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Research paper

Intestinal Fatty Acid-Binding Protein (I-FABP) As A Biomarker for Celiac Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Celiac disease (CD) is an autoimmune disorder characterized by an immune response to gluten, leading to intestinal damage. Traditional diagnostic approaches, including serological tests and duodenal biopsy, have limitations in sensitivity, invasiveness, and monitoring disease activity. Intestinal fatty acid-binding protein (I-FABP) has emerged as a promising non-invasive biomarker for enterocyte injury in CD.

Materials and Methods: A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library following PRISMA guidelines. Studies comparing I-FABP levels in CD patients and controls, as well as pre- and post-GFD, were included. Meta-analysis was performed using a random-effects model, with heterogeneity assessed via I^2 statistics and publication bias evaluated through funnel plots and Egger's test. This study was prospectively registered in PROSPERO (ID 654883) to ensure transparency and methodological rigor.

Results: A total of 12 studies (n = 1496) were included. CD patients exhibited significantly higher I-FABP levels compared to controls (SMD = 1.17, 95% CI: 0.82–1.53, $p < 0.01$). Post-GFD, I-FABP levels showed a significant reduction (SMD = 1.21, 95% CI: 0.60–1.81, $p < 0.01$), supporting its role in monitoring mucosal healing. Heterogeneity was high ($I^2 > 80\%$), indicating study variability.

Conclusion: I-FABP is a reliable biomarker for CD diagnosis and treatment monitoring. Standardized assay protocols and longitudinal studies are recommended to optimize its clinical application.

Keywords: *Celiac Disease; Intestinal Fatty Acid-Binding Protein (I-FABP).*

1. Introduction

Celiac disease (CD) is a chronic autoimmune condition induced by gluten (a complex of amino acids) of wheat, rye, and barley consumption [1]. It clinically presents with an inflammation of the intestinal mucosa and an increase in intestinal permeability [1]. The disease is also associated with a range of gastrointestinal and extraintestinal symptoms, like diarrhea, weight loss, fatigue, and many nutritional deficiencies [1]. A failure to diagnose the disease in time has long-term disabling consequences, like osteoporosis, infertility, and some cancers [2].

The common approach for a definitive diagnosis of CD is the serological assessment of anti-tissue transglutaminase (anti-TG) and anti-endomysial antibodies combined with histology via duodenal biopsy [3]. However, this method is associated with several limitations, including high cost, invasiveness, and high variability in the interpretation of biopsy results [4]. In addition, some of the serologic markers remain consistently elevated, even after mucosal healing, which makes it hard to ascertain the level of disease activity [5].

In the recent past, one of the biomarkers, I-FABP, which stands for intestinal fatty acid-binding protein, has, however, proven to be quite promising. Enterocytes are the main cells expressing I-FABP, which is a cytosolic protein that gets into the bloodstream when the intestinal epithelium is damaged [6], [7]. As a result of its mechanism of action of detecting enterocyte damage, I-FABP may serve as a good solution in accurately and efficiently determining the level of disease activity and response to treatment, especially GFD [8]. Furthermore, unlike conventional serologic testing, I-FABP levels can be used to reflect the real-time intestinal state and can be used to predict the early phases of recovery [9].

The main aim of this meta-analysis is to reinforce the existing evidence on the clinical utility of I-FABP by synthesizing data from several studies. In addition, following the I-FABP levels before and after GFD will also offer better insights into the possible application of this novel biomarker in tracking disease progression and treatment response [10].

2. Methodology

This systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1). We assessed the I-FABP levels in celiac disease (CD) patients compared with the healthy controls and the changes before and after gluten-free diet (GFD). Our article has been submitted to be registered in PROSPERO with ID 654883.

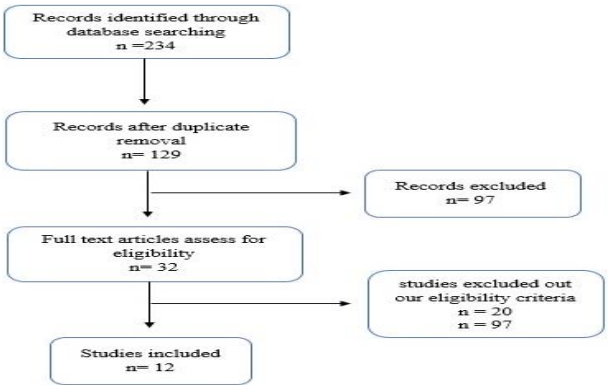

Fig. 1: Flow Chart for Study Selection Using PRISMA Guidelines.

