



Type 1 Diabetes Mellitus: Autoimmune Mechanisms and Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This article provides a comprehensive overview of Type 1 Diabetes Mellitus (T1DM), highlighting the autoimmune origins of the illness and its therapeutic options. It discusses the role of insulin in metabolism and highlights the fact that the autoimmune destruction of pancreatic beta cells is the primary characteristic of type 1 diabetes. Environmental triggers such as viral infections, cow's milk proteins, and insufficient vitamin D are studied in addition to genetic factors such as specific alleles

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associated with the disease's susceptibility. The report discusses the global epidemiology of T1DM and its increasing incidence, emphasizing the need for a comprehensive approach to treatment. Various treatment options are evaluated, emphasizing the need for customized approaches to treat this complex autoimmune disease. These options include gene therapy, insulin treatment, immunomodulatory medications, and vaccination. All things considered, the study adds to our understanding of T1DM and highlights the ongoing need to develop effective treatment modalities.

Keywords: Type 1 diabetes mellitus; autoimmune mechanisms; treatment; environmental.

1. INTRODUCTION

The main characteristic of chronic Type 1 Diabetes Mellitus (T1DM) is the body's inability to produce insulin due to the autoimmune destruction of pancreatic beta cells. An important anabolic hormone, insulin, influences growth and the metabolism of minerals, proteins, fats, and carbohydrates. Therefore, one feature of type 1 diabetes, which presents as a systemic condition, is hyperglycemia. Several studies have demonstrated that a substantial hereditary component exists for type 1 diabetes. The primary susceptibility gene is linked to alleles DR3, DR4, DQA1*0501, DQB1*0201, DQA1*0301, and DQB1*0302. It is situated in the HLA region on chromosome 6. There is a 40–50% association between the HLA complex and the incidence of type 1 diabetes [1-4].

According to recent studies, type 1 diabetes is quickly expanding globally. Globally, the frequency also varies; in the United States, it is 12.2:10,000, whereas in Africa, it is 3.5:10,000. In Europe, the prevalence increased by 3-4% yearly between 1989 and 2008 [1]. Among the immunological markers of type 1 diabetes include antibodies against insulin, tyrosine phosphatase, glutamate decarboxylase (GAD), pancreatic islet cells, and zinc transporter 8. A variety of environmental factors, such as viruses, cow's milk proteins, and low vitamin D3, have been demonstrated to start the autoimmune process in people who are genetically predisposed to it; however, none of these have been directly connected to diabetes [5].

If diabetes worsens and other autoimmune diseases emerge because of the inflammatory process that causes type 1 diabetes, managing diabetes may become more challenging. T1DM is most frequently associated with the following conditions: autoimmune thyroid diseases (17–30%), such as Graves' disease and Hashimoto's thyroiditis, Addison's disease (0.2%), celiac disease (8%), rheumatoid arthritis (1.2%), autoimmune gastritis (5–10%) and systemic lupus erythematosus (1.15%) [6-9].

Type 1 diabetes is characterized by an autoimmune response against pancreatic beta cells (T1DM). Prior to the disease's clinical signs, anti-islet autoantibodies reveal T1DM symptoms, and the syndrome frequently co-occurs with other autoimmune diseases. The natural course of the autoimmune illness may be greatly impacted by these coexisting conditions; thus, it is important to carefully consider them [10]. The review aimed to integrate all of the existing evidence critically and comprehensively about the relationship between autoimmune illnesses and T1DM, in addition to emphasizing the importance of treating the patient holistically rather than just treating T1DM.

