Autoimmune diseases in coeliac disease: effect of gluten exposure

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***Abstract*:** Introduction: the prevalence of autoimmune diseases is increased in patients with coeliac disease. Duration of gluten exposure seems to predispose adolescents with coeliac disease to autoimmune diseases. Aim: In a retrospective cohort study, we assessed the relationship between autoimmune disorders and actual gluten exposure in patients with coeliac disease. Patients and methods: the frequency of autoimmune disorders was evaluated in 64 patients (53 females, 11 males, mean age 29 years, range 16–63) with coeliac disease. The effect of age at the end of follow up, age at diagnosis of coeliac disease, actual gluten-exposure time, gender and diagnostic delay was assessed. Results: the prevalence of autoimmune diseases was 17%. Mean duration of gluten exposure was 26 and 25 years for patients with and without autoimmunity, respectively. Logistic regression showed that a longer mean follow up ($P = 0.044$) was related to the prevalence of autoimmune disorders while actual gluten exposure was not predictive. Conclusion: in this study, the prevalence of autoimmune diseases in patients with late coeliac disease diagnosis does not correlate with duration of gluten intake. Confirmatory prospective, multicentre studies of the effect of gluten-free diet are needed in adults.

***Keywords*:** coeliac disease, autoimmune disease, prevalence, gluten exposure, gluten-free diet

Introduction

Coeliac disease is a gluten-dependent disorder, triggered by ingestion of gluten and causing small-bowel mucosal inflammation, villous atrophy and crypt hyperplasia in genetically predisposed individuals. Its association with other autoimmune diseases has been well established in many studies. It has been suggested that prolonged exposure to gluten in coeliac disease may promote the development of other autoimmune diseases. Ventura *et al.* [2002] were the first to propose that gluten load might be involved in the pathogenesis of autoimmune disease in coeliac disease. Thus, a gluten-free diet has been proposed to prevent the development of autoimmune disease in coeliac subjects. However, the protective effect of a gluten-free diet has been disputed. The aim of the study was to establish the frequency of autoimmune disease in coeliac subjects and to find out how these diseases develop in relation to gluten intake.

Materials and methods

Patients

This was a retrospective study in which we reviewed the hospital medical records of adult patients in whom coeliac disease was diagnosed at our centre from 1991 to 2006. Coeliac disease was revealed by typical symptoms in 52 patients, whereas in 9 and 3 patients respectively, the disease was subclinical and silent. The diagnosis of coeliac disease was made in all cases by histology. According to Marsh criteria, the disease was mild (I, II, IIIa) in 12 patients and severe (IIIb, IIIc, IV) in 52 cases. Villous atrophy was total or subtotal in 77% and partial in 23% of the cases. Immunologic criteria were deemed positive by the presence of at least one of these antibodies: antigliadin, antiendomysium or antitissue-transglutaminase.

Methods

The presence of autoimmune disease was assessed by reviewing patient records. We searched for the

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following disorders: insulin-dependent diabetes mellitus, autoimmune thyroid diseases, Addison's disease, autoimmune hepatitis, primitive biliary cirrhosis, primary sclerosing cholangitis, pernicious anaemia, autoimmune anaemia, autoimmune neutropenia, autoimmune thrombocytopenia, connective tissue diseases, alopecia, psoriasis and dermatitis herpetiformis. The presence of one of these autoimmune diseases was searched by clinical or biological evaluation at the diagnosis of coeliac disease and by clinical evaluation during follow up. The date of the diagnosis of autoimmune disease was recorded.

For each patient, the following features were recorded:

- age at coeliac disease diagnosis;
- age at diagnosis of autoimmune disease;
- diagnostic delay (time between the first onset of symptoms and the diagnosis of coeliac disease);
- diet compliance;
- histological outcome: histological remission was defined by mucosal recovery in control biopsy;
- immunologic outcome: immunologic remission was defined by a lack of serum antibodies;
- years of follow up;
- actual duration of gluten exposure: the endpoint for actual gluten-exposure time was specified as follows: to commencement of a strict gluten-free diet, or to the diagnosis of an autoimmune disorder in cases where autoimmune disease occurred before adoption of a strict gluten-free diet or to the end of follow up in cases where patients did not adhere to a strict gluten-free diet and autoimmune disease did not develop;
- sex.

