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Role of Islet Autoantibodies in Type 1 Diabetes: A Review Article

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ABSTRACT

Background: *Type 1 diabetes (T1D) is an autoimmune illness marked by progressive destruction of pancreatic β-cells and insulin deficiency. Islet autoantibodies (AABs) are early indicators of autoimmunity and have a critical role in predicting illness onset, particularly in genetically at-risk individuals. Early seroconversion, especially in young children, is closely linked to faster progression to clinical T1D. This review discusses the role of AABs in illness staging, risk assessment, and the potential benefits of early screening.*

Objective: *Our objective is to evaluate the role and clinical significance of islet autoantibodies, including their timing, sequence, and number, and how they relate to T1D progression and early diagnosis strategies.*

Conclusion: *Islet autoantibodies are key biomarkers in the preclinical phase of T1D. Incorporating screening and early metabolic monitoring into clinical practice may decrease the possibility of diabetic ketoacidosis at identification and allow for timely intervention to delay or prevent disease onset.*

Keywords: *Type 1 diabetes, autoantibodies, seroconversion, disease progression, screening, early diagnosis.*

INTRODUCTION

Type 1 diabetes is a major chronic condition mainly influencing adolescents and kids.[1] It is classified as an autoimmune illness, in which progressive immune-mediated destruction of pancreatic β-cells results in absolute insulin deficiency. [2, 3]

It is a tissue-specific autoimmune illness marked by the immune-mediated destruction of pancreatic β-cells, causing absolute insulin deficiency. Multiple lines of evidence underscore its autoimmune origin. These include: (i) the existence of insulitis, defined as lymphocytic infiltration within and around the islets of Langerhans; (ii) the detection of circulating autoantibodies targeting islet-associated antigens; (iii) strong genetic predisposition involving both major histocompatibility complex (MHC) and non-histocompatibility complex loci; and (iv) a higher prevalence of other autoimmune conditions in individuals diagnosed with T1D.[4].

The 1st indication of autoimmune involvement in type 1 diabetes (T1D) emerged in 1974, when Bottazzo and colleagues identified islet cell antibodies (ICAs). Utilizing indirect immunofluorescence on frozen pancreatic sections, these antibodies were found to target multiple antigens within the islets of Langerhans, providing early evidence of an autoimmune response directed against pancreatic tissue.[5]

Owing to the limitations of the original islet cell antibody (ICA) assay—including its dependence on human pancreatic tissue and lack of quantitative output—subsequent research has focused on identifying specific islet autoantigens using molecular methods. So far, above ten target antigens were characterized, with glutamic acid decarboxylase (GAD) first identified in 1990. Among the key autoantibodies currently utilized in the identification and prediction of T1D are glutamic acid decarboxylase antibodies (GADA), insulin autoantibodies (IAA), zinc transporter 8 antibodies (ZnT8A), and insulinoma-associated protein 2 antibodies (IA-2A). Detection methodologies have evolved significantly, moving from traditional immunohistochemical approaches to more accurate and scalable methods like electrochemiluminescence (ECL), enzyme-linked immunosorbent assay (ELISA), and

radioimmunoassay (RIA), often employing recombinant autoantigens formed through various expression systems.[6]

Localization and Function of Autoantigens Targeted by Anti-Islet Autoantibodies:

1-Insulin

Insulin is synthesized exclusively via pancreatic β-cells and is resulting from its precursor, proinsulin, which contains A- and B-chains linked by a C-peptide. Following enzymatic cleavage of the C-peptide, mature insulin is produced. Its primary role is to regulate blood glucose concentrations through stimulating glucose uptake and storage in insulin-responsive tissues like the skeletal muscle, adipose tissue, and liver.

2. Glutamic Acid Decarboxylase (GAD)

Glutamic acid decarboxylase exists in two isoforms (GAD65 and GAD67) which are enzymes responsible for the production of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Both isoforms are expressed in the pancreatic islets and central nervous system. In β-cells, GAD65 is predominantly associated with synaptic-like microvesicles, whereas GAD67 is more diffusely distributed within the cytoplasm. GAD65 is the main isoform targeted in autoimmune diabetes.

