## Mini Review about the Differences in Genetic, Immunological, and Clinical Presentation of Type 1 Diabetes Mellitus in Young and Adult Patients



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**Abstract**

The goal of this mini-review article is to describe the differences in genetic, immunological, and clinical presentations of type 1 diabetes mellitus (T1DM) in children and adults. We believe this can add to the knowledge of clinicians treating patients with DM and improve their management skills. T1DM has traditionally been associated with younger populations with onset below the age of 30. Recent epidemiological data have shown that more than half of all new cases of T1DM occur in adults. Key genetic, immune, and metabolic differences exist between adult- and childhood–adolescent-onset T1DM, many of which are not well understood. A substantial risk of misclassification of diabetes mellitus type can result. Notably, some adults with T1DM may not require insulin at diagnosis, their clinical disease can masquerade as type 2 diabetes mellitus (T2DM), and the consequent misclassification may result in inappropriate treatment. Here, we summarize and add to the current understanding, highlighting the epidemiology and immunogenetic and metabolic characteristics of adult-onset T1DM. In adult-onset, as compared with childhood-adolescent onset T1DM, HLA-associated risk is lower, with more protective genotypes and lower genetic risk scores. Multiple diabetes- associated autoantibodies are decreased, though Glutamic-acid decarboxylase antibody (GAD65) remains dominant although at lower titers than in children-adolescents with T1DM. After diagnosis, adult patients with T1DM progress more slowly, their serum C-peptide is higher, with ketoacidosis being less frequent. Tools to distinguish types of diabetes are discussed, including body phenotype, clinical course, genetic predisposition, autoantibodies, comorbidities, and C-peptide level. By providing this perspective, we aim to improve the management of adults presenting with T1DM. Misdiagnosis in adult-onset T1DM is common due to overlapping features with T2DM , leading to inappropriate treatment. This mini-review integrates findings from recent studies to identify distinctions between T1DM in children and adolescents and adult-onset T1DM in genetic predispositions, autoimmunity, and clinical symptoms. Recognizing these differences is critical for timely diagnosis and personalized treatment strategies, ultimately improving patient outcomes.

**Key Words:** Diabetes Mellitus type 2, Diabetes Mellitus type 1, Glutamic acid decarboxylase antibodies (Gad-65), Insulin autoantibodies (IAA), Zinc transporter 8 antibodies (ZN-T8A), Tyrosine phosphatase islet antigen-2 antibodies (IA-2), Pancreatic beta-cells.

## Introduction



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* 1. Al-Badri, A. S., & Ali, E. N. (2022). Effect of IL-23 receptor gene polymorphism (rs1884444) on the prevalence of oral fungal infection in patients with type 2 diabetes mellitus: a case-control study in Iraqi Patients. *Archives of Razi Institute*, *77*(5), 1553.
  2. Kadhim, A.S., Ajah, H.A. and Ali, E.N., 2021. Investigation the role of oral candidiasis and IL 17 gene polymorphism Rs 2275913 in type 2 diabetes mellitus in Iraqi Arab patients.
  3. Kadhim, A.S., 2023. Association between Genotype of IL17A rs (22759130 G/A) and IL17F rs (763780

T/C) Polymorphism in the Type 2 Diabetes Mellitus Patients with Oral Fungal Infection. *Biomolecular and Health Science Journal*, *6*(1), pp.6-12.

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Clinically, it has been relatively easy to distinguish acute, potentially lethal, early-onset in-life diabetes mellitus from the less aggressive condition that affects adults. The experience has taught us that not all children and adolescents with diabetes mellitus are insulin-dependent and not all adults are non–insulin-dependent at the onset of their disease [1].

