

The Role of the Hygiene Hypothesis in the Pathogenesis of Type 1 Diabetes

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Abstract. Type 1 diabetes (T1D) is an autoimmune disease where the immune system mistakenly attacks pancreatic β -cells, causing chronic inflammation and inefficient production of insulin due to decreasing β cell number. As insulin production declines, the body cannot maintain glucose homeostasis, leading to diabetes. The incidence of T1D has been rising during the last few years, along with the rapidly developing industrialized world. The hygiene hypothesis could explain this trend by suggesting that exposure to microbes in early ages functions to train the immune system. If the Immune system is highly trained, it is less likely to target self-antigens, reducing the risk of allergies and autoimmune diseases such as T1D. That being said, this review aims to evaluate how the hygiene hypothesis explains the pathogenesis of T1D. The analysis covers the theoretical basis and mechanisms of the hygiene hypothesis, early-life microbial exposures, gut microbiota diversity, environmental and geographical factors, trends in T1D incidence, animal models, and clinical trials. Evidence supports the hygiene hypothesis by highlighting the impact of environmental factors on immune development. However, current research produces contradictory results and often overlooks factors such as genetics, which also influence the onset of T1D. Future research should integrate genetics and other relevant fields with longitudinal data collection to further evaluate and refine the hygiene hypothesis.

Keywords: The Hygiene hypothesis, Type 1 Diabetes, Autoimmune disease.

1. Introduction

The autoimmune disease Type 1 diabetes (T1D) occurs based on immune-mediated destruction of pancreatic β -cells. With the loss of insulin-producing β -cells, glucose homeostasis cannot be maintained. The pathogenesis of T1D is multifactorial; some factors include genetic susceptibility, environmental triggers, and immune dysregulation [1]. In T1D, patients produce autoantibodies, including anti-GAD65, anti-IA-2, anti-insulin, and anti-ZnT8, while regulatory mechanisms and immune cells, such as Tregs, are impaired. Currently, the United States and other developed countries, particularly in Europe, report the highest incidence rates of T1D. Moreover, incidence rates have been rising with industrialization, with the most rapid growth observed in newly industrializing countries [2].

As suggested by the hygiene hypothesis, exposure to a diverse microbiome at an early age train the immune system and helps prevent autoimmune diseases. Currently, the hygiene hypothesis is supported by evidence that comes from cohort studies, mechanistic research, and interventional data. For instance, some studies suggest that certain microbes stimulate and train Tregs, while others show correlations between microbial environments and the risk of autoimmune diseases. Nonetheless, the hygiene hypothesis remains insufficient to fully explain the causation of autoimmune diseases. Key gaps include causal specificity, timing of exposure, and the development of broadly applicable interventions. There is also debate regarding factors thought to reduce microbial exposure and increase the risk of autoimmunity, such as delivery by C-section [3].

This paper focuses on analyzing how the hygiene hypothesis affects the pathogenesis of T1D. Utilizing the format of a literature review, this paper aims to produce a systematic analysis of relevant epidemiological, immunological, and animal experimental research. Hoping to achieve a comprehensive analysis, this paper examines how different findings, including microbial exposure, gut microbiota, immune tolerance, and environmental influence on T1D, support or contradict the hygiene hypothesis.

With scientific evidence, this review focuses on the relationship between the hygiene hypothesis and T1D. The hygiene hypothesis provides a unique perspective when analyzing autoimmune diseases and allows diverse research to be conducted. By explaining immunological defects in autoimmunity with environmental and microbial factors, an alternative framework for studying autoimmune diseases is provided by the hygiene hypothesis that extends beyond lifestyle and genetic factors. Furthermore, by claiming the cause of autoimmune diseases as a failure of immune education, the hygiene hypothesis explored the cause of such diseases, making prevention more attainable. It also provides more context than the simple defect in self-recognition, explanation. Importantly, the claims made in the hygiene hypothesis also match the growing trend of onset in autoimmune diseases such as T1D, making it more valid [4]. Thus, research on the hygiene hypothesis provides theoretical support for future prevention strategies, therapeutic approaches, and research directions. Furthermore, this research could provide a potential contribution to the fields of public health and immunology.