3- **Insulinoma-associated protein 2 IA-2**

Insulinoma-associated protein 2 and its isoform IA-2β are transmembrane glycoproteins localized to the membrane of insulin-containing secretory granules. They belong to the protein tyrosine phosphatase (PTP) family but lack enzymatic activity. IA-2 is believed to have a role in the biogenesis and stability of insulin granules and can contribute to β-cell maturation and regulated insulin secretion.[7]

4- Zinc transporter 8 (ZnT8)

Zinc transporter 8 (ZnT8) is an integral membrane protein found in the membrane of insulin secretory granules. It facilitates the transport of zinc ions into these granules, a process essential for insulin crystallization and hexamer formation. Beyond structural roles, zinc also participates in signaling mechanisms that influence β-cell function and intercellular communication. Autoantibodies against ZnT8 are commonly found in persons with recent-onset T1D[8, 9]

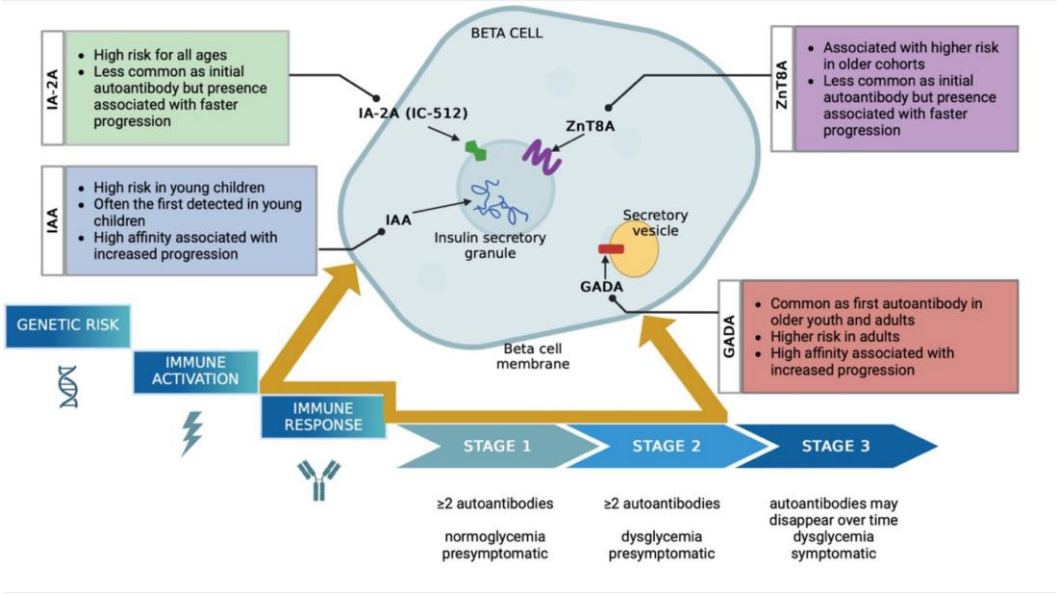

Figure No. (1): Schematic illustrating the development of type 1 diabetes from genetic susceptibility to clinical identification, highlighting the characteristics of pancreatic beta cell destruction and the appearance of islet autoantibodies (IA). It emphasizes important IAs associated with type 1 diabetes, involving zinc transporter 8 antibody (ZnT8A), glutamic acid decarboxylase antibody (GADA), insulin

autoantibody (IAA), and islet-antigen-2 antibody (IA-2A, IC-512).[10]

Islet Autoantibodies and Disease Progression:

Longitudinal research has clearly demonstrated that islet autoantibodies emerge long before the clinical manifestation of type 1 diabetes. The period between initial autoantibody seroconversion and the beginning of overt disease, however, differs considerably across individuals. Among the earliest detectable autoantibodies—especially in kids under the age of 5—are insulin autoantibodies. These are often the 1st indicators to appear and are commonly present at diagnosis, provided that exogenous insulin therapy has not yet begun, as such treatment may affect the accuracy of IAA detection.[11]

Key autoantibodies linked to type 1 diabetes involve zinc transporter 8 antibody, glutamic acid decarboxylase antibody, insulin autoantibody, and Insulinoma-associated protein 2 [12, 13]

Long-term studies in genetically susceptible individuals such as Type 1 Diabetes Prediction and Prevention Study (DIPP), Diabetes Autoimmunity Study in the Young (DAISY), the German BABYDIAB Study, Diabetes Prevention Trial of Type 1 Diabetes (DPT-1), The Environmental Determinants of Diabetes in the Young (TEDDY) Study, and TrialNet have given essential insights into the early stages of islet autoimmunity. These investigations consistently show that persons with multiple islet autoantibodies are at significantly elevated possibility of developing clinical type 1 diabetes. [14-19]

