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The follow-up of patients with celiac disease

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ABSTRACT

Celiac disease (CD) is a very common immune-mediated enteropathy resulting from the interaction between dietary gluten and the immune system in genetically predisposed individuals. The immune response leads to intestinal damage, malabsorption and, ultimately, to a broad spectrum of both intestinal and extra-intestinal symptoms. According to current criteria, a proper diagnosis of CD requires an initial phase consisting of clinical case identification and serological screening that, over time, has increased in importance. In most adults and in selected children, the diagnosis is subsequently defined by histological evidence of intestinal damage as a confirmatory test, which usually returns to normal after a suitable period of a gluten-free diet (GFD). The clinical remission and disappearance of circulating antibodies after a GFD further confirm the diagnosis and represent a goal to be achieved to improve the quality of life and reduce the risk of long-term complications. However, although the diagnostic criteria for CD are well defined and described in specific guidelines, the monitoring of CD patients undergoing GFD has been less studied and, consequently, specific guidelines for this phase are still lacking. The aim of this report was to evaluate the classical tools used to monitor the adherence and response to GFD, other non-invasive biomarkers that have been proposed for CD monitoring, and the histological follow-up of CD patients in order to provide a starting point for future discussions on this specific topic.

1. Introduction

Celiac disease (CD) is an immune-mediated enteropathy caused by an inflammatory immune response to dietary gluten in genetically predisposed individuals. This immune response initiates a cascade of events leading to intestinal damage, directly through innate immunity mediated by natural killer (NK)-like cells and, indirectly, by means of T cell-driven adaptive immunity. Specific alleles of the human leukocyte antigen (HLA) class II (HLA-DQ2.5, -DQ2.2, and -DQ8) and several non-HLA gene variants contribute to CD genetic predisposition. As a CD-specific mechanism, HLA molecules encoded by the above-mentioned alleles are able to present immunogenic peptides originating from the incomplete digestion of dietary gluten fractions to $CD4^+$ T-cells. The incompletely digested gluten fractions are rendered immunogenic by deamidation by the enzyme tissue transglutaminase (tTG). Wheat derived gluten, consisting of gliadin and glutenin, and similar storage proteins in other cereals, such as secalin in rye and hordein in barley can cause complaints in CD [1]. A careful literature review suggests that CD is one of the most common chronic disorders worldwide, with a prevalence of 1%–2% and a heavy global health burden, worsened by evidence that a significant proportion of cases remains undiagnosed [2,3]. In this scenario, interventions such as a policy of systematic case finding and pediatric screening of the general population have been suggested to reduce the health burden of CD [4]. According to current criteria [1,5], a proper diagnosis of CD initially requires the clinician's attention to evaluate the broad spectrum of both intestinal and extra-intestinal symptoms (clinical case identification), as well as the presence of specific antibodies in serum of patients (serological screening). Thereafter, in all adults and in selected children, the diagnosis is defined by histological evidence of duodenal villous atrophy, crypt hyperplasia and

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intraepithelial lymphocytosis (confirmation test), which normally recover after a suitable period of complete gluten withdrawal from the diet. The clinical remission and disappearance of circulating antibodies after a gluten-free diet (GFD) confirm the diagnosis and represent a goal to be achieved in order to improve the quality of life and reduce the risk of long-term complications, such as osteoporosis and intestinal lymphoma [1]. Although the diagnostic criteria for CD are well defined and described in specific guidelines, the monitoring of CD patients on a GFD has been less studied and, consequently, specific guidelines for this phase are still lacking.

In the present report, we evaluated both traditional and alternative treatment for CD, the classic tools used to monitor the adherence and response to GFD and, finally, other non-invasive biomarkers that have been studied and proposed for CD monitoring in order to provide a starting point for future discussions on this topic.