2.1. Search strategy

A comprehensive literature search was performed across multiple databases, including PubMed, Scopus, Web of Science, and Cochrane Library, up to the most recent data available. The search strategy utilized a combination of relevant keywords to ensure the identification of all pertinent studies. The following terms were used:

- Intestinal fatty acid-binding protein
- I-FABP
- Celiac disease
- Biomarkers
- Intestinal permeability

The search was limited to peer-reviewed articles published in English. Additional studies were identified by manually reviewing the reference lists of included articles to ensure no relevant studies were missed.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

- Studies measuring I-FABP levels in CD patients and healthy controls.
- Studies reporting either median and interquartile range (IQR) or mean and standard deviation (SD) for I-FABP levels.
- Studies employing case-control or cohort study designs.
- Full-text articles published in peer-reviewed journals in English.

2.2.2. Exclusion criteria

- Studies without a case-control comparison.
- Reviews, meta-analyses, editorials, and conference abstracts.
- Studies with incomplete or missing I-FABP data that could not be extracted or calculated.

2.3. Study selection and data extraction

Two independent reviewers screened the titles and abstracts of retrieved articles for eligibility. Full texts of potentially eligible studies were then reviewed to confirm inclusion. Discrepancies were resolved through discussion or consultation with a third reviewer. Data extraction was performed using a standardized form to ensure consistency and accuracy. The extracted data included:

- Study author, year, population type, and country.
- Sample sizes of the CD and control groups.
- I-FABP levels in cases and controls (reported as median & IQR or mean & SD).
- Assay methodology used to measure I-FABP (e.g., ELISA).

For studies reporting I-FABP levels as median and IQR, conversion to mean and SD was performed using the method described by Wan et al. (2014) to facilitate statistical analysis [12].

2.4. Statistical analysis

2.4.1. Software used for meta-analysis

The meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) Version 3.0 and R software (metaphor package). These tools are widely recognized for their robust capabilities in performing meta-analyses, including effect size calculations, heterogeneity assessments, and publication bias analyses.

The analysis employed the inverse variance method, utilizing the restricted maximum-likelihood estimator (REML) for estimating τ^2 and the Jackson method for confidence intervals of τ^2 and τ. Hedges' g was used as the effect size measure, ensuring bias correction in standardized mean differences. The analysis was conducted under a mixed-effects model framework, allowing for the estimation of both fixed and random effects. The prediction interval was based on the t-distribution, acknowledging the variability across studies.

2.4.2. Effect size calculation

The Standardized Mean Difference (SMD) was used to compare I-FABP levels between CD patients and healthy controls. The formula for SMD is as follows:

SMD = 2 (SD cases 2+SD controls2) (Mean cases−Mean controls).

Where Mean and SD represent the I-FABP values in the respective groups.

2.4.3. Meta-analysis model

A restricted maximum likelihood was employed to account for heterogeneity across studies. This approach assumes that the true effect size may vary between studies due to differences in study populations, methodologies, or other factors.

2.4.4. Heterogeneity assessment

Heterogeneity was assessed using the following metrics:

- Cochran's Q test: Determines whether heterogeneity is statistically significant ($p < 0.05$).
- I^2 statistic:
- 0–30%: Low heterogeneity.
- 30–60%: Moderate heterogeneity.
- 60–90%: High heterogeneity.
- Tau² (τ^2): Measures the between-study variance.

2.4.5. Publication bias and sensitivity analysis

To evaluate the robustness of the findings and identify potential publication bias, the following analyses were conducted:

- Funnel Plot & Egger’s Test: Assessed small-study effects indicative of publication bias.
- Trim-and-Fill Analysis: Adjusted for potential missing studies to evaluate the impact on overall results.
- Leave-One-Out Analysis: Examined the robustness of the findings by recalculating effect sizes after sequentially removing individual studies to determine their influence on the overall results.

