Coeliac disease in patients with type 1 diabetes mellitus and auto-immune thyroid disorders

M. Buysschaert

Department of Endocrinology and Nutrition, Cliniques Universitaires St Luc, Université Catholique de Louvain, B-1200 Brussels, Belgium.

Abstract

The paper aims to review the prevalence and natural history of coeliac disease in patients with type 1A diabetes mellitus and auto-immune thyroid disorders. These diseases share a similar genetic background. In diabetic children and adults, the prevalence of (mostly asymptomatic) coeliac disease varies form 0.97 to 6.4%. Diabetes is usually diagnosed first. Screening in relatives may also be positive. Recurrent hypoglycaemia in diabetic subjects (indirectly) suggest the development of coeliac sprue. Thyroid disorders (thyroiditis and Graves' disease) are also usual in coeliac disease. A common etiopathogenic mechanism for the association CD / diabetes / thyroid disorders, with gluten as the driving antigen, was postulated. Thus, screening program for coeliac disease are recommended in individuals with type 1A diabetes and/or auto-immune thyroid conditions, as well as in their first-degree relatives. (Acta gastroenterol. belg., **2003**, 66, **237-240**).

Key words : coeliac disease, type 1 diabetes, thyroiditis, hyperthyroidism, prevalence, clinical presentation.

Introduction

Coeliac disease (CD), one of the most commonest lifelong disorders in Western countries, is characterised by immune mediated damage to the jejunal mucosa which is triggered by gluten (1). Type 1A (auto-immune) diabetes mellitus as well as auto-immune thyroid diseases occur more commonly than by chance in association with CD (2). Moreover, CD, type 1A diabetes and thyroid disorders (Graves' disease and hypothyroidism) are clustered in the auto-immune polyendocrine syndrome type II (APS II), or Schmidt's syndrome (3).

The aim of this review is to determine the prevalence and natural history of the association of CD with diabetes and/or thyroid diseases. We also describe the clinical presentation of CD in patients with endocrine conditions, in particular diabetes.

Endocrine disorders

Type 1A diabetes

Type 1A diabetes mellitus occurs in genetically predisposed persons as a consequence of an immune-mediated destruction of pancreatic islet ß-cells that secrete insulin (3,4). The onset of clinical diabetes represents the endpoint of an insidious decline in the function of ß-cells after the majority of them have been damaged. Risk of diabetes can now be predicted on the basis of reliable immunological markers. Thus, islet-cell antibodies (ICA) can be demonstrated in 60-90% of new-onset type 1A diabetes. Other extensively studied auto-antibodies include insulin auto-antibodies, as well as glutamic acid decarboxylase (GAD) and tyrosine phosphatase (IA_2) auto-antibodies, which are also present in 50 to 90% of patients at the onset (and before the onset) of the disease (4).

Thyroid diseases

Two disorders, Hashimoto (chronic auto-immune) thyroiditis and Graves's disease compose the major auto-immune thyroid conditions. The diagnosis of chronic auto-immune thyroiditis is based on clinical and biological signs of hypothyroidism, in particular elevated serum thyrotrophin (TSH) levels. High concentrations of anti-thyroperoxidase and/or anti-thyroglobulin antibodies are present. Hyperthyroidism and low levels of TSH are the most common features of Graves' disease and caused by auto-antibodies to the thyrotrophin receptor. In some patients, progression from Graves' hyperthyroidism to thyroiditis and hypothyroidism is recognised as well as the converse (3).

Auto-immune polyendocrine syndrome type II

Type 1A diabetes and auto-immune thyroid diseases are associated in the APS II syndrome, together with other pathological conditions, in particular coeliac disease. Other less common disorders observed in APS II include Addison's disease, hypogonadism, vitiligo, alopecia, pernicious anemia and myasthenia gravis. APS II is strongly influenced by HLA-alleles. The majority of patients have high risk alleles DR3 and DR4 with the classic haplotype of HLA A1, B8, DR3, DQ A1*0501, DQ B1*0201 and HLA-DR4, DQ A1*0301, DQ B1*0302 (3).

Natural history of the association [cd / diabetes / thyroid diseases]

Coeliac disease and type 1A diabetes

In a recent paper, G. Holmes reviews the relationship between CD and type 1 diabetes (5). In diabetic children, when based on both serological tests and small

Address for correspondance : Prof. M. Buysschaert, Service d'Endocrinologie et Nutrition, Cliniques Universitaires St Luc, Avenue Hippocrate 54, UCL 54.74, B-1200 Bruxelles, Belgique. E-mail : buysschaert@diab.ucl.ac.be.

bowel biopsy, screening studies have shown the prevalence of CD to be between 0.97 and 6.2%, with an exception of children from Algeria who have a prevalence of 16.4%. In adults, the overall prevalence of the association CD / type 1 diabetes varies from 1.3 to 6,4% according to the studies. Barera *et al.* (6) studied prospectively 274 consecutive patients at the onset of type 1 diabetes (age : 8.3 ± 4.7 years, mean ± 1SD) for six subsequent years. Only one patient had a diagnosis of CD before the onset of diabetes. At diabetes diagnosis, 15 of 273 patients were tested positive with the antiendomysium (IgA) test. Jejunal biopsy confirmed CD in nine individuals. Twelve other patients with a negative antiendomysium antibody at diabetes onset were found positive during follow-up and seven had CD on the basis of biopsies. Thus, the overall prevalence of CD in the entire cohort of these type 1 diabetic patients was 6.2%. This means a prevalence of CD in type 1 diabetes which is twenty times higher than in the general population, with sixty percent of cases already present at diabetes onset. It is of interest to note that the majority of cases of CD were totally asymptomatic in their clinical presentation (6).