1.1. Treatment

To date, as confirmed by a very recent European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position paper aimed at providing evidence- and expertise-based tools for clinicians supporting CD patients under therapy [6], the only suitable treatment for CD consists of lifelong adherence to a strict GFD. The authors first declare that a GFD must guarantee the complete elimination of all gluten-containing cereals which, in addition to the aforementioned wheat, rye and barley, include khorasan wheat or kamut®, malt, malted barley, spelt, and most of their derivatives. Possible substitutes of gluten-containing cereals are specific grains such as maize or corn, oats, rice and sorghum, pseudocereals (amaranth, buckwheat, chia, quinoa, teff), legumes or pulses (chickpeas, lentils), and tubers (potato, yuca). Some derivatives from gluten-containing cereals such as glucose or fructose syrup, maltodextrin, malt vinegar, sugar from wheat, and wheat starch can be safe for consumption as long as they are guaranteed gluten free by the manufacturer. Indeed, any processed food must be regularly checked and, only if the amount of gluten does not exceed 20 mg/kg, it may be labelled as "gluten-free" and included in a GFD. Oats deserve a separate discussion because, even if regularly checked, it can be consumed safely only if the quantities of 20–25 g/day for children and 50–70 g/day for adults are not exceeded [7,8]. Beyond the complete description of such a diet, the same ESPGHAN position paper provides useful indications on how to read and interpret food labels, avoid cross contact with gluten and how to follow a GFD while preventing the nutritional risks related to it. Among the latter, a low intake of fibers, micronutrients and vitamins, as well as a high intake of sugars and poor quality fats have been reported [6].

On the other hand, as a direct consequence of the heavy psychosocial implications related to a GFD, research on alternative pharmacological treatments is currently very active [1]. As recently suggested by D'heedene et al. [9], therapeutic approaches alternative to a GFD may be divided into four main groups, depending on how the relative pharmacological agents act in the complex pathogenetic framework of CD. In summary: 1) by neutralizing gluten peptides before their absorption occurs; 2) by modulating intestinal permeability thus preventing paracellular uptake; 3) by regulating the gluten-dependent immune response; 4) by promoting immunological tolerance to gluten. The gluten neutralizing agents (group 1) are endopeptidases such as latiglutenase or ALV003 and TAK-062 which, by targeting specific residues (e.g., proline and glutamine), are able to proteolyze gluten peptides thus reducing their immunogenicity [10,11]. The intestinal permeability modulating agents (group 2) are molecules which, by targeting specific proteins (e.g., zonulin), serve as tight junction regulators reducing intestinal permeability and, consequently, the amount of gluten reaching the lamina propria [12]. Regarding agents that regulate the gluten-dependent immune response (group 3), promising results have been obtained with the tTG inhibitor ZED1227 which, by targeting the enzyme active site, leads to a partial interruption of the cascade of events underlying gluten-specific immune activation [13]. Among immunotherapeutic agents belonging to group 4, the most promising results have been obtained with the tolerance-inducing vaccine Nex-Vax2, specifically designed to desensitize CD patients to gluten [14]. However, despite significant efforts and promising results obtained over time, no newly proposed treatment has yet completed a phase III clinical trial and, therefore, future studies focused on therapeutic approaches alternative or supplemental to a GFD are warranted.

1.2. Tools used to monitor the adherence and response to GFD

1.2.1. Anti-tTG antibodies

In clinical practice, monitoring the adherence and response to GFD in CD patients is carried out through periodic determination of anti-tTG IgA antibody titers, except in patients who present IgA deficiency in which IgG isotype antibodies are determined [15]. In addition to this serological approach, different procedures for the assessment of adherence to GFD have been developed including clinician and dietitian interview, CD-specific adherence-based validated questionnaires such as celiac disease adherence test and Biagi score, and assessment of healing of mucosal lesions [16–18] (Table 1).

