TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

RELATIONSHIP BETWEEN CELIAC DISEASE AND IDIOPATHIC SHORT STATURE IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT
Objectives: To evaluate the prevalence of celiac disease (CeD) in children with idiopathic short stature and assess growth hormone (GH) differences between affected and unaffected children.
Methods: A systematic review and meta-analysis were conducted according to PRISMA guidelines. Studies reporting on serological or biopsy-confirmed CeD in children with idiopathic short stature were included. Data sources included PubMed, Scopus, Web of Science, ScienceDirect, and ClinicalKey. Pooled prevalence estimates and standardized mean differences in GH levels were calculated using a random-effects model using comprehensive meta-analysis software.
Results: Our results included eleven studies with a total of 1873 children with short stature and 946 (50.5%) of them were males. Ten studies were included. The pooled seroprevalence of CeD was 22.7% (95% CI: 20.6%–25.0%), while the biopsy-confirmed prevalence was 14.8% (95% CI: 12.1%–18.0%). GH levels did not significantly differ between children with and without CeD (pooled SMD = 0.023, 95% CI: -0.259 to 0.304; p = 0.874). **Conclusion:** CeD is a relatively common and often overlooked cause of idiopathic short stature in children. Routine screening for CeD in this population is recommended, as early diagnosis and treatment can improve growth outcomes. GH levels are not significantly affected, reinforcing the importance of nutritional recovery in managing growth failure.

Keywords: *Celiac Disease, idiopathic short stature, children, growth hormone, Systematic review.*

INTRODUCTION

CeD is a chronic inflammatory condition affecting the upper small intestine, triggered by an intolerance to gluten protein and commonly observed in individuals with a genetic predisposition. Gluten, a protein found in wheat, is widely consumed in Western diets, with an average intake ranging from 10 to 20 grams per person per day [1]. The classical presentation of CeD typically includes symptoms associated with malabsorption, such as diarrhea, steatorrhea, and unintended weight loss or impaired growth. In children, hallmark features often include persistent diarrhea, failure to thrive, muscle wasting, poor appetite, abdominal bloating, and, in some cases, emotional distress and lethargy [2].
Delayed puberty or short stature may be the initial signs of CeD. The likelihood of CeD in individuals presenting with isolated growth retardation or short stature ranges from 10% to 40% (9,10). In children, impaired growth due to CeD is primarily attributed to nutritional deficiencies, and significant improvements in height are often observed within two years of initiating a gluten-free diet [3].
CeD is marked by the production of autoantibodies in response to gluten exposure in genetically predisposed individuals. Current clinical guidelines agree that the most accurate and cost-effective initial serological test is the measurement of antibodies against tissue transglutaminase (tTG). While anti-endomysial antibodies (EMA) provide comparable diagnostic accuracy, this test relies on immunofluorescence, making it more subjective, operator-dependent, and costly [4]. An additional antibody test, targeting deamidated gliadin peptides, may be useful in patients

who test negative for standard CeD antibodies but continue to exhibit strong clinical indicators of the disease—especially in children under two years of age [5].

Serological testing is the first step in evaluating individuals suspected of having CeD. If the test results are positive, a small intestinal biopsy is typically recommended to confirm the diagnosis, as advised by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [4]. However, updated guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) indicate that a biopsy may be unnecessary in patients with classic CeD symptoms, tTG levels exceeding ten times the upper limit of normal, positive EMA, and presence of the HLA-DQ2 or DQ8 gene variant. In asymptomatic but high-risk children, a confirmed diagnosis of CeD requires both positive serological tests and histological evidence from a biopsy. Importantly, both evaluations should be conducted while the individual is consuming a gluten-containing diet [5].