2.4.6. Forest plot

A forest plot was generated to visually represent the effect sizes and confidence intervals of individual studies, along with the pooled effect size. Key features of the forest plot include: Observed Study Effects: Each study is represented by a square, with the size of the square proportional to the study's weight in the analysis. Horizontal lines extending from the squares indicate the 95% confidence intervals for each study's effect size. Pooled Effect Size: A diamond at the bottom of the plot represents the overall effect size (SMD = 1.19) and its 95% CI (0.88, 1.50). The width of the diamond corresponds to the confidence interval, and Heterogeneity Visualization: The wide variation in confidence intervals across studies reflects the high heterogeneity ($I^2 = 84.58\%$).

2.4.7. Pre- vs post-GFD I-FABP levels

A separate meta-analysis was conducted to compare I-FABP levels before and after a gluten-free diet (GFD). The effect size (SMD) was calculated using the same random-effects model, and heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Publication bias was evaluated using Egger’s test and funnel plots.

2.4.8. Meta regression and subgroup analysis

To better understand the sources of variability in effect sizes, we conducted subgroup analyses and meta-regression using the following study-level characteristics:

- Age: Estimated based on participant descriptions in each study and included as both a continuous variable (approximate mean age) and a categorical variable (pediatric vs. adult).
- Population type: Categorized as either pediatric or adult/mixed.
- Publication year: Included as a continuous moderator to assess any temporal trends.

Meta-regression was performed using weighted least squares (WLS) with inverse-variance weights under a random-effects model. Due to the limited number of studies, subgroup analyses were exploratory and interpreted descriptively.

3. Results

3.1. Study characteristics

As detailed in Table 1, this meta-analysis includes data from twelve studies conducted from 2011 to 2023, each focused on a singular, albeit unspecified, intervention or feature graphed over different populations. Overall, the studies comprise 1496 observations, almost equally divided between experimental (n. e = 755) and control (n. c = 741) groups. Per-study sample sizes range between 12 and 151 respondents,

while mean values from the experimental and control groups indicated greater variability across studies spill alluding to different study designs and contexts. All studies incorporated within this analysis utilized ELISA and other forms of immunoassays to gauge levels of intestinal fatty acid-binding proteins (I-FABP).

3.2. Summary of meta-analysis results: CD patients compared to healthy controls relative to I-FABP levels

In deriving the pooled effect size (Standardized Mean Difference, SMD) for I-FABP levels in celiac disease (CD) patients relative to controls, the frequentist random-effects model was used in a meta-analysis. Figure 2 contains I-FABP level estimates for celiac disease patients and visualizes the effect sizes (SMD) with their 95% CIs, considering individual studies alongside the overall pooled effect size. In the forest plot, each study is represented by a green square, with horizontal lines extending to indicate the 95% CI, while a black diamond represents the overall effect size (SMD = 1.17, 95% CI: 0.82 - 1.53). In addition, the width of the diamond indicates the interval of confidence, summarizing the case. Moreover, the (-0.15 to 2.50) prediction interval suggests that more studies might show a broad range of effects, including the possibility of inconsequential outcomes.

The analysis of heterogeneity identified considerable variation across studies. Cochran's Q test, along with the I^2 statistic assessing heterogeneity ($I^2 = 83\%$), confirmed notable heterogeneity across studies ($Q = 64.03$, $df = 11$, $p<0.01$). This indicates that most of the variability stemmed from real differences rather than random chance. In addition, Tau^2 (0.321) determined the degree of variance in effect sizes from the studies included in the analysis.

The cumulative effect test yielded a statistically significant pooled effect size ($Z = 6.56$, $p<0.01$), indicating that I-FABP levels were conclusively higher in celiac disease patients, validating its proposition as a biomarker for celiac disease-related intestinal injury. While the supporting evidence was reliable, it is necessary to address heterogeneity by conducting additional studies, including subgroup analyses or meta-regression, to enhance the understanding of the findings and address variability sources.