Recently, in order to establish best practice for CD follow-up, key points in the monitoring of CD patients have been published to determine "when, what, who, and where" should be assessed [19]. Although anti-tTG antibody monitoring is a widely established protocol, since on a GFD their levels decrease over time and are expected to normalize by 18–24 months after starting the diet [20], negative results does not necessarily indicate good adherence to GFD and also present a poor correlation with mucosal recovery [19,21–23]. In a meta-analysis of patients with biopsy-confirmed CD undergoing follow-up biopsy on a GFD, it was found that tests for serum anti-tTG IgA antibody titers had low sensitivity in detection of persistent villous atrophy [24]. Besides, the seroconversion from negative to positive result in anti-tTG IgA in CD patients with gluten consumption after GFD takes time and a high dose of gluten is necessary [25].

Furthermore, it should be noticed that the normalization of anti-tTG IgG antibodies in patients with selective IgA deficiency is slower than anti-tTG IgA in immunocompetent patients [26,27]. Elevated levels of anti-tTG IgG antibodies can persist for a long time on GFD patients and do not correlate with histological activity of CD [28].

As has been mentioned, anti-tTG antibodies decrease after starting a GFD and the assays that are commercially available are highly specific. However, the certified intended use of all anti-tTG assays present in the market is to "aid in the diagnosis of CD", and none of them is certified for monitoring purposes nor are there any available recommended cutoffs for monitoring disease activity. Likewise, the cutoffs established for diagnostic purposes are set by the manufacturers at a threshold that provides high specificity, high sensitivity or a compromise to maximize both. One limitation is that these diagnostic cutoffs are used both for diagnosis and for monitoring in daily routine, but it is not evident that these cutoffs are optimal for monitoring CD patients on a GFD [29]. This aspect is very relevant and yet it is not usually taken into account, as demonstrated by a recently published study that shows that the cutoff value for anti-tTG IgA antibodies as marker of mucosal recovery was higher than the value for diagnosis [30].

Another relevant aspect is that serological monitoring of CD patients under GFD is dependent on the assay used, showing that despite fluorochrome-enzyme immuno-assay (FEIA) and chemiluminescence immuno-assays (CLIA) have high sensitivity and specificity for CD diagnosis, after GFD the normalization of anti-tTG antibody titers is significantly higher for FEIA in comparison with CLIA [29]. Similar results have been observed in another study considering ELISA and CLIA, where CLIA results took longer to normalize [31,32]. Therefore, it would be recommended the use of the same methodology for the diagnosis of CD and for the monitoring of patients in GFD, since this could impact the interpretation by clinicians about the adherence of the patient to GFD.

Table 1
Main tools used for diagnosing and monitoring celiac disease.

Tools	CD diagnosis	CD monitoring
Clinician and dietitian interview	Not used	Used with limitations
CD questionnaires	Not used	Used with limitations
Anti-tTG antibodies	Diagnostic markers Pros: • Highly specific • Less invasive	Periodic determinations of anti-tTG antibodies is widely used in clinical practice Limitations: • Negative results does not necessarily indicate good adherence to GFD • Poor correlation with mucosal recovery • Seroconversion from negative to positive result in CD patients with gluten consumption after GFD takes time and a high dose of gluten is necessary • In patients with selective IgA deficiency, elevated levels of IgG antibodies can persist for a long time after GFD and do not correlate with histological activity of CD
Intestinal fatty acid binding proteins (iFABP)	Not routinely used Sensitive marker for enterocyte damage (correlation with severity of villous atrophy).	Not routinely used I-FABP levels decrease after GFD High I-FABP levels after GFD could indicate histological abnormalities and warrant further evaluation
Gluten immunogenic peptides (GIP)	Not used	Promising non-invasive biomarkers: direct biomarker of voluntary or involuntary gluten intake both in adult and pediatric CD patients; can be found in both symptomatic and asymptomatic CD patients after a GFD Can be performed either in clinical laboratories or point-of-care settings Limitations: GIP levels are not related to symptoms
Faecal calprotectin	Not used	Not routinely used Non-invasive marker for continued inflammation
Duodenal biopsy	Diagnostic marker Limitations: • Invasive • Correct interpretation of results highly dependent on correct sampling, correct orientation and standardized histopathological interpretation. • Low inter-observer agreement	Assess mucosal healing in response to GFD. Limitations: • Invasive • In absence of diagnostic biopsies establishing improvement may be difficult • Controverse recomendations of follow-up biopsies in asymptomatic CD patients • Follow-up biopsy in asymptomatic children is not recommended. • Recommendation of re-biopsy in case of persisting or relapsing symptoms after GFD

