World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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The interplay of environmental and genetic factors, along with the contributions of cellular and humoral immunity, in the pathogenesis of Type 1 Diabetes Mellitus

Hayam Aziz Mohammed * and Marwah Sabah Altaiee

Department of Biology, College of Education for Pure Sciences: Ibn Al-Haytham, Baghdad University, Baghdad, Iraq.

World Journal of Advanced Research and Reviews, 2025, 27(02), 1625-1631

Publication history: Received on 11 July 2025; revised on 20 August 2025; accepted on 22 August 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.27.2.2998

Abstract

Type 1 diabetes Mellitus is a long-term autoimmune condition that causes the beta cells in the pancreas that produce insulin to be destroyed. The precise causes of type 1 diabetes are unknown, but it is believed to be a complicated disease brought on by a mix of genetic and environmental factors that trigger an autoimmune response that attacks pancreatic cells. HLA gene variants are a significant cause of heightened susceptibility to the illness, in addition to environmental factors such as diet, vitamin deficiencies, and viral infections. GAD65, IAA, and ZnT8 are examples of autoantibodies that might appear years before symptoms develop and are markers of the disease's progression. The immune system's intricate mechanisms of humoral and cellular apoptosis and inflammation lead to the death of beta cells. Appropriate therapy, follow-up, and early identification of these immunological markers can enhance patients' quality of life and lessen the impact of the illness.

Keywords: Type 1 Diabetes; Environmental Factor; Genetic Factor; Cellular and Humoral Immunity

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by the body's inability to produce insulin due to autoimmune destruction of pancreatic beta cells. Insulin is the primary anabolic hormone with crucial effects on the metabolism of glucose, lipids, proteins, minerals, and growth. Type 1 diabetes presents as a systemic disorder marked by hyperglycemia [1][2]. Although the disease is associated with autoimmune responses targeting beta cells, the precise causes and mechanisms of disease progression remain incompletely understood [3]. T1DM is a complex, multifactorial disease influenced by both genetic and environmental factors affecting immune responses against beta cells. The main susceptibility genes are located in the HLA region on chromosome 6, particularly the major histocompatibility complex (MHC) genes, such as HLA-DR3 and HLA-DR4, which play a pivotal role in genetic predisposition, along with other genes like PTPN22 and CTLA4 that regulate immune responses. Despite the importance of genetic factors, environmental triggers, such as viral infections or alterations in gut microbiota, are required to initiate the disease process [4][5].

Evidence indicates that changes in the gut microbiome composition, including decreased Bifidobacterium and increased Bacteroides, promote chronic inflammation and impair immune balance, contributing to the development of autoimmunity against pancreatic beta cells. Additionally, nutritional factors such as vitamin D deficiency, low omega-3 fatty acid intake, and high consumption of dairy products, along with early viral infections (especially enteroviruses), and high birth weight or overweight during infancy, increase disease susceptibility [6][7]. In this context, the immune system targets beta cell components by producing autoantibodies that do not directly cause damage but serve as markers of immune dysregulation. These autoantibodies play a critical role in early diagnosis and prediction of disease before clinical symptoms appear [8]. The autoantibodies most commonly associated with type 1 diabetes include insulin autoantibodies (IAA), glutamic acid decarboxylase 65 (GAD65) antibodies, tyrosine phosphatase-related IA-2

* Corresponding author: Hayam Aziz Mohammed

antibodies, zinc transporter 8 (ZnT8) antibodies, and islet cell antibodies (ICA) [9]10]. These autoantibodies typically represent the earliest indication of the autoimmune process, which may or may not progress to clinical disease, and can be detected years before symptom onset. Multiple studies have confirmed their importance in predicting disease onset and progression, making them vital tools for diagnosis and prevention [11]. Although type 1 diabetes is a chronic immunological and physiological disorder, early diagnosis through detection of autoantibodies, treatment adherence, and continuous follow-up can significantly reduce complications and improve patients' quality of life. Given the complex and multifactorial nature of the disease, a deeper understanding of the genetic and environmental factors influencing its development is essential for developing more effective diagnostic and therapeutic strategies. This study aims to review the central role of HLA region genes and associated immune mechanisms, as well as to evaluate the impact of various environmental factors on the initiation and persistence of autoimmune destruction of pancreatic beta cells [12] [13].

