preventive strategies. This review underscores the complex interplay between gut microbiota and host immunity and suggests that gut-targeted interventions may serve as promising avenues for T1D prevention and management. Altered bacterial populations can weaken gut barrier integrity, allowing microbial and dietary antigens to cross into the bloodstream. This increased gut permeability promotes immune activation: innate immune cells (e.g., macrophages) respond to microbial components and release inflammatory signals, while adaptive immune cells (T cells) become dysregulated. Molecular mimicry (similarity between microbial proteins and pancreatic β-cell antigens) may further drive autoimmunity. Moreover, a depletion of short-chain fatty acid (SCFA) producing bacteria diminishes the induction of regulatory T cells (Tregs), reducing immune tolerance. Together, these mechanisms contribute to the activation and expansion of autoreactive T cells that target pancreatic β cells, leading to their destruction.

Keywords

Autoimmunity, Gut microbiota, Intestinal permeability, Microbiome, Type 1 diabetes

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1. Gut Microbiota and Its Influence on the Pathogenesis of Type 1 Diabetes

Diabetes is rapidly becoming one of the most common metabolic diseases affecting populations around the globe. T1D specifically is categorized as an autoimmune disease [1]. It is primarily characterized by a significant deficiency in insulin production due to the destructive action of T-cells, which attack and destroy the insulin-secreting pancreatic beta cells [2]. Numerous factors play a role in the onset and progression of type 1 diabetes (T1D), and these include diet, genetic makeup, and the composition of gut microbiota. Both humans and various animal species harbor a diverse array of microbial communities, with a notable majority residing in the gastrointestinal (GI) tract [3,4]. The intake of different nutrients has the capability to significantly alter the structure and functional activities of gut microbiota. These microorganisms produce a variety of metabolites and other molecules that are absorbed by the host organism and contribute to a wide range of physiological processes that are essential for maintaining health [5,6]. Gut microbiota is, therefore, crucial for the development and overall well-being of its host. The metabolites generated by gut microbes are not static; they change dynamically in response to different factors and can greatly influence the health status of the host, while also playing a role in the progression of various disease states [6,7].

The GI tract is a remarkable ecosystem that harbors complex and dynamic populations of microorganisms [8]. These microorganisms, integral to our health, possess a cellular structure that comprises DNA, RNA, proteins, polysaccharides, and lipids [9]. This intricate collection of microbes known as gut microbiota exerts significant and marked influences on the host's homeostasis, contributing to various physiological processes, and play a pivotal role in the development of metabolic diseases [10,11]. Over the past several decades, an extensive amount of research efforts has been dedicated to delineating and understanding the diverse roles of gut microbiota in the development of type 2 diabetes and obesity, both of which are critical health concerns in modern society [12,13]. More recently, compelling evidence has emerged pointing to a key role of gut microbiota in the development of T1D, showcasing the breadth of their impact on health [14,15]. Altered gut bacterial composition has been highly associated with the pathogenesis of insulin dysfunction and an increased risk of developing T1D. Notably, earlier data has indicated that gut microbiota significantly alter gut permeability, which in turn induces the translocation of gut-derived bacterial products into the systemic circulation. These changes actively promote insulitis and contribute to the pathogenesis of T1D [16]. Therefore, targeting gut microbiota may not only provide valuable insights but could also offer novel therapeutic potential for patients suffering from T1D, representing a promising area for future research and intervention.

T1D is recognized as a multifactorial autoimmune disease that arises due to a combination of various elements. While genetic factors play a crucial and critical role in the disease's development, it is increasingly understood and widely accepted that a variety of environmental triggers are also involved [17]. These environmental triggers can include infections, vitamin D deficiency, and the composition of gut microbiota, all of which contribute significantly to the initiation and progression of autoimmunity in individuals. Supporting this perspective, studies have shown that individuals who possess genetic variants associated with T1D do not always go on to develop islet autoantibodies or progress to the disease itself, indicating that other factors are at play in the disease's manifestation [18,19]. Furthermore, since the phyletic type and specific composition of gut microbiota can vary widely from one host to another and change dynamically over a person's lifetime, it is proposed that these gut microbiota, along with their interactions with the host, serve as crucial driving forces behind the development of T1D [20]. To this point, extensive research has identified significant alterations in the composition of the gut microbiome in individuals with both clinical and preclinical T1D [21]. Notably, a distinct microbial signature for preclinical T1D has also been recognized in young children who are born into families at high risk for the disease [22]. It has been estimated that these specific interactions between gut microbiota and their host are responsible for a substantial percentage of individuals who eventually go on to develop T1D later in life, underscoring the importance of understanding these environmental influences on autoimmune disease pathways.

2. Pathophysiological and Clinical Overview of T1D

T1D is a chronic autoimmune disorder that is caused by the immune-mediated selective destruction of pancreatic β-cell. The disease occurs mainly in childhood and adolescence; however, it also occurs in the later stage of human life. Insulin-producing pancreatic β-cells are selectively destroyed in T1D, resulting in decreased insulin secretion. Current T1D management relies on continuous exogenous insulin delivery; however, this therapy is not completely effective. Furthermore, T1D patients are at risk of complications, including heart disease, kidney failure, neuropathy, and amputation [23]. The early stage of T1D precedes the clinical appearance of the disease, which is characterized by autoimmunity

changes in islet autoantibodies, and dysregulation of gut microbial composition. Early identification of predictive factors for T1D will allow at-risk individuals to be targeted for interventional studies to prevent or delay the onset of clinical disease [24].

It is generally accepted that as with many other autoimmune diseases, T1D results from a complex interplay between genetic, immunological, and environment factors. Genetic susceptibility for T1D is associated with specific genes and polymorphisms in the major histocompatibility complex (MHC) and lymphocyte specific genes. Although the MHC-region predisposes to T1D, only a fraction of the genetically susceptible individuals develops overt symptomatic disease, which suggests that environmental triggers also play an important role [25]. Epidemiological studies have suggested that there are multiple environmental factors contributing to the rapid increase in T1D, such as infections, dietary changes, and gut microbiota. However, with the exception of infections, direct evidence showing that environmental factors increase the risk of T1D in humans is mostly lacking. These environmental factors could lead to the malfunction or disruption of the homeostasis of the immune system, resulting in the early activation and prolonged breakdown of insulin tolerance or autoimmunity relevant for the development of T1D [26].

2.1 Overview of T1D and Its Association with Gut Microbiota Dysregulation

Diabetes is an emerging metabolic disease across the globe. T1D has emerged as a pressing health issue in numerous countries worldwide by rapidly increasing [27]. T1D is an autoimmune disease which is caused by poor secretion of insulin. The factors contributing to the development of T1D involve different factors such as diet, genome, and gut microbiota. The gut microbiome consists of 1014 microorganisms, which colonize the GI tract. Gut microbiota has been known to have a significant effect on host homeostasis and metabolic diseases. Recent findings suggest that a distorted microflora is closely related with insulin and T1D dysfunction. Notably, the gut microbiota targeting can be a new therapeutic prospect in the T1D patients [28]. Current intervention studies, including probiotic, dietary, and short-chain fatty acid (SCFA)–based approaches, remain preliminary, small in scale, and product-specific with inconsistent outcomes; therefore, no intervention should be recommended outside clinical research, and larger standardized randomized controlled trials are required.

Humans and animals harbor various microbial communities, of which the overwhelming majority of microbiota are present in the GI tract. The gut microbiota, also termed as gut flora or intestinal microbiota, is the complex population of microorganisms that show a symbiotic relationship with the host. In general, the gut microbiota consists of at least 100 trillion microorganisms, including bacteria, viruses, archaea, fungi, and protozoa. Bacteria are the most important and abundant members, comprising about 15,000 different bacterial species and 1014 bacteria, which play a crucial role in the gut microbiota. Most gut bacteria belong to the phylum Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia [29].

GI tract is colonized within the first days after birth by gut microbiota. Dietary intake of different nutrients has the potential to modify the composition and functions of gut microbiota, which subsequently generate products that are transported into the host and engaged in different physiological activities, such as cardiovascular activity, immune homeostasis, Ca^{+} uptake, and glucose homeostasis [30]. It is also stated that gut microbiota has a significant role in host development. The overuse of antibiotics would disrupt the development of the gut microbiota leading to the disruption of the intestinal epithelial barrier, which consequently caused a reduction in the mass of pancreatic beta-cells, endoplasmic reticulum stress, and the cytotoxicity of cytokines [7].