As it has been proposed, a reasonable strategy for interpreting the results regardless of the methodology used could be the harmonization of the cutoffs at 100 % specificity. In this way, temporal differences in the normalization of anti-tTG antibody titers are eliminated [33].

Taking into account that serological monitoring has limitations, since the normalization of antibody titers is lengthy, it cannot identify occasional gluten exposure, and especially the fact that negative antibody results do not necessarily indicate good adherence to GFD or mucosal recovery, other biomarkers have been proposed for CD monitoring, such as fatty acid binding proteins [34], fecal calprotectin [35] and gluten immunogenic peptides (GIPs) in stools and/or urine [36]. It is important to note that these markers have different characteristics and clinical significance: while anti-tTG antibodies are markers of an ongoing immune response, calprotectin levels are related to the degree of inflammation, iFABP are a marker of tissue damage, and GIPs reflect adherence to gluten-free diet (Fig. 1).

1.2.2. Intestinal fatty acid binding proteins (iFABP)

Fatty acid binding proteins (FABPs) are low molecular weight (14–15 KDa) cytoplasmic proteins that play a role in the lipid transport by binding to hydrophobic ligands, mainly fatty acids, and are involved in the lipid metabolism and maintenance of lipid homeostasis [34]. Since the first description in 1972 [37], ten FABP isoforms have been identified from the organs or tissues where they are most expressed and involved in specific functions. In detail, they consist of liver (L)-, intestine (I)-, heart/cardiovascular (H)-, adipose (A)-, epidermis (E)-, ileal (IL), brain (B)-, myelin (M)-, testis (T)-, and retinal (R)-FABP [34]. I-FABP is encoded by the *FABP2* gene and expressed throughout the small intestine, primarily in the jejunum, where an increasing concentration gradient from immature enterocytes of the crypts to mature enterocytes of the villous tip is observable [34,37]. Any injury to enterocytes leads to I-FABP release at local sites, which is then absorbed and passes into the circulation, where detection of elevated I-FABP levels has been described as highly suggestive of enterocyte damage in the course of enteropathy [38]. Consistently, high serum I-FABP levels have been widely observed in untreated CD patients, in whom they correlate with the degree of villous atrophy and return to normal after a suitable period of GFD, in relation to intestinal mucosa healing [39,40]. A recent study has shown that variations in compliance to GFD, assessed by fecal measurement of GIPs, correlate with serum levels of I-FABP but not anti-tTG [41]. This finding suggests that I-FABP, with a half-life of 11 min while in circulation, could better reflects rapid changes in compliance to GFD with respect to anti-tTG, which take a longer time to normalize on a GFD or reactivate after a voluntary or involuntary gluten ingestion. This hypothesis is supported by two studies, the first of which shows that serum levels of I-FABP and anti-tTG normalized, respectively, in 82 % and 47 % of CD patients by 26 weeks of GFD [42]. The second study shows that serum I-FABP levels significantly increased in CD patients following 2 weeks of gluten challenge, while 4 weeks elapsed before a pronounced autoantibody increase was detected [43]. However, another study has shown that some adult CD patients on a GFD still present elevated serum I-FABP levels despite absence of villous atrophy and reduction or normalization of anti-tTG antibodies [44], probably due to age-dependent differences in long-term GFD adherence and intestinal mucosa healing [45]. In this context, elevated serum I-FABP levels nonresponding to GFD could be indicative of histological abnormalities and warrant further evaluation. Furthermore, high serum I-FABP levels have also been reported in patients with pathological conditions other than CD, such as neonatal necrotizing enterocolitis, acute mesenteric ischemia and inflammatory bowel disease [34,38]. Larger studies on both pediatric and adult populations also including disease controls are thus required to validate and promote the use of serum I-FABP as a non-invasive marker for diagnostic and monitoring purposes, in untreated and treated CD patients, respectively.