Idiopathic short stature in children, defined as height significantly below the average for age and sex without an identifiable medical cause, remains a diagnostic and management challenge in pediatrics. Among the potential underlying conditions, CeD has gained attention as a possible yet often overlooked contributor. CeD is an immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals. While it commonly presents with gastrointestinal symptoms, many pediatric cases manifest primarily through extraintestinal signs such as poor growth. In some children, idiopathic short stature may be the only clinical indication of CeD. However, reported prevalence rates of CeD among children with idiopathic short stature vary across studies, leading to uncertainty about the need for routine screening. A systematic evaluation of the available evidence is therefore necessary to clarify this association and inform clinical practice.

The objective of this systematic review and meta-analysis is to assess the relationship between CeD and idiopathic short stature in children. Specifically, the study aims to determine the pooled prevalence of CeD among children with idiopathic short stature and evaluate the strength and consistency of this association across different populations and research settings.

METHODOLOGY

STUDY DESIGN AND DURATION

This systematic review and meta-analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6]. The research process was initiated and completed in May 2024.

LITERATURE SEARCH

A comprehensive and structured search was performed across multiple databases, including PubMed, Web of Science, Scopus, ScienceDirect, and ClinicalKey, to identify relevant literature examining the association between CeD and idiopathic short stature in children. The search was limited to studies published in English. Customized strategies were applied to each database, using relevant keywords and MeSH terms such as "Celiac Disease," "short stature," "growth failure," "child," and "pediatric," combined using Boolean operators (AND, OR, NOT) to optimize search sensitivity and specificity.

STUDY SELECTION AND DATA EXTRACTION

The search results were independently screened and verified by two reviewers using Rayyan (QCRI) [7]. Titles and abstracts were reviewed based on predefined inclusion and exclusion criteria. Eligible full-text articles were thoroughly assessed, and disagreements were resolved through discussion. A standardized data extraction form was used to collect the following information: author(s), year of publication, country, study design, sample size, mean age, method of CeD diagnosis (serological or histological), prevalence of CeD, and criteria used to define idiopathic short stature.

SELECTION CRITERIA

Studies were included if they: (1) involved children diagnosed with idiopathic short stature, (2) reported on the prevalence or diagnosis of CeD within that population, and (3) used clinical, serological, or histological criteria to confirm CeD. (4) Studies published within the last five years (2020-2025). Studies focusing on populations with identified causes of short stature other than CeD were excluded.

RISK OF BIAS ASSESSMENT

The quality of non-randomized studies included in the meta-analysis was evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool [8]. The assessment addressed potential bias in seven domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of reported results.

STATISTICAL ANALYSIS

Data were analyzed using Comprehensive Meta-Analysis software (Version 3.0) [9]. A random-effects model was chosen to account for expected variability across studies. Statistical significance was defined as $P < 0.05$. Sensitivity analyses were conducted by sequentially excluding individual studies to assess their impact on the overall effect estimate. Heterogeneity among studies was evaluated using Cochran's Q statistic and the I^2 index. A significant Q ($P < 0.05$) indicated heterogeneity, while I^2 values quantified the proportion of total variation across studies due to real differences rather than sampling error [10,11].

RESULTS

SEARCH RESULTS

Following an extensive search, a total of 806 articles were identified. After removing 411 duplicates, 395 records remained for title and abstract screening, of which 242 were excluded. Of the four full-text reports requested, two could not be retrieved. Fifty-one articles were assessed in full, resulting in the exclusion of 27 due to irrelevant study outcomes, 10 due to ineligible population types, one editorial letter, and two abstracts. Ultimately, 11 studies met the inclusion criteria and were incorporated into the analysis. A summary of the study selection process is illustrated in **Figure 1.**