2.2 Epidemiology and Gut Microbiota Related Risks in T1D

The times of peak incidence of T1D vary from country to country and by latitude. The majority of cases in Finland and Norway occur between 4 and 6 years of age, in Alaska 10 years, and in the southern United States peak incidence occurs by age 15 [31]. In general, the incidence increases in young children by 3%-4% per year in most Western countries [32,33]. In contrast, the incidence of T1D is relatively low in the tropics and subtropics, and increases progressively from the equator to the poles, in North America and Europe reflecting a latitudinal gradient. In relation to the duration of ill health before diagnosis, there is a gradual decay in the rates of admission with symptoms of acute onset over increasing periods of time the age at which symptoms appear increases. Children over 5 years and adults may have more insidious onset than children under this age; diuresis may be a first presenting symptom and polyphagia often unnoticed. Apprehension concerning impending death may also occur. The age of children whom parents have apprehensions about pre-diagnostic behavior and dieting is between 3 years and 8 years. Factors which render children more susceptible to parent expectations include maternal education and cultural influences, differences in the early rearing environment, general educability, personality

acquisition, and early diet patterns [34]. T1D has both genetic and environmental risk factors, an understanding of which is highly relevant to prevention. HLA risk haplotypes of the class II MHC on chromosome 6q are primary susceptibility genes, but a dozen post-HLA risk genes of smaller effect have been identified around the genome, especially in immune-regulatory pathways. Twin concordance increases from 6% by age 2 to 70% by age 30 [35]. The T1D associated HLA risk regions explain approximately 50% of genetic disease risk, and affect the development and function of multiple immune and psycho-social phenotypes, which drive altered immune tolerance and immune dysregulation leading to T1D. HLA also interacts with the gut microbiota to affect risk [36,37]. Knowledge of basic disease mechanisms would help understand proxies of risk. Disease prevention via environmental risk and HLA modulation is a greater challenge. These factors must be clarified in concert with how inter-individual variation translates into altered phenotype and into 'diabetes risk' [38]. Such understanding is critical to inform rational individual-level T1D prevention strategies.

2.3 Pathophysiology

T1D is an organ-specific autoimmune disease that is characterized by the infeasibility of insulin replenishment due to the aberrant destruction of insulin-secreting pancreatic β cells by the immune system [39]. The unequivocal absence of insulin leads to a surge of hyperglycemia and other adverse complications, including diabetic vascular diseases and diabetic kidney disease [40]. Patients with T1D often need daily administration of exogenous insulin to live and can still develop long-standing hyperglycemia and secondary chronic complications, consequently affecting long-term quality of life. The pathogenesis of T1D is complex [41,42]. Recently, it has been revealed that the gut microbiome, which influences the pathogenesis of multiple autoimmune and metabolic diseases, plays an unanticipated role in T1D. However, understanding of the interaction between the gut microbiome, its metabolites, immunity, and T1D pathogenesis is still limited.

The gut microbes, primarily composed of bacteria, fungi, archaea, and viruses, significantly influence host physiology by affecting host metabolism, nutrition, development, immune system, and behavior [43]. Gut microbiota is key for gut defense against enteric pathogens and diet and host physiology. Dysbiosis is an imbalance of gut microecology that leads to GI disorder. Recent investigations using high-throughput 16S ribosomal ribonucleic acid (16S rRNA) sequencing and metabolome analyses have shown that the abundance of Firmicutes is increased while that of Bacteroidetes, Oscillibacter, and Ruminococcus is decreased in T1D-prone NOD mouse at pre-diabetes stage as compared to WT mice. Dysbiosis gut microbiome in gut-related immune regulation could influence T1D development [44]. Emerging evidence indicates that gut microbiome dysbiosis can promote systemic and pancreatic inflammation in T1D [39,43]. Altered microbial metabolites, such as short-chain fatty acids (SCFAs), bile acids, and lipopolysaccharides (LPS), can activate pro-inflammatory pathways, including cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and modulate immune cell activity [45]. This inflammatory response contributes to autoimmune-mediated destruction of pancreatic β-cells, highlighting inflammation as a critical mechanistic link between gut microbial imbalance and T1D pathogenesis (Figure 1).

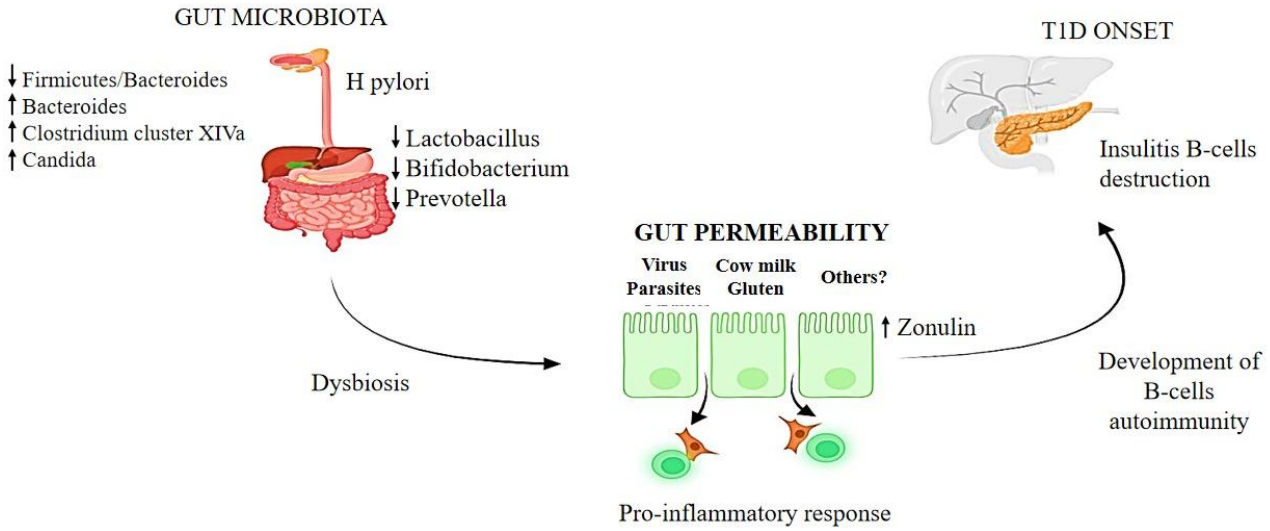

Figure 1. Role of microbiota in the pathogenesis of T1D. Abnormal microbial patterns may increase intestinal permeability ("leaky gut"), allowing luminal antigens to cross the epithelial barrier and interact with gut-associated lymphoid tissue (GALT). This can promote activation of autoreactive T cells and systemic inflammation. Reduced levels of SCFA–producing bacteria (e.g., Faecalibacterium, Roseburia) weaken regulatory immune mechanisms, particularly regulatory T-cell (Treg) responses, lowering tolerance to self-antigens.

3. The Gut Microbiome

The gut microbiome, also termed gut microbiota, was originally defined by the complex and diverse populations of gut microflora that inhabit the entire GI tract. More recently, the broad functional capabilities of the intestinal microbiome have also influenced a change in the definition, which now encompasses all microbial communities and their collective genes, genomes, and metagenomes. The gut microbiome is dominated by Bacteroidetes and Firmicutes, which comprise 90% of gut microbes [46]. Homeostasis of the gut microbiome is important for maintaining host health, as it affects intestinal morphology, epithelial cell turnover, mucosal immunity, and metabolic regulation. Dysbiosis, as defined by changes in the composition and activity of gut microbes, causes or exacerbates various diseases, including GI malignancies, inflammatory bowel disease, irritable bowel syndrome, T1D, obesity, and neurometabolic diseases [47].

The gut is colonized immediately after birth, and its composition is influenced by various factors, including diet, age, delivery mode, and antibiotic use. This microbiota gradually matures, becoming stable by approximately 3–5 years old and more similar between individuals. The gut microbiota composition and its impact on host metabolism and immunity broadly develop into adulthood. Owing to rapid developments in high-throughput sequencing technology, studies in humans and animal models have identified compositional differences in the gut microbiota that are associated with diseases. Mechanistic studies have revealed gut dysbiosis-induced aberrant production of metabolites and immune dysregulation, which shed new light on the preventive and therapeutic strategies targeting gut microbiota intervention [47].

Alterations in the composition and function of gut microbiota have been reported in patients with T1D or in nonobese diabetic mice that spontaneously develop T1D. Geographical regions, genetic background, and environmental exposures could all influence gut microbiota composition and immune system development; however, the impact of gut microbiota composition on T1D pathogenesis remains controversial. Children with T1D were reported to have gut dysbiosis years before clinical onset, while other studies on direct comparisons of gut microbiota between children with T1D and matching controls did not observe such differences [48]. Doubt has also been cast on whether reported compositional differences reflected T1D onset or simply caused altered metabolism of an ill-managed disease. Improved rigorous dietary and antibiotic exposures must be taken into account for better evaluating the impact of gut microbiota on T1D pathogenesis. It is important to acknowledge that early immune activation itself may influence gut microbiome composition, raising the possibility of reverse causation in microbiome–T1D associations. Additionally, shared covariates such as breastfeeding practices, antibiotic exposure, early-life infections, delivery mode, and socioeconomic differences can confound study results. Several cohort studies adjusted for some of these factors, while others did not, which impacts the comparability and confidence in reported associations. Therefore, the interpretation of microbiome differences must consider the extent to which each study controlled–or failed to control–for these potential confounders. Since HLA genotype is the strongest genetic determinant of T1D, it may also influence gut microbial composition and modify microbiome–disease associations. Some major cohort studies, including TEDDY, adjusted for HLA risk haplotypes when analysing microbial changes, whereas others did not, which contributes to variability across findings. Therefore, interpretation of microbiome differences requires consideration of whether HLA genotype was controlled for or whether HLA–microbiome interactions were examined.