Although its use in the clinical routine of laboratories is not established, serum I-FABP could be a sensitive marker for enterocyte damage, since there is a correlation between serum I-FABP levels and the severity of villous atrophy in celiac disease patients at the time of diagnosis. Although enterocyte damage improves upon GFD, and therefore there is a decrease in I-FABP levels, in some cases this damage could persist despite absence of villous atrophy and reduction or negativization of

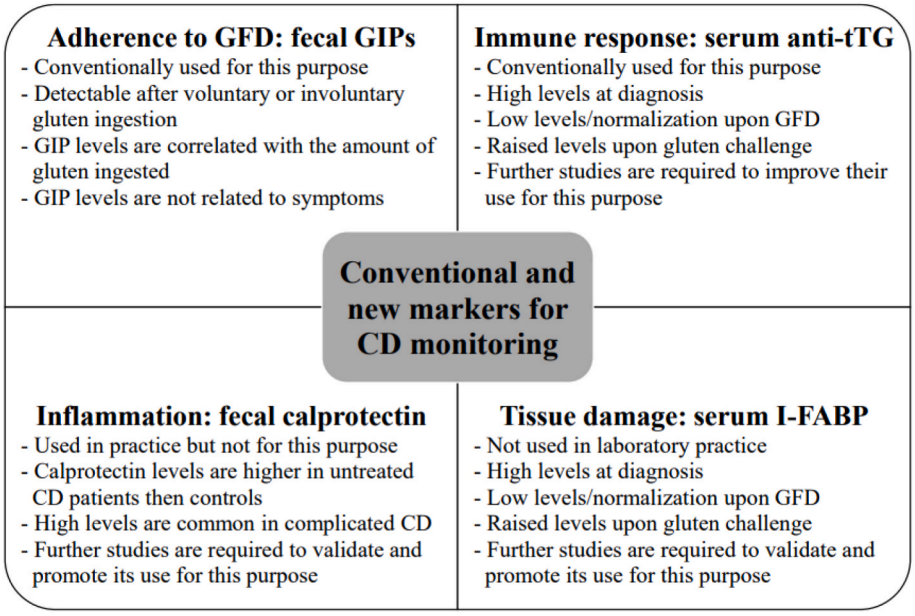

Fig. 1. Clinical and physiopathological distinction of conventional and new markers for CD monitoring: anti-tTG antibodies are markers of immune response and calprotectin of inflammation; iFABP are a marker of tissue damage, while GIPs reflect adherence to gluten-free diet.

anti-tTG IgA antibody titers.

1.2.3. Gluten immunogenic peptides (GIPs)

GIPs are fragments of gluten that are excreted undigested and can be detected in stool and urine. Due to their presence in stool up to four days after accidental exposure or voluntary gluten consumption and the correlation of the level with the amount of gluten ingested, GIPs can be used as a marker of adherence to GFD [46–49]. These peptides can also be found in urine, where they can be detected after 4–6 h after gluten intake and persist up to 48 h [50]. Therefore, GIPs are a direct biomarker of voluntary or involuntary gluten intake both in adult and pediatric CD patients. In addition, GIPs can be found in both symptomatic and asymptomatic CD patients after a GFD, consistent with the fact that persistent enteropathy is present in around 25–40 % of adult CD patients after two years on GFD and 5–19 % of pediatric CD patients after one year on GFD [51]. However, GIP levels are not related to symptoms [52]. Different assays are commercially available for GIP detection in stool and urine, based on immunochromatography/lateral flow technique, and only one commercial sandwich ELISA assay is currently available for detection of GIPs in stool (iVYLISA GIP-S test (Biomedal S.L., Seville, Spain)). All of them present CE-IVD certification but no IVDR certification. Considering the differences between the two methodologies, lateral flow immunoassays could be used either in clinical laboratories or point-of-care settings due to its simplicity, while ELISA would be more suitable for clinical laboratories when a quantitative analysis is required. Taking these aspects into account, the patients could perform the determination of GIPs at home when there is a suspicion of dietary transgression.

