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# The influence of intestinal microbiota on the development of type 1 diabetes

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**Abstract**

**Introduction and purpose**

Type 1 diabetes (T1D) is an autoimmune disease that results in the destruction of pancreatic β cells, which leads to insulin deficiency and hyperglycemia. One significant factor that may influence the development of type 1 diabetes is a change in the intestinal microbiota. This study aim is to present the significance and role of intestinal microbiota in the pathogenesis of T1D. This subject is important, as it offers prospects for new therapeutic solutions, especially given the significant social impact of T1D.

**Description**

Type 1 diabetes (T1D) causes a number of symptoms and complications, including an increased risk of developing cardiovascular diseases. Diagnosis includes measurements of glucose concentration, glycated hemoglobin, and specific antibodies in the blood. The basic therapy for T1D is insulin replacement therapy. Numerous studies have shown that both the composition and function of the intestinal microbiota are impaired in patients with T1D. It has been observed that an increase in the number of Bacterioides and a decrease in the number of Firmicutes, which are the main microorganisms of the intestinal microbiome, are correlated with a high risk of developing T1D.

**Summary**

Type 1 Diabetes (T1D) is a serious health problem that affects many people worldwide and the incidence of the disease is constantly increasing. There is a growing number of studies that emphasize the influence of the intestinal microbiota on the development of T1D. It is important to enlarge our knowledge about this disease. Further studies are needed to determine the importance and the role of the intestinal microbiota in the pathogenesis of T1D.

**Keywords:** diabetes; type 1 diabetes; T1D; diet in type 1 diabetes; gut microbiota; gut microbiota and type 1 diabetes.

## Introduction and purpose

Type 1 diabetes (T1D) is an autoimmune disease in which autoreactive T-lymphocytes play a crucial role in the pathogenesis by attacking the pancreatic β-cells. This process leads to the gradual destruction of these cells, which are responsible for insulin production [1]. As a result, the patient's pancreas is unable to produce sufficient amounts of insulin, leading to hyperglycemia- an elevated blood sugar level. The initial symptoms may include polydipsia and dry mouth, polyuria, lack of energy, fatigue, blurred vision, and weight loss [2]. This disease progresses rapidly and is most commonly diagnosed in children and adolescents, though it can also occur in adults..

T1D is a significant health issue both in Poland and globally. According to data from the Central Statistical Office (GUS), in 2022, 3.1 million people with diabetes (both type 1 and type 2) utilized public healthcare services in Poland, with approximately 10% of these individuals having type 1 diabetes. A noticeable upward trend is clear; the number of registered individuals was 2.7 million in 2017 [3]. Globally, the incidence of type 1 began to rise in the 1950s, with an average annual increase of 3-4% over the past three decades [4]. This is reflected in the statistics indicating that the prevalence of type 1 diabetes varies from 1 to 3 per 100 000 individuals annually in China and other countries in Asia and South America, around 10-20 per 100 000 individuals in Southern European countries and the USA, and 30-60 per 100 000 individuals in Scandinavia. The studies from which these data originate primarily focus on individuals under the age of 15 [4].

The highest incidence rates of type 1 diabetes (T1D) are observed in North America and Europe, suggesting a significant role of environmental factors, such as diet and lifestyle [5]. In the pathogenesis of T1D, genetic factors, including the presence of high-risk alleles of human leukocyte antigens HLA-DR and -DQ, contribute to increased susceptibility to the disease. However, exposure to environmental factors is responsible for an autoimmune response. Among genetically predisposed individuals, less than 10% develop T1D, highlighting the critical importance of environmental exposure [1, 5]. Environmental factors that may accelerate the onset of T1D include viral infections, vitamin D deficiency, antibiotic use, and changes in gut microbiota [5].

The aim of this work is to elucidate the significance and role of gut microbiota in the pathogenesis of T1D, as this is an important topic that offers prospects for new therapeutic solutions. This is particularly crucial given the continually rising incidence rates and the real social issue posed by type 1 diabetes.

## Material and methods

The review was based on the analysis of materials collected in the „PubMed”and Google Scholar. The following keywords were entered during the search for scholarly articles: diabetes, type 1 diabetes, T1D, diet in type 1 diabetes, gut microbiota, gut microbiota, and type 1 diabetes. A total of 46 articles published between 2015 and 2024 were considered for the study and verified for their relevance to the topic of gut microbiota in type 1 diabetes.