2. The Hygiene Hypothesis and Its Basic Mechanism

2.1. The Hygiene Hypothesis

The hygiene hypothesis claims that pathogenic stimulation in early years may confer protection against the subsequent development of autoimmune diseases or allergies [4]. It suggests that reduced exposure to organisms as children, resulting from improved hygiene and sanitation, can hinder the development of the immune system. Thus, this could increase susceptibility to autoimmune diseases and allergies [4].

2.2. The Hygiene Hypothesis— Origin and Developments

The concept of the hygiene hypothesis was first extensively investigated in the 1970s and 80s. The term “hygiene hypothesis” was initially coined by David Barker, who suggested that the rising incidence of appendicitis in rural British communities was the result of improved living standards [4]. The concept soon gained traction among British scholars, such as Butler and Golding, who observed the same trend in their longitudinal study of children’s health. However, early research was primarily focused on appendicitis [4].

Brought up by David P. Strachan, a British epidemiologist, the hygiene hypothesis was introduced in 1989. Strachan published this idea in the *British Medical Journal* in the form of a paper titled “Hay fever, hygiene and household size”. Strachan concluded that allergies during the post-industrial era are primarily caused by smaller family size, improving hygiene, and quality of life. As Strachan stated, these factors would result in a growing trend of atopic diseases and cross-infections are reduced during youth.

The hygiene hypothesis garnered considerable attention among scholars, with the majority of research focusing on allergies and asthma during the 1990s. It was generally believed that reduced exposure to infections in childhood would result in an insufficiently trained immune system, causing the overreaction to allergies. In the early 2000s, the scope of the hygiene hypothesis expanded to environmental microbial exposure and immune regulation, beyond the narrow focus on prior infections. Since the early 2000s, the hygiene hypothesis has also been applied to explain the pathogenesis of autoimmune diseases, such as Type 1 diabetes, in addition to simple allergies [4].

2.3. The Effect of Exposure to Microorganisms on the Development of the Immune System

It's widely recognized that exposure to a diverse range of microorganisms during youth would help prepare and train the immune system. Over time, beneficial microorganisms would develop a symbiotic relationship with the host, during which the immune system develops tolerance toward non-pathogenic species. Certain microorganisms can also trigger the production of immunoregulatory cells, such as the T cells (Tregs). This process is important to reduce inflammation, maintain immune tolerance, and prevent autoimmune diseases. Moreover, exposure to a broad diversity of microorganisms helps maintain an appropriate balance between the Th1- and Th2-mediated immune

responses, whereas insufficient exposure may lead to TH2 dominance and an increased risk of allergies [5].

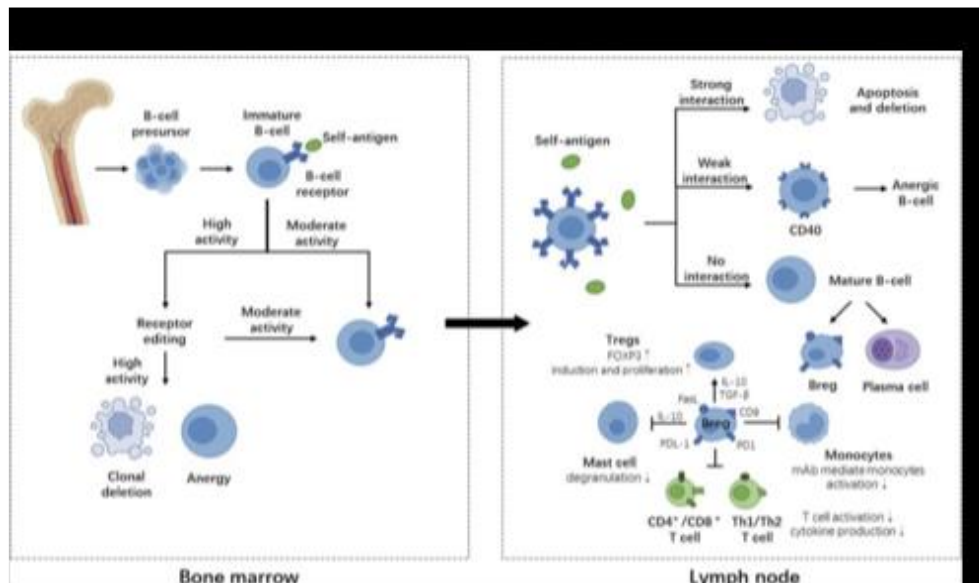


Fig. 1 The mechanism of central and peripheral immune tolerance with B lymphocytes as an example [6].

