Chapter 11

Follow-Up of CD Patient: Is Mucosal Recovery a Goal of Therapy?

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Abstract

The main aim of this chapter is to give a comprehensive guide to the follow-up of patients with CD. The compliance with a strict gluten-free diet (GFD) is the main goal in the management. Patients must be trained in the GFD and the benefits obtained from a strict adherence. There are several methods to assess the compliance of the diet and they are summarized in the text: interviews with a dietitian or a doctor, structured surveys, serology, histology and gluten detection in the feces. Furthermore, CD patients must be included into a periodical follow-up made by a physician (general or gastroenterologist) qualified on the management of CD. Periodical visits include: clinical assessment, laboratory test (detection of nutritional deficiencies and CD serology) and other test in selected cases (bone densitometry and hyposplenism detection).

The evaluation of the duodenal mucosa recovery throughout the follow-up may be important to identify those patients who require a closer monitoring to detect nutritional deficiencies or complications associated to the persistence of mucosal atrophy.

Keywords

Celiac disease, management, gluten-free diet, duodenal biopsy.

1. Introduction

Patients diagnosed with celiac disease (CD) have a permanent intolerance to the gluten contained in their diet. Removal of gluten is associated with clinical and histological improvements, while poor adherence to a gluten-free diet (GFD) is associated with lower quality of life and higher risk of CD related symptoms and complications[1,2]. However, there are two key points that patients and physicians may have to take into account for the follow-up of CD patients:

Compliance with a strict GFD is a very hard and demanding daily task. Patients need as much dietary information as possible, and also clear advice from physicians. It is estimated that less than 50% of CD patients follow a strict GFD, mainly in the adult CD population. Better dietary compliance is achieved in the pediatric population when the disease is diagnosed in early childhood[3].

The second key point is the variability in the follow-up practices among physicians and the inadequate or absence of management after the diagnosis[4]. The lack of information in non-referral populations and the variability in the guidelines may be the main reason for these inadequate practices.

The main aim of this chapter is to give a comprehensive guide to the CD follow-up with a discussion of the leading goals of management.

2. Gluten-Free Diet

2.1. Importance of a Strict GFD Compliance

The tolerance of gluten in the diet is highly variable among patients. While someone present symptoms with small amount of gluten in the diet, others can tolerate routine transgressions[5]. Furthermore, some patients are diagnosed on the basis of screening approach and they have no symptoms to improve when gluten is avoided, making more difficult the compliance with the diet[6].

The first target of the physician following CD diagnosis is to explain to the patient the importance and benefits of strictly avoiding gluten in the daily diet. The patient must understand that no transgression is allowed to avoid complications and to achieve a similar quality of life and life expectancy than that of the general population. Strict GFD is associated with a decrease in the risk of developing lymphoproliferative disease in CD, which is the worst complication and with very poor prognosis[7].

The physicians involved in the management of CD must take into account that GFD compliance is the cornerstone of therapy. They must be able to adequately explain this concept to the patient. It is not clear who should perform the follow-up to investigate adherence to GFD: gastroenterologist, primary care physician or an expert dietitian[8]. Medical follow-up by primary care physicians or gastroenterologist may be similar in terms of rates of adherence to GFD[9]. The available evidence suggests that consultation with a dietitian may be useful when gluten contamination is suspected. However, follow-up by a dietitian and a doctor together may not be better than the care provide by either alone[10]. The final decision will depend both on the availability of an expert dietitian in the different centers and on the relationship between gastroenterology departments and primary care centers.

Patient associations or support groups can provide important care to achieve adequate dietary compliance. These associations offer detailed information about the importance of a strict GFD and answer questions related to gluten-free foods and cooking recipes. They also organize meetings where patients can share information about the disease and the compliance with diet[11].

2.2. Monitoring Adherence to the GFD

Gluten-free diet compliance may be assessed by several methods (Table 1). Dietary compliance assessed via interviews by a skilled dietitian is probably the best method. While some patients will only need consultation with their physician to achieve strict adherence to the GFD, others will require a multidisciplinary approach to assess GFD compliance.

