CHAPTER 7

Gluten tolerance in adult patients with celiac disease 20 years after diagnosis?


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ABSTRACT

Background & objective: Celiac disease (CD) is believed to be a permanent intolerance to gluten. A number of patients, however, discontinue the gluten-free diet (GFD) without developing symptoms or signs. The aim of our study was to investigate whether CD patients are capable of developing tolerance to gluten.

Methods: All 77 adult patients from our hospital known to have biopsy-proven CD for more than 10 years were invited to participate. We investigated symptoms, gluten consumption, antibodies for CD and other autoimmunity, human leukocyte antigen (HLA)-typing, bone mineral density, and performed small bowel biopsies. Tolerance was defined as no immunological or histological signs of CD while consuming gluten.

Results: Sixty-six patients accepted participation, but after review of the diagnostic biopsies 53 were found to have true CD. Twenty-three percent of patients had a gluten-containing diet (GCD), 15% admitted gluten transgression (GT) and 62% followed the GFD. Patients on a GFD had significantly more osteoporosis. Normal small bowel mucosa was found in four of eight on GCD and in four of four with GT. Two patients were considered to have developed tolerance to gluten. One of them was HLA-DQ2/DQ8 negative.

Conclusion: Development of tolerance to gluten seems possible in some patients with CD. Further follow-up will show whether this tolerance is permanent or only a long-term return to latency. This feature may be associated with genetic characteristics, especially with HLA genotypes that differ from DQ2 or DQ8. More insight into the mechanisms of the development of gluten tolerance may help to distinguish those CD patients that might not require life-long GFD.
INTRODUCTION

Celiac disease (CD) is a chronic disorder caused by an inflammatory T-cell response to the gluten proteins present in wheat. Gluten causes villous atrophy of the small intestine in CD patients, which may lead to nutrient malabsorption, causing a broad spectrum of symptoms. Furthermore, CD may also be asymptomatic.

CD is considered to be a permanent disorder and, the advised treatment is life-long adherence to a gluten-free diet (GFD). GFD improves the health status of CD patients (1,2) and protects them from development of complications (3,4), but is frequently experienced as a burden on social life and on quality of life (5-7), and compliance may pose a problem (5,6,8-10). It is well known that a number of CD patients stop following the GFD after a time of treatment without developing symptoms or signs of disease. Most of them will develop CD intestinal lesions after different periods of gluten consumption, but some seem to tolerate gluten for a long time (11-13). The aim of the present study was to investigate whether there are CD patients who may develop tolerance to gluten, and if so, to explore their genetic, immunological and clinical characteristics.

METHODS

In this follow-up study, we collected all patients aged 20-80 years from the files of the medical administration of the Leiden University Medical Center who had undergone a small bowel biopsy between 1975 and 1994 and met the diagnostic criteria for CD. These were clinical signs of CD and at least one biopsy of the small intestine, showing the characteristic appearance of CD (villous atrophy, crypt hyperplasia, inflammatory infiltration) during gluten consumption, and clinical and/or histological recovery, once treated with a GFD (14).

The patients were traced using the national telephone registry or information from the municipal authority of the last known address of the patient. Informed consent to participate was asked for by letter. Non-responders were sent a reminder after 2 months and, in case of no response, were contacted by telephone after 6 months.

Food questionnaire

Patients were asked to register their degree of compliance with the diet as strict, partial (gluten transgression; GT: 0-10 g gluten/day) or none (gluten-containing diet; GCD: >10 g gluten/day). From the patients with partial or nonadherence to the diet, consumption of gluten-containing products was checked by a food frequency questionnaire. Gluten intake was estimated by multiplying the grams of vegetable protein from gluten-containing cereals by 0.8 (15).
Assessment of symptoms

Specific gastrointestinal symptoms were evaluated according to the Gastrointestinal Symptom Rating Scale (GSRS) (2,16,17) which rates symptoms from 1 ‘no discomfort at all’ to 7 ‘very severe discomfort’. Furthermore, 27 items on associated diseases and other CD-related symptoms such as vomiting, anorexia, weight loss, aphthous ulcers, lassitude, anaemia, alopecia, muscular cramp and weakness, erythema nodosum, osteoarthropathy, dental enamel defects and peripheral neuropathy were asked and also scored from 1 to 7.