The rate of development differs and is affected by both the age at which autoantibodies first appear (seroconversion) and the specific types involved. As such, early identification of high-risk individuals is essential for timely intervention and for selecting suitable candidates for preventive or disease-modifying therapies.[20]

Autoantibody Seroconversion and Age-Related Risk in Type 1 Diabetes

Kids with a genetic predisposition to type 1 diabetes typically develop islet autoantibodies early in life. Studies such as TEDDY, BABYDIAB, and DIPP have shown that seroconversion—the initial appearance of these autoantibodies—most often occurs between six months and three years of age, with insulin autoantibodies (IAA) commonly being the first detected around 9 months.[15-17, 21]

Early seroconversion, especially before age three and in the existence of multiple autoantibodies, is strongly related to faster development to clinical T1D. Each autoantibody tends to appear at specific ages: IAA usually develops in the first 2 years, glutamic acid decarboxylase antibody between ages three TEDDY data further reveal that IAA-only seroconversion typically occurs around 1.8 years, while GADA-only appears later, around 4.3 years. When these antibodies appear as second markers, they follow the first by a few months (e.g., GADA by 3.7 months, IAA by 5.9 months, and IA-2A/ZnT8A by about 13.3 months). On average, a second autoantibody appears roughly 6.8 months after the first, regardless of which one comes first.[17, 23]

Crucially, younger kids with multiple autoantibodies develop to type 1 diabetes more quickly compared to older individuals, highlighting age at seroconversion as a key predictor of disease development [24].

Number and Sequence of Autoantibodies as Predictors of Type 1 Diabetes Progression:

The number of islet autoantibodies (AABs) observed in an individual is one of the most robust predictors of both the possibility and rate of development to clinical type 1 diabetes. Findings from prospective cohort investigations like DIPP, DAISY, and BABYDIAB have consistently demonstrated a dose-dependent relationship between AAB number and disease progression. For example, children without detectable AABs had a 10-year risk of only 0.4%, compared to 14.5% in those with a single autoantibody. The possibility increased substantially to nearly 70% in kids with multiple autoantibodies, with lifetime risk approaching 100%.[22]

The TEDDY research further supported these results, demonstrating a five-year progression possibility of eleven percent with 1 autoantibody, thirty-six percent with 2, and forty-seven percent with 3. Similar risk gradients were observed in the DPT-1 and Fr1da studies, where individuals with four autoantibodies demonstrated significantly higher risk compared to those with two, with a reported hazard ratio of

1.85.[16, 17, 25]
TrialNet data emphasized the combined predictive power of autoantibody status and glycemic measures: over 85% of persons with multiple autoantibodies and impaired glucose tolerance progressed to type 1 diabetes within five years. A retrospective analysis involving over 3,000 first-degree relatives found that more than 80% of individuals under 20 years old with multiple AABs developed T1D within a decade, whereas older individuals or those with only a single autoantibody showed markedly lower progression rates.[19, 24]
Beyond the number of autoantibodies, their sequence and specific type also influence disease risk and timing. In young children, insulin autoantibodies are most commonly the 1st to appear, although their prevalence declines with age. Information from the Diabetes Autoimmunity Study in the Young study indicate that kids with persistently high levels of insulin autoantibodies develop more rapidly to clinical diabetes—100% within approximately 5.6 years—in comparison with those with variable or declining insulin autoantibodies titers. In this cohort, age at seroconversion and insulin autoantibodies concentrations were the strongest predictors of progression, whereas IA-2A and glutamic acid decarboxylase antibody were less predictive in isolation.[26]
The presence of IAA as the initial autoantibody is particularly significant. Children who developed IAA first had a markedly elevated risk of T1D—71.4% within 10 years and 92.1% within 20 years—compared to lower risks (47.6% and 61.6%, respectively) in those who did not initially test positive for IAA.[20]

In contrast, glutamic acid decarboxylase antibodies (GADA) are more frequently the initial autoantibody in older children and adults. In younger persons, glutamic acid decarboxylase antibody is typically related to a slower rate of illness development. However, in older populations, its existence confers a relatively greater possibility of developing type 1 diabetes.[27]
Goals and Benefits of Type 1 Diabetes Screening

The primary objective of screening for type 1 diabetes is to recognize persons at risk or in the preclinical phase of the illness, enabling timely intervention through preventive or disease-modifying strategies aimed at delaying or potentially avoiding the beginning of clinical symptoms.