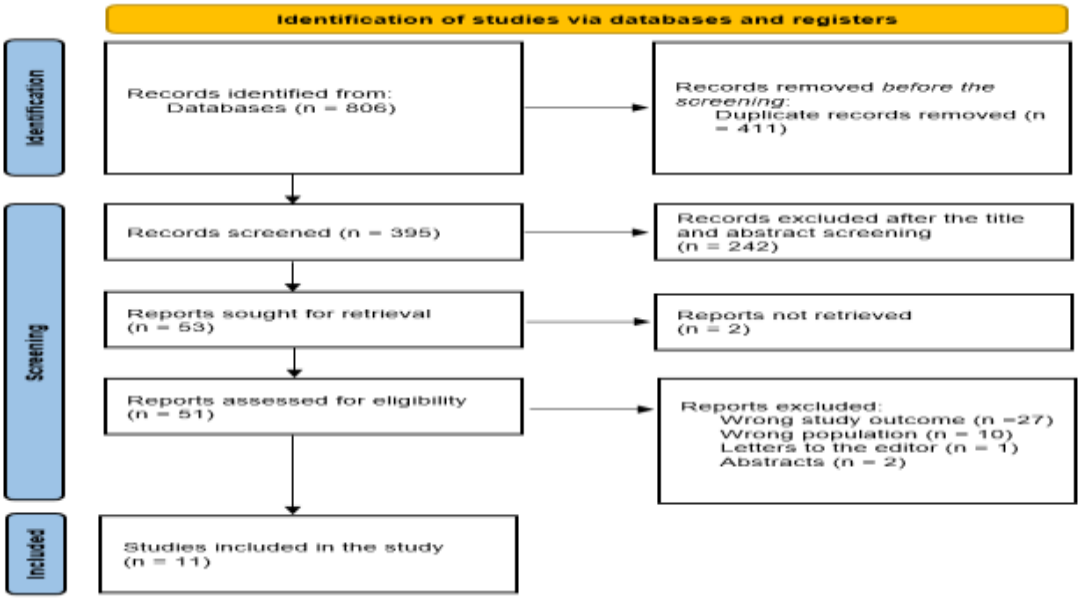

Figure (1): Study selection is summed up in a PRISMA flowchart.

CHARACTERISTICS OF THE INCLUDED STUDIES

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included eleven studies with a total of 1873 children with short stature and 946 (50.5%) of them were males. Ten studies were observational cross-sectional studies [12, 14-22], and one study was a retrospective cohort [13]. Four studies were conducted in Pakistan [14, 16, 19, 21], two in Saudi Arabia [13, 18], two in Egypt [15, 17], two in Iraq [12, 22], and one in India [20].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age/ range	Males (%)	Diagnosis of celiac	ROBIN-II
Hayawi, 2020 [12]	Observational cross-sectional	Iraq	177	3 - 17	107 (69.4%)	Biopsy positive	Moderate
Saadah et al., 2020 [13]	Retrospective cohort	Saudi Arabia	275	9.4 ± 4	151 (54.9%)	Biopsy/ serology positive	Moderate
Jalil et al., 2023 [14]	Observational cross-sectional	Pakistan	149	10.2 ± 3.1	80 (53.7%)	Serology positive	Moderate
Sayed Hemeda et al., 2020 [15]	Observational cross-sectional	Egypt	100	6.7 ± 2.8	48 (48%)	Serology positive	Moderate
Muhammad et al., 2022 [16]	Observational cross-sectional	Pakistan	151	5 - 16	76 (50.3%)	Serology positive	Low
Abdel-Megeid et al., 2024 [17]	Observational cross-sectional	Egypt	100	10.37±3.28	58 (58%)	Serology positive	Low
Saadah, 2020 [18]	Observational cross-sectional	Saudi Arabia	351	9 ± 3.7	199 (56.7%)	Serology positive	Moderate
Masood et al., 2020 [19]	Observational cross-sectional	Pakistan	300	2 - 15	126 (42%)	Serology positive	Moderate
Mahli et al., 2024 [20]	Observational cross-sectional	India	40	2 - 18	14 (35%)	Biopsy/ serology positive	Moderate
Javed et al., 2023 [21]	Observational cross-sectional	Pakistan	151	7.7±3.3	50 (33.1%)	Serology positive	Moderate
Abdullah & Mahmood, 2024 [22]	Observational cross-sectional	Iraq	79	8.3±3.3	37 (46.8)	Serology positive	Moderate