Anthropometry

Patients were instructed to perform three measurements of their own height and weight at home following written instructions and the average was used for further analyses.

Blood tests

Participants were asked to have blood puncture. Human leukocyte antigen (HLA)-typing was performed at our hospital (Professor F.H.J. Claas), and serum ferritine, folic acid, vitamin B12, 25(OH) vitamin D and calcium were measured according to routine testing. Titers of serum immunoglobulin (Ig)-A against gliadin (AGA), tissue transglutaminase (tTGA) and endomysium (EMA) were measured, respectively, using enzym-linked immunosorbent assay techniques and indirect immunofluorescence on monkey oesophagus (BME von Blomberg) (18,19). In case of IgA deficiency (total IgA concentration <0.06 g/l), serum IgG-AGA and IgG-tTGA were measured.

To check the development of other autoimmune phenomena, the following parameters were measured in serum (MR Batstra, BME von Blomberg): thyroperoxidase (TPO) and thyroglobulin antibodies, by haemagglutination (Thymune-M and Thymune-T; Remel Europe, Ltd, Kent, UK), thyroid stimulating hormone receptor (TSH-R) antibodies by radioimmunoassay (TRAK assay; BRAHMS diagnostica GmbH, Berlin, Germany), glutamic acid decarboxylase antibodies (anti-GAD), insulinoma-associated protein-2 antibodies (IA2) by radioimmuno-assay (RSR Ltd, Cardiff, UK) and islet cell antibodies (ICA) by indirect immuno-fluorescence on human bloodgroup O pancreas.

Bone mineral density

Bone mineral density (BMD) of both right and left femoral neck and the lumbar spine were assessed by dual-energy X-ray absorptiometry (DEXA). Osteopenia was defined as BMD of –1 to –2.5 SD and osteoporosis as BMD of less than -2.5 SD.

Histology

Duodenal biopsies were offered to all patients consuming gluten (GT, GCD), and to patients with positive celiac antibodies or decreased BMD while following a GFD. Biopsies were performed according to routine procedures. All study and diagnostic
biopsies were reviewed by the same pathologist (H.M.) who was unaware of the clinical situation of the patient and classified according to the modified Marsh criteria (20,21).

**Tolerance**
Tolerance to gluten was defined as no immunological or histological signs of CD while the patient was consuming a GCD for more than 2 years.

**Statistical analysis**
All analyses were carried out using SPSS 11.5. Results with normal distribution are presented as means with standard deviations and with skewed distribution as medians with ranges. To compare patient characteristics and results, the Kruskall Wallis and Mann-Whitney U-tests were used for skewed distribution and the analyses of variance for normal distribution. Percentages and numbers of patients were compared using the Fisher's Exact test. P-values less than 0.05 were considered as significant.

**Ethics**
The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center.

**RESULTS**

The patient flow chart is presented in Fig. 1. Of the 114 patients with villous atrophy, 37 were not eligible to be invited. Reasons for ineligibility were death (n=18), diagnoses different from CD (n=8: lactose intolerance, tropical sprue, isolated short stature, chronic nonspecific diarrhea or giardiasis), severe psychiatric or social problems (n=2) and psychomotor retardation (n=1). In addition, eight could not be invited due to unknown address, emigration or failure to contact them by telephone.
Figure 1. Flow chart of all the patients aged 20-80 years known in the files of the medical administration of the Leiden University Medical Center, with a small bowel biopsy with villous atrophy between 1975 and 1994.