Previous human studies show considerable heterogeneity in gut microbiome alterations associated with T1D. For example, several cohorts reported a marked increase in Bacteroides abundance [49-52], whereas others found a reduction in butyrate-producing Firmicutes with no consistent change in Bacteroides [68-73]. Similarly, some studies described elevated Escherichia coli and endotoxin-producing taxa [56-59], while others highlighted decreases in beneficial genera such as Bifidobacterium or Akkermansia [64-66]. These inconsistent findings likely arise from differences in age groups, dietary habits, geographic regions, sequencing platforms, and HLA genotypes across cohorts. Therefore, the heterogeneity of human evidence should be acknowledged when interpreting gut–immune interactions in T1D (Table 1).

Table 1. Key studies investigating gut microbiome dysbiosis in T1D mellitus: A comparative table.

Study Details	Age & HLA Genotype	Gut Microbiome Changes	Findings Related to T1D & Gut Role	Sample Type	Analysis Method	Reference
16 cases, 16 controls	7.48±0.87 years, Caucasians	↑ Clostridium, Bacteroides, Veillonella ↓ Actinobacteria, Firmicutes, Lactobacillus, Bifidobacterium, etc.	↑ pro-inflammatory cytokines (TNF-α, IL-1β), ↓ beneficial bacteria linked to inflammation	Stool	16S rRNA sequencing	[49-52]
15 cases, 13 controls	<18 years, Caucasians	↑ Bacteroides, Ruminococcus, Veillonella ↓ Bifidobacterium, Roseburia, Faecalibacterium	↑ gut permeability, immune activation via NF-κB pathway	Stool	16S rRNA sequencing	[50,51,53]
20 cases, 28 controls	23.1±8.6 years, Caucasians & Afro-descendants	↑ Bacteroides vulgatus, rodentium ↓ Bifidobacterium, Lactobacillales	Leaky gut, systemic inflammation, β cell destruction	Stool	Metagenomics	[54,55]
903 children with T1D risk	3-46 months, HLA positive	↑ Parabacteroides, Streptococcus ↓ Ruminococcaceae, Akkermansia	Molecular mimicry linked to T1D initiation	Stool	16S rRNA sequencing	[56-59]
11 cases, 11 controls	0-77 months, Finland & Estonia	↑ Bacteroides ovatus, fragilis, vulgatus ↓ Lachnospiraceae, Veillonellaceae, Bifidobacterium	Toxins cause DNA damage, leaky gut, bacteriophages modulate seroconversion	Stool	Metagenomics	[55,60,61]
28 cases, 27 controls	1.3-4.6 years, European countries	↑ Streptococci, Bacteroides ↓ Butyrate-producing Clostridium clusters	Molecular mimicry stimulating autoimmunity, reduced butyrate production	Stool	16S rRNA sequencing	[62]
10 cases, 8 controls	0-3 years, Finland & Estonia	↑ Escherichia coli	LPS and bacteriophage products initiate autoimmunity and epigenetic changes	Stool	16S rRNA sequencing	[48,63]
73 cases, 103 controls	3-19 years, Africa & Middle East	↑ E. coli ↓ Eubacterium, Roseburia, Clostridia clusters	LPS drives inflammation via NF-κB pathway, gut barrier dysfunction	Stool	Metagenomics	[64-66]
12 cases, 10 controls	12-33 years, Han Chinese	↑ Bacteroides/Firmicutes ratio, Bilophila	High HbA1c linked to increased Bacteroides, ↓ Faecalibacterium	Stool	16S rRNA sequencing	[64,67]
47 children with autoimmunity	5.3-16.3 years	↓ Prevotella, Butyricimonas, SCFA producers, diversity	Butyrate modulates Treg/T Helper 17 Cell (Th17) balance, promotes anti-inflammatory cytokines	Stool	Metagenomics	[68-73]

3.1 Methodological Variability Across Studies

Differences in methodological approaches across microbiome studies contribute substantially to the heterogeneity observed in human T1D research. The key cohorts included in this review vary in sequencing strategy (16S rRNA *vs*. shotgun metagenomics), DNA extraction kits, primer sets, sample collection timing, and bioinformatics pipelines. These inconsistencies introduce batch effects and limit the comparability of microbial profiles across studies. A summary of these methodological differences is provided in Table 2, highlighting how technical variations may influence taxonomic resolution, detection of low-abundance taxa, and interpretation of functional pathways. Addressing such variability in future research will be essential for generating standardized, reproducible, and interpretable microbiome–T1D associations.

Table 2. Methodological differences across key gut microbiome studies in T1D.

Study/Cohort	Sequencing Method	DNA Extraction Method	Primers Used	Bioinformatics Pipeline	Sample Timing	Reference
Study 1	16S rRNA	Qiagen Stool Kit	515F/806R	QIIME/DADA2	At diagnosis	[49-52]
Study 2	16S rRNA	MoBio PowerSoil	V3-V4 region	QIIME	Pre-autoimmunity	[50,51,53]
Study 3	Shotgun metagenomics	Phenol–chloroform	None	MetaPhlAn2/HUMAnN2	Mixed	[54,55]
TEDDY	16S rRNA	MoBio PowerMag	V4	QIIME v1.9	Monthly	[56-59]
Finland-Estonia	Shotgun	Qiagen AllPrep	None	Kraken+Bracken	Before seroconversion	[55,60,61]
EU Multi-country	16S rRNA	ZymoBIOMICS	V1-V3	QIIME2	Early childhood	[62]
Infant cohort	16S rRNA	Bead-beating Kit	V4	DADA2	0-3 years	[48,63]
Africa/Middle East	Shotgun	PowerSoil	None	MetaPhlAn3	Longitudinal	[64-66]
Han Chinese	16S rRNA	Stool DNA Kit	V3-V4	USEARCH	At diagnosis	[64,67]
Autoimmunity cohort	Shotgun	Qiagen Stool Kit	None	HUMAnN2	Before autoimmunity	[68-73]

3.2 Importance of Gut Microbiota on T1D

Despite T1D being primarily regarded as a genetic disorder, with high heritability estimates of around 60%-90%, the complexity and incompleteness of T1D susceptibility genes suggests that a substantial proportion of the genetic component cannot be accounted for by genetic factors alone [74]. The increasing incidence rates suggest that environmental factors have a substantial impact, quickly and in a way that cannot be explained by genetic predisposition alone. Several research initiatives have been established to identify environmental factors that potentially contribute to the onset of T1D autoimmunity and the progression of disease in children/young adults.

Recent research implicates the gut microbiota and its interplay with the immune system in T1D pathogenesis. The GI tract is one of the largest immune organs in the body and is colonized with trillions of microorganisms, which collectively comprise the microbiota. These microorganisms greatly impact the development and regulation of the host immune system and maintain homeostatic immunity. In particular, mechanisms by which gut microbiota education of the immune system can become aberrant leading to T1D pathogenesis are reviewed, as well as recent human mechanistic microbiota studies [75].

3.3 Composition of the Gut Microbiome

The human gut microbiome is a complex ecological community composed of trillions of microorganisms, including bacteria, viruses, fungi, archaea, and protozoa. Among these, bacteria are the most extensively studied and account for the majority of microbial genes in the intestine. These microbial populations are not uniformly distributed but vary along the GI tract depending on oxygen levels, pH, nutrient availability, and host secretions. The gut microbiome has become a pertinent aspect of the environment in the progression and pathogenesis of T1D. Changes in the composition of the gut microbiome and the gut microbiome functional ability have been shown to occur in both animal models and human cohorts before the development of T1D. Besides protecting against diseases, it has been also suggested that the gut microbiome is capable of also compromising the immune system paving way to the emergence of autoimmune diseases such as T1D [76].

A seminal study of T1D cases *vs.* controls in terms of microbiome composition was capable of defining compositional changes that clustered around T1D cases and controls (i.e. at age prior to 10 years). In such studies, a reduction in bacterial diversity was noted in cases of T1D which were accompanied with a high abundance of Rikenellaceae family, in addition to Blautia, Ruminococcus and Streptococcus genera. Following these preliminary findings, TEDDY study analysed the metagenomes of more multicenter study. The aim of this study was to reveal changes in the microbiota among children initiating at 3 months of age, to clarify perturbs that could be in the lead to the diagnosis of IA and T1D. In this instance, inter-subject differences had been found to explain most of the variability in the metagenomes, followed by age, geographical location, and breast-feeding of the subjects [77]. In this regard, it has been identified that ingestion of human milk and high abundance of Bifidobacterium species in the initial phase of colonization of the gut were strongly correlated with variability in the metagenomes.