2. EPIDEMIOLOGY

Of those with T1D, 42% happen beyond the age of 30, and 58% happen before or at that time in the first 60 years of life. New data from the UK Biobank suggests that T1D can appear at any age, even though the condition can show at any age [11]. Given that both men and women get sick at the same rates, there doesn't appear to be any overall gender bias. Despite what many people may believe, the illness is not as widespread as one may believe. According to Harjutsalo et al. [12,13], China has a considerably lower incidence of 1 case per 100,000 person-years, whereas Finland had 62.5 instances per 100,000 person-years, which is the highest incidence. According to Redondo et al. [14], 65% of twins of individuals with T1D acquired the disease by the time they were 60 years old. In addition, children in the US who have a family member with Type 1 diabetes have a 5% chance of developing the illness by the time they are 20, compared to a 0.3% risk in the general population. These findings highlight the part inheritance plays in the risk of T1D. Furthermore, during the 20th century, North America and Europe had a 2% to 3% yearly increase in the number of T1D cases. This rate suggests that behavioral and/or environmental signals may have a role in the development of T1D, as it is much greater than that which could

be explained by genetics alone [15]. Based on a review of 84,000 children in 22 European countries between 1989 and 2013, the incidence rate appeared to stabilize in high-risk countries such as Finland and Norway, while the country-pooled incidence rates in all pediatric age groups were increasing [16].

3. IMMUNE PATHOGENESIS

Understanding the immunological mechanisms behind type 1 diabetes has allowed for the development of novel treatments targeted at both disease prevention and reversal, as well as the identification of those who are more susceptible to the condition. T-cell lysis of B-cells, triggered by a loss of self-tolerance, is the first step in the immunological pathogenesis of type 1 diabetes. Two characteristic hallmarks of this autoimmune disease are anti-b cell antigen-specific antibodies and insulinitis. As therapy goals, identifying specific processes that may make the illness polygenic and addressing the roles of genetics and environment in an individual's total risk function are important. Combining the nonobese diabetic (NOD) mouse model with rare cases of monogenic T1D, such as those associated with mutations in the FoxP3 gene (immune dysregulation, enteropathy, polyendocrinopathy, X-linked syndrome) and Autoimmune Regulator gene (autoimmune polyglandular syndrome type 1), has allowed for a thorough understanding of the peripheral and central mechanisms of immune tolerance compromised in the disease [17]. According to Bluestone et al., these findings have sparked optimism that immunological tolerance-targeting therapies may be able to delay or prevent Type 1 Diabetes. Islet autoimmunity in Type 1 Diabetes (T1D) manifests as low C peptide and persistent hyperglycemia months to decades before clinical disease because over 70% of the b cell mass has been irreversibly destroyed [18].

4. GENETICS

Various genetic variations, also known as alleles, can function as protective or risk factors in the onset of type 1 diabetes. In monozygotic twins, the probability of a first-degree relative acquiring T1DM is around 6%, and the disease's concordance is over 50% [19]. Siblings of T1DM patients are 15 times more likely to get T1DM when comparing this most recent incident to the 0.4% incidence of T1DM in the general population. It's crucial to remember that while relatives of T1DM patients have a much higher

risk of getting the illness, most people who have it (around 85%) do not have a first-degree relative with this pathology. The approximately 40% of the general population with high-risk HLA alleles is the main reason for the high frequency of sporadic occurrences. Through association and linkage studies, a number of susceptibility genes have been found to be important causes of the illness. As a result, at least 60 loci that affect the chance of having the illness have been found [20].

Major Histocompatibility Complex (MHC), situated at the DDM1 locus on the short arm of chromosome 6, is the primary genetic component responsible for the disorder. Only 40% of healthy controls have these HLAs, but 90% of people with type 1 diabetes have either the DR3 or DR4 antigens or both [21]. DR3-DR4 heterozygosity is lower in adults (20–30%) and higher in children (50%) who acquire the condition, compared to the 2.4% prevalence in the US population [21]. There is a strong association, according to studies, between an individual's resistance or susceptibility to illness and the amino acid located at the HLA-DQ β location on the chain. Diabetes is unlikely to develop if both chain alleles include an aspartic acid residue at position 57. But its lack of it is an obvious indication of weakness. The relative risk (RR) of contracting the disease was 107 for those without both aspartic acid alleles. Recent research has demonstrated a connection between elevated disease risk and arginine, an amino acid located at position 52 of the DQ α chain. The danger is increased when aspartic acid is absent from position 57 in the DQ β chain. Since the final amino acid is missing from position 57 of the DQ α chain and arginine is present at position 52 of the HLA antigen presentation site manager, it is believed that the T-cell receptor (TCR) can recognize an autoantigen if it interacts with it [21]. IDDM2 is another locus linked to genetic risk that has been found. It is connected to the chromosome 11 insulin gene. Ten percent or so of the FA of illness is caused by this gene [22]. This locus is linked to the variable number of nucleotide repeats (VNTR) polymorphism region. Research has demonstrated a correlation between the frequency of type 1 diabetes and variations in the sizes of the VNTRs for the insulin gene. Class III, or extended VNTR (> 100 repeats), has been associated with immunity to disease [23]. It has been suggested that this phenomenon is due to enhanced immune tolerance to a larger insulin gene with elevated thymic expression and the