Table 1. Methods proposed to monitor the adherence to GFD.

Interviews with a skilled dietitian
Consultation with the doctor
Structured surveys
Decrease of serological markers
Improve of villous atrophy
Detection of gluten peptides in feces

Resolution of symptoms may not be an accurate method to assess GFD adherence at the physician consult. On the other hand, persistence of symptoms is associated in most of the cases to continuous gluten ingestion[12]. Moreover, there are other issues different from gluten ingestion that may contribute to the perseverance of symptoms (see previous chapter). Structured short surveys have been employed as an alternative to dietitian consultation for quick assessment of GFD adherence. Questionnaires are easy and quickly to fill in the clinic. Their correlation with the antibody levels and duodenal biopsy appears be high and useful in the follow-up. However, they may be validated in different countries and clinical context before their widespread use[13].

Serologic levels of antibodies employed for CD diagnosis are gluten-dependent: a decrease is expected within months of strict GFD, a gluten challenge increase their values and the persistence of elevated levels suggest a lack of adherence to GFD[14]. Periodical testing for deaminated gliadin IgA and/or tissue-transglutaminase IgA antibodies may be useful for monitoring GFD compliance[15]. However, the normalization of these antibodies' titers does not identify minor dietary transgressions, and their usefulness may only be for predicting non-adherence but not for assessing strict adherence. Diagnosis of CD in adults is actually common in the absence of positive

antibodies (5-16% of biopsy confirmed CD) and serology is useless if antibody levels are not elevated before the start of the GFD[16].

Small bowel histology is the definitive way of assessing the healing of the mucosa. Villous atrophy recovery confirms that strict GFD is followed independently of serological titers or symptoms[1]. Intestinal biopsies in the follow-up may be important in adults where villous atrophy persists despite absence of symptoms and negative serology[17].

A novel method to monitor GFD compliance was recently described. This method can detect the presence of immunodominant gluten peptides in human feces based on the use of the anti-gliadin 33-mer G12 antibody. This antibody is able to detect small amounts of ingested gluten and would represent a quantitative method to assess gluten intake in CD patients. However, ongoing studies will clarify their role in CD management[18].

3. What Should We Test?

3.1. Clinical Assessment

Follow-up visits serve to check the improvement of initial symptoms or the manifestation of newly developed ones. The presence of gastrointestinal symptoms similar to those presented by patients complaining irritable bowel syndrome is common in patients with CD. The persistence or new onset of symptoms may be investigated as related to CD or as another entity. Furthermore, clinicians may be vigilant for symptoms associated with serious intestinal complications: unexplained fever, weight loss, severe diarrhea or signs of malnutrition[19]. Body weight and height in children may reflect adequate nutritional requirements and a correct absorption in the small intestine.

Autoimmune diseases are frequently associated with CD and they can develop at any time during the follow-up. Physicians must be aware of autoimmune and other related diseases associated with CD so to investigate them at the follow-up visits[20].

It is important to screen first-degree relatives and other relatives especially if they have some clinical symptoms. The index case must be informed about this family risk and recommend the screening of relatives[6].

3.2. Laboratory Tests

Laboratory test are important to recognize nutritional deficiencies and the development of associated diseases or complications. Physicians should check on the intestinal absorption status. The basic laboratory panel to analyze previous to each visit may include: full blood count, ferritin, vitamin B12, folate, calcium, alkaline phosphatase, thyroid-stimulatin hormone and thyroid hormone, glucose, aspartate and alanine aminotransferases and antibodies against deaminated gliadin IgA or tissue-transglutaminase IgA[21].

3.3. Other Tests

Decrease in the bone mineral density is probably due to vitamin D deficiency. However, the risk of fracture in CD patients is unclear and the predictive value of bone densitometry is not enough to identify individuals at high-risk of fracture. It seems reasonable to perform bone densitometry to those adult CD patients at high-risk situations that include post-menopausal women, men >55 years and those with known osteopenia before the diagnosis of CD[22]. Further studies are required to identify the efficacy and cost-effectiveness to perform bone densitometry to all the adult CD patients at diagnosis and to identify the follow-up frequency of performing this analysis[23].