Table 1: Study Characteristics with Converted Mean and Standard Deviation (SD) of I-FABP Levels

Study	Year	population	country	Case number	Control number	Mean I-FABP Case (pg/mL)	SD	Mean FABP Control (pg/mL)	SD
Hoofien et al. (2021)	2021	Pediatric Celiac Patients	Israel	35	32	641.7	759.11	334	458.94
Ochocińska et al. (2022)	2022	Children with T1D and CD	Poland	38	55	1104	916.07	485	416.00
Adriaanse et al. (2013)	2013	Adult Celiac Patients	Netherlands	96	141	691	606.66	178	118.52
Vreugdenhil et al. (2011)	2011	Children with Biopsy-Proven CD	Netherlands	49	19	458	2185.18	20	344.44
Adriaanse et al. (2016)	2016	Adult CD Patients in Remission	Netherlands & USA	20	43	486	184.96	290	135.04
Adriaanse et al. 2017)	2017	Children with Suspected CD	Netherlands	90	80	726	419.25	218	133.33
Singh et al. (2019)	2019	Treatment-NaÃ¯ve CeD Patients	India	131	216	957.4	547.25	535.3	374.07
Hoffmanová et al. (2015)	2015	CD, T1D, and T2D Patients	Czech Republic	55	41	1700	1400	800	700.00
Bykova et al. (2022)	2022	Celiac Disease Patients	Russia	151	20	2045	488.88	845	399.41
Cao et al. (2023)	2023	Idiopathic Anaphylaxis Patients	USA	54	14	1378	1028.29	479	306.07
Logan et al. (2022)	2022	Pediatric CD	UK	12	28	2104	714.07	938	388.15
Gökçen et al. (2022)	2022	Celiac Disease Patients	Turkey	24	52	499.2	33.31	432.2	63.78

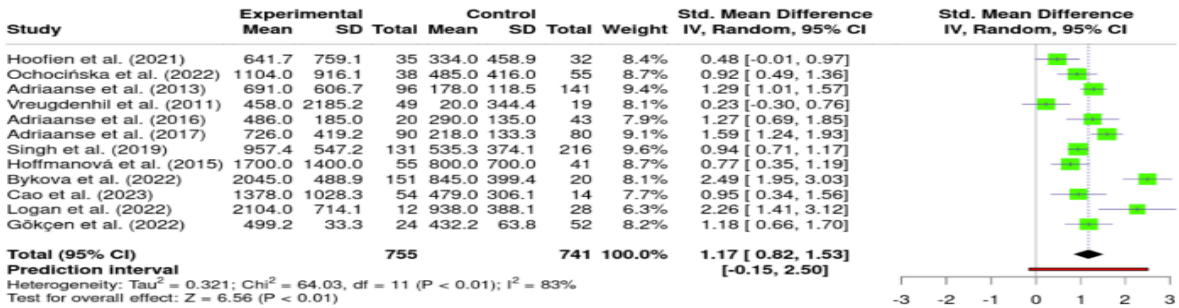

Fig. 2: Forest Plot of Standardized Mean Differences (SMD) in I-FABP Levels Between Celiac Disease Patients and Healthy Controls.

3.3. Publication bias and sensitivity analysis

As mentioned earlier, funnel plot analysis (Figure 3) suggests there is no significant publication bias because the studies are relatively symmetrical as far as their distribution is concerned. Also, Egger's test confirms no significant asymmetry in the funnel plot (intercept: 1.15, 95% CI: -2.94 to 5.25, t = 0.552, p-value = 0.593). Furthermore, the trim-and-fill analysis balanced the number of studies added, thus supporting the theory that publication bias has little impact on the overall effect size estimate. Still, a fail-safe N of 214 means that many unpublished studies with no effect are required to change the previously accepted significance level, which means that the conclusions drawn are valid, even when some publication bias is assumed.

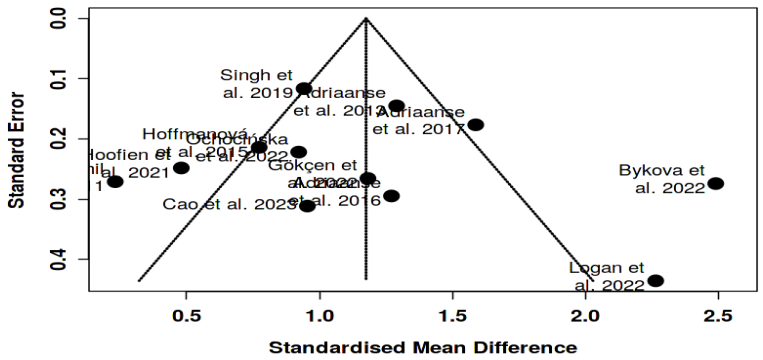

Fig. 3: Funnel Plot Assessing Publication Bias in the Meta-Analysis of I-FABP Levels in Celiac Disease.