2. The Pathogenesis of Type 1 Diabetes Mellitus: Genetic, Immunological, and Environmental Mechanisms Working Together

2.1. Genetic factors

Type 1 diabetes Mellitus is a multifactorial autoimmune disorder resulting from a complex interplay between genetic susceptibility, immune dysregulation, environmental triggers, and gut microbial composition. Genetic predisposition remains a cornerstone in determining risk, particularly through polymorphisms in genes related to immune recognition and regulation [14]. Human leukocyte antigen (HLA) class II alleles, especially HLA-DR3 and HLA-DR4, play a critical role in modulating antigen presentation to T cells. These alleles are strongly associated with heightened risk of autoimmune responses and are consistently linked to T1D pathogenesis. Despite the presence of high-risk genotypes in approximately 90–95% of T1D cases, less than 5% of the general population actually develops the disease, indicating that genetic predisposition alone is insufficient and requires environmental and immunological cofactors [15]. Among non-HLA genes, PTPN22, CTLA4, IFIH1, and IL2RA have been implicated in modulating T cell activation and immune tolerance. The transcription factor AIRE, crucial for thymic expression of tissue-specific antigens, contributes to central tolerance by eliminating autoreactive T cells. Mutations in AIRE are associated with autoimmune polyendocrine syndrome type 1 (APS-1), which frequently includes T1D. Similarly, FoxP3, a marker of regulatory T cells (Tregs), ensures peripheral immune homeostasis, and its deficiency—seen in IPEX syndrome—often leads to T1D among other autoimmune conditions [16][17]. The gut microbiota has emerged as a significant environmental factor influencing the immune landscape in T1D. Dysbiosis, characterized by reduced microbial diversity and altered abundance of specific bacterial taxa, may compromise intestinal barrier function and promote systemic inflammation. Studies have shown that children with high genetic risk for T1D often exhibit early-life shifts in gut microbiota composition, including a reduction in Bifidobacterium and Lactobacillus species, and an increase in pro-inflammatory microbes such as Bacteroides [18]. These changes can impair the development of immune tolerance, enhance gut permeability ("leaky gut"), and facilitate the translocation of microbial antigens or toxins, which may act as triggers for islet autoimmunity. Moreover, short-chain fatty acids (SCFAs), such as butyrate, produced by commensal bacteria, are known to enhance Treg function and intestinal barrier integrity—both of which are often deficient in individuals progressing toward T1DM [19].

In conclusion, the pathogenesis of T1D is not dictated by genetics alone but is the result of cumulative interactions between genetic variants, immunological imbalances, environmental insults, and gut microbiota disturbances. This holistic understanding is crucial for identifying individuals at highest risk, developing biomarkers for early detection, and designing preventive strategies that may include immunomodulation, microbiota-targeted therapies, and tailored lifestyle interventions [20].

2.2. Environmental Factors in the Development of Type 1 Diabetes (T1D)

Available evidence from animal and clinical studies suggests that dietary factors early in life may play a role in inducing or suppressing the autoimmune response leading to type 1 diabetes (T1D). Animal models, particularly in NOD mice, have shown that a gluten-free diet during pregnancy or weaning may delay or reduce the onset of the disease, highlighting the potential role of gluten as an environmental trigger [21]. In human studies, some epidemiological analyses have shown that introducing gluten before 4 months of age is associated with an increased risk of developing islet autoimmunity, compared to introducing it between 4–9 months or after 9 months [22]. However, not all studies agree on this finding. Other studies have not shown a clear association between the timing or amount of gluten introduction during the first year of life and the risk of type 1 diabetes, suggesting that dietary factors alone may not be decisive without concomitant genetic factors Breastfeeding is a potential protective factor, as the duration of breastfeeding, particularly beyond 6 months, is associated with a slightly reduced risk of developing autoimmunity

