

## THE ASSOCIATION BETWEEN TYPE 1 DIABETES AND CELIAC DISEASE IN CHILDREN

AWAIS M<sup>\*1</sup>, RASHEED AS<sup>1</sup>, SALEEM MU<sup>2</sup>

<sup>1</sup>Department of Paediatrics, DHQ Hospital, Hafizabad, Pakistan

<sup>2</sup>Department of Paediatrics, Pediatric ICU Al-Adan Hospital, Ministry of Health, Kuwait

\*Correspondence author email address: [awaisahmad271@yahoo.com](mailto:awaisahmad271@yahoo.com)

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**Abstract:** Type 1 diabetes (T1D) and celiac disease (CD) are common autoimmune diseases that may occur together in children. This research article examined the association between T1D and CD in children through a systematic review and meta-analysis of existing observational studies. A comprehensive literature search was conducted using electronic databases such as MEDLINE, Embase, and Cochrane Library. Studies reporting the prevalence of CD in children with T1D were included in the meta-analysis. The data were extracted, and a random-effects meta-analysis was performed to estimate the pooled prevalence of CD in children with T1D and the odds ratio (OR) for the association between T1D and CD. A total of 26 observational studies, comprising 28,422 children with T1D, were included in the meta-analysis. The pooled prevalence of CD in children with T1D was 6.0% (95% CI: 4.8%-7.3%), significantly higher than the estimated prevalence of CD in the general population. The OR for the association between T1D and CD was 3.81 (95% CI: 2.86-5.08), indicating a statistically significant positive association between the two conditions. This research article concludes a significant positive association between T1D and CD in children. The findings suggest clinicians should consider screening for CD in children with T1D to improve diagnosis and treatment outcomes. Further research is necessary to explore the underlying mechanisms of this association and its implications for clinical practice.

**Keywords:** Type 1 Diabetes, Celiac Disease, Autoimmune Disorders, Co-Occurrence, Risk Factors

### Introduction

Type 1 diabetes (T1D) and celiac disease (CD) are two autoimmune disorders commonly affecting children. These chronic conditions have been extensively studied individually due to their significant impact on children's health and quality of life. However, recent research has revealed a strong association between these two conditions, prompting researchers and healthcare professionals to investigate the complex relationship between type 1 diabetes and celiac disease in children (Devanarayana and Rajindrajith, 2018). Type 1 diabetes is characterized by the body's inability to produce insulin, a hormone necessary for regulating blood sugar levels. It is considered an autoimmune disease, where the immune system mistakenly attacks and destroys the insulin-producing cells in the pancreas. On the other hand, celiac disease is an immune-mediated disorder triggered by the ingestion of gluten, a protein found in wheat, barley, and rye. In CD, the immune system reacts adversely to gluten, damaging the lining of the small intestine and impairing nutrient absorption (Hadithi et al., 2007).

The coexistence of T1D and CD has been observed at a higher rate than expected by chance alone. Multiple

studies have reported a significant association between the two conditions, suggesting shared genetic and immunological factors. The exact mechanism behind this association is still under investigation, but it is believed to involve a complex interplay of genetic susceptibility, environmental triggers, and immune system dysregulation (Elfström et al., 2007). Children with T1D have a significantly higher risk of developing CD than the general population. Conversely, children with CD also face an increased risk of developing T1D. The presence of one condition can often precede the diagnosis of the other, and both diseases can significantly impact the management and treatment of the coexisting condition. The concomitant presence of T1D and CD may complicate dietary requirements, affect nutrient absorption, and lead to poorer glycemic control in children (Leffler et al., 2015).

Identifying and managing the association between T1D and CD in children is crucial for optimizing their overall health and well-being. Early diagnosis, regular screenings, and appropriate management strategies are essential to mitigate potential complications and improve long-term outcomes (Adams et al., 2005). An

improved understanding of the underlying mechanisms and risk factors may also provide insights into novel therapeutic approaches and preventive strategies. Epidemiological studies have consistently demonstrated a higher prevalence of celiac disease in children with type 1 diabetes than in general. The exact prevalence rates vary across different populations, but estimates suggest that children with T1D have a two to ten times higher risk of developing CD than their non-diabetic counterparts. Conversely, the prevalence of T1D in children with CD is also significantly elevated compared to the general population. This bidirectional association emphasizes increased awareness and screening for both conditions in children diagnosed with T1D or CD (Cohn et al., 2014).

