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Immunoglobulin a Deficiency in Coeliac Disease: A Scoping Review

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ABSTRACT

Coeliac disease (CeD) and immunoglobulin A deficiency (IgAD) frequently co-occur and share a genetic background within the HLA-DQ2 region. Although this has been known for decades, the underlying mechanisms linking the two conditions remain unclear. We conducted a scoping review to evaluate the prevalence, clinical characteristics, diagnostic challenges and histopathological features of IgAD in patients with CeD. Thirty-one studies published between 1985 and 2024 were included. IgAD was more prevalent among individuals with CeD, 1.4%–4.8% than in the general population, and CeD occurred in 5.9%–14.1% of patients with IgAD. Most patients presented with gastrointestinal symptoms, although selection bias was common. IgG-based serology remains essential for diagnosis and monitoring, but its reliability during follow-up is limited by the slow decline of antibodies. Histological findings indicate compensatory IgM and IgG responses and persistent mucosal immune activation. Improved strategies for diagnosis and long-term monitoring of patients with both conditions are warranted.

1 | Introduction

Coeliac disease (CeD) is a chronic inflammatory condition triggered by gluten, which affects the gastrointestinal tract and involves autoimmune mechanisms [1]. The histopathology in the small bowel is characterised by villous atrophy, crypt hyperplasia and inflammation. CeD is closely associated with specific genes and is primarily linked to the haplotypes HLA-DQ2.5 (encoded by DQA1*05:01/DQB1*02:01) or DQ8 (encoded by DQA1*03:01/DQB1*03:02) [2]. The prevalence of CeD among adults and children ranges from 0.5% to 2%, with an average of about 1% [3]. The immunoglobulin A tissue transglutaminase antibody (TGA-IgA) serves as the most prominent diagnostic biomarker for CeD; its diagnostic accuracy exceeds 95% [4].

Immunoglobulin A (IgA) is the dominant immunoglobulin in luminal secretions, such as saliva, tears, bronchial and nasal

mucosal secretions and mucous secretions of the small intestine. It has important roles in maintaining immune homeostasis in mucosal surfaces by binding microbes and regulating their sampling at the mucosal surface [5, 6]. This is a crucial step in developing regulation or tolerance to luminal antigens, whether food or microbial in origin. It also shapes the mucosal-associated microbiome and maintains mucosal barrier protection [7]. It is conceivable that a lack of IgA alters the microbiota and proinflammatory responses to pathogens.

Selective immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency, and has a prevalence of approximately 1 in 600 in the Western world [8, 9]. According to the current definition, the disorder is defined by serum IgA levels < 0.07 g/L with normal IgM and IgG levels in people > 4 years old [10]. When the serum IgA level is higher than 0.07 g/L but two standard deviations below normal for the age

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in question, the condition may be referred to as partial IgAD [8], which is not discussed here. A large proportion of individuals with IgAD are clinically asymptomatic, but the condition is associated with a higher risk of infections, allergies and autoimmune diseases [11, 12]. IgAD is a heterogeneous disorder arising from multiple underlying mechanisms, including abnormalities in B-cell proliferation and maturation, as well as genetic alterations involving chromosome 18 and genes such as JAK3, TACI, CXCR4, and STAT1 [13–15]. The defect in immune regulation involves a blockade of cytokine effects, in particular TGF β and IL-10 that regulate the switch between the initial + IgM + IgD B cell production to IgG and IgA [16, 17]. In addition, IgAD is genetically associated with the HLA region, in particular with HLA-B8, DR3 and DQ2 [18–20].

In clinical practice, IgAD may lead to negative results for TGA-IgA in serum when screening for CeD [21]. In addition, there is no definitive clinical procedure for diagnosing and monitoring patients with both conditions [22, 23].

On this background, we systematically evaluated the existing literature, particularly for the clinical and diagnostic challenges of IgAD in CeD, both in children and adults. Our findings may add to future discussions regarding clinical practices and patient management strategies for individuals with IgAD and CeD.

2 | Methods

2.1 | Study Design

This systematic scoping review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) reporting guidelines [24] (Supporting Information S1: Appendix 1). The protocol followed the Joanna Briggs Institute's (JBI) guidance on conducting scoping reviews [25]. The protocol was developed in consultation with the Centre for Evidence Based Medicine Odense and Cochrane Denmark and was made publicly available at the Open Science Framework [26].

2.2 | Search Strategy

We performed a literature search of MEDLINE, Embase, Cochrane Library, Web of Science and Scopus for all publications from inception to 19 June, 2024. No filters for study design and language were used. Supplementary searches for grey literature (i.e., not peer-reviewed) were conducted through one search on Google Scholar, of which the first 100 search results were assessed. In addition, the reference lists of publications citing them were assessed using the Web of Science. Authors of relevant conference abstracts were contacted to identify additional data.

The searches were conducted as a two block search. One block contained keywords related to CeD and the other one contained keywords related to IgAD. A librarian was consulted to ensure that all keywords and concepts were covered (Supporting Information S2: Appendix 2).

2.3 | Eligibility Criteria

The criteria for the inclusion of studies were:

1. Studies on humans (children and adults)
2. Studies investigating patients with both conditions (CeD and IgAD), which reported measures for the prevalence, clinical presentation, diagnostic challenges, or relevant pathology descriptions.
3. Randomised controlled trials, case-control studies, cohort studies (prospective or retrospective) and cross-sectional studies.
4. Studies published in English.

The exclusion criteria included the following:

1. Studies on animals
2. Studies with irrelevant information about patients with IgAD.
3. Studies aiming to test a commercial assay in populations with the primary outcome of diagnosis of CeD.

2.4 | Study Selection

References identified in the database registry and Google Scholar search were imported into Covidence. Duplicates were automatically removed. Two independent reviewers (K.B., C.C.) screened all remaining references at the title and abstract level. After initial screening, the studies considered eligible were evaluated in full length.