Patients
n=114

Eligible/invited
n=77

Informed consent

No
n=11

Stop

Yes
n=66

Biopsy-confirmed CD, including review of diagnostic biopsy
n=53

Dietary regimen

GCD
n=12
HLA: 11/12
DQ2 n=7
DQ1,6 n=1
DQ 6 n=1
DQ1,7 n=1
DQ3,5 n=1

GT
n=8
HLA: 6/8
DQ2 n=3
DQ8 n=1
DQ8,7 n=1
DQ5,9 n=1

GFD
n=33
HLA: 31/33
DQ2 n=31

Actual small bowel histology

Marsh 0-1
n=4/8

Marsh 3
n=4/8

Marsh 0-1
n=4/4

Marsh 0-1
n=9/10

Marsh 3
n=1/10

GCD, gluten-containing diet; GFD, gluten-free diet; GT, gluten transgression; HLA, human leukocyte antigen.
Of the 77 patients invited (67%), 66 agreed to participate (86%). Through review of the diagnostic biopsies 53 patients were found to have true CD and only these patients were taken into account in this study. Characteristics of the patients are presented in Table 1, grouped according to their dietary habits. Patients on GCD and those with GT were diagnosed with CD at a significantly younger age (median: 2 years; range: 0.7-32) than patients who strictly adhered to the GFD. The duration of CD was, however, comparable in all three groups.

Table 1. Clinical characteristics of 53 patients with biopsy-confirmed celiac disease according to their dietary habits.

<table>
<thead>
<tr>
<th></th>
<th>GCD (n=12)</th>
<th>GT (n=8)</th>
<th>GFD (n=33)</th>
<th>Overall</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m)</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>0.07b</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>30 (25-53)</td>
<td>26 (22-66)</td>
<td>57 (21-77)</td>
<td>0.0001a,b</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>2 (0.7-15)</td>
<td>4 (0.9-32)</td>
<td>24 (1-65)</td>
<td>0.0001a,b</td>
<td></td>
</tr>
<tr>
<td>Duration of CD (y)</td>
<td>28 (16-44)</td>
<td>24 (17-34)</td>
<td>25 (12-52)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Duration of GFD (y)</td>
<td>6 (1-28)</td>
<td>14 (0.2-23)</td>
<td>24 (8-36)</td>
<td>0.0001a,b</td>
<td></td>
</tr>
<tr>
<td>Duration of actual gluten consumption (y)</td>
<td>18 (1-32)</td>
<td>8 (2-34)</td>
<td>0</td>
<td>0.0001a,b</td>
<td></td>
</tr>
<tr>
<td>Gluten intake (g/day)</td>
<td>15 (10-24)</td>
<td>0.9 (0.004-3)</td>
<td>0</td>
<td>0.0001a,b,c</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>22.4 ± 3.3</td>
<td>22.8 ± 2.5</td>
<td>24.6 ± 3.6</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

GCD, gluten-containing diet (>10 g gluten/day); GFD, gluten-free diet (0 g gluten/day); GT, gluten transgression (0 – 10 g gluten/day); aSignificance between GCD and GFD; bSignificance between GT and GFD; cSignificance between GCD and GT.

Food questionnaire
All participating patients completed the questionnaire on gluten consumption. A strict compliance with the GFD was self-reported by 62% of the patients. Twelve patients (23%) reported a GCD with a median gluten intake of 15 g/day for a median of 18 years, which was, of course, significantly higher than the gluten intake (0.9 g/day) of the eight patients with GT (Table 1). The reasons for restarting gluten consumption were: ‘according to the doctor CD was cured’ (n=4) or ‘no complaints after gluten ingestion’ (n=8).

Health status
No differences were found in the results of the Gastrointestinal Symptom Rating Scale and in the other CD-related symptoms among patients in the 3 groups (Table 2).
Table 2. Comparison of the Gastrointestinal Symptom Rating Scale scores and other CD-related symptoms in patients with biopsy-confirmed celiac disease according to their dietary habits.

<table>
<thead>
<tr>
<th>GSRS symptom</th>
<th>GCD (n=12)</th>
<th>GT (n=8)</th>
<th>GFD (n=33)</th>
<th>Overall P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>1.8±1.5</td>
<td>1.6±0.7</td>
<td>1.6±0.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Indigestion</td>
<td>2.0±1.2</td>
<td>2.5±1.1</td>
<td>2.1±0.9</td>
<td>0.63</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.5±0.7</td>
<td>2.1±1.5</td>
<td>2.0±1.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.9±1.6</td>
<td>1.9±1.3</td>
<td>2.6±1.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Other CD-related symptoms</td>
<td>1.4±0.4</td>
<td>1.4±0.2</td>
<td>1.5±0.4</td>
<td>0.52</td>
</tr>
</tbody>
</table>

CD, celiac disease; GCD, gluten-containing diet (>10 g gluten/day); GFD, gluten-free diet (0 g gluten/day); GSRS, Gastrointestinal Symptom Rating Scale (with scores from 1 'no discomfort at all' to 7 'very severe discomfort'); GT, gluten transgression (0 – 10 g gluten/day).