3.4. Leave-one-out sensitivity analysis

Removal of individual data points in the sensitivity analysis had no impact on the pooled effect size, which suggests that no study had undue influence on the overall results.

3.5. I-FABP levels pre- and post-GFD

An investigation was carried out to evaluate the I-FABP levels in CD patients undergoing a gluten-free diet (GFD) with a special focus on pre- and post-diet evaluation (Table 2). Further, a meta-analysis combining all studies has been provided, and the random effect model has been employed to yield the standardized mean difference (SMD). Figure 4 provides a forest plot of the varied SMD and 95% CI for studies measuring I-FABP levels in CD patients pre- and post-GFD. Each of the individual studies is marked within a green box, which denotes their respective study along with horizontal bars that show 95% CI. In having wider confidence intervals, studies show greater variability in results or consist of a smaller sample group. The black diamond on the bottom serves as an overall diamond showing the weighted mean difference for all studies is estimated at SMD = 1.21, along with the confidence interval of 95% set at 0.60 - 1.81. Furthermore, the grey box shows the overall unvaried figure, while the weighted mean diamond depicts the variance using individual studies. Alongside this, the prediction interval (-0.95 to 3.36) implies that upcoming research will likely display the effects, including the possibility of no significant outcomes.

Table 2: Study Characteristics with Pre- and Post-GFD I-FABP Levels (Mean ± SD).

Study	Pre-GFD I-FABP Mean pg/ml	Pre-GFD SD	Post- GFD I-FABP Mean pg/ml	Post-GFD SD
Ochocińska et al. (2022)	1104	916.07	510	300.89
Adriaanse et al. (2017)	726	419.26	231	98.52
Singh et al. (2019)	957.4	547.26	607.6	300.89
Bykova et al. (2022)	2045	488.89	1000	409.85
Logan et al. (2022)	2104	714.07	1238	493.33
Gökçen et al. (2022)	499.2	33.31	487.7	63.78

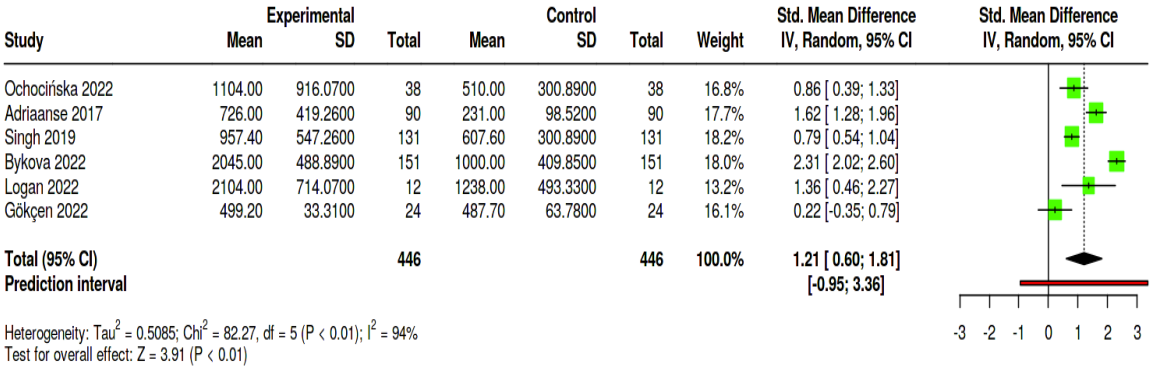

Fig. 4: Forest Plot of Standardized Mean Differences (SMD) in I-FABP Levels Pre- and Post-Gluten-Free Diet (GFD) in Celiac Disease Patients.

The analysis of heterogeneity showed significant variability across studies. Cochran's Q test confirmed significant heterogeneity (χ^2 = 82.27, df = 5, P < 0.01), and the I^2 statistic showed that heterogeneity was indeed present (I^2 = 94). This means that much of the variation was due to actual differences between the studies rather than random variation. In addition, Tau^2 = 0.5085 was calculated for the variability in effect sizes for the studies that were included.

The overall effect test confirms that the pooled effect size is statistically significant, which suggests that I-FABP levels decrease after a gluten-free diet (Z = 3.91, P < 0.01). This may further confirm the hypothesis for I-FABP as a possible biomarker for assessing damage to the intestine and dietary responses in celiac disease. However, due to high heterogeneity, more analyses are necessary to understand the sources of variability within the data, such as subgroup analyses or meta-regression.