3 | Results

3.1 | Search Results and Study Selection

The study selection is summarised in the PRISMA flow diagram (Figure 1), including the identification and screening of the studies through the searches, the eligibility criteria and the inclusion and exclusion processes. 31 studies were included in the final analysis, of which three were conference abstracts. The authors of the conference abstracts were contacted. Only one of them responded, and there was no peer-reviewed publication.

3.2 | Summary of the Included Studies

The studies were published between 1985 and 2024. The population studies were from North and South America and from Europe.

Twelve studies were retrospective reviews of medical records, nine were case-control studies, seven were cross-sectional studies, and three were prospective studies.

We sorted the outcome of the full-length evaluations into the following subheadings: Prevalence, pathogenesis, histology, clinical findings and follow-up. Each study was included in one or more subheadings.

In line with the scoping review format, no formalised bias analysis or meta-analysis was performed. A forest plot illustrating the prevalences was constructed.

3.3 | Prevalence

The prevalence of IgAD in CeD populations ranged from 1.4% (95% CI: 0.9%–2.0%) [11] to 4.8% (95% CI: 2.2%–7.4%) [27]

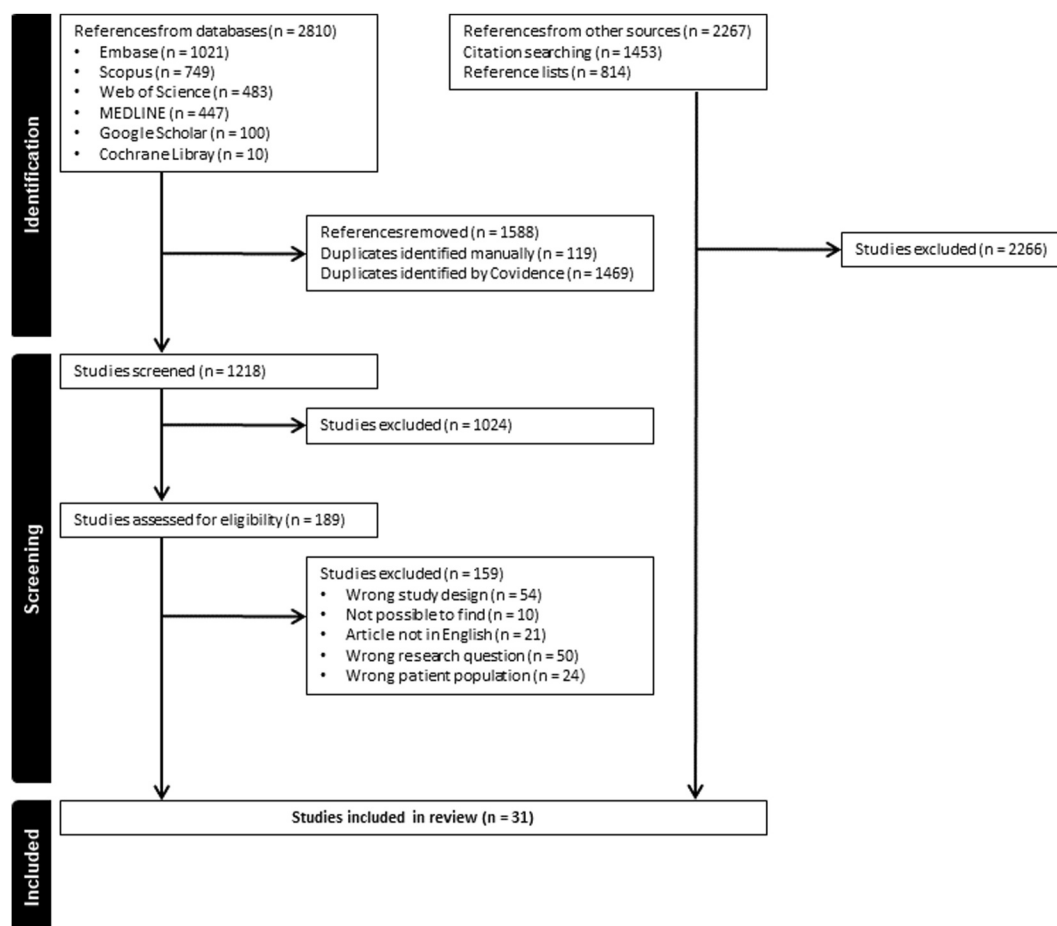


FIGURE 1 | PRISMA flowchart of the search strategy.

(Figure 2, Table S1). The prevalence of CeD in IgAD populations ranged from 5.9% (95% CI: 1.7%–10.2%) [28] to 14.1% (95% CI: 9.1%–19.2%) [29] (Figure 2, Table S2). Ludvigsson investigated the largest cohort ($n = 2100$) of patients with IgAD and found that 6.7% had CeD compared to 0.19% in healthy controls ($n = 18,653$) [30]. Notably, the prevalence in hospital populations may well underestimate the prevalence of the unselected population.

3.4 | Pathogenesis

An early study by Cataldo et al. showed an increased production of the cytokine TNF- α and a reduction of IL-10 in IgAD and CeD patients (Table 1) [35].

HLA-DQA1*05:01/DQB1*02:01, which encodes the HLA-DQ2 allele, may play a role in determining the total serum IgA levels, particularly in individuals predisposed to IgAD. This finding underscores the close relationship between the two conditions IgAD and CeD [36]. Furthermore, CTLA4 (cytotoxic T-lymphocyte associated protein 4)-ICOS (inducible co-stimulator) was identified in a large European dataset as a shared risk locus for IgAD, common variable immune deficiency (CVID), and CeD [32].

One study suggested that patients with CeD and IgAD have an increased number of HLA low-risk genotypes [33].