Dietary assessment

At diagnosis, the patient met with a dietician for explanation of the gluten-free diet. During follow-up, adherence to the gluten-free diet was evaluated on every visit by the physician in charge of the patient. In addition, whenever a lapse was suspected, the patient was seen by a dietician who ascertained compliance and the absence of unintentional gluten ingestion. The diet was classified as strict (no dietary lapses), partial (regular dietary lapses) or a normal gluten-containing diet.

Statistical analysis

Statistical data were generated using SPSS version 11.5. For all statistical analyses, a two-tailed P-value <0.05 was considered significant.

Results

A total of 64 patients were enrolled in the study. The demographic data on coeliac disease patients are presented in Table 1.

Prevalence of autoimmune disease

The overall prevalence of autoimmune disease was 17%. In only one patient, autoimmune disease was diagnosed before coeliac disease while 91% of autoimmune disease diagnoses were subsequent to the diagnosis of coeliac disease. Hypothyroidism and pernicious anaemia were the most frequent disorders, retrieved in two cases respectively. The different types of autoimmune disease are presented in Table 2. The coeliac disease patients were then grouped according to the absence (group 1) or presence (group 2) of associated autoimmune disease.

Logistic regression analysis

The logistic regression model, using a univariate approach, showed an increased prevalence of autoimmune disease in older patients, in female patients and in those with longer diagnostic delay; however, these results were not statistically significant. Indeed, a longer mean follow up was a significant predictor of an increased risk for developing autoimmune disease ($P=0.044$). None of the other clinical–epidemiological

Table 1. Demographic data on coeliac disease patients.

	Coeliac disease ($n=64$)
Female%	83
Race%	
Caucasian	100
Age at diagnosis of coeliac disease, mean (range) (years)	29 ± 11 (16–63)
Age at end of follow up, mean (years)	33
Strictness of gluten-free diet (%)	
Strict	64
Partial	25
Gluten-containing diet	11
Not known	0

features, in particular actual gluten exposure, reached statistical significance. These results are described in Table 3.

Discussion

Coeliac disease seems to meet the criteria of a true autoimmune disease triggered by an environmental agent (gluten) in genetically predisposed individuals and causing production of autoantibodies [Meize-Grochowski, 2005; Ventura *et al.* 2002; Kumar *et al.* 2001]. The exposure of an immature immune system to gliadin in susceptible individuals is a prominent cofactor in modifying the immunological response earlier in life and thus predisposing susceptible individuals, not only to overt coeliac disease, but also to autoimmune disease [Ventura *et al.* 2002]. Thus, patients with coeliac disease are at high risk of having autoimmune disease [Ventura *et al.* 2002; Kumar *et al.* 2001]. Moreover, untreated patients with coeliac disease have been found to have a higher than expected prevalence of organ-specific autoantibodies. Duration of gluten exposure seems to predispose children and adolescents with coeliac disease to autoimmune diseases [Toscano *et al.* 2000; Ventura *et al.* 1999]. Gluten-free diet treatment has been proposed to prevent development of autoimmune disease in coeliac subjects. In fact, Ventura *et al.* [2000] showed in an uncontrolled study that serum insulin-related antibodies disappeared and antithyroid antibodies decreased in coeliac children during a gluten-free diet. However, Sategna Guidetti *et al.* [2001] reported that gluten withdrawal did not protect against the development of autoimmune disease in adults. Similar results in adults and children were subsequently published [Viljamaa *et al.* 2005]. A recent French study showed that strict adherence to a gluten-free diet was associated with a decreased risk of subsequent autoimmune disease, but does not give total protection [Cosnes *et al.* 2008].

Table 2. Frequency of autoimmune diseases in coeliac disease.

Autoimmune disorder	*n*
Hypothyroidism	2
Pernicious anaemia	2
IDDM	1
AIH	1
Overlap AIH/PBC	1
PSC	1
Sarcoidosis	1
Scleroderma	1
Psoriasis	1

IDDM, Insulin-dependent diabetes mellitus; AIH, autoimmune hepatitis; PBC, primitive biliary cirrhosis; PSC, primary sclerosing cholangitis.

Table 3. Univariate logistic regression analysis of different variables as predictors of the presence of autoimmune disease in coeliac disease patients.