against beta cells [23]. This is thought to result from reduced early exposure to foreign proteins such as cow's milk proteins. A link between early introduction of cow's milk and an increased risk of diabetes has also been suggested, although the evidence remains conflicting. Vitamin D is also considered a nutrient that may have a protective immunological role [24].

Some studies suggest that low levels of it in early childhood may contribute to the stimulation of autoimmune responses. Furthermore, it is hypothesized that early viral infections, such as those caused by enteroviruses, may lead to aberrant activation of the immune system and the targeting of pancreatic beta cells [25]. On the other hand, viral infections, particularly those caused by coxsackie B viruses from the enterovirus family, play a potential role in inducing autoimmunity directed against pancreatic beta cells. These infections have been linked to the activation of interferon production and increased expression of HLA class I molecules, making beta cells more susceptible to attack by cytotoxic T cells [26]. These effects interact with genetic predisposition, as mutations in genes such as IFIH1 and TYK2 contribute to amplifying the inflammatory response. Some data indicate that viral infections may precede the appearance of autoantibodies by a long period, supporting the hypothesis of their role in the onset of autoimmunity.

As for the gut microbiome, numerous studies have demonstrated an imbalance in its composition in patients with type 1 diabetes compared to healthy individuals [27]. T1D patients are characterized by reduced bacterial diversity and instability, with lower proportions of Firmicutes, Actinobacteria, and Lactobacillus, compared to increased proportions of Bacteroidetes, Clostridium, Veillonella, and Bacteroides. Also noted is a decreased abundance of Faecalibacterium prausnitzii, a butyrate-producing bacterium that plays a role in immune regulation. This imbalance often results from cesarean delivery, an unbalanced early diet, or the use of antibiotics in childhood, leading to the development of an intestinal environment unfavorable for proper immune system maturation [28]. The gut microbiota plays a crucial role in regulating intestinal permeability and the immune system's balance between regulatory and inflammatory pathways. Beneficial bacteria such as Lactobacilli and Bifidobacterial promote the proliferation of Treg cells, which play a role in suppressing autoimmunity, while proteobacteria (such as Escherichia and Helicobacter) promote Th1 and Th17 inflammatory pathways, which can contribute to beta cell destruction if chronically present. Therefore, modifying the microbiome's composition is a potential target for preventive intervention [29].

Experiments in NOD mice have shown that a diet rich in acetate and butyrate reduced the development of diabetes, and studies using probiotics (such as Bifidobacterial and Lactobacilli) have demonstrated efficacy in reducing disease-causing immune responses. Although animal studies have shown promising results, human clinical evidence remains limited and inconsistent [30]. While the TEDDY study showed that probiotic administration in the first weeks of life was associated with a reduced risk of autoimmunity in children with a genetic predisposition, other studies have not demonstrated a long-term protective effect of probiotic use on the development of type 1 diabetes [31].Based on these data, it appears that the risk of developing type 1 diabetes does not depend on a single factor, but rather on a complex interaction between genetic predisposition and environmental, immunological, and nutritional factors during early childhood. Therefore, further longitudinal and systematic studies remain necessary to accurately determine the impact of these factors and provide effective preventive recommendations.