Immune, genetic, and metabolic analysis of these two, apparently distinct, forms of diabetes mellitus revealed inconsistencies, such that insulin-dependent and immune-mediated diabetes in adults was redefined as T1DM, while most other forms were relabeled as T2DM. Recent understanding is that more than half of all new cases of T1DM occur in adults [1,2]. However, many adults may not require insulin at diagnosis of T1DM and have a more gradual onset of hyperglycemia, often leading to misclassification and inappropriate care. Indeed, misdiagnosis occurs in nearly 50% of adults with new T1DM and this misdiagnosis is increasing with the age of the patients [1,2,3,4].

T1DM constitutes approximately 5-10% of all diabetes cases worldwide. It is characterized by autoimmune destruction of pancreatic beta cells, leading to absolute insulin deficiency.

Traditionally considered a pediatric disease, recent evidence highlights a significant prevalence of adult-onset T1DM, with over 50% of new cases diagnosed in adulthood. The clinical distinction between T1DM and T2DM in adults can be challenging due to overlapping features, resulting in frequent misdiagnoses [1]. This review will add additional understanding to the

existing knowledge and further explore the differences in genetic, immunological, and clinical presentations of T1DM in children and adults to improve diagnostic accuracy and therapeutic strategies [2].

**Genetic and Immunological Differences**

The natural history of T1DM involves genetic predisposition related to the HLA system, and factors of the environment. This is usually viral leading to autoimmune destruction of the pancreatic beta-cells in predisposed patients [1].

Individuals who develop T1DM later in life have a lower concordance rate between identical twins, lower risk of HLA heterozygosity, lower association with both HLA Class I and Class II genes, and lower gene risk scores (GRS), estimated by summing the Odds Ratio of disease- associated genes [2]. In younger patients with T1DM, the higher risk genes for the disease are HLA DR3-DQ2/DR4-DQ8 haplotype, as well as A\*2402 alleles and B39\*06 were more common.

If present, they were associated with an earlier onset of the disease. The protective genes

against T1DM are DR15-DQ6 and DR7-DQ3, which were least common in younger patients with the disease [3]. Adults on the other hand with T1DM have more protective genotypes such as HLA-DR15 and DQ6, which was associated with a slower rate of beta cell destruction [4].

Like in children and adolescents, T1DM is caused by the autoimmune destruction of beta cells in adults. Evidence of this is autoimmunity are the autoantibodies glutamic acid decarboxylase (GAD65), insulin autoantibodies (IAA), tyrosine phosphatases islet antigen-2 antibodies (IA-2), and zinc transporter-8 antibodies (ZnT8A) [5,6].

The autoimmune process in T1DM is more pronounced in children. Multiple autoantibodies, including GAD65, IA-2, ZnT8A, and insulin autoantibodies (IAA), are commonly detected in younger patients at diagnosis with higher titers. The presence of multiple autoantibodies correlates with rapid beta-cell destruction and severe clinical presentation [5,6].



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Kadhim, A. S., & Al-Karawi, A. S. (2025). Investigating the multifactorial correlation between obesity and rheumatoid arthritis: A study of immunological and biochemical markers. *Obesity Medicine*, *53*, 100578.

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IAA and Zinc transporter-8 antibodies are associated with more severe inflammation of islet cells and abrupt onset of overt diabetes mellitus that is usually seen in children-adolescent patients with T1DM. Early-onset disease is also more likely to be associated with high levels of

multiple antibodies [5,6]. Glutamic acid decarboxylase antibodies (GAD65) are associated with a less severe autoimmune response and slower disease progression and are usually seen in adult- onset disease [6]. Other auto-antibodies are not as commonly seen compared to patients who are younger at diagnosis of T1DM.

Additionally, inflammatory markers differ between children and adults. Younger patients with T1DM typically exhibit higher levels of islet cell inflammation, driven by a robust immune response. In children and young adults, there was higher concordance with identical twins with T1DM. Adults, however, often have less pronounced inflammation, allowing for a more gradual decline in beta-cell function [6].