CD-related symptoms=vomiting, anorexia, weight loss, aphthous ulcers, lassitude, anaemia, alopecia, muscular cramp and weakness, erythema nodosum, osteoarthropathy, dental enamel defects, peripheral neuropathy.

A significantly higher number of patients following a GFD reported osteoporosis: 13 compared to none of the patients in the other two diet groups (P=0.008). In addition, two new cases of osteoporosis were found during the study in patients following a GFD, but none were found in the other groups. The present median age (61 vs. 40 years, P=0.001) and median age at diagnosis (32 vs. 11 years, P=0.001) of patients on a GFD with osteoporosis was significantly higher compared with the ones on a GFD without osteoporosis. No difference was, however, observed in the sex distribution among those with and without osteoporosis (P=0.41). In two cases, osteoporosis was the presenting symptom of CD. Osteopenia was found to be equally distributed throughout the three dietary groups: in two of 10 (20%) patients on a GCD, in four of six (67%) with GT and in six of 30 (20%) on a GFD (NS).

An associated disease was reported for 27 times (by 32% of the patients). Some patients had more than one associated disease. Divided over the three diet groups, there were five patients with selective IgA deficiency, three with dermatitis herpetiformis, three with hypothyroidism, two with diabetes mellitus type 1, two with rheumatoid arthritis, one with secondary hyperparathyroidism, two with Sjogren syndrome, two with cancer, one with ulcerative colitis, one with multiple sclerosis, one with auto-immune hypothyroidism, one with systemic lupus erythematosus, one with scleroderma and one with fertility problems and miscarriages. No significant differences exist in the distribution of patients with an associated disease among the three groups.
**Blood tests**

Fourty-six of the 53 participating patients (87%) were consented to blood puncture. No deficiencies were found in any of the patients. Five patients were IgA deficient: one of them (GCD) had IgG-AGA and another one (GFD) had IgG-tTGA. IgA positivity for CD antibodies was found in four of 41 patients (10%) (Table 3). A significant difference was found in the number of patients with positive IgA-EMA among the three dietary groups ($P=0.043$).

HLA-typing was performed in 48 patients: 41 (85%) were HLA-DQ2 and one (2%) was HLA-DQ8 (Fig. 1).

<table>
<thead>
<tr>
<th>Antibody</th>
<th>GCD ($n=9$)</th>
<th>GT ($n=6$)</th>
<th>GFD ($n=26$)</th>
<th>Overall $P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA-AGA</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>IgA-EMA</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0.043</td>
</tr>
<tr>
<td>IgA-tTGA</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>TPO</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.77</td>
</tr>
<tr>
<td>ICA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.77</td>
</tr>
<tr>
<td>IA-2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AGA, antigliadin antibody; anti-GAD, glutamic acid decarboxylase antibodies; EMA, antienormysium antibody; GCD, gluten-containing diet (>10 g gluten/day); GFD, gluten-free diet (0 g gluten/day); GT, gluten transgression (0 – 10 g gluten/day); IA2, insulinoma-associated protein-2 antibodies; ICA, islet cell antibodies; TPO, thyroperoxidase antibodies; tTGA, tissue transglutaminase antibody.