The TEDDY IA cases and controls were parsed to show that more Lactobacillus rhamnosus and Bifidobacterium dentium was present in the controls and more Streptococcus species was present in IA cases. The same findings were obtained with the TEDDY T1D cases and controls showing that the controls had greater abundance of lactic acid-producing bacteria and the T1D cases had greater abundance of Bifidobacterium pseudocatenulatum, Roseburia hominis, and Alistipes shahii. Collectively these results would indicate a protective role of SCFA as has been reported previously in rodent models in addition to other human T1D cohorts. Disturbed intestinal permeability has been also found as a pathogenesis mechanism in T1D [45] composition of the gut microbiome in Figure 2.

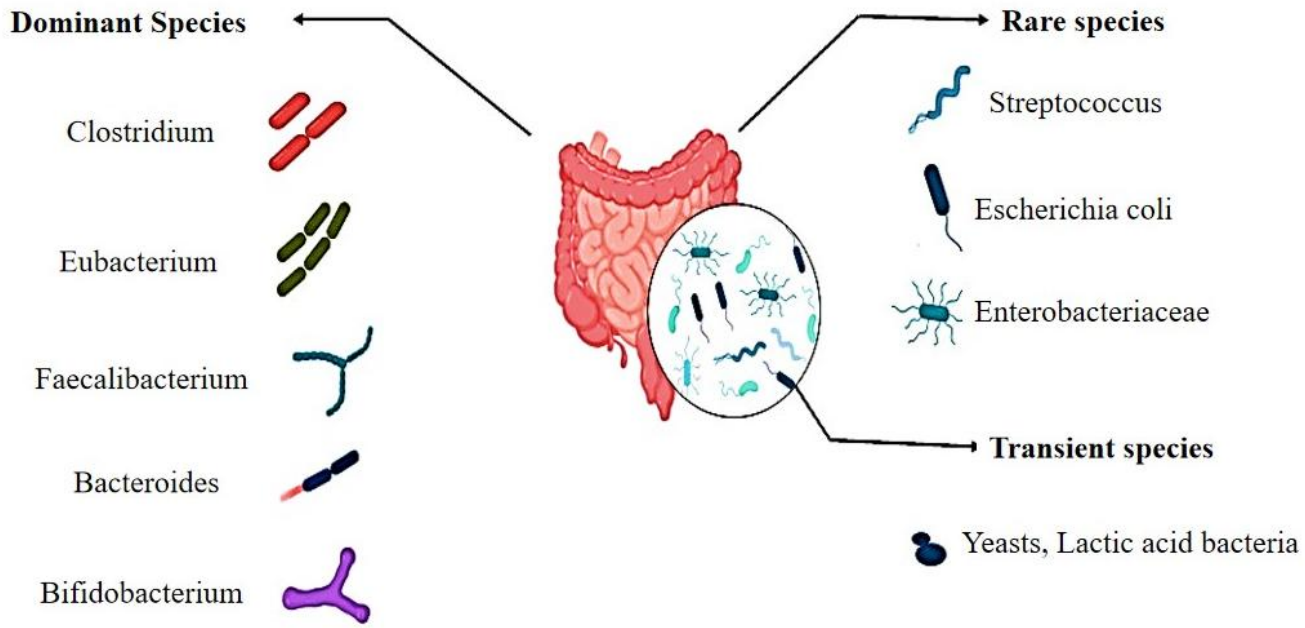

Figure 2. Composition of the gut microbiota.

3.4 Factors Influencing Gut Health

Obesity and malnutrition have emerged as two global epidemics, presenting health concerns across all nations and populations. Gut microbiota (aka gut microbes) is a diverse group of microorganisms living in the colon and a key factor in shaping the accessibility of energy from food and maintaining metabolic homeostasis. Gut microbes become home to both partially digested food and a number of immune cells, creating a central network governing the interface between the diet, GALT, and metabolism. During this life-long separation of the gut and its microbial inhabitants, the gut immune system must build up nutrients-sensitive tolerogenic mechanisms to avoid chronic inflammation. A growing body of evidence suggests that they are enormously influential in metabolic disorders [78].

Gut microbes develop with ontogeny and respond to dietary changes across life. The mammalian gut is colonized by microbes within hours of birth and achieves a stable community within one to two years, which is dominantly governed by the mode of delivery. Following weaning, the gut microbiome continues to develop in response to switching from a liquid milk diet to solid foods, ensuring both the quality and quantity of fermentation products reach the gut. With the prolongation of antibiotic use, this life-long succession of gut microbiota may be disrupted and lead to health consequences [79]. For example, the development of enteric infections is likely to occur following weaning and solid food introduction, which terminate the oral tolerance period and lead to intestinal inflammation. Microbe-encoded virulence factors can be transferred to activate a vicious cycle of inflammation, leading to systemic immunological changes and metabolic disturbance.

Accumulating evidence has shown compositional changes in gut microbiota as risk factors for diet-induced obesity. Mechanistic studies using germ-free mice and microbiota-transplant experiments strongly support causation and involvement of gut microbiota in obesity onset. Coupled with metagenomic and metabolomic studies, research has also expanded to functional investigation and offer targets for intervention. Clinical applications of microbiome-modifying therapeutic strategies are under development to restore gut microbiota dysbiosis encountered in obesity. Advances in fecal microbiota transplantation (FMT) have shown promise in treating obesity. However, safety concerns and management complexity must be examined before generalization. The hypothesis that gut microbiota predisposes individuals for development of T1D is based on several clinical observations in children developing T1D [79].

3.5 Functional Evidence: Microbial Metabolites Linking the Gut Microbiome to T1D Autoimmunity

Functional evidence strongly supports the link between gut microbiome alterations and autoimmune activation in T1D [80]. SCFAs such as butyrate regulate Treg induction and maintain epithelial integrity. Altered bile acid composition influences FXR/TGR5 signaling, affecting immune homeostasis [81]. Tryptophan-derived metabolites act through the aryl hydrocarbon receptor (AHR) to modulate inflammation [82]. Increased LPS and zonulin levels disrupt gut barrier function, promoting systemic inflammation and autoimmunity [83]. Metabolomics studies in children at risk for T1D reveal reduced SCFAs, increased pro-inflammatory lipid mediators, and altered amino-acid metabolism, supporting a mechanistic link between gut metabolites and β-cell autoimmunity [84].

4. Gut Health and Immune Function

Gut health, which is a complex interaction between the gut microbiome and gut and intestinal mucosal health, is ruled by the gut–blood barrier or intestinal barrier (IB) [85]. The gut environment is the first point of contact for the majority of antigens, microorganisms, and nutrients, which are then absorbed into the circulatory system, influencing immune responses and affecting the function and activation of T and B lymphocytes. Since the GALT has both immune, endocrine, and excretory functions, gut health is critical for good health. An impaired intestinal permeability or “leaky gut” permits free passage across the intestinal epithelium of luminal macromolecules, pathogens, and gut microbiota products. Macromolecules and bacteria connect with the Toll-like receptor immune system, changing their immune responses and production of interleukin-1 (IL-1) and interleukin-6 (IL-6), and ultimately driving a cascade of proinflammatory changes systemically, leading to β-cell damage and loss of glucose homeostasis. GAD65 and ZnT8, which are produced by beta cells and released into circulation, can cross the gut–blood barrier. Proinflammatory macrophages recruit proinflammatory T cells, interfering with insulin production [86,87].

Gut microbiota modulation has been studied in T1D prevention. Most gut microbiota studies have focused on children at high risk of T1D, while a few have looked at adults with new-onset T1D. Changes in the gut microbiota of individuals genetically prone to developing T1D are detectable as early as 1-2 years before the clinical onset of the disease and involve a decrease in species richness and diversity. Significant changes in microbiota are correlated with the development of T1D. Changes in intestinal permeability have been seen before and at T1D diagnosis. In prediabetic children, increased gut permeability, altered fecal microbiota composition, and increased plasma zonulin (in pathogenesis of T1D by regulating intestinal permeability) levels have been shown [79]. Evidence indicates that increased intestinal permeability during beta cell autoimmune damage enhances gut health and allows the gut microbiota to promote inflammatory and autoimmune responses, thereby accelerating the onset of clinical disease [76].