## Clinical Presentation

In adults, T1DM typically has an insidious onset, with hyperglycemia-related symptoms developing gradually. Adults may present with higher body mass indices (BMIs), minimal weight loss, and less frequent Diabetic Ketoacidosis (DKA). Residual beta-cell function often delays the need for insulin therapy, further complicating diagnosis. Misdiagnosis as T2DM is common, leading to initial treatment with oral hypoglycemic agents, which are inadequate for managing autoimmune diabetes [7]. T1DM in children has an abrupt onset, likely due to high-risk HLA genes and autoimmunity leading to rapid inflammation and destruction of the beta cells.

Symptoms include rapid weight loss, polyuria, and polydipsia. As many as half of patients present with DKA [7].

In contrast, adults with T1DM have a more insidious onset. Ketonuria and DKA are much less common at the onset of the disease. One of the reasons might be because of better-preserved beta cell function at the beginning of the disease, because of higher endogenous insulin production due to less aggressive destruction of the pancreatic beta cells. Due to the more protective genotypes associated with later onset of the disease, the rate of autoimmune destruction of beta cells is slower. Many adult individuals are therefore misdiagnosed as having T2DM and managed with lifestyle modifications and oral hypoglycemic agents which are frequently insufficient. These patients eventually develop DKA and require insulin replacement due to poor glycemic control on oral agents [8,9].

One tool to help distinguish the type of diabetes in older individuals is the AABBCC one. Age (age < 35 is more concerning for T1DM, autoimmunity (family or personal history of

autoimmunity), body habitus (BMI less than 25 is more likely in T1DM, background (family history of T1/T2 DM/MODY), diabetes mellitus control (patients’ response to oral hypoglycemic

agents) and comorbidities (history of pancreatitis or medications that can predispose to



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autoimmune phenomena) [9]. This tool is helpful, but is not 100% accurate, especially in older, overweight patients with T1DM. To complicate the differentiation between type 1 and T2DM, in adults is the presence of GAD65 antibodies in lower titers in patients with classical T2DM. Additionally, normal or high-C peptide levels in these patients together with a lack of DKA and other autoantibodies besides GAD 65, and higher BMI suggest in these instances that we are dealing with T2DM and not with adult T1DM.

## Discussion

The main goal of this article is to summarize the key differences in genetic, immunological, and clinical features among early and late-onset T1DM It is important to understand how the same disease presents differently in the two different age groups of patients. This provides clues as to why late-onset diabetes mellitus can be mistaken for T2DM. The adults with T1DM have lower- high risk genotypes HLA-DR3/DR4 and more protective genotypes- HLA-DR15 and DQ6. They have fewer more aggressive type antibodies in lower titers like IAA and ZnT8 antibodies, and adults have a more gradual loss of beta cell function, leading to a more insidious onset ofT1DM. This slow progression of disease in adults is one of the reasons for misclassification.

Another reason for misdiagnosis is the misconception that autoimmune diabetes is a disease only seen in children-adolescents and that adults are more likely to have T2DMwhich leads to confirmation bias. In addition, frequently adult patients with T1DM are overweight compared to younger patients with the disease [10]. Diagnosis and management differ significantly among T1DM and T2DM focuses primarily on lifestyle modifications, which may or may not be in conjunction with oral hypoglycemic agents.

T1DMon the other hand necessitates treatment only with specific insulin regimens that are tailored to each patient. Inaccurate diagnosis in adults can lead to patient confusion/distress, improper treatment, and increased risk of micro and macrovascular complications due to poor glycemic control, DKA, and mortality [11].

As mentioned above, identifying patients with adult-onset T1DM can be challenging. One way to help diagnose patients is by using the AABBCC approach as mentioned earlier.