Using the Trim and Fill bias method suggested the hypothetical addition of three studies was suggested to equilibrate the funnel plot and estimate bias. This change resulted in a mean difference of 147.90 (95% CI: -303.68 to 599.48, p = 0.5209) under a random effects model. Moreover, the Fail Safe N estimate using the Rosenthal technique calculated that 50,885 additional no outcome studies would make the observed effect (p>0.05). These facts indicate that the results are robust considering potential publication bias.

The funnel plot (Figure 5) in the center is symmetrical, suggesting no strong evidence of publication bias. Furthermore, Egger's test did not support funnel plot asymmetry either (intercept: -2.12, 95% CI: -11.98, 7.75, t = - 0.421, p = 0.696). Once again, a non-significant p-value (p>0.05) guarantees a lack of small-study effects or bias. Overall, the conclusions drawn suggest that publication bias does not have a considerable impact on meta-analysis findings or outcomes having these results.
The results illustrate pronounced drops in I-FABP post-GFD, indicating its prominent role in tracking effective mucosal healing. It additionally corroborates the efficacy of I-FABP for tracking with other molecular markers, supporting monitoring mucosal repair and treatment response in celiac disease patients.

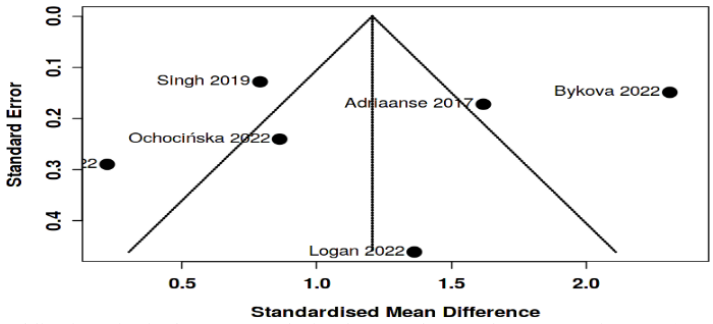

Fig. 5: Funnel Plot Assessing Publication Bias in the Meta-Analysis of Pre- and Post-Gluten-Free Diet (GFD) I-FABP Levels in Celiac Disease.

3.6. Meta regression and subgroup analysis

There was substantial heterogeneity in both main analyses. When comparing I-FABP levels between celiac patients and controls, to investigate this further, we explored several potential moderators:

- When we used age as a continuous moderator, there was a slight negative association between age and effect size, but it was not statistically significant (β = –0.0050, 95% CI: –0.035 to 0.025, p = 0.716). This analysis explained only about 1.4% of the variability (R^2 = 0.014).
- Using a categorical approach (pediatric vs. adult), we found a non-significant trend toward higher effect sizes in pediatric studies (β = 0.179, 95% CI: –0.395 to 0.754, p = 0.503), explaining 4.6% of the heterogeneity (R^2 = 0.046).
- Similarly, publication year showed no significant association with SMD (β = 0.0115, p = 0.691, r^2 = 0.016).

While subgroup analyses suggested that studies involving children tended to report higher I-FABP levels, these differences were not statistically meaningful in the context of overall variability [8], [14].