4.1 Immune System Overview

The immune system is made up of complex physiological responses, architectures, and cells [88]. The immune system is classified into two categories: nonspecific and specific defense mechanisms. The nonspecific system consists of the skin, phagocytic macrophages or macrophages, mucous membranes, histiocytes, free macrophages, and the reticuloendothelial system. Physical and chemical barriers protect membranes. The specific or adaptive defense mechanism consists of specialized cells located in the lymphoid organs, such as the spleen, lymph nodes, and thymus. Antigens are molecules seen as foreign by the immune system. Lymphocytes are white blood cells that bind to and destroy foreign antigens. T lymphocytes, which mature in the thymus gland, are involved in cell-mediated immunity, whereas B lymphocytes give rise to plasma cells that secrete antibodies in humoral immunity. T lymphocytology presents cartridge-type syringes ready for use. In terms of physiology, T lymphocytes migrate via the blood, being recruited into the tissues with the help of chemokines, and usually interrogate antigen-bearing dendritic cells. It has been conclusively shown, in both humans and mice, that the gut microbiome plays a role in both types of host immunity involved in T1D, adaptive and innate. The gut microbiota is comprised of bacteria, predominantly within the phyla Firmicutes and Bacteroidetes. Microbial DNA from both bacterial phyla is often detected in the circulation of healthy subjects. The gut microbiome assumes a perennial role in sensing gut bacteria and transducing signals through either the short chain fatty acid butyrate or toll-like receptor signaling. Allocatabolism of secondary bile acids by the gut microbiome directly modulates T cell activity, enabling the production of TH1 and Th17 cells and improving the synthesis of insulin. These types of cells become dysregulated in children with autoimmunity, potentially leading to T1D [89]. Generally, the gut microbiome affects T lymphocytes through conventional mechanisms, including dendritic cells and Treg cells. The gut microbiome directly modulates the spleen and lymph nodes through MyD88 signaling and metabolites. Exposure to gut microbiome products regulates dendritic cell proliferation, which is critically involved in the activation and polarization of naïve T cells. A few hours after birth, gut microbiome

colonization begins in the healthy gut, allowing beneficial bacteria to be integrated. Disruption of this process is often involved in the pathogenesis of many diseases, including T1D and other autoimmune diseases [90].

4.2 GALT

The GALT comprises gut, tonsils, and the appendix. The GALT is of key importance for host immunity as it contains the highest density of immune cells in the body. The gut epithelium tightly cooperates with the GALT to protect against luminal pathogens while allowing the tolerogenic response to food antigens and gut microbiota. Mechanisms of cell contact and/or cytokine-mediated cross-talk between GALT-resident APC and lymphocytes maintain the homeostasis of mucosal immunity. Aberrant GALT function implicated in the pathogenesis of several autoimmune diseases [90]. GALT appears to play a dual role in T1D. Certain GALT-associated signals can support tolerogenic immune responses that help prevent disease, while disturbances within this system may instead contribute to autoimmune activation and disease progression. However, the involvement of GALT in T1D is still poorly understood. Structurally and functionally, GALT is a highly organized immune network that maintains gut homeostasis. It includes Peyer's patches, isolated lymphoid follicles, and mesenteric lymph nodes, all of which help regulate immune responses to gut microbes. The intestinal lining consists of a single layer of epithelial cells joined by tight junctions, forming a crucial barrier that prevents harmful antigens from entering systemic circulation [91].The gut epithelium has a variety of functions, including barrier function, secretory function, nutrient transport, and immunity. The gut is abundantly infiltrated with intraepithelial lymphocytes (IEL), most of which are T lymphocytes that express αβ or γδTCR. Gut-resident Treg (TRG) are required for the maintenance of gut immune homeostasis and protection against gut inflammation. Peyer's patches (PP), an organized form of GALT, constitute important sites of gut mucosal immunity. The PPs are specialized follicles that protrude into the intestinal lumen, which is lined by follicle-associated epithelium (FAE) [92]. M Cells covering the FAE take up luminal antigens and transport them to underlying immune cells. Other immune cells like T, B cells, and APC are present in the PP follicles, germinal centers (GC), and inter-follicular areas. Naive T and B cells enter the PPs through high endothelial venules (HEV) and undergo a localized humoral/T cell immune response; memory T and B cells then migrate to the gut lamina propria and lamina-associated gut tissues, such as mesenteric lymph nodes (MLN), both of which participate in gut mucosal immune responses.

4.3 Role of Gut Microbiota in Immunity

The gut microbiota–the microbiome of the large intestines–is an intricate and extensive community of microorganisms in a symbiotic relationship with their host. The gut microbiota composition is determined by a combination of host genetics and environmental factors and is notably influenced by diet. The gut microbiota contributes to the development and training of the immune system and protects against pathogens. Conversely, dysbiosis can lead to immune disorders, one of which is T1D [93].

Immune cells mature and develop peripheral tolerance primarily in the thymus and peripheral lymphoid organs, and GALT accounts for the majority of these organs. Although the thymus and spleen are major immune organs, most naive T cells travel to the gut and encounter the gut microbiota [90]. Gut microbiota metabolites, especially SCFAs, shape gut immunity and maintain immune homeostasis through several mechanisms. SCFAs directly affect the migration, proliferation, and differentiation of various immune cells in the gut and distant lymphoid tissues. They can also affect immunity through the production of secondary metabolites.

Initial microbial colonization of the gut occurs shortly after birth, accompanied by the maturing immune system. The composition of the gut microbiota gradually stabilizes around 2 y of age. The gut microbiota is thought to be altered in immune disorders, which raises the question of whether the gut microbiota plays an etiological role in these disorders. Initially, most studies focused on a limited number of gut microbiota and immune disorders. The rapid development of high-throughput sequencing technology provides more detailed information on the gut microbiota and its pathogenic mechanisms in T1D [76]. Recent studies have reported that the composition and function of gut microbiota differ between healthy and T1D individual's/disease animal models. Furthermore, dietary modification, fecal transplantation, and novel procedures to manipulate gut microbes and their metabolites may alter the risk of T1D. Figure 3 shows the role of gut microbiota in immunity and inflammatory disease.

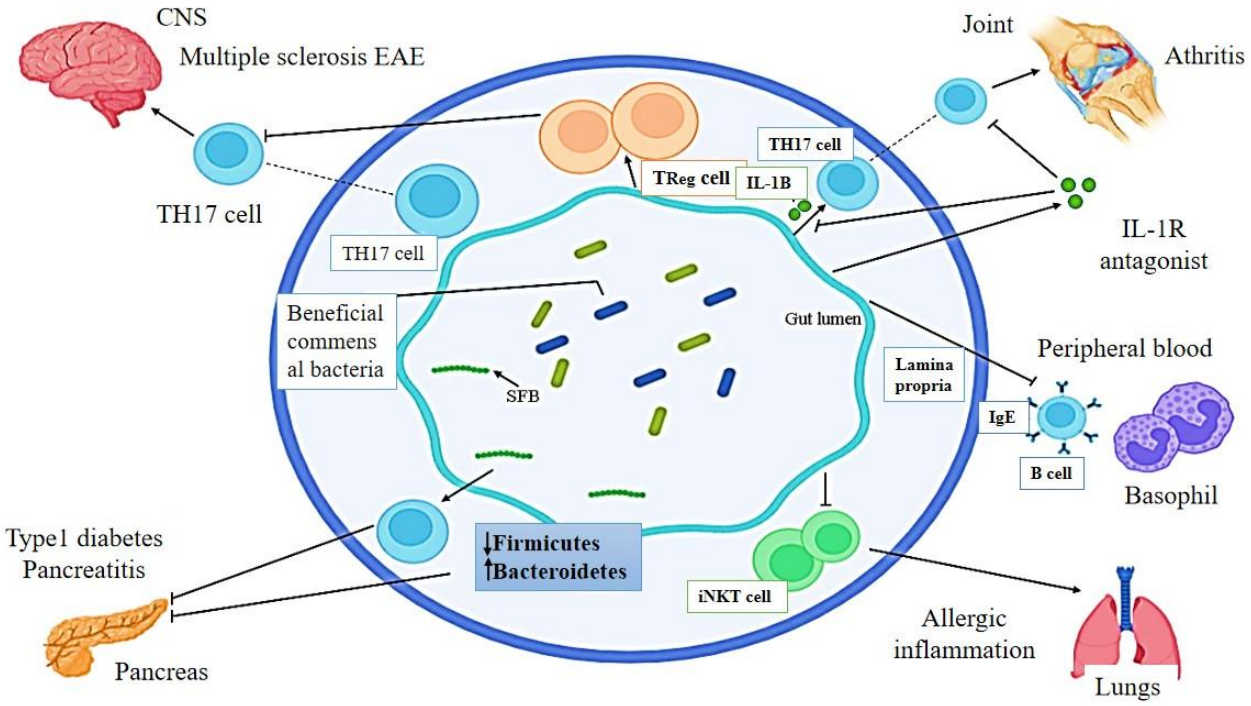

Figure 3. Role of the gut microbiota in immunity and inflammatory disease. Figure illustrates how commensal gut microbes regulate intestinal and systemic immunity. Microbial metabolites such as SCFAs support epithelial barrier integrity and promote Treg differentiation. In contrast, dysbiosis impairs barrier function, enhances pro-inflammatory Th1/Th17 responses, and facilitates systemic immune activation, contributing to autoimmune disorders including T1D.