**Symptoms of diabetes**

Type 1 diabetes can manifest with various symptoms, including increased thirst (polydipsia), more frequent urination (polyuria), and uncontrolled weight loss [6, 7]. T1D increases the risk of developing cardiovascular diseases such as peripheral artery disease and coronary artery disease [8]. Patients may also experience complications such as retinopathy, neuropathy, hypertension, and an increased risk of overweight or obesity [9, 10]. A significant number of children develop diabetic ketoacidosis (DKA), which is a serious condition requiring immediate medical attention. [6]. Furthermore, both chronic hyperglycemia and hypoglycemia in patients with T1D are associated with cognitive function impairments in memory, concentration, and attention [11, 12].

T1D can be divided into three main stages: the asymptomatic phase, characterized by the presence of autoantibodies in the blood with normoglycemia; the phase of early metabolic changes with an asymptomatic state, marked by the presence of autoantibodies in the blood with dysglycemia indicating functional damage to pancreatic β cells; and clinical diabetes, characterized by the occurrence of clinical symptoms such as hyperglycemia and other classic signs. [13, 14].

**Diabetes diagnosis**

Diagnosis of T1D involves measuring blood glucose levels or glycated hemoglobin (HbA1c). T1D is diagnosed when fasting glucose levels are twice found to be above 126 mg/dL (7.0 mmol/L), random glucose levels exceed 200 mg/dL (11.1 mmol/L) in the presence of hyperglycemia symptoms, or an abnormal result from an Oral Glucose Tolerance Test (OGTT) (glucose level above 200 mg/dL two hours after administering 75 g of glucose). A glycated hemoglobin (HbA1c) level exceeding 6.5% (48 mmol/l) is also a criterion for diagnosis of diabetes [6, 7]. For patients with T1D, the preferred diagnostic criterion is blood glucose level [6].

The measurement of autoimmune antibodies directed against insulin (insulin autoantibodies, IAA), insulinoma-associated antigen 2 (IA-2), glutamic acid decarboxylase (GAD65), zinc transporter 8 (ZnT8 autoantibodies), and islet cell antibodies (ICA) plays a significant role in assessing the risk of developing and diagnosing type 1 diabetes. These antibodies indicate dysfunction of pancreatic β-cells [15, 16]. Although antibody levels can predict the development of diabetes, there are no effective methods to prevent its onset. Therefore screening for T1D should not be performed in the general population [16].

**T1D Treatment**

Intensive insulin therapy, discovered in the 1920s, is a groundbreaking treatment for type 1 diabetes. Prior to insulin therapy, patients with type 1 diabetes had an average life expectancy of just one to two years following diagnosis. Today, the life expectancy of individuals with type 1 diabetes has increased significantly. Moreover, both the mortality rate and Disability-Adjusted Life Years (DALYs) associated with the disease have declined [13,17]. Another significant event that impacted the treatment of this condition was the publication of the

Diabetes Control and Complications Trial in 1993, which demonstrated that maintaining glucose concentrations as close to normal physiological levels as possible leads to a reduction in microvascular and cardiovascular complications of type 1 diabetes [6].

Currently, the most commonly used method for managing glycemia involves manual blood sugar measurements, followed by multiple subcutaneous insulin injections throughout the day. An alternative to traditional injections is the insulin pump, which enables the continuous delivery of rapid-acting insulin through a small catheter inserted into subcutaneous tissue. This method is particularly useful for patients with severe glycemic control issues. The use of an insulin pump in conjunction with continuous glucose monitoring (CGM) technology improves blood glucose control, thereby reducing the risk of complications [13,18]. A more advanced method is the artificial pancreas, which combines CGM with continuous insulin infusion, allowing for better glycemic outcomes and reducing the burden on patients. The programmed device maintains target glycemia, which decreases the effort required from the user of this method, while also enhancing their quality of life. Some models can also administer glucagon based on real-time glucose readings. The most advanced commercially available methods are closed-loop systems, which require patients to manage their mealtime insulin doses. Systems that completely remove the need for manual blood glucose monitoring are still in clinical trials [13,19].

Alternatives or supplements to insulin therapy are constantly being sought. Among the options being considered is the addition of the GLP-1 analogue liraglutide to standard insulin treatment, as well as the application of immunomodulatory therapy. There are also high hopes for stem cell therapy. It has been proven that stem cells can transform into insulin-producing and secreting cells, allowing for better glycemic control. However, these methods remain in the research phase [20,21].

**The microbiome**

The microbiome includes all saprophytic microorganisms, commensals, and parasites within the human body. Through evolution, microorganisms have colonized human surfaces, as well as the digestive and respiratory systems, in search of ecological niches and food sources [22].

Colonization begins at birth, when the fetus is exposed to the mother’s vaginal microbiota while passing through the birth canal [22]. Subsequent environmental exposure further shapes an individual's microbiota. Microbial colonization occurs throughout the body, but the largest population is found in the intestines [23].