*NA=Not-applicable

META-ANALYSIS OF PRIMARY EFFECT SIZE

RESULTS OF T1D

A meta-analysis of 10 eligible studies involving 1696 children showed a pooled event rate was 22.7% (95% CI: 20.6% to 25.0%), indicating that nearly one in five children with idiopathic short stature tested positive for CeD-specific serological markers **Figure (2).** Significant heterogeneity was observed among the included studies, as indicated by a Cochran's Q value of 93.31 with 9 degrees of freedom ($P < 0.001$). The I^2 statistic was 93.3%, reflecting considerable heterogeneity across studies. This suggests that the variation in effect sizes is unlikely to be due to chance alone. The between-study variance (Tau-squared) was estimated at 0.600, with a corresponding Tau value of 0.774, indicating substantial variability in the true effects **Figure (5A).**

In 4 eligible studies involving 843 children showed a pooled event rate was 14.8% (95% CI: 12.1% to 18.0%), indicating that approximately one in seven children with idiopathic short stature had CeD confirmed through histological examination **Figure (3).** Substantial heterogeneity was detected among the included studies, as evidenced by a Q-value of 75.879 with 3 degrees of freedom ($P < 0.001$). The I^2 statistic was 96.0%, indicating considerable heterogeneity across studies. The between-study variance (Tau-squared) was estimated at 1.611, with a Tau value of 1.269. The standard error and variance of Tau-squared were 1.524 and 2.322, respectively **Figure (5B).**

In 2 eligible studies involving 63 children showed pooled standardized mean difference was 0.023 (95% CI: -0.259 to 0.304), with a p-value of 0.874, indicating no statistically significant difference in GH levels between the two groups **Figure (4).**