5. Genetic Predisposition to T1D

T1D is a multifactorial disease involving genetic susceptibility and triggering factors possibly interacting with environmental risk factors [94]. Underlying genetic susceptibility is well characterized with hundreds of genetic variants associated with T1D now identified. Of the genetic factors determining T1D susceptibility, the human leukocyte antigen (HLA) region is the most important accounting for more than 50% of the genetic risk for T1D. Within the HLA region, HLA-DR3 and/or DQ2 in combination with HLA-DR4 and/or DQ8 strongly predispose to T1D, and these high-risk HLA genotypes can be detected years before the onset of the disease. Progression from the appearance of islet autoantibodies to T1D is a dynamic and heterogeneous process influenced by intrinsic and extrinsic factors. Genetic predisposition to develop islet autoantibodies has been associated with the HLA class II region. Interestingly, the pre-diagnostic genetic risk profile of T1D has also been found to be influenced by environmental factors in early life.

A previous report showed that environmental factors may modify diabetes-related autoimmunity, but a comprehensive analysis of the time frame of the interaction was lacking. The broad aim was to investigate how genetic and environmental factors interact to affect the development of diabetes-related autoimmunity in the TEDDY cohort during the first 6 years of life [77]. As the results, it was found that 12 environmental factors either significantly increased or significantly decreased the risk of diabetes-related autoimmunity. Genetic and environmental interactions modifying the risk of diabetes-related autoimmunity by 6 years of age were discovered. This revealed a more complex picture of the interaction between genetic and environmental risk factors than previously believed. These findings contribute to the long-term aim of identifying environmental risk factors that can be prevented by lifestyle changes or modified through pharmacological intervention.

6. Gut Health and T1D Risk

The human GI tract harbors a high abundance and diversity of microbes, collectively referred to as the gut microbiota. The most abundant microorganisms include bacteria, archaea, fungi, protozoans, and viruses. Recent research has established that gut microbiota plays essential and diverse roles in host metabolism, physiology, immune system development, and health, and are relevant to metabolic, autoimmune, inflammatory, and neurological disorders [95].

A growing body of literature indicates that gut microbiota influence host diabetes susceptibility, and gut microbiota dysbiosis is highly associated with T1D development. A better understanding of the relationship between gut microbiota

and T1D may help develop effective preventive or therapeutic strategies for T1D managements. T1D is an autoimmune disease characterized by a progressive destruction of insulin-secreting β-cells within the islets of Langerhans in the pancreas [88]. T1D is more prevalent in children and is associated with several putative environmental risk factors. The disease is caused by a complex interplay between genetic susceptibility and largely unknown environmental triggers. Each year, nearly 600,000 newly diagnosed cases of T1D are identified globally, with over 60,000 of these cases identified in children under the age of 15. T1D is classified into two broad subtypes based on clinical and pathophysiological characteristics [88].

T1D has an insidious onset pattern preceded by an asymptomatic phase referred to as islet autoimmunity. The pathogenesis of T1D is thought to involve multiple factors, predominantly genetic susceptibility, and environmental triggers, such as stress, infections, and dietary change. Among dietary components, addition of dietary gluten during weaning has been associated with increased risk of islet autoimmunity. Conversely, breastfeeding is thought to protect against T1D risk. Several epidemiological studies have proposed a role of gut microbial dysbiosis in T1D pathogenesis, leading to the hypothesis that specific environmental factors may trigger disease onset in genetically susceptible individuals by ultimately affecting gut microbiota composition [74,96,97].

Several studies have shown that the gut microbial composition differs between heathy hosts and hosts with T1D or at risk of T1D (Table 3). Bio-Breeding (BB) rat and non-obese diabetic (NOD) mouse exhibit similar characteristics to human disease [98]. In Bio-Breeding diabetes-prone (BB-DP) rats, the gut microbiota composition differs significantly even before the onset of T1D between those that eventually will might go on to develop the disease and those that will not [99]. Similarly, Luiz et al.(2009) observed a significant decrease in the number of Lactobacillus, Bryantella, Bifidobacterium, and Turicibacter in BB-DP rats, whereas the number of Bacteroides, Eubacterium, and Ruminococcus increased in BB-DP rats compared with the Bio-Breeding diabetes-resistant (BB-DR) rats [100].

Table 3. Gut microbiota alterations in experimental and clinical models of T1D.

Model/System	Observed Microbiota Changes	Associated Implications	Reference
Bio-Breeding diabetes-prone (BB-DP) *vs*. diabetes-resistant (BB-DR) rats	↑ *Bacteroides*, ↓ *Lactobacillus*, *Bifidobacterium*	Loss of protective commensals and increased immune activation	[99]
Bio-Breeding rats (BB-DP *vs*. BB-DR)	↓ *Turicibacter*, *Bryantella*; ↑ *Eubacterium*, *Ruminococcus*	Shifts toward a more inflammatory microbiome	[100]
Children with new-onset T1D	↓ *Actinobacteria*, *Firmicutes*, ↑ *Bacteroidetes*, ↑ *Veillonella*, ↓ *Prevotella*	Early dysbiosis linked to increased intestinal permeability and immune dysfunction	[49]
Case-control study in children	↓ *Firmicutes*, ↑ *Bacteroidetes*	Suggests a microbial signature of increased T1D risk	[101]
NOD mice	↓ *Lactobacillus reuteri* and *Clostridium* species	Reduced SCFA production and compromised gut barrier	[102]
Germ-free NOD mice colonized with microbiota	Restoration of gut bacteria delayed onset of diabetes	Indicates protective role of healthy microbiota	[103]

7. Environmental Factors Influencing Gut Health

T1D is regarded as an autoimmune disease characterized by insulin deficiency resulting from destruction of pancreatic β-cells. However, a growing body of evidence suggests that the components of the gut-associated immune system and gut microbiota are important in the pathogenesis of T1D. Within a timeline of months to years, T1D follows a pre-clinical phase during which functional autoantibodies against islet antigens can arise [74]. Pathogenetic studies should therefore be performed in the early pre-clinical stages of T1D. Knowledge of environmental factors influencing diversity and composition of the gut microbiota is crucial to elucidate the contribution of these factors to T1D risk. Methodological and technical challenges in microbiota studies are outlined with emphasis on issues specifically relevant to studies of NOD mice and the human gut microbiota.

The incidence of T1D is increasing rapidly in many populations, but the majority of identical twins of affected individuals remain healthy, suggesting that environmental factors play an important role in T1D pathogenesis. Several research initiatives to identify possible environmental risk factors of T1D have been undertaken worldwide [20]. A large number of studies have focused on infectious agents in particular, but none has yet been found to convincingly explain increases in incidence. Gut microbiota composition has been shown to be affected by many of the environmental factors, such as birth mode, diet, and antibiotic treatment, and is now also being considered as a possible factor contributing to T1D development. Improved understanding of the interactions between environmental factors, gut microbiota composition, and T1D risk may offer new avenues for prevention.

7.1 Antibiotic Use

Antibiotics are some of the most widely used medications. They are used primarily for the treatment of bacterial infections, and their usage has been steadily increasing worldwide. In the last couple of decades, it has become evident that their use can dramatically modify the composition and the function of the gut microbiome. A large number of publications have provided evidence of the possible role of the gut microbiota and especially its early-life perturbations in metabolic disorders, including T1D. While not yet targeted in studies, a close relationship between antibiotic therapy and T1D has already been indicated by a smaller set of findings in the recent literature [104].

The gut microbiome is an important regulator of human health and indeed might even be considered a non-chemical organ. The relations between the gut and metabolic diseases, including obesity and type 2 diabetes, have been widely investigated, resulting in a large body of scientific literature [99]. A large number of publications provided evidence for the possible role of the gut microbiota in metabolic diseases, including T2D. Recently it has been suggested that specific bacteria of the gut microbiome contribute to the development of T2D [105]. Such studies on the relation of the gut microbiome and its perturbations with T1D, even concerning axenic animals, have started only recently. Dysbiosis of the gut microbiome has been indicated as a contributing factor to the emergence of T1D. The specific gut taxa of the bacterial phylum Bacteroidetes have been correlated with the emergence of T1D; the abundances of two members of this phylum would precede the appearance of islet autoantibodies.

7.2 Infections and Gut Health

Infection with common gut and respiratory viruses is associated with an increased risk of T1D. Gut mucosal tissues are a potential site of early target organ damage. Enterovirus infections of the pancreas coincide with the appearance of autoimmunity to the islet autoantigen GAD in the NOD mouse model, and an enteroviral RNA signature has been observed in pancreas specimens of recent-onset T1D children [106]. These data together with evidence of abnormal gut mucosal immunity in T1D suggest that gut mucosal tissues may be early sites of immune dysregulation leading to the development of autoimmunity.