Variables	Group I: CD ($n=53$)	Group II: CD + AID ($n=11$)	*p*
Age at diagnosis of CD	26 ± 11	27 ± 12	0.943
Gender			0.44
Female	83%	91%	
Male	17%	9%	
Smoking status	12%	0%	0.44
Diagnostic delay (months)	50 ± 62	83 ± 127	0.22
Actual gluten-exposure time (years)	25 ± 12	26 ± 11	0.82
Family history of AID	6%	9%	0.546
Family history of CD	11.5%	9%	0.647
Mean follow-up (months)	45 ± 53	82 ± 56	0.044
Strictness of gluten-free diet			0.2
Strict	67%	46%	
Partial	25%	27%	
Gluten-containing diet	8%	27%	
Immunologic remission	66%	100%	0.5
Histological remission	54%	57%	0.617

CD, coeliac disease; AID, autoimmune disease.

The effect of a gluten-free diet on the development of autoimmune disease is still under debate. Thus, it can be hypothesized that gluten ingestion plays a central role in modifying the immunological response earlier in life [Norris *et al*. 2005]. As observed by Ventura and coworkers, the prevalence of autoimmune disease in children in whom coeliac disease was diagnosed before the age of two years and who later did not undergo gluten challenge, was comparable with that of controls [Sategna Guidetti *et al*. 2001; Ventura *et al*. 1999].

The variable extent of actual gluten exposure not only reflects more accurately the duration of gluten exposure but also eliminates confounding factors that contribute to the apparently significant relationship between age at diagnosis and outcome. However, actual gluten exposure is difficult to interpret. The exposure time might be overestimated, because many autoimmune diseases could remain undetected for many years, and also coeliac disease may have been subclinical for years before the diagnosis is made [Viljamaa *et al*. 2005; Sategna Guidetti *et al*. 2001]. It might also be underestimated because of dietary lapses. Moreover, this variable can be biased by screening procedures and medical awareness. This hypothesis may explain the effect of a longer mean follow up as a predictor of an increased risk for developing autoimmune disease as found in our series.

The results of this pilot study, as well as an earlier study [Sategna Guidetti *et al*. 2001], showed that in patients with late coeliac disease diagnosis, duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disease, and that gluten withdrawal did not protect from autoimmune disease. However, these conclusions must be tempered by the small size and the retrospective character of this study. Confirmatory prospective long-term multicentre studies of the effect of gluten-free diet are needed in adults.

Conflict of interest statement

None declared.

References

Cosnes, J., Cellier, C., Viola, S., Colombel, J.F., Michaud, L., Sarles, J. *et al*. (2008) Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet, *Clin Gastroenterol Hepatol* 6: 753–758.

Kumar, V., Rajadhyaksha, M. and Wortsman, J. (2001) Celiac disease-associated autoimmune endocrinopathies, *Clin Diagn Lab Immunol* 8: 678–685.

Meize-Grochowski, R. (2005) Celiac disease: a multisystem autoimmune disorder, *Gastroenterol Nurs* 28: 394–402; quiz 403–404.

Norris, J.M., Barriga, K., Hoffenberg, E.J., Taki, I., Miao, D., Haas, J.E. *et al*. (2005) Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease, *JAMA* 293: 2343–2351.

Sategna Guidetti, C., Solerio, E., Scaglione, N., Aimo, G. and Mengozzi, G. (2001) Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders, *Gut* 49: 502–505.

Toscano, V., Conti, F.G., Anastasi, E., Mariani, P., Tiberti, C., Poggi, M. *et al*. (2000) Importance of gluten in the induction of endocrine autoantibodies and organ dysfunction in adolescent celiac patients, *Am J Gastroenterol* 95: 1742–1748.

Ventura, A., Magazu, G., Gerarduzzi, T. and Greco, L. (2002) Coeliac disease and the risk of autoimmune disorders, *Gut* 51: 897; author reply 897–898.

Ventura, A., Magazzu, G. and Greco, L. (1999) Duration of Exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Sigep Study Group for autoimmune disorders in celiac disease, *Gastroenterology* 117: 297–303.

Ventura, A., Neri, E., Ughi, C., Leopaldi, A., Citta, A. and Not, T. (2000) Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease, *J Pediatr* 137: 263–265.

Viljamaa, M., Kaukinen, K., Huhtala, H., Kyronpalo, S., Rasmussen, M. and Collin, P. (2005) Coeliac disease, autoimmune diseases and gluten exposure, *Scand J Gastroenterol* 40: 437–443.