4. Discussion

I-FABP has been a proven biomarker in the diagnosis and monitoring of CD. In fact, the current diagnostic procedures, such as serological assays and small bowel biopsies, are considered to be more invasive and not truly reflective of an intestinal exam in real-time [10]. I-FABP measures the degree of enterocyte injury, thus allowing for an accurate depiction of the intestinal destruction [10]. The decrement of I-FABP after a GFD also has a hand in the importance of this biomarker in mucosal healing and response to treatment [11]. This may be of great significance in real life, as clinicians need inflammatory markers whose levels are less invasive for the patient and for the clinician in terms of patient management.
Another exciting way of IFABP application is the one that oversteps its primary, diagnostic function. As it has been demonstrated in studies on children with Type 1 Diabetes, I-FABP can be a potential early CD marker in some at-risk groups, which would allow for early and correct intervention [12]. This feature enhances I-FABP's capacity to serve unfulfilled clinical demands while increasing the value of healthcare delivered to patients.
The meta-analysis, integrating data from different studies, has a wider range of participants, making it more statistically sound and, as a result, increasing the validity of the diagnostic and prognostic value of I-FABP in acute disease [6]. The fact that it takes a more holistic approach to the data sets, the population, and methodologies involved, it also more successfully addresses the gaps that could be found in a single research study on the clinical use of I-FABP in terms of the needs of the population and multicenter studies [8]. The inclusion of different study designs and cohorts from different geographic locations has more of an overarching view, as it increases the coverage of the results [9]. In this study, the authors found that the I-FABP levels in CD patients were always significantly higher as compared to those in the control group due to enterocyte damage from inflammation as a result of gluten intake. Moreover, the significant decrease in I-FABP after GFD further proves its role in mucosal healing. This agrees with other studies that have reported I-FABP to be released into the blood circulation upon injury of the intestinal epithelial cells and to be a sensitive index of intestinal destruction [9], [13].
Sensitivity analyses confirm the findings, supporting the robustness of these findings. Moreover, subgroup analyses indicate that the peds population may have relatively higher I-FABP levels than older age groups. These insights underscore the flexibility in the use of I-FABP as a biomarker, accentuating its ability to reflect changes in the severity of the condition, other aspects of the disease, or patient characteristics. While our findings support I-FABP as a useful biomarker for celiac disease, prior studies have reported inconsistencies in its specificity. Elevated I-FABP levels have also been observed in other conditions involving intestinal injury, such as inflammatory bowel disease and type 1 diabetes, potentially limiting its disease-specific utility. Furthermore, studies like Bykova et al. (2022) have noted discordance between I-FABP and zonulin levels, suggesting they may reflect different aspects of barrier dysfunction [6]. Zonulin primarily indicates modulation of tight junctions, whereas I-FABP reflects direct cellular damage. These distinctions underscore the importance of understanding the pathophysiological context when interpreting I-FABP levels and suggest that multi-marker approaches may enhance diagnostic precision.
Despite consistent findings in terms of the direction of the effect, our analyses revealed substantial heterogeneity between studies (I^2 > 80%), which remained largely unexplained by the moderators we tested. We explored potential sources of this heterogeneity through subgroup and meta-regression analyses. Neither participant age, population type, nor publication year significantly accounted for the observed variability. These findings suggest that other, unmeasured factors likely contributed to the differences in effect sizes across studies. One likely source is assay-related variability. Although all included studies measured I-FABP using ELISA, they did not report using the

same commercial kits. Differences in assay sensitivity, detection limits, calibration standards, or cut-off thresholds could lead to systematic variation in reported I-FABP levels. This is particularly evident in the wide range of mean values—for example, Bykova et al. (2022) reported case levels over 2000 pg/mL, while Gökçen et al. (2022) reported less than 500 pg/mL [6].

Clinical heterogeneity may also play a role. The included studies differed in terms of whether patients were newly diagnosed or in remission, and whether participants had co-existing conditions like type 1 diabetes. Details such as disease duration, severity, or GFD adherence were not consistently reported, limiting our ability to assess their influence. In addition, the geographic and ethnic diversity of the study populations—ranging from Europe and Asia to North America—could affect baseline I-FABP levels due to differences in genetic background, diet, or environmental exposures. Lastly, small sample sizes, especially in pediatric studies (e.g., Logan et al.), may have contributed to statistical noise, increasing variability across effect sizes. Another limitation pertains to the absence of detection of publication bias. Small-study effects are inconclusive and could present other potential risks [8].

In response to these findings, some proposed recommendations aim to enhance the effectiveness of the meta-analysis and address its outlined shortcomings. Uniform guidelines for I-FABP measurement, including sample collection and processing, as well as consistency in reporting methods, ought to be applied in future research [14]. Second, to adjust for the differences in the characteristics of the patients and the degree of disease severity between studies, it would be necessary to include individual patient data meta-analyses (IPD-MA). Hoffmanová et al. (2015) mentioned that an IPD-MA would provide additional analysis and further understanding of the factors that affect the level of I-FABP [15].