Infection with common gut and respiratory viruses is associated with an increased risk of T1D in a nested case-control study. This study demonstrates that serological responses to 22 viral infections are more strongly associated with T1D than any other risk factor. Gut mucosal tissues are a potential site of early target organ damage in T1D [107]. Infection with enteroviruses, rotaviruses, and HCV, but not adenoviruses, leads to an increase in risk of T1D. In NOD mice, enteroviral infection early in life is sufficient to accelerate disease progression. Enterovirus infections of the pancreas coincide with the appearance of autoimmunity to the islet autoantigen GAD in the NOD mouse model, and an enteroviral RNA signature has been observed in pancreas specimens of recent-onset T1D children. These data together with evidence of abnormal gut mucosal immunity in T1D suggest that gut mucosal tissues may be early sites of immune dysregulation leading to the development of autoimmunity. Studies are warranted to try to detect enteroviral RNA in gut mucosal tissues, and to better understand the developmental immunobiology of gut viral infections in such children.

7.3 Hygiene Hypothesis

Washing of hands before eating, frequency of bathing and total stress score showed positive correlation with incidence of T1D. Pre-eating hand washing and frequency of house cleaning were separately linked with an increased risk of T1D, whereas getting dirty was linked to a decreased risk. These results are in line with the hygiene hypothesis according to which microbial exposure during early life stages is lacking, which predisposes an individual to T1D. This also allows the hypothesis of the old friend, according to which the decrease in the number of organisms within the urban environment can serve as one of the factors contributing to the growing prevalence of chronic inflammatory diseases [108]. Prior to eating, bathing and getting dirty, hand washing influences the microbiome of the skin and gut. Such data imply that influences on the skin or gut microbiome may be of greater significance than infections or influences on the microbiome in other locations. Regular washing could reduce skin organisms. Being dirty with soil can prove counter-effective as soil is a good provider of ammonia-oxidizing bacteria and archaea. Washing or bathing frequently may lead to the decrease in the production of nitrite and nitric oxide and potentially lead to the negative impact on the physiology of T cells, disregarding immunomodulation and immunoregulation [109].

8. Preventive Strategies for T1D

T1D is one of the most common chronic diseases of childhood and the most common autoimmune disease at younger ages. Although T1D can occur throughout life, an early peak in incidence rates occurs in childhood, especially between 4 and 8 years of age. The pathogenesis of T1D is multifactorial and not completely understood. It involves an abnormal immune response to pancreatic islet antigens primarily occurring in genetically predisposed individuals [110]. This aberrant

autoimmune process leads to the progressive destruction of insulin-producing beta cells, thus depriving the body of its principal source of glucose and energy. The role of environmental factors in the pathogenesis of T1D is actively being investigated, and recent observations suggest that the gut microbiota may influence the onset of T1D. The gut microbiota is composed of complex, diverse, and relatively stable communities of microorganisms, mainly bacteria, residing in the GI tract. A number of environmental factors shape the gut microbiota and its mature composition. T1D is characterized by an altered gut microbiota composition, called dysbiosis. Furthermore, gut microbiota dysbiosis in infancy predicts the development of islet autoimmunity (IA) and eventual T1D in genetically predisposed children. Therefore, the gut microbiota may contribute to the onset of T1D by influencing both immunological and metabolic processes but also via an indirect mechanism [111].

Since the development of IA/MS, T1D onset may occur at any time point, ranging from weeks to many years later, and preventive strategies aimed at delaying balancing both efficacy and safety are much needed. The gut microbiota is a promising target for intervention due to its accessibility and the evidence that it can be modulated early in life. However, the nature and effectiveness of early-life interventions on the microbiota/gut/peripheral immune system has not been investigated in a large-scale randomized clinical trial thus far. Hence, knowledge of the effects of microbiota modulation on T1D prevention is limited and no strategies are currently available to prevent T1D in the general population. Various approaches including dietary intervention, pre-, pro- and postbiotics, FMT, biotherapeutics, and probiotics are all potential avenues to reduce or halt T1D onset, and most are technically feasible. Diacyclopropylsulfamide in a particular human gut model has even been shown to reduce pathogenic enterovirus production. Further studies involving biotherapeutics paired with ideal prebiotics on T1D prevention are warranted. Assessment of diet composition and dietary habits is relatively simple, and there is strong evidence that diet shapes gut microbiota composition long-term (ca. 6 months) to such an extent that improvement of prediction in multiple diseases is seen [110]. Approaches held up for additional studies, particularly in selected cohorts include probiotics (evidence-of-mechanism studies that include immunology are awaited with particular interest as several studies have commenced to this end), prebiotics (modulation of CAI of GBS and related outcome measures), diet composition, and diet habits (studies with higher engagement using mobile apps combined with internet-based diet monitoring are foreseen).

8.1 Dietary Interventions

Recently, scientists have shown a greater understanding of human intestinal microbiota, physiology, and its study methods, with a focus on its excellent function at the molecular, structural, and functional levels. The reason why this exquisitely engineered functionality is being explored is to treat and eliminate various diseases, particularly diabetes. Consequently, it is important to briefly explain several avenues for improved intestinal microbiota and gut health [88]. Moreover, the gut microbiome is important in the prevention and treatment of diabetes. The microbiome demonstrates a lack of inverse association with the abundance of butyrate-producing bacteria but does not play a significant role in a proinflammatory pathway, consistent with previous reports. Thus, a better understanding of the gut microbiome and its function could be useful to improve gut health and prevent or treat T1D [111]. From birth, members of the microbiota colonize the intestine and establish an intimate association with the host, benefiting them with the acquisition of complex carbohydrate-degrading enzymes and vitamins. Such arrays of enzymes in the microbiota digest dietary polysaccharides to liberate monosaccharides, which are then fermented to produce SCFA. Through extensive metabolomics screening, it has been discovered that interactions between the microbiota and various gut cell types lead to alterations in deranged immune responses. SCFA administration significantly impacted α-diversity, increased Roseburia, Lachnospira, and Clostridium metabolism of soluble fiber, and improved glycemic control. The extent of gut microbiome alterations was unrelated to gut permeability changes. At the same time, it remains an enticing and unexplored avenue that holds the promise of reasonably better mechanisms and greater effectiveness than available pharmacological options to alleviate diseases of gut origin [112].

8.2 Probiotic Supplementation

A probiotic strain, Lactobacillus casei (or Lacticaseibacillus casei strain Shirota, LcS), which has potent immunomodulating activity, has been confirmed as worthy of further investigation as a diabetes-preventive probiotic strain [113]. Spontaneous autoimmune diabetes in NOD mice can be halted by oral administration of LcS on postnatal day (PD) 18. LcS-induced IL-10 production in lamina propria mononuclear cells attenuates proinflammatory cytokine production in monocyte-derived cells. The oral probiotic administration protects against autoimmune diabetes in NOD mice after weaning by modulating intestinal immune homeostasis.

LcS induces robust IP-10 and IL-10 production from lamina propria mononuclear cells (LPMCs). Anti-inflammatory IL-10 production attenuates the production of proinflammatory TNF-α and interferon-γ (IFN-γ) in LPS-activated monocyte-derived macrophages [111]. These findings indicate that LcS supplementation, one of the probiotics that has immunomodulating activity in humans, may be clinically applicable for T1D prevention.

Table 4. Completed and ongoing clinical trials of probiotics, prebiotics, and FMT for T1D prevention and treatment.

Clinical Trial Identifier	Status	Phase	Study Population	Intervention	Sponsor	Location	Estimated Completion	Primary Outcome(s)	Trial Link
Probiotics									
NCT03961854	Recruiting	Phase 2	T1D <1 Year; 8-17 years	Drug: *L. johnsonii* N6.2 Probiotic *vs.* Placebo Capsule	University of Florida	USA	Dec 2025	C-peptide levels, safety	Link
NCT03961347	Recruiting	Phase 2	T1D <3 Years; 18-45 years	Drug: *L. johnsonii* N6.2 Probiotic *vs.* Placebo Capsule	University of Florida	USA	Jan 2026	Beta-cell function preservation	Link
NCT03423589	Completed	Phase 3	Full siblings of T1D patients; 6-17 years	Dietary Supplement: VSL#3	Medical College of Wisconsin	USA	Jun 2022	Safety, immunological markers	Link
NCT04141761	Recruiting	Phase 3	T1D <90 days; 6-17 years	Dietary Supplement: Visbiome (VSL#3) *vs.* Placebo	Medical College of Wisconsin	USA	Dec 2025	Preservation of endogenous insulin secretion	Link
NCT03880760	Recruiting	Phase 2	T1D diagnosis; 6-18 years	Probiotics: *L. johnsonii* MH-68, *B. animalis* subsp. lactis CP-9, *L. salivarius* AP-32 *vs.* Placebo	China Medical University Hospital	China	Nov 2025	Safety, gut microbiome changes	Link
Prebiotics									
NCT02442544	Active, not recruiting	Phase 2	T1D >1 year; 8-17 years	Dietary Supplement: Prebiotic (1:1 oligofructose:inulin) *vs.* Placebo	Alberta Children's Hospital	Canada	Mar 2025	Gut microbiota composition, metabolic markers	Link
NCT04114357	Not yet recruiting	Phase 1	T1D >4 months, <24 months; 12-16 years	Drug: Acetylated and Butyrylated High Amylose Maize Starch	Indiana University	USA	Sep 2026	Safety, gut barrier integrity	Link
NCT02903615	Active, not recruiting	Phase 2	T1D diagnosis; 18-70 years	Other: Novel diet (lower carb, Mediterranean-style, prebiotic fiber focus) *vs.* Standard diabetes diet	Garvan Institute of Medical Research	Australia	Apr 2025	Glycemic control, inflammation markers	Link
ACTRN12618001391268	Completed	Phase 2	T1D >6 months; 18-45 years	Dietary Supplement: Acetylated and Butyrylated High Amylose Maize Starch	Monash University	Australia	Aug 2023	Insulin use, beta-cell function	Link
FMT									
NCT04124211	Recruiting	Phase 2	T1D diagnosis; 18-65 years	Biological: FMT	Third Affiliated Hospital of Southern Medical University	China	Dec 2025	Beta-cell function, immune modulation	Link
NTR3697	Completed	Phase 1	T1D <6 weeks; 18-30 years	Biological: FMT	University of Amsterdam	Netherlands	Dec 2021	Safety, insulin requirement	Link