3.5 | Histology

Five studies evaluated the duodenal histology (Table 1). In all cases, biopsies from patients with CeD with IgAD were evaluated by the Marsh–Oberhuber classification [42, 43]. The studies focused on IgG- and IgA-producing immunocytes. Unsurprisingly, Klemola et al. observed that both patients with IgAD and patients with IgAD and CeD on a GFD had decreased numbers of IgA-containing cells [37]. In patients with IgAD without CeD, an increased number of IgM-containing cells was found and most IgAD patients had compensatory jejunal immunocytes with IgM and IgG isotypes [37, 39]. Compared to healthy controls, patients with IgAD differed in the proportions of various IgG subclasses, with a higher IgG1 and a corresponding decrease in the proportions of IgG2, IgG3 and IgG4 [39]. The association between TGA-IgG levels and the severity of the intestinal mucosal damage was evaluated and no statistical correlation was found [40]. In an abstract, TGA-IgM deposits were observed in biopsies from 6/7 patients with untreated CeD and IgAD [41]. IgAD patients without CeD had a higher number of CD3⁺ and T cell receptor (TCR) $\gamma\delta$ ⁺ intraepithelial lymphocytes (IELs) than controls, but lower than IgAD patients with CeD [44].

3.6 | Clinical Findings and Follow-Up

The clinical findings in patients with IgAD and CeD are diverse (Table 2). Children with IgAD and CeD reportedly had a higher incidence of silent forms than patients with only CeD [46],

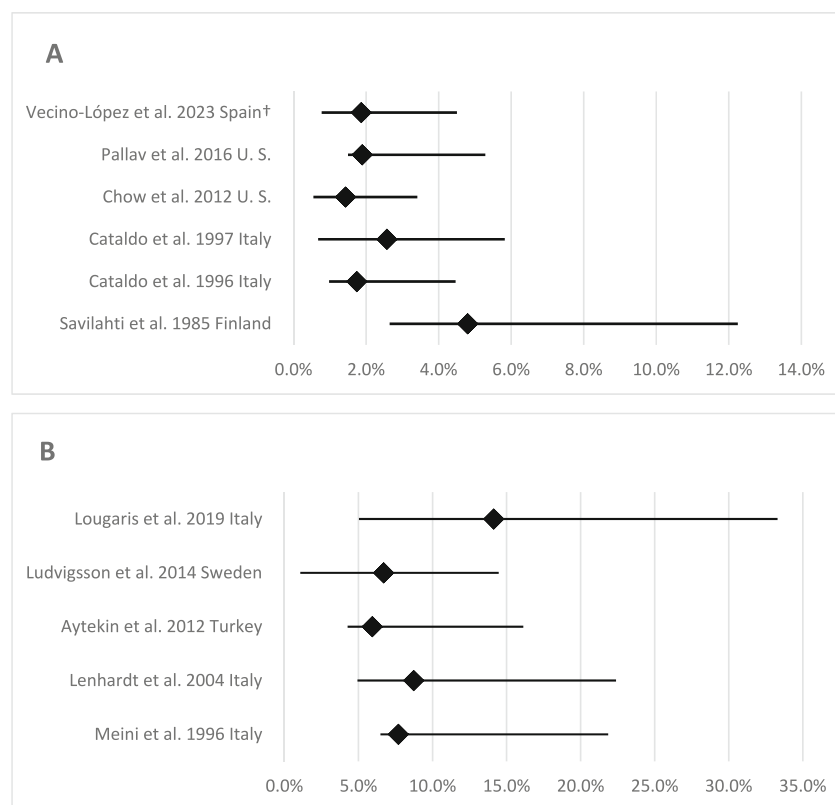


FIGURE 2 | Forest plots illustrating the prevalence of A: IgAD in CeD populations and B: CeD in IgAD populations.

which the same authors subsequently did not confirm [48]. In an early report, 4/15 children did not have symptoms, whereas 11/15 children had growth failure, iron deficiency, and diarrhoea [27]. López et al. described 86 children with both CeD and IgAD, 91% were symptomatic, predominantly with diarrhoea, weight loss, abdominal distension and abdominal pain [22]. In an abstract, the most frequent symptoms in children with CeD alone were abdominal pain (41%) and weight loss (37.2%) and in children with both CeD and IgAD, the most frequent symptom was diarrhoea (45.5%) [45]. The major symptoms in adults were related to malabsorption and malnutrition [51]. Chow observed no difference in symptoms between children and adults with only CeD versus both CeD and IgAD; most were symptomatic [11]. Korponay-Szabó et al. found that the majority of children with both IgAD and CeD exhibited symptoms of malabsorption; out of 78 children, 53 had diarrhoea, 34 had a distended abdomen, 65 had iron deficiency, 57 had weight loss and 34 had short stature [52]. Two small studies reported similar distributions of symptoms [50, 55]. In conclusion, most patients with CeD and IgAD experience symptoms from the gastrointestinal tract; however, the populations were prone to selection bias. All authors recommend screening for CeD in all patients with IgAD as well as the reverse, regardless of symptoms.

3.7 | Autoimmunity

Among 22 adults with CeD and IgAD, a concomitant autoimmune disease was present in 29% compared to 12% of patients with normal IgA levels ($p = 0.0081$) [11]. Ludvigsson, based on a much larger sample, also observed that adults with IgAD had a higher prevalence of several other autoimmune diseases and

that CeD and type 1 diabetes were the most prevalent [30] (Table 2). In a paediatric population with only IgAD ($n = 189$) the prevalence of autoimmunity, excluding CeD, was 9% [29].