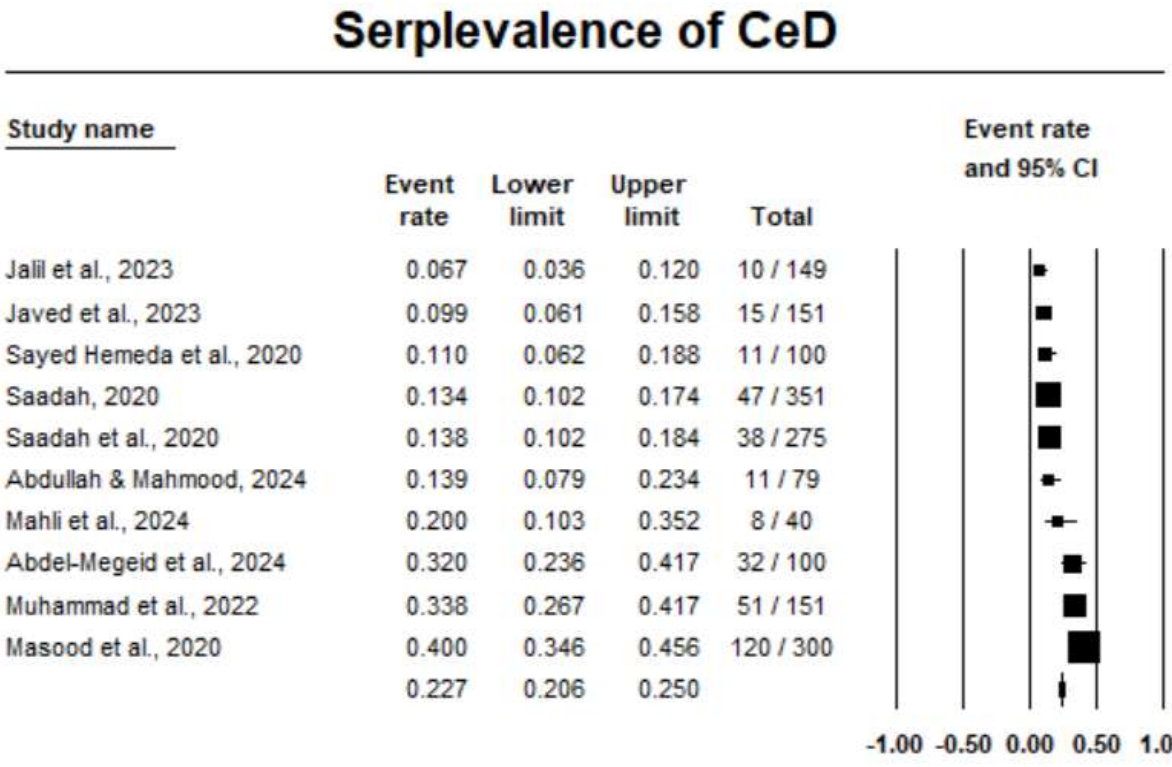

Figure (2): Forest plot of the seroprevalence of CeD in children with idiopathic short stature.

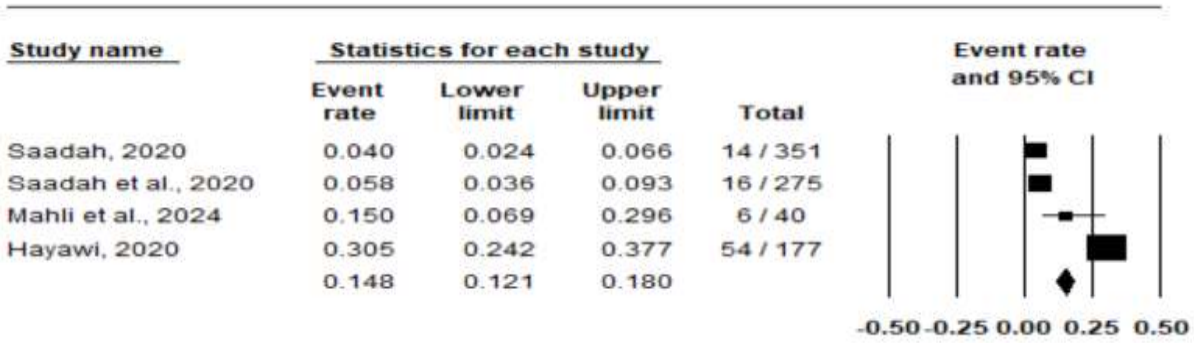

Figure (3): Forest plot of the biopsy-detected CeD in children with idiopathic short stature.

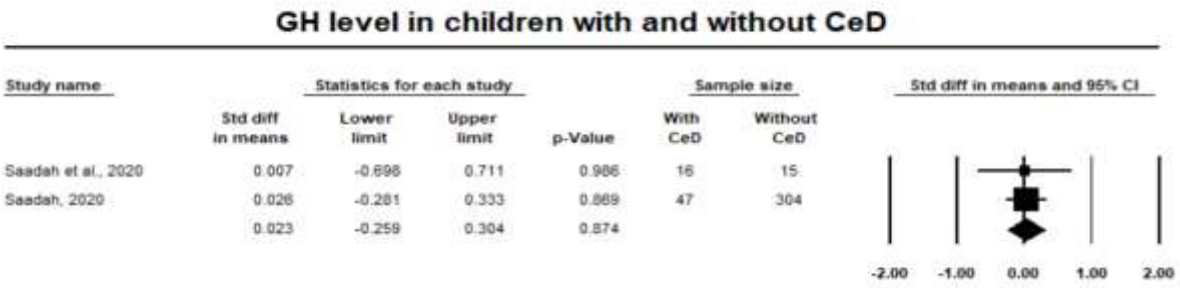

Figure (4): Forest plot of the difference of GH level between children with and without CeD.