In the gastrointestinal system, variations in conditions and functions across sections result in different compositions of bacteria, fungi, and archaea. In the oral cavity, bacteria from groups such as Streptococcus, Peptococcus, Bifidobacterium, Staphylococcus, Lactobacillus, and Fusobacterium are predominant. Due to the very low pH in the stomach and duodenum, the growth of many bacterial species is limited, with Helicobacter pylori, Lactobacillus, Streptococcus, and the yeast Candida albicans being the main inhabitants. In subsequent sections of the intestine, the number of bacteria increases, reaching its highest quantity in the large intestine. Here, most of the bacteria are obligate anaerobes: Bacteroides, Clostridium, Ruminococcus, Fusobacterium, Butyrivibrio, Peptostreptococcus, Eubacterium, and Bifidobacterium; aerobic and facultative anaerobic bacteria include Gram-negative rods from

the Enterobacteriaceae family, Gram-positive rods like Lactobacillus, cocci from the genera Enterococcus and Streptococcus, and small amounts of fungi from the genus Candida spp [22].

The gut microbiota plays a crucial role in supporting host health. It participates in the digestion of complex carbohydrates, the synthesis of essential vitamins, and regulates the immune system. The microbiota also competes for resources and space with pathogenic microorganisms, thereby preventing their potential invasion. In addition, the gut microbiota produces short-chain fatty acids that have anti-inflammatory effects and contribute to maintaining the integrity of the intestinal barrier in the large intestine [23].
It is estimated that around 30% of microbial species are common across most individuals, forming a specific core microbiome. The rest is modifiable by physiological processes, including the immune system, genotype, lifestyle, and the host's living environment [22].

**The influence of diet on microbiota**

Diet is a major factor influencing gut microbiota composition. Research shows a positive correlation between plant-based protein intake and increased levels of Lactobacillus. The same protein reduces the number of Bacteroides and Clostridium perfringens. Such changes in microbiome composition lead to an increase in the production of short-chain fatty acids (SCFAs), which in turn strengthens the intestinal barrier and decreases inflammation [24]. In addition to protein, fat intake also affects the composition of gut microbiota. Studies in mice have shown that a high-fat diet rich in saturated fats leads to an increase in the proportion of Bacteroides. This change in gut microbiota may be associated with the development of T1D [24,25]. Conversely, the consumption of unsaturated fats, such as those found in olive oil, has an opposite effect [24,26,27]. The intake of carbohydrates like glucose, fructose, sucrose, and lactose results in a decrease in the proportion of Bacteroides in gut microbiota [24]. A study examining the impact of a Mediterranean diet on the microbiome demonstrated that plant fiber ferments in the large intestine and produces SCFAs. This process increases anti-microbial peptides (AMP) and regulates β-cell function. Thus, it has been shown that adequate fiber intake can protect against the onset of T1D in genetically predisposed individuals [26]. Research indicates that an anti-inflammatory diet enhances the structure and composition of the intestinal mucus layer, supporting gut integrity [27].

**The Influence of Microbiota on the Occurrence of Type 1 Diabetes (T1D)**

Gut dysbiosis is a condition characterized by an imbalance in the composition and function of the microorganisms that constitute the gut microbiota. Numerous studies have demonstrated the presence of dysbiosis in individuals with type 1 diabetes (T1D) [1, 28, 29, 30]. Specifically, children diagnosed with T1D exhibit a higher prevalence of Bifidobacterium spp. but lower levels of Streptococcus thermophilus and Lactococcus lactis than healthy children [31].
The two primary microbial groups within the gut microbiome are Bacteroidetes and Firmicutes. An increase in the abundance of Bacteroidetes spp. along with a decrease in Firmicutes has been correlated with a heightened risk of developing T1D [30, 31, 32]. Furthermore, elevated levels of Clostridiales and Dorea bacteria, coupled with reduced

Akkermansia, have been observed in T1D patients and their siblings, suggesting that similar environmental conditions may predispose these individuals to T1D.

Disruptions in the balance of specific bacterial strains can lead to a deficiency in bacteria responsible for producing short-chain fatty acids (SCFAs) [33]. SCFAs, primarily acetate, propionate, and butyrate, exert their effects through G protein-coupled receptors, influencing not only the colon but also other organs such as adipose tissue and immune cells via the bloodstream. SCFAs play a critical role in regulating gastrointestinal function, motility, and integrity [34]. Due to the similarities in pathomechanisms underlying T1D and genetic loci between humans and non-obese diabetic (NOD) mice , NOD mice are frequently used in research studies [35]. Feeding NOD mice diets rich in SCFA-producing bacteria has been shown to reduce the incidence of T1D in these animals [28, 35].

