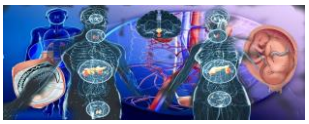
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# Chronic Autoimmune Disease: Type 1 Diabetes Pathophysiology and Management

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**Abstract**

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Individuals with T1D require life-long insulin replacement with multiple daily insulin injections daily, insulin pump therapy, or the use of an automated insulin delivery system. Without insulin, diabetic ketoacidosis (DKA) develops and is life-threatening. In addition to insulin therapy, glucose monitoring with (preferably) a continuous glucose monitor (CGM) and a blood glucose monitor if CGM is unavailable is recommended. Self-management education and support should include training on monitoring, insulin administration, ketone testing when indicated, nutrition including carbohydrate estimates, physical activity, ways of avoiding and treating hypoglycemia, and use of sick day rules.

**Keywords:** Type 1 diabetes mellitus; autoimmune disease; immunogenetic characteristics; blood glucose monitoring

## Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. There is heterogeneity in the metabolic, genetic, and immunogenetic characteristics of T1D and age-related differences, requiring a personalized approach for each individual. Loss of insulin secretion can occur quickly or gradually. Residual insulin production (detectable/higher c-peptide) is more common in adult-onset compared to youth-onset T1D, whereas diabetic ketoacidosis is more common in youth with T1D. Detectable c-peptide is associated with better glycemic control. The presence of other autoimmune conditions, obesity, comorbidities, and the development of diabetes-related complications is also variable.

## Etiology

In T1D, there is autoimmune destruction of the beta cells in the pancreatic islets over months or years, causing an absolute deficiency of insulin. Although the exact etiology of T1D is still unknown, researchers believe there is a genetic predisposition with a strong link with specific HLA (DR and DQ) alleles. This association is more pronounced in youth-onset T1D compared to adult-onset T1D. Multiple other genes contribute to heritability as well.

The presence of circulating pancreatic islet autoantibodies suggests that the individual is at risk for or has developed T1D. These antibodies include islet cell cytoplasmic antibodies (ICA), antibodies to insulin (IAA), glutamic acid decarboxylase isoform 65 (GAD65), insulinoma antigen 2/islet tyrosine phosphatase 2 (IA-2) and zinc transporter isoform 8 (ZnT8). IAAs are primarily detected in children. GAD65 is the most common autoantibody detected in adults. ICA is no longer routinely recommended, as it is an imprecise assay. The greater the number of detectable antibodies and the higher their titers, the greater the risk of developing T1D.

## Epidemiology

T1D is one of the most frequent chronic diseases in children but can have its onset at any age. In adults, new-onset type 1 diabetes may be misdiagnosed as type 2 diabetes and is more common than youth-onset T1D. There has been a steady increase in the incidence and prevalence of T1D, representing approximately 5% to 10% of people with diabetes. A systematic review and meta-analysis reported that the worldwide prevalence of T1D was 9.5%, with an incidence of 15 per 100,000 people.

## Pathophysiology

The development of T1D occurs in 3 stages. Stage 1 is asymptomatic and characterized by normal fasting glucose, normal glucose tolerance, and the presence of ≥2 pancreatic autoantibodies. Stage 2 diagnostic criteria include the presence of pancreatic autoantibodies (usually multiple) and dysglycemia: impaired fasting glucose (fasting glucose 100 to 125 mg/dL) or impaired glucose tolerance (2-hour post-75 gm glucose load glucose 140 to 199 mg/dL) or an HbA1c 5.7% to 6.4%. Individuals remain asymptomatic. In stage 3, there is diabetes, defined by hyperglycemia (random glucose ≥200 mg/dL) with clinical symptoms, fasting glucose ≥126 mg/dL, glucose ≥200 mg/dL two hours after ingesting 75 g of glucose during an oral glucose tolerance test and/or HbA1c ≥6.5%.

## Genetics

Type 1 diabetes is a heritable polygenic disease with identical twin concordance of 30–70%, sibling risk of 6–7%, and a risk of 1–9% for children who have a parent with diabetes. The overall lifetime risk varies greatly by country and geographical region but overall is around one in 250 people. The disease is slightly more common in men and boys than in women and girls. Two HLA class 2 haplotypes involved in anti gen presentation, *HLA DRB1*0301-DQA1*0501-DQ*B10201* (*DR3*) and *HLA DRB1*0401-DQA1*0301-DQB1*0301 (DR4-DQ8)*, are linked to approximately 50% of disease heritability and are prevalent in white people.

## The β-cell phenotype of type 1 diabetes

At diagnosis, people with type 1 diabetes have reduced β-cell function compared with healthy controls. With amelioration of hyperglycaemia, these β cells can have a partial recovery of insulin secretory function, leading to a so-called honeymoon period after diagnosis with minimal or no exogenous insulin needed. Over time, many of these residual cells are lost. However, analysis of pancreatic sections from individuals with long-term type 1 diabetes show the presence of residual β cells decades after diagnosis. When sensitive C-peptide measure ments are performed, 30–80% of people with long-term type 1 diabetes are found to be insulin microsecretors. So, although endogenous β-cell quantity and function decline with longer disease duration, this decline does not progress to a complete loss of all β cells.

## Management of clinical disease

Methods of managing type 1 diabetes continue to improve, and although progress is generally slow and incremental, occasionally it is punctuated by rapid change. One such moment of change happened in 1993 with the publication of the Diabetes Control and Complication Trial. This trial and the follow-up observational Epidemiology of Diabetes Interventions and Complications trial convincingly showed that achieving and maintaining glucose concentrations as close to those seen in people without diabetes as possible leads to a reduction in microvascular and cardiovascular type 1 diabetes complications.

## Enhancing Healthcare Team Outcomes

Self-management of T1D includes administering insulin multiple times daily with glucose monitoring and attention to food intake and physical activity every

day, which is a considerable burden. Whereas newer technologies have helped people improve their glycemic control, they are costly, complex, and require education and training. Many people with diabetes fear hypoglycemia, hyperglycemia, and the development of complications, and depression, anxiety, and eating disorders can develop.

**Disease-modifying therapies**

For over 30 years, most efforts to cure type 1 diabetes have focused on altering the immune system's attack on β cells. This approach began with trials of ciclosporin, an immunosuppressant that was given to inhibit T-cell activation. Although ciclosporin was unable to induce a durable disease remission, insulin requirements of patients decreased during active treatment, generating enthusiasm that immune modulation could treat type 1 diabetes.

**Conclusion**

Over the past 50 years, people with type 1 diabetes and their medical-care providers have been tantalised with optimism and subsequently disappointed at the seemingly unobtainable cure on the horizon. However, this long journey has been punctuated by several pivotal successes, including the discovery of insulin in 1922, the first pancreatic transplantation in 1966, the first insulin-pump studies, the first immunomodulatory trial in 1986, and the first definitive evidence linking glycaemic control with complication status in 1993. The past 25 years has brought an upsurge of technological advances, including designer insulin analogues, smart insulin pumps, continuous glucose sensors, and closed-loop insulin delivery systems.

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