1.2.4. Calprotectin

Calprotectin is a protein primarily expressed by neutrophils. Elevated levels of calprotectin in faeces are a sign of Inflammation associated with neutrophil infiltration in the gastrointestinal tissue. Faecal calprotectin is therefore widely used as a non-invasive marker for inflammation and disease activity in Inflammatory Bowel Disease (IBD), which is characterized by neutrophilic infiltration [**35**]. Calprotectin is usually measured in faecal extracted samples by (automated) ELISA or binding assays which are IVDR/FDA approved. CD is classically associated with mononuclear infiltration in the epithelial layer (intraepithelial lymphocytosis), villous atrophy and crypt hyperplasia. Usually, neutrophilic infiltration is not taken into account. However, studies show a significant increase in neutrophils in up to 50 % of CD cases at diagnosis which were associated with more severe disease [53, 54]. It is however not clear if this neutrophilic infiltrate reduces upon treatment with GFD. Nevertheless, faecal calprotectin may be a non-invasive marker for continued inflammation in CD. Recently 10 case control studies investigating faecal calprotectin as a marker for small intestinal damage in CD were reviewed by Kivelä et al. [55]. Six of these studies found a significant increased faecal calprotectin in untreated CD patients compared to controls, while the other four showed no significant differences. These differences in outcome of these studies may not only be due to study design but may also be due to the proportion of patients with increased neutrophil infiltration at the start of the study. In addition, the mean calprotectin levels, although significantly higher in active CD compared to controls, were in 4 out of the 6 positive studies lower than the reference value used by most diagnostic laboratories (<50 μg/g); i.e the mean calprotectin levels are not considered to be elevated in these patients making it difficult translating these findings to daily practice. Interestingly, a more recent retrospective study in CD patients and non-celiac enteropathy patients showed that elevated (>50 μg/g) faecal calprotectin was significantly more common in complicated CD and non-celiac enteropathy compared to uncomplicated CD [56]. Prospective follow-up studies carefully taking confounding factors and pre-treatment neutrophil infiltration are needed to establish whether faecal calprotectin is indeed a valuable marker for small intestinal inflammation in the management and follow-up of CD patients.

1.3. Histological follow-up

The triad lymphocytosis, crypt hyperplasia and villous atrophy in duodenal biopsies has been the cornerstone of celiac disease diagnosis. However, the correct assessment of these signs of inflammation and mucosal damage is highly dependent on correct sampling of biopsies (at least two from the bulb and four from the second part of the duodenum are recommended [57]), correct orientation of the biopsies and standardized histopathological interpretation. Efforts to standardize interpretation of biopsies by applying quantitative parameters such as villous height to crypt depth ratio (VH; CrD) and IEL counts based on CD3 staining [58] have been made but are not widely implemented and most

pathologists use qualitative methods such as the Marsh and Marsh-Oberhuber classifications. Unfortunately, these scoring systems generally suffer from low inter-observer agreement, which may be better in experienced centers under controlled circumstances [59]. Establishment of the above mentioned changes in the duodenal mucosa have been the golden standard to diagnose CD up until the 2012 ESPGHAN criteria were published. These guidelines recommended diagnosis in pediatric cases without esophagogastroduodenoscopy (EGD) and histology of duodenal biopsies, provided the anti-tTG antibody levels are high and confirmed in a separate serum sample [60]. It is debated whether this approach is applicable in adults but if patients are unwilling or unable to undergo EGD, CD may be diagnosed without histology [22]. This means that CD is diagnosed more frequently without evaluation of the duodenal mucosa at diagnosis. On the other hand, the goal of evaluation of follow-up biopsies is to assess mucosal healing in response to GFD, but when diagnostic biopsies are lacking establishing improvement may prove difficult, particularly when low grade lesions are observed in follow-up biopsies.