2.4. The Basic Mechanisms of Immune Tolerance and Immune Regulation

Although definitions of immune tolerance would be different for each distinct disease, it generally explains how the immune system distinguishes between pathogenic and non-pathogenic antigens [6]. There are two main types of tolerance: central and peripheral, as shown in Figure 1. Central tolerance is the selection of T cells and B cells in the thymus and bone marrow, respectively. T cells undergo negative selection, whereas B cells undergo receptor editing. During maturation, both immature T and B cells are exposed to self-antigens. If lymphocytes exhibit excessive reactivity to self-antigens, they are considered potentially autoreactive and therefore are removed via apoptosis [6]. Peripheral tolerance operates outside the primary lymphoid organs. This system prevents the immune system from attacking the normal cells by inactivating them when a self-antigen is encountered in a process called anergy. Cells like Tregs also belong to this system due to their immune suppressive functions and contribute to reducing inflammation. In extreme cases, this system may also trigger apoptosis to delete immune cells that are causing harm to normal tissues [6].

Immune regulation is a mechanism aiming to ensure effective elimination of pathogens while minimizing collateral damage to healthy tissues. This goal is often achieved by controlling 2 different aspects of immune responses: the intensity and duration of immune responses. Tregs directly control this process by secreting immune suppressive cytokines such as IL-10 and TGF- β , allowing the body to maintain immune homeostasis [7]. Said homeostasis is achieved when an ideal balance between infection-combating pro-inflammatory cytokines and immune suppressive anti-inflammatory cytokines is maintained. For instance, when the balance of such as IL-6 and IFN- γ (pro-inflammatory) and IL-10, and TGF- β (anti-inflammatory) levels is maintained, the risk of chronic inflammation will decrease [7].

2.5. The Hygiene Hypothesis's Explanation on the Occurrence of Autoimmune Diseases

The hygiene hypothesis suggests that the cause of autoimmunity is the lack of microbial exposure during early childhood. Specifically, these exposures are viewed as helpful training mechanisms for the immune system to distinguish between non-pathogenic and pathogenic antigens. Most importantly, certain microorganisms are believed to be responsible for stimulating Tregs, which is important to battle autoimmunity. Therefore, when the body lacks microbial signals, the number and efficiency of Tregs may be lower compared to a body with rich microbiota. As a result, self-reactive

immune cells are not effectively suppressed, and cytokine homeostasis is disrupted. Under such conditions, individuals are more likely to develop chronic inflammation or autoimmune diseases [8].

3. Pathogenesis and Epidemiology of T1D

3.1. Autoimmune Characteristics and Immune Cell Function in T1D

In T1D, the immune system loses tolerance to antigens expressed by pancreatic β -cells in the islets of Langerhans [9]. These β -cells function to maintain homeostasis in blood glucose levels by secreting insulin. Specifically, the insulin binds to target cells near blood vessels and stimulates glucose uptake for ATP production. In T1D, immune cells infiltrate the pancreatic islets and destroy the β -cells, leading to a rapid decline in insulin production and chronic inflammation [9].

Multiple immune cell types contribute to T1D pathogenesis. CD8⁺ cytotoxic T cells are a major effector population; they identify β -cells via MHC class I molecules and induce apoptosis, causing extensive β -cells destruction. CD4⁺ Helper T cells activate cytotoxic T cells and B cells and secrete pro-inflammatory cytokines that further damage β -cells. B cells produce autoantibodies against β -cell antigens while activating more CD8⁺ T cells. Macrophages release inflammatory cytokines such as IL-1 β and TNF- α , causing damage to the tissue. Dendritic cells recognize the β -cell antigens as foreign and present them to CD8⁺ T cells, thereby initiating the autoimmune cascade [9].