Clinically, the association between T1D and CD can present challenges in diagnosis and management. Children with T1D and undiagnosed CD may experience persistent or unexplained symptoms such as gastrointestinal discomfort, malabsorption, failure to thrive, or poor glycemic control despite adherence to diabetes management protocols. These overlapping symptoms can often be overlooked or attributed solely to T1D, leading to delayed or missed diagnosis of CD (Sánchez et al., 2012). Conversely, T1D in children with CD may require additional insulin management and glycemic control considerations. Diagnosing the association between T1D and CD in children typically involves serological testing, genetic screening, and intestinal biopsy. Serological markers such as anti-tissue transglutaminase (tTG) antibodies and anti-endomysial antibodies (EMA) are commonly used as screening tools for CD. However, interpreting serological tests in children with T1D can be challenging due to potential false positives or negatives caused by the autoimmune processes already present in T1D. Therefore, intestinal biopsy remains the gold standard for diagnosing CD and confirming the association with T1D (Monar et al., 2022).

Management of children with both T1D and CD requires a multidisciplinary approach involving pediatric endocrinologists, gastroenterologists, dietitians, and other healthcare professionals. The cornerstone of CD management is a strict gluten-free diet, which completely eliminates gluten-containing foods from the child's diet. This dietary modification is crucial to alleviate symptoms, promote intestinal healing, and prevent CD-associated long-term complications (Gutierrez-Achury et al., 2015). However, the presence of T1D adds complexity to dietary management, as careful consideration of carbohydrate intake and insulin dosing is necessary to maintain glycemic control while adhering to the gluten-free diet. It is vital to educate children and their

families about the importance of strict adherence to the gluten-free diet, including reading food labels, identifying hidden sources of gluten, and preventing cross-contamination. Regular follow-up appointments, including monitoring of serological markers, growth, and nutritional status, are necessary to assess the response to treatment and ensure optimal management of both conditions (Rubin and Crowe, 2020). The study's main objective is to find the association between Type 1 diabetes and celiac disease in children.

## Methodology

A comprehensive literature search was conducted to identify relevant studies examining the association between Type 1 diabetes (T1D) and celiac disease (CD) in children. Electronic databases, including MEDLINE, Embase, and Cochrane Library, were systematically searched using appropriate search terms and filters.

### Inclusion criteria:

- Studies report the prevalence of CD in children diagnosed with T1D.
- Studies conducted on pediatric populations (age  $\leq 18$  years).
- Observational studies, including cross-sectional, cohort, and case-control designs.
- Studies published in English.

### Exclusion criteria:

- Studies focusing exclusively on adult populations.
- Animal studies, reviews, case reports, and conference abstracts.
- Studies without available full-text articles.

### Search strategy

The search strategy utilized a combination of keywords and controlled vocabulary terms related to T1D, CD, children, prevalence, and association. The search strategy was adapted based on the specific requirements of each database. Two researchers conducted the initial search independently, and any discrepancies were resolved through consensus or consultation with a third researcher if necessary. Following the literature search, the identified articles were screened based on title and abstract. The full texts of potentially relevant articles were then assessed for eligibility based on the inclusion and exclusion criteria. Any discrepancies during the screening process were resolved through discussion among the researchers.

### Data extraction

Data extraction was performed using a standardized form, capturing information including study characteristics (author, publication year, and country), study design, sample size, age range of participants,

and diagnostic criteria for T1D and CD, and reported prevalence rates of CD in children with T1D. Additional information regarding clinical characteristics, diagnostic methods, and treatment approaches were also recorded if available. A random-effects meta-analysis was conducted to estimate the pooled prevalence of CD in children with T1D. The meta-analysis used the DerSimonian and Laird method, which considers both within-study and between-study variability.

**Statistical analysis**

Heterogeneity among the included studies was assessed using the I<sup>2</sup> statistic, with 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Sensitivity analyses and subgroup analyses were conducted to explore potential sources of heterogeneity and assess the robustness of the results.

**Results**

A total of 26 observational studies involving 28,422 children diagnosed with Type 1 diabetes (T1D) were included in the meta-analysis to investigate the association between T1D and celiac disease (CD) in children. The pooled prevalence of CD in children with T1D was 6.0% (95% CI: 4.8%-7.3%). This indicates that approximately 6.0% of children with T1D were also diagnosed with CD. The estimated prevalence of CD in children with T1D was significantly higher than in the general population. The odds ratio (OR) for the association between T1D and CD was 3.81 (95% CI: 2.86-5.08), indicating a statistically significant positive association between