Children may have reduced bone mass at the time of diagnosis. However, they are more likely than adults to have fully restored bone mass after 6-12 months of a GFD. Bone densitometry is not generally required in newly diagnosed pediatric patients with uncomplicated CD. In children, special attention to assure normal growth and development is recommended[24].

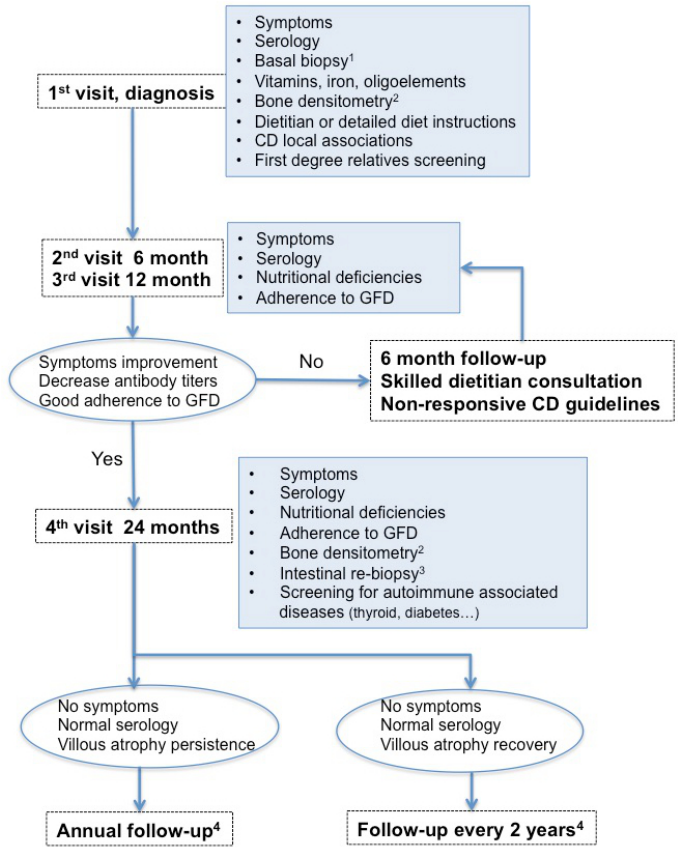
Hyposplenism may affect more than one-third of CD adult patients, while it is not a complication in pediatric patients. The incidence of hyposplenism

correlates with the duration of pre-exposure to gluten and it is higher in those with concomitant autoimmune disorders or pre-malignant conditions[25]. Based on this associated factors, the splenic function may be determined in a selected group of adult CD patients: older patients at diagnosis, concomitant autoimmune or premalignant disorders, and previous history of major infections or thromboembolism. As a diagnostic tool, pitted red cell counting remains an accurate, quantitative and inexpensive method[26]. Protein-conjugate vaccines should be recommended in patients with major hyposplenism, defined by a pitted red cells value higher than 10% and/or and IgM memory B cell frequency lower than 10%.

4. How Often Should We Test?

An algorithm that shows an approach to the monitoring and scheduled visits is shown in Figure 1. After the first visit we have established the diagnosis with a basal biopsy, nutritional status and bone mineralization in high-risk subjects. The second and third visits may be done at 6 months intervals and we must check the following items: symptoms, decrease of basal antibody titers, nutritional deficiencies and the grade of adherence to GFD.

After de first year of diagnosis the patient may experience one of the following situations: (i) symptoms persistence, (ii) elevated antibody titers or (iii) bad adherence to GFD. In these cases, the follow-up may continue at 6 months intervals and with the consultation of a skilled dietitian to ensure a strict GFD. When CD patient continue in this situation physicians must take into account the possibility of a non-responsive CD and follow the applicable guidelines.