Key benefits of screening include:
Reduction in Diabetic Ketoacidosis (DKA):
Early detection through screening substantially decreases the frequency of **diabetic ketoacidosis** at the time of identification—from rates as high as 80% in the general population to less than 5% among individuals undergoing regular monitoring. Preventing DKA is critical, as it is associated with acute complications such as cerebral edema, shock, neurocognitive deficits, and increased mortality. Moreover, experiencing **diabetic ketoacidosis** at identification was correlated with a higher likelihood of recurrent **diabetic ketoacidosis**, severe hypoglycemia, and suboptimal long-term glycemic control.[28]
Improved Immediate Clinical Outcomes:
Screening facilitates earlier diagnosis, often before the beginning of severe symptoms like unintentional weight loss, metabolic decompensation, or hospitalization. This can lead to a more stable and manageable clinical presentation at disease onset.[29]
Enhancing Quality of Life and Mental Health:
Knowledge of autoantibody status can help families prepare psychologically and practically for future insulin dependence. While a positive screening result may induce initial anxiety, structured education and emotional support programs were demonstrated to enhance adaptation and reduce long-term stress for both kids and caregivers.[30]
Facilitation of Research Participation:
Early identification of individuals at risk permits enrollment in clinical trials focused on prevention or early-stage intervention. These studies are crucial for advancing therapeutic development. However, it is important to acknowledge that screening may also bring emotional challenges, particularly when families struggle to understand the implications of pre-symptomatic T1D or when no immediate

treatment is available..[31]

Screening and Monitoring Strategies

Screening for Type 1 Diabetes (T1D) is becoming increasingly widespread around the world. Although most current efforts are part of research or pilot programs, routine screening may soon become standard medical practice in many regions. Notably, in 2023, Italy became the 1st country to legally adopt a national public health policy which mandates screening for both celiac illness and type 1 diabetes in all kids.[32]

Several screening programs employ a two-step approach that integrates genetic testing—such as HLA genotyping or the use of polygenic risk scores—with islet autoantibody analysis to enhance the recognition of persons at highest possibility for developing type 1 diabetes. This strategy improves cost-effectiveness by narrowing the pool of individuals requiring frequent monitoring. However, it may overlook individuals who develop autoantibodies despite lacking high-risk genetic markers. Notable programs adopting this combined screening model include DIPP and BABYSCREEN in Europe, the international Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) initiative, and U.S. based efforts such as Combined Antibody Screening for Celiac and Diabetes Evaluation (CASCADE) and PLEDGE.[33-35]

In contrast to combined genetic and autoantibody strategies, screening programs based solely on islet autoantibody detection may identify a broader spectrum of at-risk individuals. However, this approach is more resource-intensive and raises unresolved questions regarding the optimal age and frequency of testing. In Europe, initiatives such as EDENT1FI and Fr1da represent large-scale efforts to implement generalized population-based autoantibody screening. In the United States, the ASK (Autoimmunity Screening for Kids) program screens kids for pre-symptomatic type 1 diabetes and celiac illness. Similarly, Australia's Type 1 Diabetes National Screening Pilot is exploring various models, involving genetic testing at birth or in early infancy, followed by autoantibody screening among the ages of two and six.[36]

Kids who exhibit a single persistent islet autoantibody frequently progress to Stage 1 T1D within approximately two years, particularly when seroconversion occurs before the age of five. This progression is typically marked by the development of additional autoantibodies, indicating advancing islet autoimmunity.[37]

For children under the age of three who present with a single islet autoantibody, the Juvenile Diabetes Research Foundation (JDRF) recommends follow-up autoantibody testing every six months for the 1st three years, followed by annual testing for an additional three years. In parallel, routine metabolic assessments—such as annual random blood glucose and HbA1c measurements—are advised to monitor early glycemic changes. Nonetheless, the potential financial burden and psychological impact of ongoing surveillance should be carefully considered when implementing long-term screening protocols.[38]