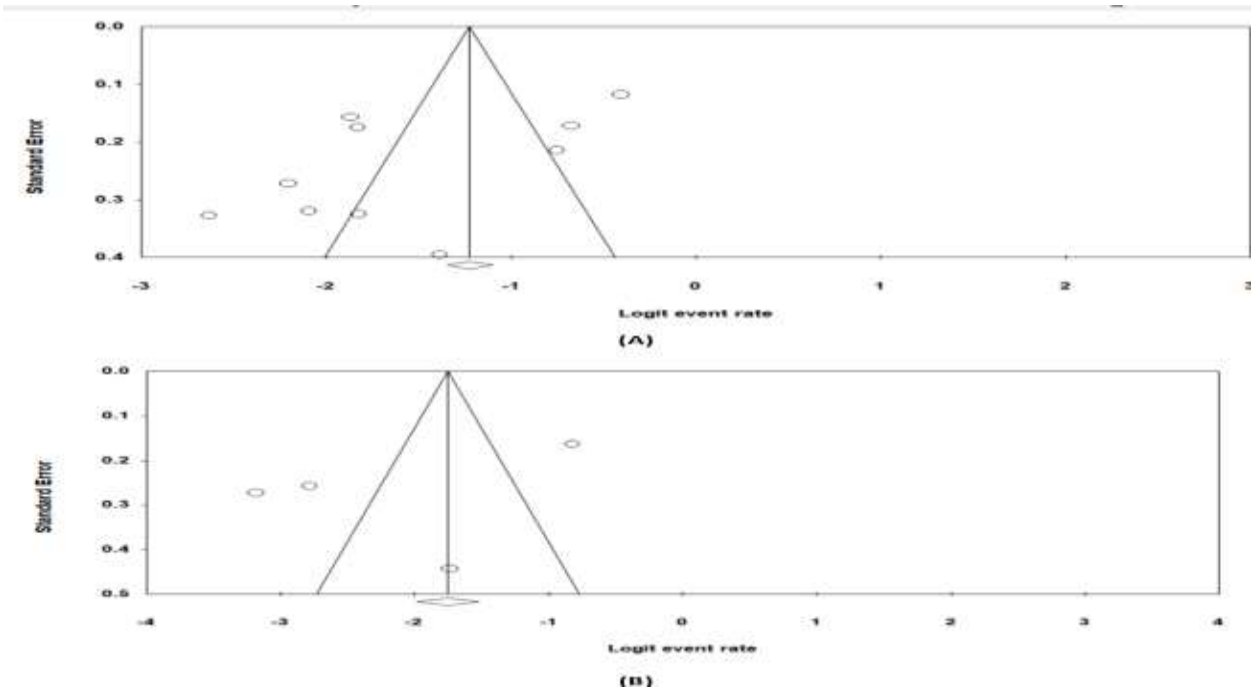

Figure (5): Funnel plot of the risk of bias assessment of the previously included studies.

DISCUSSION

This systematic review and meta-analysis assessed the association between CeD and idiopathic short stature in children, examining both seroprevalence and biopsy-confirmed prevalence, as well as the role of GH levels. The pooled seroprevalence of CeD among children with idiopathic short stature was 22.7%, highlighting that CeD is a relatively common yet potentially underdiagnosed cause of growth failure in pediatric populations.

Van Rijn and colleagues conducted a compilation of data on CeD prevalence among patients with short stature, reporting rates ranging from 1.7% to 8.3% in individuals who had not undergone prior evaluation for short stature, and higher rates ranging from 18.6% to 59.1% in those where endocrine causes had already been ruled out [23]. Notably, many of the studies analyzed in their review were published before standardized diagnostic criteria for CeD were established [24].