resultant tolerance. One of the signs and symptoms of monogenic polyendocrinopathy, which is connected with genes like XPID and AIRE (type 1 autoimmune polyendocrine syndrome is linked to an autoimmune regulator), is diabetes.

T1DM risk has been linked to PTPN22, a gene that generates a lymphoid-specific phosphatase that affects TCR signaling (Bottini et al., 2004). Polymorphisms in the CTLA4 (IDDM 12) gene seem to be associated with the onset of autoimmune diabetes and Graves' disease [24], albeit not in all populations. Additionally, a region linked to the IL-2 receptor has shown statistical association [25]. In conclusion, a considerable number of genetic loci have been linked to an increased risk of diabetes. Among these, the person's link to an index case of diabetes and their HLA type at birth are the foundations upon which certain communities calculate the risk of the illness. For instance, the DR3-DQ2/DR4-DQ8 genotype increased the risk of diabetes by almost 50% in siblings of T1DM patients.

5. ENVIRONMENTAL ASPECTS

Numerous characteristics point to a major environmental component in T1DM. Environmental variables appear to trigger the autoimmune process in different nations, as demonstrated by the genetically comparable populations' heterogeneity and the rapidly rising prevalence (incidence twice as high in the UK as in France, for example). There are two reasons why the incidence has recently increased. First, the spread of infectious processes is encouraged by increased public exposure to infectious agents such as viruses [26]. The disease often manifests in the winter, and certain T1DM epidemic relapses suggest that certain viruses, such as rotavirus (Yoon, J. W., 1979) and Coxsackie virus [27] as well as certain dietary factors, may influence an individual's risk of developing T1DM. Despite several associations with various other environmental variables and viruses, prenatal rubella infection is the sole agent that reliably links T1DM to a virus after more than 40 years of research [28]. High-risk HLA alleles and a high incidence of AITD are typically present in children with this type of diabetes [29]. It's unclear exactly how a congenital rubella infection raises the risk of type 1 diabetes. Furthermore, the presence of antibodies or viral antigen at the time of diagnosis has been the basis for correlations with a specific viral agent. Since the illness develops after a protracted immune

response, establishing a pathogenic link between these infectious organisms and the illness is difficult. An increased insulin need during an ongoing sickness might have been the reason for the identification of viral particles at the time of diagnosis. It was by accident that the infectious agent was present.

One other environmental factor linked to the disorder's development is early consumption of cow's milk, namely cow's serum albumin, or BSA. Retrospective research that found this component led to the development of this concept. Numerous follow-up investigations, however, were unable to corroborate these findings. For example, research conducted in Denver, Colorado, where newborns were evaluated, found no correlation between any condition with breastfeeding, enteric virus infections, or a history of vaccines before delivery [29].