In another study, administration of butyrate—known for its anti-inflammatory properties and ability to strengthen the intestinal barrier—resulted in increased production of C-peptide, improvements in damaged pancreatic beta islets, and notably, an increase in insulin-producing islets. Additionally, reaserch confirmed that the abundance of butyrate-producing bacteria was inversely proportional to the levels of autoantibodies involved in pancreatic cell destruction. This led to the conclusion that a reduced quantity of butyrate-producing bacteria contributes to the pathogenesis of T1D [36].

Moreover, correlations have been established between elevated levels of anti-GAD antibodies and decreased abundance of Roseburia, Faecalibacterium, and Alistipes [5, 31]. There is also a noted relationship between Bacteroidetes, Veillonella, and Prevotella populations with increased zonulin levels; conversely, lower zonulin levels are associated with Faecalibacterium and Roseburia presence. This may influence what is referred to as "intestinal permeability" [38].

Research confirms that individuals with T1D experience gut dysbiosis, leading to what is commonly termed "leaky gut." However, there is no consensus on whether this condition is a cause or a consequence of T1D. According to studies involving animal models and works by Bosi et al. and Harbison et al., dysbiosis appears prior to symptom onset [29, 37-41]. The mechanisms underlying this phenomenon are complex. The intestinal epithelium represents the largest surface area for contact between the human organism and the external environment; thus, its integrity is crucial for overall health [42]. The intestinal barrier consists of several layers including epithelial cells coated with mucus—a habitat for gut microbiota—tight junction proteins, and immune cells [25, 31, 43]. Mucins are the primary constituents of mucus and can be degraded by certain strains of Bifidobacterium, Bacteroides, and Ruminococcus. Consequently, these bacteria can compromise the first layer of the intestinal barrier. In contrast, Firmicutes act antagonistically by stimulating mucin production, thereby reinforcing the intestinal barrier [34].

The integrity of the intestinal barrier is primarily maintained by tight junctions (TJs). These structures comprise a network of proteins, including claudins, occludin, cingulin, and the cytoplasmic proteins zonula occludens (ZO) 1, 2, and 3 [25, 29, 31, 43, 44]. The tightness of these junctions determines the rate and type of molecules that can permeate into the

circulatory system [43]. Zonulin plays a crucial role in regulating intestinal permeability by modulating the opening and closing of TJs between enterocytes [42]. Dysbiosis has been shown to stimulate enterocytes to produce zonulin.This initiates a cascade of biochemical reactions resulting in phosphorylation of tight junction proteins (TJ), their loosening, and consequently increased intestinal permeability [29, 41, 44]. A "leaky gut" allows exogenous antigens to enter the systemic circulation.

Two hypotheses arise from current studies: one posits that antigens induce generalized inflammation and direct damage to pancreatic cells while the second suggests that this occurs indirectly through antigen-presenting cells (APCs) presenting antigens to autoreactive T lymphocytes. Both mechanisms activate the immune system, promote inflammation, and contribute to T1D development [36, 37].

Additionally, one study demonstrated that decreased blood pH during conditions such as diabetic ketoacidosis significantly correlates with gut microbiota functionality [45].

Understanding the relationship between microbiota and T1D development is essential. Insights into these connections may pave the way for innovative treatment approaches for T1D .

**Summary**

Diabetes is a significant health issue that negatively impacts the quality of life for patients and their families, leading to long-term complications and, consequently, a reduction in lifespan. Diabetes affects many people worldwide, and in recent years, the prevalence of this disease has been steadily increasing. A growing body of research emphasizes the importance of gut microbiota in developing T1D. These studies have shown that alterations in gut microbiota may contribute to the onset of type 1 diabetes [46] .

Further understanding of diabetes its pathomechanisms, risk factors, prevention strategies, diagnostics, and treatment options is essential. Continued research is needed to determine the significance and role of gut microbiota in the pathogenesis of diabetes, including T1D.

**DISCLOSURES**

**Author's contribution:**

Conceptualization: Katarzyna Augustowska, Agnieszka Protasiuk;
Methodology: Rafał Sierzpowski, Patrycja Tymoszuk;
Formal analysis: Agnieszka Protasiuk, Rafał Sierzpowski;
Investigation: Patrycja Tymoszuk, Agata Żak;
Writing-rough preparation: Katarzyna Augustowska, Patrycja Tymoszuk, Agata Żak;
Writing-review and editing: Agnieszka Protasiuk, Rafał Sierzpowski;
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