In addition, there can be some clues in the patient’s history, physical examination, and disease course that can help differentiate between the two types of DM. The most discriminative feature is the younger age at diagnosis. T1DMis more likely to occur in those younger than 30- 40 years of age. A systematic review done in 2015 analyzed some studies that used clinical

criteria to predict insulin deficiency. The variable with the greatest discriminatory power for T1DM was the age at diagnosis- age below 30 was the most predictive parameter. The next best predictor was time to insulin treatment. The need for Insulin within 2- years after diagnosis favoredT1DM. Factors such as BMI, hypertension, history of DKA, or ketonuria contributed little

to nothing toward the diagnostic probability differentiation [12]. Unfortunately, in real life, physicians experience exceptions to this data.

If the clinical suspicion of T1DM is high, laboratory testing can be pursued. Autoantibodies to beta cell antigens can be measured, preferably within 3- years of diagnosis. The absence of antibodies does not rule out T1DM but makes T2DM or MODY more likely in adults.

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GAD65 antibody positivity is common in later-onset T1DM and can detect up to 60-80% of patients [13]. As mentioned above, because GAD 65 might be positive in low titers in T2DM its positivity should be viewed in the context of the whole clinical picture and the presence of normal or increased postprandial C- peptide in patients with T2DM.

C-peptide may also be used to give insight into the type of diabetes and its management. It should be measured when BS is between 80- 200 mg/dl. A C-peptide <0.2 nmol/l is indicative of severe insulin deficiency raising the possibility for T1DM in the appropriate clinical context

[13].

A meta-analysis done in 2023 studied the predictive value of C-peptide in distinguishing T1DMfrom T2DM. It concluded that plasma C-peptide levels were highly associated with

accurate classification, diagnosis, and treatment of the different diabetes types. C peptide cut- off of < 0.2 mmol/L was indicative of T1DM [14,15]

Above are some tools that might help diagnose the type of diabetes. There is, however, no specific test that can either confirm or rule out T1DM from T2DM. Pursuing a diagnosis requires careful analysis of patient history, clinical features, and laboratory tests simultaneously. This simple algorithm is not foolproof, and some individuals with T1DM may remain unidentified throughout their lifetime [ 16].

In general, summarizing what was stated above adults with T1DM have a lower incidence of HLA-DR3 and DR4, and lower concordance of the disease with identical twins, but a higher incidence of metabolic syndrome and higher C- peptide at the diagnosis of theirT1DM. They have a lower incidence of DKA at the onset of their disease and lower titers and numbers of antibodies against the pancreatic beta-cells. Up to 50% of them are not initially treated with insulin. They have a similar incidence of other autoimmune conditions as patients who are younger with T1DM. The prevalence of T1DM in patients above the age of 20 is between 21- 50% which should alarm the physician to change their outlook about this disease.

Epidemiological trends indicating an increase in adult-onset T1DM highlight the need for heightened awareness among healthcare providers. Increased use of genetic, immunological, and serological markers as well as the clinical presentation in diagnostic workflows can help differentiate T1DM from other diabetes types, ensuring timely and appropriate treatment.

## Conclusion

T1DMpresents significant differences in genetic, immunological, and clinical features between

children and adults. T1DMin children and adolescents is driven by strong genetic predisposition and aggressive autoimmunity, leading to rapid disease progression and acute clinical



presentations. Conversely, patients with adult-onset T1DM often have more protective genotypes against the disease, milder autoimmunity, and slower beta-cell destruction, contributing to a more gradual onset and frequent misdiagnoses as T2DM. Understanding these distinctions is essential for improving diagnostic accuracy and treatment strategies, ultimately enhancing patient outcomes across all age groups.