3.2. Recent T1D Incidence trends Around the Globe and Specific Regions

The global incidence rate of T1D has been increasing, with around 8.4 million diagnosed cases in 2021, and an estimated 9.5 million in 2025, showing a 13% increase [9]. The increase is particularly pronounced in lower-income countries, where incidence has risen by approximately 20% [9]. Nevertheless, incidence remains highest in high-income countries, showing a strong positive correlation with national GDP [10]. Currently, the United States has the highest T1D incidence, with a rate of 12.2 per 10,000 individuals [9].

3.3. The Environmental Factors' Impact on the Onset of T1D

The onset of T1D is influenced by various environmental factors. C-section at birth has been suspected to have a direct correlation with the increasing onset of T1D [11]. Since 1990, C-section rates have increased by approximately 50%, paralleling the increase in T1D incidence. Infants delivered via C-section lack contact with protective vaginal bacteria and exhibit lower gut microbial diversity. Thus, C-section delivery may increase susceptibility to T1D [3]. Early-life antibiotic use can also change the gut microbiota. This may result in the depletion of beneficial gut microorganisms and reduce immune tolerance. Thus, early and repeated antibiotic exposure may increase the incidence of T1D [12]. Growing up in overly hygienic or sterile environments may further increase the risk of T1D. Microbial exposure is effective in training the immune system during childhood and in balancing the Th1/Th2 response. Areas with low pathogen exposure, such as urban areas in developed countries, exhibit the highest T1D incidence [11].

3.4. Epidemiological Evidence Related to the Hygiene Hypothesis in T1D

Geographical variations in T1D incidence provide key epidemiological evidence supporting the hygiene hypothesis. High-income countries, which typically feature improved hygiene and reduced contact with microbes and pathogens during childhood, exhibit higher T1D incidence rates. When immigrants move from less to more developed countries, their offspring show a growing risk of T1D over time [2]. When immigrants reproduce 5 years after the migration to Sweden, the baby's risk of T1D onset will be 22% lower compared to when the mother lives in Sweden for 11 years or more [13]. Furthermore, children raised in an agricultural (rural) environment during the first year of their lives have less chance of developing T1D than those raised in developed cities. This protective effect is attributed to greater exposure to environmental microbial diversity in rural settings [2].

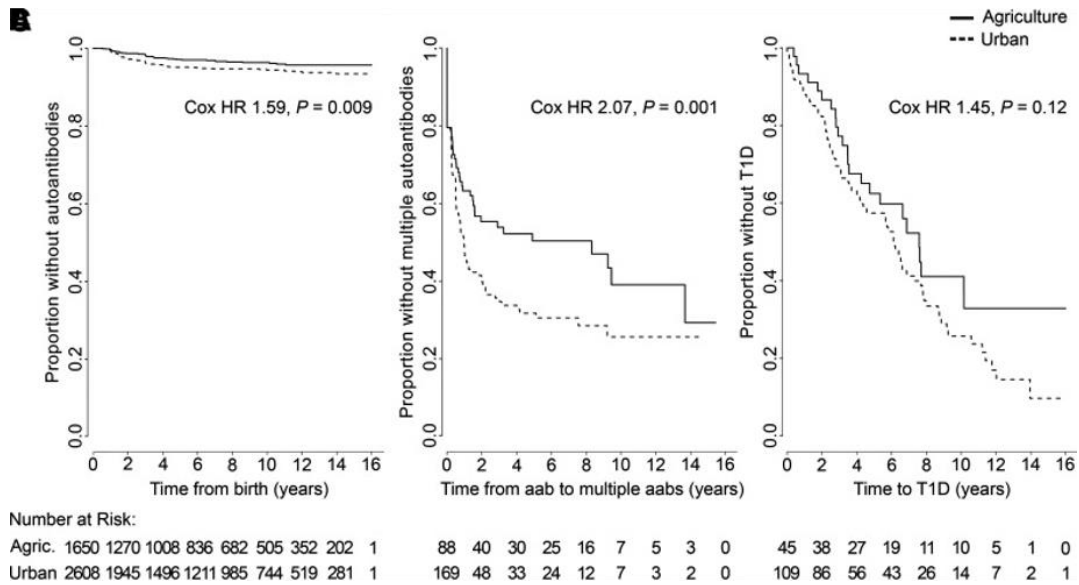


Fig. 2 The incident rate of T1D of people who settle in rural and urban areas [2]

As shown in Figure 2, people from agricultural areas consistently exhibit a higher proportion without autoantibodies compared to those from urban areas. A lower prevalence of autoantibodies corresponds to a reduced risk of T1D among individuals from agricultural areas [2].