3.8 | IgG Antibodies During Follow-Up

Eight studies evaluated antibodies in patients with CeD and IgAD during the follow-up period (Table 2). Cataldo et al. evaluated the diagnostic usefulness of IgG-EMA and TGA-IgG and concluded that both IgG-EMA and TGA-IgG appeared useful for the identification of CeD in IgAD patients, whereas they were less satisfactory for monitoring dietary compliance [56]. Korponay-Szabó et al. evaluated the diagnostic potential of TGA-IgG compared with EMA-IgG and calculated the sensitivity for TGA-IgG of 98.7% and specificity of 98.6%. Both measures showed a decrease in treated patients, but the reduction in IgG autoantibodies was slow, and most patients remained antibody-positive even after more than 2–3 years on a gluten-free diet (GFD) [52]. The slow decrease of IgG autoantibodies was later confirmed [50]; after 1 year on GFD, 18% of patients with IgAD achieved normalisation of TGA-IgG compared to 36.3% of IgA competent patients; and after 2 years, 30% compared to 80%, respectively.

Measurement of IgA levels during CeD monitoring was evaluated in a study by Kavarian et al. and presented as an abstract, 28/290 (10%) were IgA deficient, and of these, 9 patients were initially IgA competent and became deficient, 6 patients were deficient and became competent and 13 patients remained deficient [57].

TABLE 1 | Studies included evaluating the pathogenesis and histology.

Study [reference]	Population	Key findings
Haimila et al. 2008 Finland [31]	663 families with CeD from Hungary and Finland. 575 patients with CeD from Finland, Hungary and Sweden. 275 patients with IgAD from Sweden and Finland. 87 patients with CVID.	An association between CTLA4-ICOS and both IgAD and CVID was found. There was an association between CTLA4-ICOS and CeD. The study identified a shared risk locus for IgAD, CVID and CeD and confirmed the association between CeD and CTLA4-ICOS in a large European dataset.
Schirru et al. 2021 Italy [32]	516 patients with CeD. 16 patients with CeD and IgAD.	Patients with CeD-IgAD showed an increased frequency of mild villous atrophy. These patients showed an increase in HLA low-risk genotypes. Autoimmune liver disease was more frequent in CeD-IgAD patients.
Clerici et al. 1993 Spain [33]	45 children with IgAD. 12 of them with CeD. 166 healthy controls (mean age 35.4 years) and 51 children with CeD without IgAD.	In patients with CeD-IgAD, the frequency of HLA-B14 was increased, and the A1,B8,Cw7, DR3,DQw2 haplotype was present at a higher frequency. DR2 may protect against severe enteropathy, as it was decreased in CeD-IgAD patients.
Cataldo et al. 2003 Italy [34]	32 patients with CeD. 34 patients with CeD-IgAD. 96 healthy controls.	CeD-IgAD and CeD patients had an increase of the TNF -308A allele. The frequency of the three IL-10 promotor polymorphisms was not significantly different in any of the three groups. CeD-IgAD patients were positive both for 308A TNF and 1082A. HLA-8.1 haplotype may play a role in predisposing to CeD and IgAD. Genetically determined increased production of TNF- α and reduction of IL-10 may be relevant for susceptibility to CeD, in IgAD patients.
Fabris et al. 2009 Italy [35]	19 patients with IgAD without CeD. 26 patients with CeD and IgAD. 73 patients with CeD and normal IgA. 77 healthy blood donors.	Compared to controls, patients with IgAD demonstrated an increase of BLYS and APRIL levels. No difference between patients with or without CeD. BLYS was overexpressed in IgAD and CeD patients. APRIL was increased only in IgAD patients.
Abdukhakimova et al. 2023 Kazakhstan [36]	108 serum samples from the bone marrow donors' registry were analysed for total IgA concentration with respect to HLA-DQB1*02:01.	There was a statistically significant difference in total serum IgA levels in donors with low IgA concentration (< 80 mg/dL) between HLA-DQB1*02:01 positive and negative donors. All complete IgAD cases were observed among HLA-DQB1*02:01 carriers only.
Klemola et al. 1988 Finland [37]	13 patients with IgAD, 4 of them with CeD. 12 controls.	Both IgAD patients and CeD-IgAD (on GFD) patients had decreased numbers of IgA-containing cells. In patients with IgAD without CeD, an increased number of IgM-containing cells was found.
Borrelli et al. 2009 Italy [38]	Biopsies from 25 children with IgAD; 9 untreated CeD, 7 potential CeD and 9 without CeD. 16 children with normal IgA and without CeD as controls.	IgAD patients without CeD had a higher number of CD3 ⁺ and T cell receptor $\gamma\delta$ ⁺ intraepithelial lymphocytes compared to controls, but lower than IgAD patients with CeD. Intestinal IgM anti-TG2 and immunohistochemical markers do not discriminate between IgAD and potential CeD with IgAD. The serum IgG CeD-associated autoantibodies remain very important for the diagnosis of CeD in IgAD patients.

(Continues)

TABLE 1 | (Continued)

Study [reference]	Population	Key findings
Nilssen et al. 1991 Norway [39]	14 patients with IgAD, 6 of them with CeD. 28 controls with normal IgA.	Most IgAD patients showed compensatory jejunal immunocyte population consisting of IgM and IgG classes. A notable difference was found in the proportions of various IgG subclasses, with IgG1 being higher and IgG2, IgG3, and IgG4 being reduced.
Donat et al. 2022 Spain [40]	2917 children with CeD. 38 children with CeD and IgAD.	Marsh 3b-c lesion was observed in 26/38 (68.4%). No statistically significant difference was found between TGA-IgG and the changes in intestinal mucosa or symptoms.
Romagnoli et al. 2012 Italy ^a [41]	Biopsies from 60 children suspected of having CeD. 20 children with another gastrointestinal disease as a control group.	5.6% of the patients had IgAD. IgA anti-TGA2 deposits were detected in low or negative serum IgA anti-TGA2 and in patients with IgA deficiency.