Kids who test positive for multiple islet autoantibodies (AABs) are considered at high possibility for developing type 1 diabetes and should undergo glycemic staging alongside regular clinical monitoring. This approach facilitates early identification of candidates for preventive interventions or enrollment in clinical trials. The intensity and frequency of monitoring must be individualized depending on the child's estimated risk of progression, family preferences, and healthcare system resources. While some high-risk individuals may benefit from comprehensive assessments like the oral glucose tolerance test (OGTT), others may be adequately monitored using less intensive methods including periodic HbA1c or random blood glucose measurements.[39]

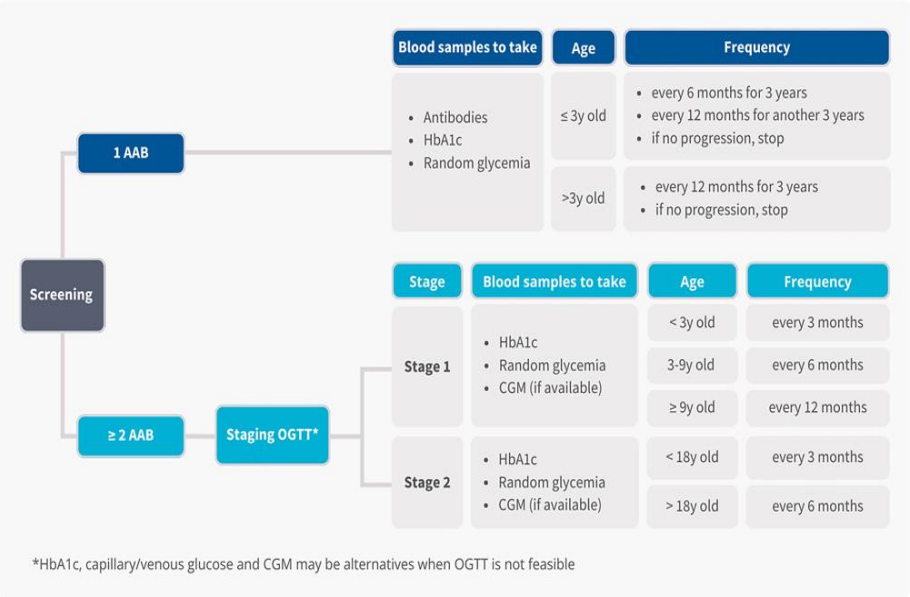

Figure No. (2): Screening and monitoring in adolescents and kids with multiple or single autoantibodies. Age and number of islet autoantibodies dictate the incidence and intensity of suggested monitoring for individuals with multiple or single autoantibodies. The status of multiple or single autoantibodies must be verified in a 2nd sample. CGM, continuous glucose monitoring; OGTT, oral glucose tolerance test; AAB, autoantibodies.[40]

All families of kids with multiple islet autoantibodies should receive comprehensive education regarding the natural development to Stage 3 type 1 diabetes (T1D), strategies for managing earlier stages of the disease, available monitoring options, and the early signs and symptoms of hyperglycemia. Access to a multidisciplinary healthcare team and provision of home glucose monitoring tools are essential components of care. In the absence of structured follow-up and educational support, these children face a significantly increased possibility of presenting with diabetic ketoacidosis at diagnosis.[41]

CONCLUSION:

Type 1 diabetes is a chronic, organ-specific autoimmune illness with a well-defined natural history that begins long before clinical diagnosis. The existence of islet autoantibodies (AABs) serves as a reliable biomarker for identifying individuals at risk, especially when multiple AABs are detected in early childhood. Extensive longitudinal investigations have confirmed that the number, type, and sequence of AABs along with age at seroconversion—are critical predictors of disease progression. Early detection of at-risk individuals through screening programs enables timely metabolic monitoring, psychosocial support, and potential enrollment in clinical trials targeting disease prevention or delay.

Screening strategies vary, ranging from targeted approaches based on genetic predisposition to broader population-level screening using autoantibody detection. While cost and emotional burden must be considered, the benefits of early detection—including the reduction of diabetic ketoacidosis (DKA) at onset, enhanced initial glycemic control, and enhanced quality of life—are substantial. Importantly, education and support for families remain essential to optimizing outcomes and ensuring successful management during the preclinical and clinical phases of T1D.

As assay technologies and public health initiatives continue to advance, the integration of autoantibody screening into routine pediatric care represents a promising step toward the early prevention and more effective treatment of T1D.

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