**Histology of the small bowel mucosa**

A small bowel biopsy was offered to 41 patients and 22 patients consented. A normal small bowel mucosa (Marsh 0-1) was found in four of eight patients on a GCD, in all four patients with GT and in nine of 10 patients adhering to a GFD. Marsh 3a-c lesions, suggestive of active CD, were found in four patients on a GCD and in one following a GFD (Fig. 1). The patient on a GFD with Marsh 3a lesion is now being studied for possible refractory CD.
**CD patients with possible tolerance to gluten**

Four patients were considered as possibly tolerant to gluten. None of them had serum antibodies for CD or other (auto) antibodies and none of them had osteoporosis. The first patient is a 31-year-old man, with HLA-DQ1/DQ6, diagnosed with CD at the age of 2.7 years. He presented with vomiting, chronic diarrhoea, abdominal pain and weight loss. The patient's small bowel biopsy showed Marsh 2 lesions. The symptoms improved on a GFD. A gluten challenge was performed at the age of 6 years: he developed high IgA-AGA (at that time measurement of EMA or tTGA was not available) and the small bowel biopsy showed Marsh 3a lesions. At present, after 13 months of gluten consumption he has Marsh 1 lesions. This short period of gluten consumption, however, is not enough to consider him tolerant to gluten.

The second patient is a 37-year-old, HLA-DQ2 positive, woman diagnosed with CD at the age of 1 year. She presented with growth retardation, weight loss, distended abdomen, lassitude and chronic diarrhoea with steatorrhoe (78% fat absorption). Small bowel histology showed total villous atrophy, Marsh 3c. After GFD, her symptoms, fat absorption (93%) and small bowel mucosa improved significantly. A small bowel biopsy after gluten challenge at the age of 3 years showed again Marsh 3c lesions. At present, after consuming gluten for more than 21 years, the patient has Marsh 1 lesions. The patient reported fertility problems and miscarriages and has recently been diagnosed with a basal cell carcinoma of the skin, she, therefore can not be considered tolerant to gluten.

Patient 3 is a 25-year-old woman, with HLA-DQ1/DQ2, diagnosed at 2.3 years of age. She presented with chronic diarrhoea. Her small bowel biopsy showed Marsh 3a lesions. After GFD, both her symptoms and her small bowel biopsy improved: a control biopsy at the age of 7 years was normal (Marsh 0). After that she has been eating gluten, but control biopsies taken after 2, 3, 7, 10 and 18 years of gluten consumption showed normal or almost normal mucosa without significant increase of IEL: Marsh 0-1 lesions, with IEL counts of 10-30/100 epithelial cells. The patient’s mother and brother also have CD. She may be considered as having developed tolerance to gluten.

Patient 4 is a 32-year-old man, with HLA-DQ3/DQ5, diagnosed with CD at the age of 2.2 years. He presented with vomiting, chronic diarrhoea and distended abdomen. His small bowel biopsy showed Marsh 3a lesions. The symptoms and small bowel mucosa improved after GFD. Gluten challenge resulted in growth retardation, lassitude and diarrhoea, and his small bowel mucosa showed Marsh 2 lesions at the age of 9 years. After reintroduction of the GFD, the clinical symptoms improved again. The patient has now been consuming gluten for more than 22 years and has Marsh 0-1 lesions. The only alteration found in this study was osteopenia so we consider him to have developed tolerance to gluten.
DISCUSSION

In this study, we have found two patients with biopsy-confirmed CD who show no signs of active CD after a mean gluten consumption period of 20 years. These observations suggest that the development of gluten tolerance may be possible in CD patients. The intestinal immune system has several arms of defence aimed at avoiding systemic and peripheral inflammatory immune responses. This can occur by activation of regulatory T cells to tolerate innocuous antigens, such as food proteins. This hyporesponsiveness to antigens in the intestine is a phenomenon termed ‘oral tolerance’ (22-24). The immunopathological origin of CD, however, may be explained by poorly developed intestinal tolerance against gluten leading to disrupted proximal gut homeostasis in genetically susceptible individuals (25).

In this study, we defined tolerance to gluten as no immunological or histological signs of CD while the patient was consuming gluten for more than 2 years. Two years is a generally accepted, although not proven, period in which histological relapse will occur on gluten consumption, but much longer durations have been described (26-28). The two patients who may be considered tolerant both consume gluten for a considerable longer period: 18 and 22 years, respectively. It is arguable whether the term of tolerance is appropriate to describe our two patients, as it is known that CD patients may relapse after a long period of apparent tolerance (28) and the term ‘return to latency’ has been used before in this context. Only further follow-up will make clear whether our patients are permanently tolerant to gluten. We consider them now as possibly tolerant and indeed have returned to latency for a (very) long period of time.