^aConference abstract, Coeliac disease (CeD), common variable immunodeficiency disease (CVID), Gluten-free diet (GFD), Human Leukocyte Antigen (HLA), Immunoglobulin A Deficiency (IgAD), Immunoglobulin M (IgM), Immunoglobulin G (IgG), transglutaminase antibody (anti-TGA2), tumour necrosis factor (TNF), interleukin (IL).

4 | Discussion

We identified 31 studies addressing IgAD in CeD and sorted the outcome into four subheadings: Prevalence, pathogenesis, histology, clinical findings and follow-up.

CeD occurred at a frequency of 5.9%–14.1% in IgAD populations. A previous systematic review based on 17 studies estimated the prevalence of CeD in IgAD populations to be 6.6% [58]. We only included five studies under this subheading due to a stricter screening process. The studies reviewed showed that IgAD occurred more frequently in CeD patients, 1.4%–4.8%. One abstract, based on 115 studies, reported a systematic review with a 3.6% prevalence of IgAD in CeD [59]. The selection of patients may lead to underestimation, as IgAD populations are often based solely on symptomatic patients, clinically seen for allergies, infections, or autoimmune diseases. In addition, some studies only performed duodenal biopsies in patients with symptoms related to CeD, whereas in other studies, all patients were biopsied.

A strong common genetic background has been identified, particularly within the HLA region close to genes associated with autoimmunity, such as HLA-DQB1*02 [60]—almost a *sine qua non* for coeliac disease [36]. In a study involving 772 patients with IgAD and 1976 controls, Ferreira et al. [61] surveyed 118 non-HLA autoimmunity loci and found a significant enrichment of associations with autoimmunity loci compared to non-autoimmunity loci or random single-nucleotide polymorphisms (SNPs) across the genome. These findings support the hypothesis that autoimmune mechanisms contribute to the pathogenesis of IgAD.

The microbiota may influence the symptomatology of IgAD and CeD and it has been shown to be perturbed in IgAD [62], in which IgM may partly replace IgA as mucosal protection [63]. The same variation has been observed in CeD [64]. However, a firm conclusion has not been reached.

The intestinal damage in CeD may cause symptoms such as diarrhoea, weight loss, fatigue, and iron-deficiency anaemia. There have been concerns that patients with IgAD and CeD more frequently present with silent forms. However, most patients with both IgAD and CeD, both children and adults, experience symptoms from the gastrointestinal tract. Further studies should provide information on both asymptomatic and symptomatic patients from larger screening studies to avoid selection bias. All reports have stressed the practical importance of screening for CeD in patients with IgAD, including asymptomatic individuals, in line with the recommendations in the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines [4] and the American College of Gastroenterology ACG guidelines [65]. The screening should be based on an IgG-based test (IgG TGA, IgG DGP, or IgG EMA), and the final diagnosis requires a duodenal biopsy [4].

In immunocompetent patients with CeD, a clear correlation was observed between extent of histological damage and TGA-IgA [66]; however, this was not the case for patients with IgAD and CeD [40]. The result may be due to the small sample size and deserves to be investigated in a larger study.

In patients with CeD and IgAD, IgG-based antibodies are used for monitoring the response to GFD, but the accuracy has not been well studied. The studies [50, 52, 56] found that IgG TGA, DGP, and EMA persist for a long time in affected patients despite treatment with GFD [67]. More studies are needed to examine how to monitor the GFD and to evaluate the long-term implications of positive serum antibodies despite normalisation of the intestinal biopsy.

The reason for the slower disappearance of TGA-IgG antibodies in IgAD and CeD is unclear. Differences in immunoglobulin production may well be different for IgA and IgG antibodies. However, more probable are differences in isotype half-life. Metabolism of serum and mucosal IgA occurs by Fc

TABLE 2 | Studies included evaluating the clinical findings, antibodies and follow-up.

Study [reference]	Population	Symptoms in relation to CeD or IgAD	Main clinical findings at diagnosis	Follow-up
Savilahti et al. 1985 Finland [27]	250 with CeD. 12 with CeD and IgAD.	4/12 without any gastrointestinal symptoms. 11/12 with growth failure, iron deficiency or diarrhoea.		3/12 had elevated IgA levels early during the disease, which decreased 3 months after GFD.
Collin et al. 1992 Finland [45]	25 children and adults with CeD and IgAD. 1975–1989.	Major symptoms were malabsorption or malnutrition and abdominal complaints.	Increased risk of autoimmune diseases. IgG reticulins was positive in 94%. IgG AGA was positive in 43%.	
Cataldo et al. 1997 Italy [46]	688 patients with CeD. 797 patients with other gastrointestinal diagnoses. 988 healthy patients 1992–1994.	CeD-IgAD patients had typical clinical presentations as patients with only CeD. The median age of diagnosis was 3.8 years. None had other concomitant diseases.	All CeD-IgAD patients were IgG AGA positive.	Antibodies returned to normal after 1 year of follow-up.
Cataldo et al. 1998 Italy [44]	2098 patients with CeD, of whom 54 had IgAD. 1776 children and 322 adults. January 1990 to December 1995.	Children with CeD and IgAD had a higher incidence of silent forms and recurrent infections. The median age was 4.5 years in children. The median age in adult was 26 years.	Higher incidence of atopic diseases. Autoimmune and malignant diseases were similar in the two groups. AGA IgG was high in 51/54. Patients with IgAD had a higher frequency of HLA-DR3 and HLA-DQW2, as well as a lower HLA-B8.	7 of the patients with IgAD showed normalisation of serum IgG after 36–48 months. Control biopsy was performed in 16 cases with SIgAD.
Chow et al. 2012 U. S [11].	1498 adults and 317 children with CeD. Of them 26 patients with selective IgAD and 11 with partial IgAD.	No difference in clinical presentation between patients with CeD and CeD with IgAD.	Among adults with IgAD, autoimmune diseases were present in 29% versus 12% of CeD patients with normal IgA levels. Patients with CeD and IgAD had positive IgG TGA and IgG AGA.	4 patients with CeD and IgAD had persistently positive IgG antibodies but had a normal repeat biopsy.
Pallav et al. 2016 U. S [47].	1000 adults undergoing TGA-IgA testing. 243 healthy controls. August 2010 to March 2011.	Patients with IgAD showed a lower frequency of GI symptoms.	Patients with IgAD showed more co-morbid autoimmune disease when compared to CeD with normal IgA levels, 67% versus 23%. 1/6 patients with CeD and selective IgAD tested positive for TGA-IgA and all with partial IgAD tested positive for TGA-IgA.	
López et al. 2020 Spain [22]	86 children < 15 years with CeD and sIgAD. January 2006 to December 2016.	91% were symptomatic with predominantly diarrhoea, weight loss, abdominal distension, and abdominal pain. Median age at diagnosis 4.1–4.4 years. 23 did not	8% were associated with an autoimmune disease. All patients had at least one positive IgG based antibody. HLA was performed, and 91% were positive.	After 2 years of follow-up half of the children remained positive. The use of IgG serology was extrapolated to IgA isotypes, and the biopsy was