4. The Specific Mechanism of the Hygiene Hypothesis in T1D

4.1. The Role of Microbial Diversity and Gut Microbiota in Immune Regulation

Early exposure to microorganisms directly influences microbial diversity and the autoimmune diseases, such as T1D, risks. A more diverse microbial community would provide constant, low-level stimulation of immune pathways, thereby increasing Treg number and maintaining immune balance [14]. Specifically, the gut microbes' role is crucial in promoting the development of Tregs in early life. Certain microbes (e.g., *Bacteroides fragilis*, *Klebsiella*) and microbial metabolites such as SCFAs contribute to the production of cytokines like IL-10 and TGF- β . These cytokines exert immune suppressive functions by stimulating Th2 cells and promoting Tregs differentiation [14]. When the gut microbial environment is disturbed, the balance of immune regulation is disrupted, contributing to the development of autoimmune diseases, such as T1D. Through complex mechanisms and signaling pathways, gut microbes ultimately modulate the release of inflammatory factors, as shown in Figure 3 [15].

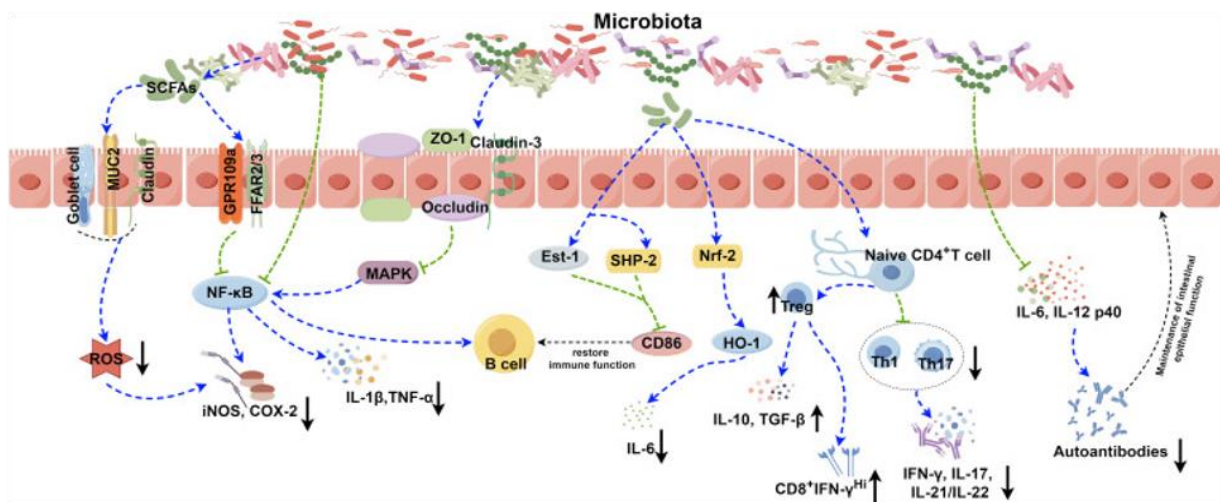


Fig. 3 The disrupted gut microbial environment leading to imbalanced immune regulation causing autoimmune disease [15].

4.2. How Early Microbial Exposure Promotes the Formation of Immune Tolerance

Early microbial exposure shapes immune regulation by functionally training immune cells. Microbial exposure during the critical neonatal window is crucial for the maturation and functional programming of innate immune cells, such as MAIT, NKT, $\gamma\delta$ T-cells, and B-1 cells [16]. These cells acquire the ability to protect the body from pathogens while tolerating beneficial microbes, thereby establishing immune tolerance [17]. Moreover, a healthy IgE level could be maintained throughout the whole lifespan, given that a balanced microbial colonization is established during early life. Specifically, IgEs can bind efficiently with the mast cells and basophils, releasing chemicals that lead to allergy. Although it may seem like IgE is more relevant to the formation of allergies, it still plays an important role as a contributor to autoimmune diseases [16].