The gut is populated with vast numbers of microorganisms, collectively known as the gut microbiota, the total genome of which is defined as the gut microbiome. Recent research has emphasized the critical role of the gut microbiome in human health and disease, particularly in the development of T1D in both humans and rodent models. The gut microbiome may serve as a novel target for the prevention as well as treatment of diabetes. This is particularly true for several existing and widely used probiotics that are non-pathogenic in humans and known to exert immunomodulating activity. Clinical trials using one of these probiotics are under consideration. Table 4 provide the complete and ongoing clinical trials of probiotics, prebiotics, and FMT for T1D prevention and treatment.

8.3 Lifestyle Modifications

The multifactorial etiology of T1D involves the interplay of genetic, environmental, and immuno-hormonal factors. That imbalance between effector and regulatory components of the immune system results in the progressive failure of insulin secretion by pancreatic β cells. The gut microbiota modulates the various arms of immunity and adaption to a suboptimal diet triggers a chronic low-grade inflammation. Environmental factors influence the onset and pathophysiology of T1D, acting across the lifetime. Genetic factors contribute to the autoimmune process of T1D but those susceptibility genes affect immunity rather than β cell function. Several interventions aimed at modulating the gut microbiota have been studied in order to delay or prevent T1D in high risk individuals [114].

Gut microbiota composition contributes both to the hygiene hypothesis and to inadequate dietary habits in promoting obesity and type 2 diabetes and other inflammatory conditions. Infants are initially exposed to maternal gut microbiota during delivery while additional microbial communities colonise the gut during the first months of life. This exposure, together with diet composition, lead to the establishment of infant gut microbiota, this period also acting as a window for T1D immunological risk factors. Gut microbiota of children with β cell autoimmunity early on the natural history of T1D shows a slower maturation towards that of healthy children, with a reduced Actinobacteria and Faecalibacterium prausnitzii. Modulating gut microbiota composition with pre-or probiotics may delay the start or progress of β cell autoimmunity. The first study assessing flora in high risk youngsters showed a reduced prevalence of Lactobacillus and Streptococcus. Follow up studies are needed to see whether an association exists between T1D onset and the reduction of probiotic strains.

The Mediterranean diet is a rich source of polyunsaturated fatty acids, phytochemicals, flavonoids, and polyphenols, with pre- and pro-biotic properties with a diverse and balanced gut microbiota considered key to gut health. Dietary intake in prediabetic mice resulted in infectious dysbiosis and reduced Faecalibacterium, Ruminococcaceae, Bifidobacterium. Also increase in Enterobacter and salmonella were also observed with symptoms including increased IL-1β, IL-6, IFN-γ, and glycaemia [76]. Weight gain (BMI) and diabetes risk are heaviest at age 0-2 significantly engendering diabetes incidence. Prenatal maternal years, especially maternal T1D, was linked with inheritance of increased T1D-risk-associated gut microbiota. Removal of dietary gluten resulted in the second apparent shift of fecal microbiota structure, with significant beta diversity differences since the point of gluten removal.

9. Future Directions in Research

To address whether the gut microbiome plays a role in the development of TID, it is essential to examine the gut microbiome of individuals with an increased risk of T1D. Addressing the gap in understanding both the nature of the changes in gut microbial composition and functional capacity as well as the subsequent impact on the host immune system, metabolism, and microbiome-host interactions in current population studies would provide important information. Understanding the microbiome changes associated with disease progression and the role of genetic susceptibility factors on gut colonization and stability would aid in the identification of microbial targets for disease prevention [74]. Current knowledge is limited on the functions of gut microbiome in individuals with an increased risk for T1D, but important information does exist. Differences in the capacity of the gut microbiome to produce SCFAs appear to either reduce or augment the autoimmune risk associated with genetic susceptibility factors [92]. Understanding the gut microbial functional capacity in individuals with an increased risk for T1D would allow for a better understanding of the mechanisms involved in the interaction between genetic, environmental, and microbiome factors in T1D pathogenesis. Importantly, knowledge of how microbial diversity is regulated in response to biologically relevant stimuli would benefit the design of future targeted interventions aimed at restoring a healthy microbiome.

Future research should focus on clarifying whether gut microbiome alterations actively contribute to the development of T1D. This requires detailed investigation of the gut microbial composition and functional capacity in individuals who are genetically or clinically at higher risk for T1D. Current studies show associations, but the causal mechanisms linking microbial shifts to immune dysregulation remain insufficiently understood. For example, children with IA progressing to T1D exhibit reduced microbial diversity, diminished SCFA–producing bacteria, and higher intestinal permeability [68] A major gap lies in identifying the specific microbial pathways that influence host immunity, metabolism, and microbiome–host interactions during the early stages of disease progression–SCFAs like acetate have been shown to modulate IgA responses and reduce insulitis in NOD mice [115]. Longitudinal microbiome profiling in high-risk individuals

would help determine how genetic susceptibility affects gut colonization, microbial stability, and SCFA–producing capacity, which may either mitigate or enhance autoimmune risk.

Understanding these functional microbial changes is essential for discovering precise microbial targets for prevention. Indeed, metabolite-based dietary interventions in humans (e.g., HAMSAB starch delivering acetate and butyrate) have been shown to increase SCFA levels and shift immune profiles toward tolerance [84]. Furthermore, defining how microbial diversity responds to diet, infections, antibiotics, and other environmental triggers will guide the development of targeted microbiome-based interventions–such as next-generation probiotics, dietary modulation, or SCFA-focused therapies. Recent preclinical data demonstrate that SCFA biotherapy remodels gut mucosal immunity and delays diabetes onset in humanized mouse models [112]. Collectively, such research will improve our mechanistic understanding of how genetic, environmental, and microbial factors converge in T1D pathogenesis and support the design of personalized strategies to maintain or restore a resilient gut microbiome.

10. Conclusion

T1D appears most frequently in childhood, with an increasing incidence in the last decades. Although the genetic predisposition is a major risk factor, it cannot explain the complex etiology of T1D which is still not fully understood. Gut health is a prerequisite for well-being and crosstalk between host and gut microbiota is crucial for immune, metabolic and intestinal homeostasis. Early nutrition could have a crucial impact on the bacterial colonization of the gut and on the maturation of the functions of the gut, leading to alterations of gut microbial ecosystem dynamics with downstream effects on the metabolism and immune system. This review is focused on T1D prevention. As the risk of T1D is related to the genetic susceptibility, it cannot be explained by the genetic background only. Environmental factors are also involved. There is now evidence that gut microbiota and gut health are involved in hormonal, immune and metabolic homeostasis with the possibility to influence the onset of chronic diseases such as T1D. The gut microbiota is involved in the control of gut permeability, immune education and maturation, production of vitamins, utilization of polysaccharides and protection from pathogens. There are qualitative and quantitative differences between gut microbiota of healthy and diseased individuals. Data also show the presence of a dysbiotic gut microbiota earlier in life which may predispose to T1D. Early nutrition is involved in the modulation of microbial composition, metabolism and activity with relevant consequences on immune development and function as well as glucose metabolism. Feeding habits that have been found useful to prevent other conditions such as obesity, atopy and inflammatory bowel disease, may have a detrimental effect in the case of T1D. The importance of preventing a gut dysbiotic state in the T1D-prone and early-life window is emphasized. Dietary interventions aimed at favoring the establishment of a gut microbiota that is more similar to that of healthy children should be devised. Probiotics, prebiotics and synbiotics should be tested in the T1D-prone population considering the specific features of their gut microbiota and the recipient expectancies. The implementation of national programs for the prevention of T1D focused on nutrition is advisable.

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Conflict of Interest

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