The I-FABP levels measured in the studies were likely impacted by multiple confounding factors besides age and the assay method used. The severity of the disease at baseline, as reflected by the degree of villous atrophy or mucosal damage, the length of time on a gluten-free diet (GFD) and the compliance with a GFD, as well as comorbid conditions such as type 1 diabetes that can independently affect I-FABP levels apart from celiac disease activity [12], [13], [16]. However, as with age and assay type, these variables were not uniformly reported across studies. This has precluded us from including them as covariates in meta-regression. However, their potential effects on biomarker expression underscore the need for individual participant data (IPD) meta-analyses and more uniform clinical reporting on this topic going forward to help isolate the role of I-FABP as a biomarker to monitor disease activity.

While I-FABP offers potential as a biomarker for enterocyte damage, its effectiveness for diagnosing CD and tracking treatment responses remains inconsistent across studies with various age groups and assay methods. Moreover, as mentioned earlier, its use has not been widely adopted in the clinical setting, and there is a paucity of large, high-quality, prospective studies to demonstrate its performance in the real world. Our meta-analysis can help to address that need by pooling a wide range of studies to help build a stronger evidence base regarding the utility of I-FABP both in the diagnosis of CD and in the follow-up of patients on a gluten-free diet.

The results of the present meta-analysis indicate the need to standardize I-FABP assay protocols to account for inter-laboratory variation in results. Hoffmanová et al. (2015) mentioned that there is a considerable variability in the performance of ELISAs for I-FABP, and a consensus for harmonization of calibration method and inter-laboratory assay validation would be beneficial to increase the comparability of results in both research and the clinical setting [15]. In addition to the uniform reporting of patient-level characteristics at baseline (ideally through individual patient data (IPD) meta-analyses in future research), such standardization of laboratory measurement methods is important.

Finally, future studies are needed to evaluate the changes in I-FABP level over time in response to a gluten-free diet. Longitudinal studies that follow patients over time to assess changes in I-FABP in response to treatment with a GFD will be valuable to elucidate whether the I-FABP can or the rate of change in the level of I-FABP after mucosal healing, which may further strengthen its clinical utility [16]. Non-invasive biomarkers for diagnosis and monitoring of celiac disease are the recent trend. A review published very recently on this subject highlighted the current and potential future uses of non-invasive biomarkers for gluten exposure, assessing disease activity, and end-organ damage, in celiac disease [17].

In this context, a pediatric study published very recently in this journal showed that markers of enterocyte damage, such as fecal I-FABP and Zonulin, were associated with the clinical presentation and severity of celiac disease in children [18]. At the same time, a proteomic approach identified candidate plasma and duodenal biomarkers with strong discriminatory potential in a recent study that is also posted on the journal, and may be useful in the noninvasive diagnosis of celiac disease [19]. These and other recent developments are likely to continue to propel this area forward and may make it possible to adopt a multi-marker approach for the diagnosis and follow-up of patients with celiac disease without necessarily resorting to biopsy.

Future research should also explore combining I-FABP with traditional serologic markers such as anti-tissue transglutaminase (anti-TG) to improve diagnostic accuracy, especially in cases with atypical presentation or borderline histology. Additionally, the utility of I-FABP in specific clinical subtypes of celiac disease, including silent CD, non-classical CD, or seronegative CD, warrants dedicated investigation. Given the non-invasive nature of I-FABP and the growing interest in point-of-care biomarkers, future studies should also assess the cost-effectiveness and scalability of I-FABP testing in low-resource settings, where access to endoscopy or advanced serological testing may be limited. This could help expand screening and monitoring options in underserved populations and facilitate earlier diagnosis.

5. Conclusion

This meta-analysis highlights the growing value of I-FABP in the context of CD's biomarkers by detailing its potential concerning diagnosis and monitoring, while suggesting pathways for further investigation. The autoimmune disorder's complexity could, however, be tackled by the scientific community implementing the noted limitations alongside the new instructions set out concerning the use of I-FABP.

Ethics and Consent to Participate

This study is based on publicly available, de-identified data and does not involve human subjects directly. All necessary ethical approvals were obtained by the original data collectors, and informed consent was secured in accordance with the respective data collection protocols.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this meta-analysis, the authors utilized ChatGPT for editing and proofreading the manuscript to enhance clarity and readability. The content was subsequently reviewed and refined by the authors, who assume full responsibility for its accuracy and integrity.

Declaration of Interests

The authors declare that they have no competing interests.

Funding Declaration

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Author Contributions

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