(1) Basal biopsy is not always necessary in children. (2) In selected cases explained in the text. (3) Control biopsy in the follow-up may be useful in adult CD. (4) Monitoring in children may be performed annually until complete growth.

Figure 1. An algorithm for a suggest approach to the monitoring of celiac disease.

Those patients that remain without symptoms, decreased antibody titers and good adherence to GFD at one year after diagnosis, may be revised at 24 months. At this time, in adult CD, duodenal biopsy may be offered to the patient to assess duodenal atrophy recovery. So, in the case of persistence of mucosal atrophy, the interval of follow-up may be annual to rule out nutritional deficiencies and to check for other complications related to CD.

However, if the duodenal mucosa shows normal architecture, the follow-up visits may be delayed, and intervals of visits scheduled every two years.

Pediatric CD may be followed with the same scheme than adults. However, bone densitometry and follow-up biopsy would be done only in selected cases. The children with good adherence to GFD and normal antibodies levels would probably be followed yearly instead of every two years. The main reason for this shorter interval is the need for an early recognition of conditions associated to pediatric CD and specially to assure normal growth and development.

5. Biopsy Control: Is Mucosal Recovery a Goal of Therapy?

As statement in the latest EPSGHAN criteria, CD children diagnosed with CD do not need a histological re-evaluation on a GFD[27]. Thus, follow-up biopsy is not recommended as a routine in children, and may be offered only to those children with non-responsive CD.

Celiac disease shows several differences between children and adults that may be taken into account in the follow-up of the disease. A large number of patients in the adult age are asymptomatic or minimally symptomatic at presentation. These cannot be followed up using symptom relief as the main determinant of clinical response. Other adult patients are diagnosed with normal antibody titers showing histological abnormalities in the duodenal biopsy. In these "seronegative" subjects, serology is not useful to assess gluten adherence or to predict mucosal healing. Finally, histological recovery is achieved in most of children but is variable in adults where complete histological recovery is reported in less than 50% of the cases[17,28].

The American College of Gastroenterology recently published guidelines include the recommendation that it is reasonable to do a follow-up biopsy in adults after two years of starting a GFD in order to assess mucosal healing, but it is not recommended as routine in children[1]. The British Society of Gastroenterology guidelines are less categorical and suggest that there is little

evidence to address whether clinical outcomes are significantly altered as a result of re-biopsy. Furthermore, the British guidelines highlight the lack of data about the cost-benefit analysis of repeated biopsy, and their final recommendation is that follow-up biopsies are not mandatory if the patient is asymptomatic on a GFD and has no other features that suggest an increased risk of complication[29].

In Figure 1 we can see that a great benefit of re-biopsy on GFD is the stratification of patients with CD in two groups: those suitable for less strict controls when mucosal recovery is achieved and those requiring more intensive clinical management when the atrophy persists in duodenal mucosa. It is clear that the persistence of villous atrophy is associated with CD complications and adverse outcomes. Even the persistence on GFD of mild forms of enteropathy (Marsh I or duodenal lymphocytosis) may be associated with nutritional deficiencies or complications[30]. As the median time to mucosal recovery has been reported as two to three years, the control biopsy may be offered to adult patients at this time (Figure 1)[31].

Patients with villous atrophy persistency may require closer clinical supervision, and strict GFD compliance is mandatory for them. Subsequent re-biopsies may be offered when there is no evidence of gluten contamination in the diet. There is less evidence for duodenal re-biopsy in those cases with persistent mild forms of enterophaty where other causes different from gluten could be responsible (mainly the *Helicobacter pylori* infection and the NSAID ingestion)[32].

6. Conclusions

The compliance with a strict GFD is the cornerstone of CD management. Patients must be followed-up along their lives by a health-care practitioner with knowledge of CD, and in some cases with the support of a skilled dietitian. Duodenal biopsy in the follow-up is a useful practice in adult CD to assess mucosal recovery and would be helpful to detect those individuals at-risk for complications.

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