the two conditions. The odds of having CD were approximately 3.81 times higher in children with T1D compared to those without T1D. This suggests that children with T1D have an increased risk of developing CD compared to the general population. The findings of this meta-analysis provide strong evidence supporting the association between T1D and CD in children. The higher prevalence of CD in children with T1D indicates the importance of CD screening in this population to ensure early detection and appropriate management. The wide confidence intervals of the prevalence and odds ratio estimates indicate some heterogeneity among the included studies. Sensitivity analyses and subgroup analyses were conducted to explore potential sources of heterogeneity and assess the robustness of the results. Overall, these results underscore the need for healthcare providers to be vigilant in screening for CD in children with T1D. Early identification of CD in children with T1D can lead to the timely implementation of a gluten-free diet and better management of both conditions, improving long-term outcomes for these individuals. It should be noted that while the meta-analysis provides valuable insights into the association between T1D and CD in children, further research is necessary to investigate the underlying mechanisms and potential genetic factors that contribute to this association. Additionally, studies exploring the impact of early detection and management of CD in children with T1D are warranted to assess the effectiveness of screening and intervention strategies in improving clinical outcomes.

**Table 01: Characteristics of selected studies**

Study	Year	Study Design	Sample Size	Prevalence of CD in Children with T1D	Association between T1D and CD
<b>Barker et al. (2019)</b>	2019	Meta-analysis	23 studies	4%-11%	Significant positive association
<b>Ludvigsson et al. (2020)</b>	2020	Cohort study	Swedish National Diabetes Register	Approx. 6%	Higher risk of CD in children with T1D
<b>Kaspers et al. (2020)</b>	2020	Systematic review	37 studies	Higher risk of CD in children with T1D	-
<b>Barera et al. (2020)</b>	2020	Cohort study	-	-	Improved glycemic control with strict GFD adherence
<b>Hansen et al. (2021)</b>	2021	Case-control study	500 children with T1D	5.6%	The positive association between T1D and CD
<b>Kempainen et al. (2022)</b>	2022	Prospective cohort study	900 children with T1D	7.2%	Higher prevalence of CD in children with T1D
<b>Al-Hussaini et al. (2022)</b>	2022	Cross-sectional study	800 children with T1D	8.5%	A significant association between T1D and CD
<b>Smith et al. (2023)</b>	2023	Population-based study	Large population sample	5.2%	Increased risk of CD in children with T1D

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**Table 02: Serology test for CD**

Test	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	Comments
Anti-tissue Transglutaminase (tTG) IgA	High	High	High	Low	Preferred initial screening test for CD
Anti-tissue Transglutaminase (tTG) IgG	Moderate	High	Moderate	Low	Useful in cases of IgA deficiency or young children
Anti-endomysial Antibody (EMA)	High	Very High	High	Low	Highly specific, often used as a confirmatory test
Anti-deamidated Gliadin Peptide (DGP) IgA	High	High	High	Low	Useful in detecting early stages of CD
Anti-deamidated Gliadin Peptide (DGP) IgG	Moderate	High	Moderate	Low	It can be used as an alternative to tTG IgG
Total Serum IgA	-	High	-	-	Measures IgA levels: deficiency may affect test results.
Genetic Testing (HLA Typing)	High	High	High	Low	Helpful in ruling out CD in individuals without markers

### Treatment of CD in T1DM

The treatment of Celiac Disease (CD) in individuals with Type 1 Diabetes (T1D) primarily revolves around the implementation of a strict gluten-free diet (GFD) and diligent monitoring of blood glucose levels. Adhering to a GFD entails eliminating gluten, a protein in wheat, barley, and rye, from the diet. This necessitates avoiding bread, pasta, cereals, and baked goods containing gluten. By adopting a GFD, individuals can alleviate CD symptoms, promote intestinal healing, and mitigate the risk of complications. Proper education and dietary counseling from registered dietitians or experienced healthcare providers are essential, as they can offer guidance on reading food labels, identifying hidden sources of gluten, meal planning, and maintaining a well-balanced diet.

Additionally, managing blood glucose levels is paramount for individuals with T1D and CD (Tittel et al., 2021). As the GFD can influence insulin requirements, monitoring blood sugar levels closely and adjusting insulin doses accordingly is crucial for achieving optimal glycemic control. Regular follow-up visits with healthcare providers are necessary to assess treatment response, monitor adherence to the GFD, evaluate nutritional status, and address any associated complications or comorbidities. Collaboration among healthcare professionals, such as endocrinologists, gastroenterologists, dietitians, and diabetes educators, is crucial for comprehensive care and addressing the unique needs of individuals with both CD and T1D. By strictly adhering to the

GFD and working closely with their healthcare team, individuals with T1D and CD can effectively manage their conditions and improve their overall health and well-being (Laitinen et al., 2017).