(Continues)

TABLE 2 | (Continued)

Study [reference]	Population	Symptoms in relation to CeD or IgAD	Main clinical findings at diagnosis	Follow-up
Vecino-López et al. 2023 Spain ^a [48]	22 children with CeD and IgAD. 1179 with CeD only.	undergo a biopsy. The remaining 63 had villous atrophy, Marsh-Oberhuber 2–3. In children with CeD the most frequent symptoms were abdominal pain (41%) and weight loss (37.2%). In children with CeD and IgAD the most frequent symptom was diarrhoea (45.5%). No difference in median age at diagnosis (4.8 vs. 3.9 years).	21/22 were tested for TGA-IgG: All were positive. 14/22 were tested for IgG DGP and 12 were positive. 13/22 were tested for IgG EMA and 11 were positive. No correlation between the TGA-IgG levels and the degree of villous atrophy.	frequently omitted. Control biopsy was performed in 6 cases.
Meini et al. 1996 Italy [49]	60 children with IgAD, 5 children with IgAD and CeD. 1989–1993.	All 5 children with IgAD and CeD were symptomatic: 4/5 growth failure, 2/5 diarrhoea, 1/5 abdominal pain, 1/5 aphthous stomatitis, 1/5 iron deficiency.		
Aytekin et al. 2012 Turkey [28]	118 children with IgAD. 2006–2011.		51/118 allergic. 99/118: Infectious disease. 20/118 autoimmune disease. 7/118 with CeD. None of the 7 patients with CeD were positive for AGA-IgA or TGA-IgA. Four patients were positive for AGA-IgG and two for TGA-IgG.	
Ludvigsson et al. 2014 Sweden [30]	2100 patients with IgAD. 18653 controls matched on gender, sex and residence. 1980–2011.		Patients with IgAD versus controls: CeD 6.7 versus 0.19%, PR = 35. Type 1 diabetes: 5.9% versus 0.57%, PR = 10. Juvenile idiopathic arthritis 0.76% versus 0.09%, PR = 8.9. SLE 0.57% versus 0.06%, PR = 8.9. IBD 3.9% versus 0.81%, PR = 5.0. Rheumatoid arthritis 2.2% versus 0.50%, PR = 4.5. Hypothyreosis 0.76% versus 0.16%, PR = 4.5. Hyperthyreosis 1.7% versus 0.43%, PR = 3.9. Myasthenia gravis 0.05% versus 0.02%, PR = 3.0.	

(Continues)

TABLE 2 | (Continued)

Study [reference]	Population	Symptoms in relation to CeD or IgAD	Main clinical findings at diagnosis	Follow-up
Lougaris et al. 2019 Italy [29]	184 children with SIgAD. Follow-up 1989–2011.	The mean age at diagnosis was 7.7 years. Symptoms leading to the diagnosis: Respiratory infections 114/184 (62%). Positive family history of antibody deficiencies 29/184 (16%). Allergic manifestations 42/184 (23%). During follow-up, 50/184 (27%) reported gastrointestinal symptoms.	Allergic manifestations 30/184 (16%). 9% had autoimmune diseases (not CeD). CeD was found in 26/184 (14%). 3/184 (2%) progressed to CVID.	
Cataldo et al. 2000 Italy [50]	20 untreated IgAD/CeD patients, 34 IgAD/CeD patients on GFD, 10 IgAD/CeD not on GFD, 11 untreated CeD patients.		In all untreated IgAD with CeD patients, IgG EMA and TGA-IgG were positive. IgA antibodies were all negative. Both IgG EMA and TGA-IgG are useful for identifying patients with IgAD and CeD. However, it is less satisfactory for monitoring dietary compliance.	
Cataldo et al. 2003 Italy [34]	32 with CeD. 27 with CeD and IgAD. 30 healthy controls.		IFN- γ levels were higher in patients with CeD and CeD with IgAD compared to controls. TNF- α and IL-10 levels were higher in CeD with IgAD compared to those in CeD and controls. IL-2 was increased in patients with CeD with IgAD compared to controls. IL-4 and IL-13 both at diagnosis and after GDF were not different in both groups and controls.	
Korponay-Szabó et al. 2003 Hungary [51]	325 patients with IgAD and 78 patients with CeD and IgAD. 73 controls with CeD and 174 healthy controls.	IgAD and CeD patients: 53/78 had diarrhoea, 34/78 had distended abdomen, 65/78 had iron deficiency, 57/78 had weight loss and 34/78 showed short stature.	TGA-IgG had a sensitivity of 98.7% and a specificity of 98.6%. The correlation with IgG EMA was high ($rs = 0.91$). TGA-IgG and IgG EMA showed a significant decrease in treated patients.	The decrease in IgG autoantibodies was slow. Most patients were still positive after more than 2–3 years on GFD.
Lenhardt et al. 2004 Italy [52]	126 children with IgAD.	5/11 had abdominal pain, 5/11 had anaemia, 1/11 had oral aphthosis and 2/11 were asymptomatic.	3/11 had a concomitant autoimmune disease. 27/126 tested positive for IgG AGA. 18/126 tested positive for IgG TGA. 5 were positive for both tests. A biopsy was performed in 37/40	