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## References

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1. Leslie R., Evans-Molina C., Freund-Brown J., et al. Adult-Onset Type 1 Diabetes: Current Understanding and Challenges. *Diabetes Care* 2021;44(11):2449–2456, doi:

<https://doi.org/10.2337/dc21-0770>

1. Burahmah J, Zheng D, Leslie RD. Adult-onset type 1 diabetes: A changing perspective. European Journal of Medicine 2022;104, 7-12, doi: [10.1016/j.ejim.2022.06.003](https://doi.org/10.1016/j.ejim.2022.06.003)
2. Redondo M, Concannon P. Genetics of Type 1 Diabetes Comes of Age. Diabetes Care 2019 Dec 12;43(1):16–18, doi: [10.2337/dci19-0049](https://doi.org/10.2337/dci19-0049)
3. Gomes M, Santos Jr G, Azulay R, et al (2024). Association between HLA alleles and

haplotypes with age at diagnosis of type 1 diabetes in an admixed Brazilian population: A nationwide study. HLA;104(1): e15574, doi: <https://doi.org/10.1111/tan.15574>

1. Sørgjerd E (2019), Type 1 Diabetes-related Autoantibodies in Different Forms of Diabetes, Current Diabetes Reviews; 15(3), 199-204, doi:

10.2174/1573399814666180730105351

1. Sanyal D. Current Perspective on Auto-antibodies in Type 1 Diabetes. Indian J Endocrinol Metab. 2020 May-Jun;24(3):233-234. doi: 10.4103/ijem.IJEM\_206\_20
2. Peters A, Kanapka L, Hirsch I, et al; Characteristics of Adult vs. Childhood-Onset Type 1 Diabetes (T1D) in the T1D Exchange Registry. *Diabetes* 1 July 2018; 67 (Supplement\_1): 182–LB. doi: <https://doi.org/10.2337/db18-182-LB>
3. Kim, C.S., Song, M.K., Park, J.S. *et al.* The clinical and immunogenetic characteristics of adult-onset type 1 diabetes mellitus in Korea. *Acta Diabetol* 44, 45–54 (2007). Doi: <https://doi.org/10.1007/s00592-007-0241-y>
4. American Diabetes Association Professional Practice Committee; 2. Diagnosis and

Classification of Diabetes: Standards of Care in Diabetes—2025. *Diabetes Care* 1 January 2025; 48 (Supplement\_1): S27–S49. <https://doi.org/10.2337/dc25-S002>

1. Leslie R., Evans-Molina C., Freund-Brown J., et al. Adult-Onset Type 1 Diabetes: Current Understanding and Challenges. *Diabetes Care* 2021;44(11):2449–2456, doi:

<https://doi.org/10.2337/dc21-0770>

1. Holt R, DeVries J, Hess-Fischl A, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the study of Diabetes. Diabetes Care 2021;44(11):2589–2625, doi: <https://doi.org/10.2337/dci21-0043>
2. Shields BM, Peters JL, Cooper C*, et al.* Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. *BMJ Open* 2015; **5:** e009088. doi: 10.1136/bmjopen-2015-009088



1. Tatovic D, Jones AG, Evans C, Long AE, Gillespie K, Besser REJ, Leslie RD, Dayan CM; Type 1 diabetes UK Immunotherapy Consortium. Diagnosing Type 1 diabetes in adults: Guidance from the UK T1D Immunotherapy consortium. Diabet Med. 2022

Jul;39(7):e14862. doi: 10.1111/dme.14862

1. Iqbal S, Jayyab A, Alrashdi A, et al. The Predictive Ability of C-Peptide in Distinguishing Type 1 Diabetes From Type 2 Diabetes: A Systematic Review and Meta-Analysis. Endocrine Practice, 29 (5), 379-387. doi: [10.1016/j.eprac.2023.01.004](https://doi.org/10.1016/j.eprac.2023.01.004)

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1. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013 Jul;30(7):803-17. doi: 10.1111/dme.12159. PMID: 23413806; PMCID: PMC3748788.

Andre E. Manov, Sukhjinder Chauhan et al. Unmasking-type-1-diabetes-in-adults-insights-from- two-cases-revealing-misdiagnosis-as-type-2-diabetes-with-emphasis-on-autoimmunity-and- continuous-glucose-monitoring. Cureus,07/25/23. PMCID: PMC10450099|PMID: 37637512.doi: 10.7759/cureus.42459