It is arguable whether the absence of clinical symptoms should be included in the concept of possible tolerance. Our results show that the frequency of symptoms in CD patients within the three groups with different gluten consumption was comparable (Table 2). In other words, patients adhering to a strict GFD also had gastrointestinal and other CD-related complaints. This confirms that the presence of health complaints is not an indicator of the histological status (29,30).

In contrast to expectations, we found osteoporosis only in patients on a GFD. This may be explained by their old age (61 years) and high age at diagnosis (32 years), an age before which formation of bone peak mass is reached in healthy situations. Furthermore, some patients started to adhere to the GFD with a delay of 6 years after CD diagnosis. It is well known that GFD improves reduced bone mineral density frequently present in newly diagnosed adult CD patients, although in contrast to children in adult patients it may not normalize (31-32).

The development of gluten tolerance in CD patients is controversial and the main question with regard to our patients is whether they ever had CD in the first place. For that reason, together with their medical files, the diagnostic small bowel biopsies were
revised by one experienced pathologist (H.M.). In 13 patients CD could not be
confirmed, but in the ones who developed tolerance to gluten CD was confirmed in this
way. This interobserver variation in the histopathological diagnosis of CD has also been
found by others (33,34) and, when in doubt, an experienced gastrointestinal pathologist
should be consulted (Dr. J.W. Meijer, personal communication). Forty-two of the 48
patients for whom HLA-typing was available were HLA-DQ2 and/or -DQ8 positive.
The other six patients had various HLA-typings of whom two (HLA-DQ6/DQ7 and
HLA-DQ3/DQ5) were found to express a functional homolog of the DQA1*0501
chain of HLA-DQ2, thus one of the two chains of the disease associated HLA-DQ2
dimer. The presence of half of the HLA-DQ2 chain in HLA-DQ2/DQ8 negative CD
patients has been described earlier (35). CD is associated with HLA-DQ2 and -DQ8 (36-
38) and the chance of having CD without these haplotypes is very low, although not
absent (37,39,40). The other four non-HLA-DQ2 or non-HLA-DQ8 patients (HLA-
DQ6/DQ7, HLA-DQ6, HLA-DQ5/DQ9, and HLA-DQ1/DQ7) are exceptions among
the CD population, but they were diagnosed with CD according to the accepted
ESPGHAN criteria (14), two of them including deterioration of the small bowel mucosa
after gluten challenge (41), so we consider them as CD patients.

CD patients who tolerate gluten have been reported by a French group of well-known
CD researchers (11-13,28). Recently they have described eight adult CD patients without
clinical symptoms or no immunological or histological signs of CD while consuming
gluten for a median period of 14 years. One of the reasons to consider that CD is a
permanent disorder is the result of a large study in young children showing that 95% of
them had histological alterations characteristic of CD after gluten challenge (42). It is
possible that gluten sensitivity, however, may decrease or increase during different
periods of life. Adult CD patients, who had been a few years on a GFD during childhood
and now consume gluten, show a less severe clinical picture than observed in newly
diagnosed adult CD patients, suggesting some patients develop resistance to gluten after
a period of GFD (43). Indeed our two patients who returned to latency were both
diagnosed during childhood.

In conclusion, in this follow-up study we have found two CD patients who returned to
latency and have possibly developed tolerance to gluten. This phenomenon may be
associated with specific genetic characteristics, especially with HLA genotypes, as we
have found that one of the CD patients who returned to latency has HLA-typing other
than DQ2 or DQ8. The factors and mechanisms that play a role in the development of
tolerance in CD patients are unclear and more studies are needed to unravel this
phenomenon to allow us to identify these exceptional CD patients that may not require
life-long GFD. Further follow-up is, however, needed to investigate whether these
patients remain at this level and confirm whether CD can be transient. Meanwhile, CD
patients should be aware of the potential risk they are at for complications and the
possibility of relapse when they have gluten consumption and therefore, regular dietary and medical follow-up remains necessary (3,4,28).

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REFERENCES