3. The involvement of immunity in Type 1 diabetes.

3.1. Cellular immunity

Type 1 diabetes (T1D) is a complicated autoimmune illness caused by dynamic combinations between genetic, immunological, and environmental variables that ultimately destroy pancreatic beta cells, which produce insulin. Among the primary immunological pathways implicated in disease progression, cell-mediated autoimmunity is critical to T1D's slow and prolonged pathogenesis [33]. Cell-mediated immunity, a critical component of the adaptive immune response, coexists with humoral immunity but is primarily dependent on T lymphocytes, which include helper T cells (CD4+), cytotoxic T cells (CD8+), and regulatory T cells (Treg). Antigen recognition is the first step in this immune mechanism. Antigens are presented to T cells via major histocompatibility complex (MHC) molecules, which activates them and causes the release of pro-inflammatory cytokines that coordinate a wider immune response, specifically targeting islet cell antigens [34]. When CD4+ and CD8+ T lymphocytes invade the pancreatic islets in type 1 diabetes, they coordinate the immune system's killing of beta cells via a variety of mechanisms, including direct cytotoxicity and the release of inflammatory cytokines, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ). Beta-cell damage is exacerbated by these reactions, which also activate natural killer cells and macrophages. Furthermore, Th17 cells support the autoimmune process and contribute to tissue inflammation by secreting interleukin-17 (IL-17) [35]. By identifying beta-cell antigens presented by MHC class I molecules, triggering cellular apoptosis by releasing granzymes and perforin, or activating the Fas/FasL pathway, cytotoxic CD8+ T lymphocytes are essential for the direct destruction

of beta cells. Pro-inflammatory cytokines such as IL-1, TNF-α, and NF-κB, which change the islet microenvironment and affect beta-cell activity, intensify these damaging processes [36].

Although regulatory T cells (Tregs) are essential for inhibiting autoreactive immune responses, there is a well-established deficit in the number and capacity of these cells in people with type 1 diabetes. A persistent autoimmune attack on beta cells is made possible by this deficit, which compromises immunological tolerance. Early in the illness, T cells are unable to distinguish between self and non-self, which causes CD4+ and CD8+ cells to become activated against endogenous antigens and starts a chain reaction of inflammatory responses [37]. It is thought that apoptosis, which is mediated by the activation of caspase pathways involving cysteine-aspartic proteases, is the main cause of beta-cell death in T1D. In both human investigations and experimental models, apoptotic cell death is thought to be the primary cause, while necrosis may also play a role [38]. These apoptotic pathways are triggered by autoreactive T-cell infiltration and high levels of inflammatory cytokines in the islet microenvironment. Fas/FasL signaling or perforin-mediated pathways can interact with beta cells, and both eventually lead to beta-cell death. Cytokine secretion, however, continues to be a key element of this damaging process [39]. According to histopathological analyses, insulitis is defined by the infiltration of immune cells into the islets of Langerhans, including dendritic cells, T cells, B cells, and macrophages. Long before diabetes manifests clinically, this chronic inflammatory condition usually starts. In the pre-symptomatic stage, even in the absence of obvious clinical symptoms, patients have dysregulated glucose metabolism and islet autoantibodies. Before hyperglycemic symptoms appear, 70–90% of functional beta-cell mass must be lost, so this "silent" autoimmune phase is a crucial time to comprehend pathophysiology and create preventive measures [40] [41].

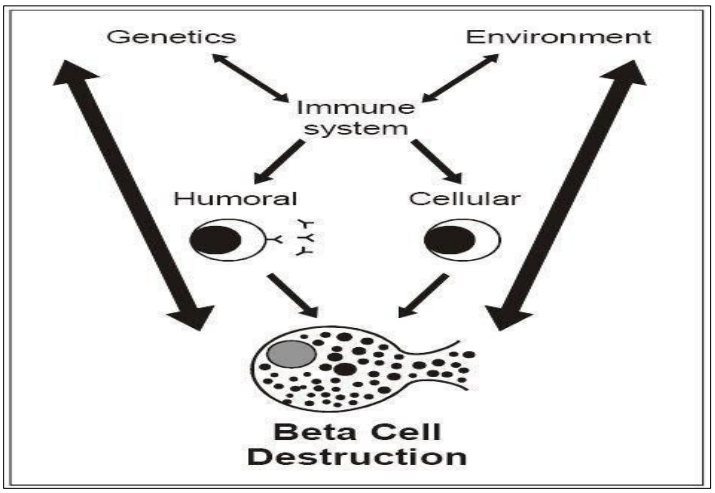

Figure 1 Genetics, environment, and the immune system interact to cause type 1 diabetes by destroying beta cells [42]