4.3. Animal Test Evidence of the Hygiene Hypothesis and T1D

The hygiene hypothesis is supported by many studies and research, including Olszak et al.'s study. This study focuses on two types of mice, the germ-free (GF) mice and the specific-pathogen-free (SPF) mice. The two mouse types are compared and analyzed throughout the study, mostly by measuring iNKT cell numbers. The result shows a higher level of iNKT cells accumulation in the GF mice, and severe colitis and asthma were also observed in the GF mice in comparison with the SPF mice. The SPF mice also show signs of a less intensive autoimmune response through less inflammation. The study demonstrated that higher exposure to microbes can enhance immune tolerance and reduce autoimmunity [18].

4.4. Clinical Trial Evidence in Explanation of the Hygiene Hypothesis and T1D

The hygiene hypothesis is also supported by a variety of clinical trials. In a randomized, double-blind trial, 25 children (aged 2–7) with high genetic risk of T1D were enrolled. All these children showed no islet autoantibodies despite the high genetic risks. During the study, all the children received daily oral insulin at increasing doses: 2.5 mg, 7.5 mg, 22.5 mg, up to 67.5 mg [18]. The result showed that at the highest insulin intake (67.5 mg per day), the body would develop an immune response to insulin. Specifically, increased insulin-specific IgG and increased IL-10 indicated that the body recognized insulin as non-pathogenic and developed immune tolerance [19]. Although not a direct test of microbial exposure, this supports the principle of the hygiene hypothesis.

4.5. Advantages and Limitations of The Hygiene Hypothesis in Explaining the Change in Risk of T1D

The advantages of the hygiene hypothesis in explaining the change in risk of type 1 diabetes can be summarized in four aspects. First, in the rapidly industrializing modern world, epidemiological trends show an increasing trend of T1D incidence rate, and the hygiene hypothesis matches this trend [20]. Furthermore, when individuals migrate from less to more developed countries, the risks of T1D of their offspring also increase [13]. Thirdly, having a highly diversified gut microbial environment at an early age also contributes to the development of a healthy immune tolerance, which matches the hygiene hypothesis [14]. Lastly, some laboratory evidence, such as animal tests and clinical trials, does show results supportive of the hygiene hypothesis. Together, these findings strengthen its explanatory power.

The hygiene hypothesis's explanation of autoimmune diseases such as T1D is also somewhat limited. The original hygiene hypothesis only explained allergies on a very general level, but to yield more preferable results in the case of T1D, such as how only certain microbes or antigens may be relevant. Environmental and lifestyle factors such as diet, obesity, vitamin D deficiency, and pollutants were not considered by the hygiene hypothesis. Some clinical trials also show little to no associations, such as how C-section delivery was often believed to increase the risk of T1D, but the Norwegian Population-Based Cohort Study found that it has no significant association with T1D risk [21].

5. Conclusion

This review examines the hygiene hypothesis's method of explanation for the onset of T1D by analyzing its strengths and limitations. T1D incidence is increasing in highly developed regions with better hygiene, which is indicated by a variety of evidence, including Geographical, environmental, and immigration evidence. The hygiene hypothesis claims that reduced microbial exposure increases the risk of autoimmune diseases, and it is supported by these results. Laboratory evidence, such as animal tests and clinical trials, all support the hypothesis to different degrees. A major strength of the hygiene hypothesis is how it clearly establishes the relationship between microbes and the immune systems of the host, and such a connection is also supported by valid evidence. The hygiene hypothesis is still very limited in many aspects; it oversimplifies trends, lacks detailed mechanistic explanations, and struggles to account for genetic and environmental interactions.

Future research should explore the genetic aspects of T1D, along with the hygiene hypothesis, to address its weaknesses. Integrating genetic perspectives may help advance the hypothesis. Longitudinal studies tracking microbial exposure and environmental factors from an early age would also be valuable to examine the hypothesis. Microbial-based interventions could also be explored, offering therapeutic as well as explanatory insights. It's also important to investigate the hygiene hypothesis in relation to other autoimmune diseases and allergies to better assess its validity. Ultimately, the hygiene hypothesis provides an insightful explanation of the growing incidence of T1D and its onset mechanism. However, it requires further refinement to provide a truly comprehensive explanation.

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