(Continues)

TABLE 2 | (Continued)

Study [reference]	Population	Symptoms in relation to CeD or IgAD	Main clinical findings at diagnosis	Follow-up
McGowan et al. 2008 Canada [53]	9533 patients tested for IgA EMA.	3 patients with IgAD and CeD had iron deficiency or anaemia. 1 had diarrhoea.	patients (3 refused) who tested positive. 11/37 had a positive biopsy and all of them tested positive for TGA-IgG, but only 5 also tested positive for IgG AGA. 22 who tested positive for IgG AGA had normal biopsy. 11 were diagnosed with CeD and carried the HLA DQ2/DQ8 alleles.	
Nazario et al. 2021 Argentina [54]	1122 patients who underwent screening for CeD.		4698/9533 (49%) were tested for IgAD. IgAD occurred in 35/4698 (0.75%). 17/35 (49%) with IgAD were diagnosed with a biopsy and 3/17 (18%) had CeD. The prevalence of omitting serum IgA determination was 20.5%. The prevalence of IgAD was 49/937 (5.16%), but most of them were partially deficient.	
Donat et al. 2022 Spain [40]	2917 children with CeD. 38 children with CeD and IgAD.	Mean age at diagnosis 4.7 years.	18/38 (47.4%) had TGA-IgA ≥ 10 times ULN. 27/38 (70.4%) were IgG EMA positive. Marsh 3b-c lesion was observed in 26/38 (68.4%). No statistically significant difference was found between TGA-IgG and the changes in intestinal mucosa or symptoms.	
Giner-Pérez et al. 2023 Spain [55]	11 children with CeD and IgAD. 20 patients with CeD without IgAD.	CeD-IgAD: Median age at diagnosis 4.3 years. 8 children were tested and carried the HLA DQ2/DQ8. 5/11 had gastrointestinal symptoms. All had positive TGA-IgG and IgG EMA. CeD: Median age at diagnosis 5.8 years. 19 children were tested and carried the HLA DQ2/DQ8. 12/20 had gastrointestinal symptoms. All had positive TGA-IgA.	At diagnosis, there was no difference when comparing TGA-IgA levels of IgA competent patients with TGA-IgG levels of IgAD patients. Normalisation rates were slower for patients with IgAD.	After 1 year on GFD 18.2% of patients with IgAD normalised TGA-IgG versus 30% in IgA competent patients. After 2 years on GFD 36.3% of patients with IgAD normalised TGA-IgG versus 80% in IgA competent patients.

(Continues)

TABLE 2 | (Continued)

Study [reference]	Population	Symptoms in relation to CeD or IgAD	Main clinical findings at diagnosis	Follow-up
Kavarian et al. 2024 U. S. ^a [56]			28/290 (10%) were IgA deficient. Of these, 9 patients were initially competent and became deficient; 6 patients were initially deficient and became competent; and 13 patients remained competent. 30% of paediatric gastrointestinal practitioners obtained a total IgA level during follow-up.	

^aConference abstract, Immunoglobulin A Deficiency (IgAD), Coeliac Disease (CeD), Immunoglobulin G (IgG), anti-gliadin antibody (AGA), Human Leukocyte Antigen (HLA), transglutaminase antibody (TGA), Deamidated Gliadin Peptide (DGP), Endomysial antibody (EMA), common variable immunodeficiency disease (CVID), Interferon (IFN), tumor necrosis factor (TNF), interleukin (IL), Gluten-free diet (GFD).

alpha R receptors [68] and IgA based crosslinking of the Fc alpha R receptor is more efficient than Fc gamma receptor binding [69].

One interesting finding is the higher risk of an additional autoimmune disease in patients with IgAD and CeD. Particularly, type 1 diabetes and the risk of additional autoimmune diseases may increase during adulthood [30]. This underlines the importance of follow-up with a focus on concomitant autoimmune diseases. However, the markedly higher prevalence of CeD and type 1 diabetes in patients with IgAD may be biased by the fact that IgA levels frequently are measured as a part of the screening for CeD in patients with type 1 diabetes, which is routinely performed in most Western countries.

Ludvigsson et al. observed that patients with IgAD had increased mortality in the first 10–15 years after diagnosis compared with the general population [70]. This underscores that IgAD patients constitute a risk group with a higher risk of autoimmune diseases and a higher mortality.

IgAD may be accompanied by transfusion reactions [71] caused by anti-IgA antibodies in plasma, in particular of the IgE isotype, which commonly occurs in IgAD patients [72]. Furthermore, anti-IgA antibodies may potentially be implicated in the pathogenesis of IgAD. This aspect has not been studied in relation to CeD and may deserve attention.

IgAD is usually regarded as existing before the development of CeD. The intake of gluten, for example, as a gluten challenge, may stimulate IgA production. One case report described two girls who developed IgAD after the diagnosis of CeD and the start of GFD [31]. The development of IgAD after the start of GFD was also described in a larger sample [57]. These limited data require further confirmation. Furthermore, IgA may persist in the intestinal mucosa in children with CeD and complete lack of IgA in plasma [31].

This review has limitations. Most reviewed studies drew on hospitalised subjects, not on unselected populations, which may underestimate prevalence calculations. These studies originate from several decades, and definitions of CeD as well as IgAD have changed over time. Lastly, the concept of a scoping review did not include a critical interpretation of the included studies.