3.2. Humoral immunity

The body's immune defense depends heavily on humoral immunity, which is mainly based on B cells that produce specific antibodies that target foreign antigens and circulate in bodily fluids like blood and lymph. The ability of these cells to recognize antigens and generate targeted antibodies is a core function of these cells [43]. B cells work closely with helper T cells within a regulated immune response that normally distinguishes between “self” and “non-self.” However, this balance can be upset in autoimmune diseases, such as type 1 diabetes, which causes the body to produce autoantibodies against its own tissues, especially the beta cells in the pancreas that produce insulin. In type 1 diabetes, the autoimmune response often starts early in life, years before clinical symptoms appear [44][45]. According to research, autoantibodies against islet cell constituents such as zinc transporter (ZnT8), insulin (IAA), glutamic acid decarboxylase (GAD65), and tyrosine phosphatase (IA-2) are crucial biochemical indicators for the early identification of autoimmune alterations that result in the illness. Since gene deletion studies in animal models have shown a significant reduction in disease incidence, highlighting its critical role in initiating autoimmunity, proinsulin is believed to be a primary autoantigen in this process [46]. Despite the fact that autoantibodies are not directly harmful in type 1 diabetes, B lymphocytes are essential because of their ability to deliver antigens. It has been demonstrated in NOD mice that illness prevention is achieved by reducing the ability of B cells to present antigens while preserving antibody production. Specifically, NOD animals lacking T cell responses to the islet autoantigen GAD [47][48] and B cells unable to internalize islet antigens via their B cell receptors were shielded from DT1 development. On the other hand, it was discovered that in these models, the selection of B cells with a high affinity for insulin accelerated the onset of diabetes.

According to human research, patients' insulin-reactive high-affinity B cells lose their ability to tolerate insulin both before and after diagnosis. Particularly in genetically predisposed populations, autoantibody profiling has emerged as a critical prediction method for identifying people at risk of developing type 1 diabetes. GAD autoantibodies usually show up between the ages of 4 and 5, whereas insulin autoantibodies usually show up between the ages of 1 and 2. Age, sex, and HLA-DR genotype have been found to have an impact on the formation of autoantibodies in large prospective cohort studies with over 24,000 participants. In particular, the HLA-DR3 haplotype is more typically linked to GAD autoantibodies, while the HLA-DR4 haplotype is more often linked to insulin autoantibodies. At the moment, the most precise model for forecasting the development of type 1 diabetes combines genetic risk scores with the quantity of islet autoantibodies found [49]

[50]. However, the first cause of autoantibody formation is still unknown. According to certain theories, the autoimmune process may be started by beta cell stress or injury, which could be the result of viral infections. This is corroborated by recent research showing modest increases in postprandial glucose levels about two months before seroconversion, which raises the possibility that beta cell malfunction may precede or possibly trigger the formation of autoantibodies. Crucially, the severity of the condition seems to be influenced by the age upon diagnosis. According to studies, children with DIT diagnosed before the age of seven had more B cell infiltration in the pancreatic islets and had less functioning beta cells than children diagnosed later. This finding is consistent with the theory that rapid beta cell death and a more robust immune response are hallmarks of early-onset type 1 diabetes [51] [52].

4. Conclusion

Type 1 diabetes is an autoimmune disease caused by immunological dysregulation, environmental exposures, and genetic predisposition. The cause is not solely genetic; islet-specific autoantibodies and cellular immunity also contribute. Focused preventive measures, continuous monitoring, and early detection are crucial for improving patient outcomes and slowing the disease's progression.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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