According to some studies, introducing grains to infants as early as three months of age may encourage the development of islet autoimmunity [30]. Vitamin D and omega-3 fatty acids have been associated with an increased risk of diabetes, but they may also impact immune function [31]. The development of islet autoimmunity, leading to type 1 diabetes (T1D), is influenced by genetic predisposition and environmental factors such as early introduction of grains, vitamin D, and omega-3 fatty acids. Introducing grains to infants as early as three months can compromise the immature gut barrier, alter gut microbiota, and cause molecular mimicry, triggering an autoimmune response against pancreatic beta cells. Vitamin D plays a dual role in immune modulation and inflammation regulation, with imbalances potentially increasing autoimmunity risk through disrupted immune tolerance and heightened inflammatory responses. Omega-3 fatty acids, known for their anti-inflammatory properties, can enhance regulatory T cells and reduce autoreactive T cells, potentially mitigating autoimmune processes, although their impact may vary based on genetic and environmental contexts. These factors together underscore the complex interplay of diet, immune function, and genetic susceptibility in the pathogenesis of T1D. Furthermore, consideration must be given to the toxins generated by the soil-dwelling *Streptomyces* bacteria, which can potentially infect food products such as vegetables. In studies on animals, it has been demonstrated that these toxins damage pancreatic cells [32].

For children who are genetically predisposed to diabetes, vaccination has been linked to an elevated risk of the condition. Further investigation has, however, disproved this notion [33].

The second scenario, which is sometimes referred to as the "hygiene hypothesis," postulates that environmental factors may prevent immune responses from initiating. The more sanitary surroundings in which today's kids grow up might be a factor in immune system dysfunctions leading to Th1-patterned disorders like type 1 diabetes or Th2-mediated response patterns like asthma [34,35]. Additional epidemiological data emphasizes the illness's environmental component. Identical twins share their whole genome, but non-twin brothers and dizygotic twins share half of their genetic makeup. Given that dizygotic twins are typically exposed to the same environmental stressors, such as the same diet and illnesses when comparing twins to non-twin siblings, there can be a higher concordance of the disease due to environmental factors.

6. PREVENTION

Two large-scale trials investigating the prevention of type 1 diabetes have been carried out to ascertain if a regimen based on the antigen—insulin—both oral and parenteral will prevent or postpone the development of diabetes in families with high or moderate risk. The European intervention trial with nicotinamide (ENDIT) showed no statistically significant difference in disease prevention between the oral nicotinamide and placebo groups.

Early research on treatments aimed at halting the death of pancreatic β cells was largely supported by immunosuppressive medications. Studies using cyclosporine showed improved metabolic performance and a halt to further beta cell loss when this medication was used [36], but the benefits of this treatment were small and would vanish quickly if started after the onset of clinical diabetes; the treatment's therapeutic usage for diabetes has been abandoned due to its inability to "cure" the condition and the severe toxic consequences that follow (including nephrotoxicity and an increased risk of cancer).¹ Other immunosuppressive treatments, like azathioprine or prednisolone, have not had much of an impact [37]. Methotrexate has not been shown to be efficacious.

Despite the fact that diabetes is mediated by the immune system, immunomodulating medications or current suppressors are not currently employed to treat the illness. Thus, research to prevent T1DM from starting is necessary, and some of these are now under progress. In Phase 2 and Phase 3 investigations, people with newly diagnosed type 1 diabetes received modified anti-CD3 treatment. After a 12- to 14-day infusion of modified anti-CD3 (e.g., teplizumab), patients demonstrated preservation of the C-peptide response, a measure of insulin secretion, a reduction in the requirement for exogenous insulin, and better glycemic management [38,39]

7. VACCINATION

Numerous therapies have been tried in animal models to stop diabetes from starting. The immunological vaccine is an exceptional treatment option since it has a lower risk and more specificity when compared to standard immunosuppression. The generation of lymphocytes that are specific to an islet antigen is the fundamental idea. Following identification, they begin to secrete cytokines that protect against tissue damage and autoimmune reactions [40]. Th2 T cells produce more IL-4 and experience less cell-mediated death compared to Th1 cells that produce IFN- γ or IL-2. The method of antigen administration (for example, oral tolerance) and the use of modified antigens can both influence the establishment of a protective immune response. For example, giving insulin subcutaneously or orally to NOD mice protects them from developing diabetes [41]. However, even without intact insulin, this reaction is still possible [42]