5 | Conclusion

The exact pathogenesis of IgAD in CeD is not fully understood, but the overlapping HLA genes are associated with the shared risk of both conditions. Since IgAD is more prevalent in individuals with CeD than in the general population, the identification of IgAD during diagnostic work-up for CeD is warranted. A flow-chart is shown (Figure 3). Patients with both IgAD and CeD may or may not present symptoms from the gastrointestinal tract, and all patients with IgAD, even asymptomatic ones, should be screened for CeD. Screening should be based on an IgG-based test, and the final diagnosis requires a duodenal biopsy. The follow-up may include attention to other autoimmune diseases.

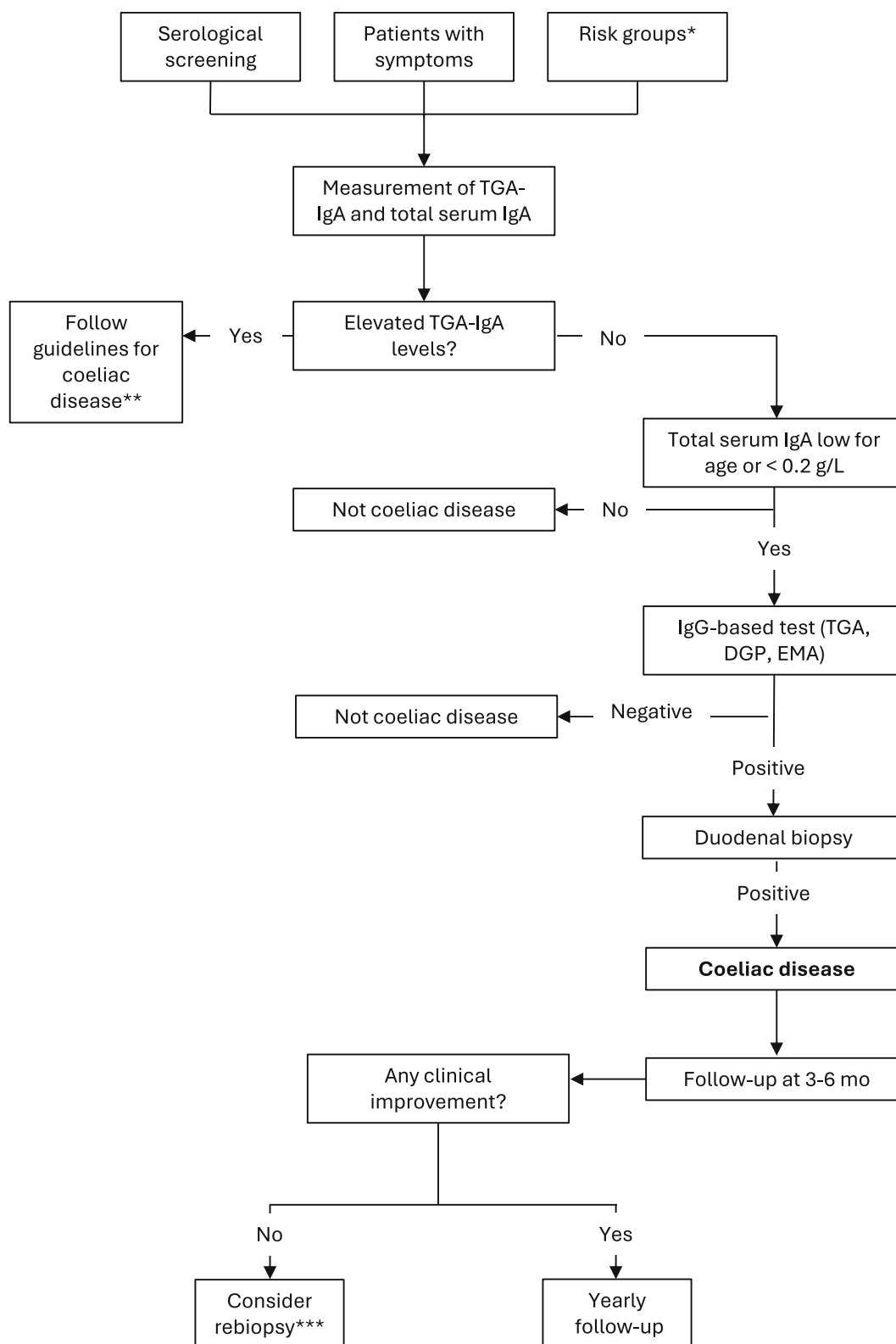


FIGURE 3 | Flowchart for the diagnosis and the management of CeD in IgAD patients. Please note that the cut-off for s-IgA in the flowchart is 0.2 g/L due to the risk of false-negative IgA antibody levels. *Risk groups are family history of CeD, autoimmune diseases and chromosomal aberrations associated with CeD or IgAD. **ESPGHAN guidelines for children [4] and ACG guidelines for adults [65]. ***Regardless of IgG-based serology.

Author Contributions

Kristine Bech: Guarantor of the review. Protocol development and search strategy. Primary reviewer of literature search and evaluation. Manuscript development for publication. **Cæcilie Crawley:** Secondary reviewer of literature search and evaluation. **Rok Seon Choung:** Expert guidance regarding coeliac disease. **Joseph A. Murray:** Expert guidance regarding coeliac disease. **Steffen Husby:** Protocol development. Corresponding author. Expert guidance regarding coeliac disease. Manuscript development for publication.

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Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270296-sup-0001-suppl-data.docx.

Supporting Information S2: ueg270296-sup-0002-suppl-data.docx.

Table S1: Studies included evaluating the prevalence of IgAD in CeD populations. **Table S2:** Studies included evaluating the prevalence of CeD in IgAD populations.