Biopsy-confirmed CeD in our analysis was found in approximately 14.8% of cases, further validating this relationship through histological evidence. More recently, a systematic review focused on the prevalence of CeD among children with short stature in Saudi Arabia reported a pooled seroprevalence of 16.1%, with biopsy-confirmed prevalence estimated at 6.75% [25]. Among the five studies included in that review, only one overlapped with the studies incorporated into our current analysis [26].

While CeD is traditionally associated with gastrointestinal symptoms, these findings underscore that short stature may be the sole presenting feature in some children. The variation in prevalence among studies could be attributed to differences in sample size, diagnostic methods, and regional prevalence of CeD. Importantly, the analysis of GH levels between children with and without CeD showed no significant difference, suggesting that growth impairment in CeD is more likely related to nutritional deficiencies due to intestinal damage rather than GH deficiency. The underlying mechanisms linking CeD to short stature remain not fully understood. It is generally accepted that damage to the small intestinal mucosa leads to nutrient malabsorption, which contributes to impaired linear growth. Affected children commonly exhibit decreased levels of insulin-like growth factors (IGF1 and IGF2) and insulin-like growth factor binding protein-3 (IGFBP-3), along with elevated levels of IGFBP-1 and IGFBP-2, and a diminished GH response to stimulation. Studies have demonstrated a significant inverse correlation between the duration of gluten exposure and circulating IGF1 levels, with prolonged exposure to gluten associated with a reduction in IGF1 even before the onset of measurable growth failure [27]. These hormonal patterns closely resemble those seen in children suffering from chronic malnutrition [27, 28]. Upon adherence to a gluten-free diet, re-assessment of the somatotropic axis has shown prompt improvement, characterized by increased concentrations of GH binding protein (GHBP), IGF1, IGF2, and IGFBP-3, along with a decline in IGFBP-1 levels. These shifts indicate enhanced GH sensitivity and a progressive normalization of growth-related endocrine function [27, 29].

The findings support the inclusion of CeD screening in the diagnostic workup of children presenting with idiopathic short stature, even in the absence of gastrointestinal symptoms. Early identification of CeD through serological testing, followed by confirmatory biopsy if needed, can allow timely initiation of a gluten-free diet, potentially leading to significant improvements in growth and overall health. Routine screening may prevent unnecessary endocrine evaluations and expedite appropriate intervention.

STRENGTHS AND LIMITATIONS

One of the strengths of this meta-analysis lies in its focus on a clearly defined pediatric population with idiopathic short stature, assessing both serological and biopsy-confirmed CeD using a consistent analytical approach. The use of a fixed-effect model allowed for a more precise estimate of the overall effect size by assuming a common true effect across studies, which is appropriate given the relatively similar design and outcome measures among the included studies. Additionally, the analysis incorporated both clinical and laboratory endpoints, including GH comparisons, offering a comprehensive perspective on the relationship between CeD and growth impairment.

However, this review also has limitations. Most of the included studies were cross-sectional in design, which limits the ability to establish causal relationships between CeD and idiopathic short stature. The cross-sectional nature also introduces potential selection and reporting bias, as temporal associations cannot be determined. Furthermore, variations in diagnostic criteria, serological cutoffs, and biopsy thresholds across studies may have introduced subtle inconsistencies. Finally, although the fixed-effect model provides precise estimates under the assumption of homogeneity, it may not fully account for unmeasured variability between study populations or settings.

CONCLUSION

This meta-analysis highlights a strong association between CeD and idiopathic short stature in children. The findings emphasize that CeD is a commonly overlooked but important cause of unexplained growth failure in the pediatric population. While classical gastrointestinal symptoms may be absent, many children with CeD present solely with poor linear growth. The absence of significant differences in GH levels between children with and without CeD suggests that the growth impairment is not due to hormonal deficiency but rather to malabsorption and chronic intestinal inflammation. These insights support the inclusion of routine CeD screening in the clinical evaluation of children with idiopathic short stature. Early identification and dietary intervention can significantly improve health outcomes and reduce the need for unnecessary hormonal investigations.

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