Even though the 2023 US guideline [22] suggests setting a goal of intestinal healing as the end-point of GFD, there is little evidence to support that healed mucosa is related to improved outcome in CD. Most studies investigating mucosal healing in relation to clinical course are, for understandable reasons, retrospective. Retrospective studies suffer from selection bias as only patients that had a follow-up biopsy are included. If follow-up biopsies are not routinely performed, patients that have persistent complaints will be overrepresented in these studies. Wide ranges between 34 % and 65 % after two years and 66–85 % after five years of mucosal healing in adult patients are reported [61–63]. In pediatric patients mucosal healing rates are generally higher, 90–95 % after two years [61,62]. A study that included patients that routinely underwent a follow-up biopsy 5–18 months after diagnosis and were re-biopsied for the study 2–22 years after diagnosis showed an increase in mucosal healing from 50 % at follow-up biopsy to 98 % at study biopsy [64], suggesting that mucosal healing generally takes more than two years in adults but eventually occurs in the majority of patients. The question remains whether persisting duodenal damage in the absence of complaints is detrimental for the long-term outcome of CD. In a Swedish study of 7648 patients with established villous atrophy that had a follow-up biopsy within five years after diagnosis, persistent villous atrophy was not associated with increased mortality after a mean follow-up of 11.5 years [65]. In line with these data, guidelines generally do not recommend routine follow-up biopsies in CD patients that are asymptomatic on a GFD [66,67]. Nevertheless, recent guidelines of the American College of Gastroenterologists [22] state that “follow-up biopsy could be considered for assessment of mucosal healing in adults in the absence of symptoms after two years of starting a GFD” and the recent monitoring guidelines endorsed by the North American and European celiac disease scientific societies included a weak recommendation to repeat duodenal biopsy 12–24 months after the start of the GFD in treated patients with CD [23]. Follow-up biopsy in asymptomatic children is not recommended [22,68]. On the other hand, all guidelines recommend to re-biopsy in case of persisting or relapsing symptoms after GFD, although the time frame is not clearly stated [22,23,66,67].

2. Conclusions

The only effective treatment for CD consists of lifelong adherence to a strict GFD. Currently, in clinical practice, the same serological approach used to diagnose CD is also employed to monitor treated CD patients. However, anti-tTG antibody negative results do not necessarily indicate good adherence to GFD and also present a poor correlation with recovery of intestinal injury. Furthermore, all commercially available assays have been validated for diagnostic use and not for follow-up. All these limitations should be carefully considered before using an anti-tTG IgA or IgG antibody test to monitor the adherence and response to GFD and, at the same time, represent a starting point for further studies aimed at improving the monitoring of treated CD patients.

Beyond the serological approach, different procedures for the assessment of adherence to GFD have been proposed. Among these, GIPs present the most promising results since they can be used as a non-invasive marker of GFD adherence able to detect voluntary or involuntary gluten intake in both adult and pediatric CD patients. Small intestine biopsies, which are normally used for diagnosing CD and to evaluate its severity, could be used to monitor the adherence of patients to GFD and mucosal healing. However, this is an invasive procedure, expensive and not practical for this purpose.

In conclusion, the monitoring of treated CD patients is poorly studied and, accordingly, specific guidelines are still lacking. Further studies aimed at improving the assessment of adherence and response to GFD would be desirable.

CRediT authorship contribution statement

Marco Di Tola: Writing – original draft, Conceptualization. **Hetty J. Bontkes:** Writing – original draft, Visualization. **Juan Irure-Ventura:** Writing – original draft, Visualization. **Marcos López-Hoyos:** Visualization, Validation. **Nicola Bizzaro:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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