8. TREATMENT

Insulin is the primary therapy for individuals with T1DM. According to the Diabetes Control and Issues Trial (DCCT) [43], strict metabolic management is necessary to prevent and delay diabetes-related chronic consequences. Still, the possibility of hypoglycemia during treatment is a considerable obstacle to attaining sufficient metabolic control. The discovery of fast-absorbing insulin analogs has decreased absorption variability and made it possible to deliver insulin even during meals. In recent years, novel insulin analogs that function more like basal insulin production instead of peaking have hit the market. The available insulin is classified as fast-acting, intermediate-acting, or

long-acting based on its pharmacokinetic properties [44].

An external mechanical pump can also be used to provide insulin. In addition to patient-directed boluses given before to meals or snacks or in reaction to rises in blood glucose concentration above the intended range, the pump administers insulin as a pre-programmed basal infusion. Candidates for the insulin pump should only be those who are highly driven to achieve better glucose control and who are prepared to collaborate with their healthcare provider to assume significant daily care responsibilities. Patients with type 1 diabetes use metformin more frequently than those who just use insulin. Metformin may benefit T1DM patients who are overweight, use high insulin dosages, or whose HbA1c is more than 8%, according to certain studies [45]. Insulin resistance was formerly thought to be exclusively associated with type 2 diabetes, although type 1 diabetics are starting to show interest in its coexistence. Diabetes may potentially be cured with pancreatic islet transplantation when paired with the right immunosuppressive medication. This transplant is being explored for the small but significant subset of patients who regularly have episodes of severe hypoglycemia and who do not respond well to standard medical treatment [46]. The shortage of eligible donor organs, as well as the complications involved with treating autoimmune and alloimmunity illnesses, limit the use of islet transplantation. Bone marrow transplantation is another option in addition to pancreatic islet transplantation. Both allogeneic and syngeneic transplantation offers potential benefits in the treatment or prevention of sickness; this is likely owing to the generation of immunoregulatory cytokines and the better performance of strong regulatory systems over effector mechanisms [47]. Numerous alternatives for diabetes treatment and prevention are provided via gene therapy. Insulin or other alternative treatment approaches may be used in gene therapy. Gene therapy has also been used in other immune-related investigations. One approach might be to develop or overexpress cytokines or receptors that respond to the pharmacological effects of endogenous medication. Among these have been investigations into the release of cytokines from systemic or pancreatic islets. This work used viral and non-viral vectors, including IL-4, IL-10, the fusion protein IL-4-Ig, IFN- γ -receptor, and TGF- β , to prevent sickness in mice [48]. Among the infusion options under consideration are various types of stem cells, dendritic cells,

and genetically altered or unmanipulated regulatory T cells. Another therapy option is to mix them with other approaches. Future therapy for type 1 diabetes patients may include cell-based medications aimed at inhibiting the abnormally high autoimmune response [49]. While several published clinical trials have used immune-modifying medicines and antigen-specific strategies, the bulk of these treatments have proven to be dangerous or have not demonstrated long-term cell protection.

9. CONCLUSION

In conclusion, because Type 1 Diabetes Mellitus (T1DM) is so complicated, a comprehensive approach is required to understand and manage the condition. Our research sheds light on the autoimmune mechanisms that underlie type 1 diabetes and emphasizes the crucial roles that environmental factors and genetic predispositions play in the onset and development of the condition. Our comprehensive analysis sheds light on the many aspects of type 1 diabetes, such as the immunological landscape, immunological pathogenesis, and possible therapeutic approaches. Furthermore, our study into prophylactic strategies like gene therapy and vaccination highlights the ongoing need to find effective ways to decrease or diminish the autoimmune response. Ultimately, by understanding how a number of elements, including genetics and environmental triggers, are interrelated and by utilizing cutting-edge therapy modalities, we may work toward developing more individualized and efficient ways to treat this intricate autoimmune disease.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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