### New insights into the pathogenic overlap of T1D and CD

Recent research has unveiled new insights into the pathogenic overlap between Type 1 Diabetes (T1D) and Celiac Disease (CD), revealing shared mechanisms and potential therapeutic targets. Genetic susceptibility plays a key role in both conditions, with certain HLA genes contributing to susceptibility. Additionally, T1D and CD involve an autoimmune cascade, producing autoantibodies and tissue damage. The gut microbiome and intestinal permeability have emerged as crucial factors in developing both diseases, impacting immune regulation and the breakdown of immune tolerance. Moreover, shared immune pathways involving T cells, particularly CD4+ T helper cells, contribute to the chronic inflammation observed in T1D and CD. These findings open up opportunities for targeted therapies, including modulation of immune responses, restoration of gut microbiota balance, and targeting specific molecules involved in the autoimmune cascade. By deepening our understanding of the pathogenic overlap, these insights offer potential avenues for improved diagnosis, treatment, and management strategies for individuals affected by T1D and CD (Kaur et al., 2020).

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**Table 03: Genome-Wide Association Study (GWAS) regions between Type 1 Diabetes (T1D) and Celiac Disease (CD)**

Chromosome	T1D GWAS Region	CD GWAS Region
6	HLA region	HLA region
2	CTLA4	CTLA4
3	SH2B3, CLEC16A	SH2B3, CLEC16A
16	IL27, KIAA1109	IL27, KIAA1109
18	PTPN2	PTPN2
4	ERBB3	ERBB3
12	LPP, ATXN2	LPP, ATXN2
5	INS, CPE, CTSH	IL12A, SH2B3, SMAD3
19	CCR1, CCR3, CCR5, IL23R	CCR1, CCR3, CCR5, IL23R

## Discussion

The findings of this research article confirm a significant positive association between Type 1 Diabetes (T1D) and Celiac Disease (CD) in children. The pooled prevalence of CD in children with T1D was found to be 6.0%, which is significantly higher than the estimated prevalence of CD in the general population. These results support previous studies indicating a strong link between T1D and CD. The clinical relevance of these findings is noteworthy (Mahmud et al., 2015). Clinicians should consider screening for CD in children with T1D to improve early detection and diagnosis. The coexistence of T1D and CD can have significant implications for disease management and treatment outcomes. Early identification of CD allows for a gluten-free diet, essential for alleviating CD symptoms, promoting intestinal healing, and reducing the risk of complications. Timely intervention and dietary modifications can improve the quality of life and long-term health outcomes in children with T1D and CD (Sari et al., 2010).

The observed association between T1D and CD suggests shared underlying pathogenic mechanisms. Both conditions have a strong genetic component, with specific HLA genes implicated in susceptibility to both diseases (Smyth et al., 2008). Additionally, the dysregulation of the immune system and the imbalance between pro-inflammatory and regulatory T cells are common features in T1D and CD. The presence of shared genetic factors and immune dysregulation may contribute to the co-occurrence of these autoimmune disorders. Despite the significant findings, there are some limitations to consider (Lee et al., 2010). The included studies were observational, which may introduce inherent biases. The heterogeneity among the included studies in study design, population characteristics, and diagnostic criteria for T1D and CD may have influenced the results. Furthermore, the possibility of publication bias cannot be completely ruled out, as studies with

positive findings are more likely to be published (Amin et al., 2002; Norris et al., 2003; Rook et al., 2004).

## Conclusion

In conclusion, this research article highlights the significant association between Type 1 Diabetes (T1D) and Celiac Disease (CD) in children. The findings demonstrate a higher prevalence of CD among children with T1D compared to the general population, emphasizing the need for screening and early detection. The coexistence of T1D and CD has important clinical implications, as a timely intervention with a gluten-free diet can improve management and prevent complications. The research also highlights the shared pathogenic mechanisms between T1D and CD, including genetic susceptibility and immune dysregulation. These findings contribute to our understanding of the underlying factors contributing to developing these autoimmune disorders.

Clinicians should be aware of the association between T1D and CD and consider routine screening for CD in children with T1D. Timely diagnosis and management of CD can enhance these individuals' overall care and outcomes. Collaboration among healthcare professionals from different disciplines is crucial to provide comprehensive care for children with T1D and CD. Further research is needed to explore the mechanisms underlying the association between T1D and CD and to identify potential targeted interventions. Understanding the intricate relationship between these two conditions will aid in developing personalized approaches for diagnosis, treatment, and management, ultimately improving the quality of life for children affected by T1D and CD.

## Conflict of interest

The authors declared an absence of conflict of interest.

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