Not *et al.* found a prevalence of CD among 491 type 1 diabetic patients of 5.7% ($n = 28$). In three patients, CD was diagnosed at the same time as diabetes. However, in the majority of subjects ($n = 25$), CD was identified after diabetes onset (median age at diagnosis of diabetes and CD : 11 and 25 years respectively) (7).

Our own data, based on serological screening tests, in 163 consecutive (june-september 2002) type 1 diabetic patients showed that antigliadine antibodies (IgA/IgG) were positive in twelve (7.3%), and immunoglobulin antiendomysium (IgA) antibodies in seven subjects (4.3%). Combined positive antigliadine and antiendomysium antibody tests were found in four patients (2.4% of the cohort) (8).

In most cases, diabetes is diagnosed first. However, diabetes-related auto-antibodies also occur in patients with CD as reported by Galli-Tsinopoulou *et al.* (9). It is of interest to mention that somewhat contradictory results were published by Vitori *et al.* who found only a few patients with CD showing potential auto-immunity toward β-cells (10).

Some (but not all) papers report a significant proportion of relatives of patients with type 1 diabetes with CD associated auto-immunity (7,11,12). Thus, Not *et al.* (7) found a higher prevalence of CD among 824 first-degree relatives than in 4.000 control subjects (1.9 *vs.* 0.25% ; $P < 0.001$). Additionally, the frequency of auto-immune disorders in diabetic patients with CD was also significantly higher than in subjects with type 1 diabetes alone (35,7 *vs.* 6,3% ; $P < 0.0001$). Auto-immune diseases were also more frequent in (non diabetic) relatives with CD than in those tested negative for the antiendomysial antibody (18,7 *vs.* 2.6% ; $P = 0.01$) (7).

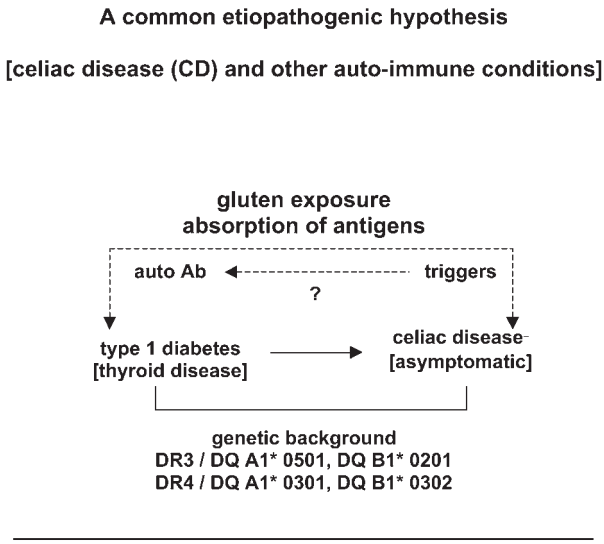
In summary, CD commonly occurs in type 1 diabetic patients and their relatives. In most individuals at diagnosis of CD, no clinical signs could be related to gluten intolerance. Therefore, it is recommended that screening for CD should be part of the routine investigation at the onset of diabetes and regularly thereafter (5,7,11-13). G. Holmes suggests a yearly test for three years, then at five years and five years thereafter or at any other time if there are clinical indications (5).

Coeliac disease and thyroid status

The frequency of subclinical or asymptomatic CD is also increased in patients with chronic auto-immune thyroiditis. Berti *et al.* found 3.4 and 0.25% of CD in 172 patients with auto-immune thyroiditis and 4.000 sex-matched control subjects, respectively (14). Comparable data were previously reported by Collin *et al.* (4.8 *vs.* 0.4% in auto-immune thyroid disorders and controls respectively) (15) and more recently confirmed by Volta *et al.* (3.0 vs. 0.4%) (16). It is of interest to note that patients with both auto-immune thyroid diseases and type 1 diabetes do not seem more likely to have (occult) CD when compared with those with type 1 diabetes only (17). On the other hand, studies published between 1974 and 1984 have shown a prevalence of thyroid diseases in patients with CD varying from 3.5 to 10.8% (Ref in 15). A more recent metaanalysis by J.L. Sadoul showed that thyroid auto antibodies were present in 14 to 30% of cases of CD. In most cases, thyroid disorders were due to Hashimoto thyroiditis. A few authors however observed a high percentage of Graves' disease (18).

A tentative common etiopathogenic hypothesis

The association of CD, type 1A diabetes and/or thyroid auto-immune diseases is principally due to a similar genetic background. Another hypothesis is that, in genetically susceptible persons, one disease (CD) could predispose to another. M. Pocecco and A. Ventura (19) suggest that untreated (latent or silent) CD could be an immunological trigger and induce diabetes and/or thyroid disorders due to gluten as a driving antigen (Fig. 1). In accordance with this, the prevalence of auto-immune disorders in CD is closely related to age at diagnosis or, in other words, to the duration of exposure to gluten (20). Moreover, like serum antiendomysium auto antibodies, diabetes and thyroid-related antibodies seem to be "gluten-dependent" and tend to disappear during a twelve month gluten-free diet (21). Both studies indirectly suggest that early elimination of gluten may prevent the development of other auto-immune diseases. A recent of paper of Hummel *et al.* in high risk subjects (first-degree relatives of patients with type 1 diabetes) did not support the latter hypothesis by failing to observe a reduction in serum titers of type 1 diabetes associated auto antibodies upon commencement of a gluten-free diet (22). Additionally, the frequency of diabetes observed in the gluten re-exposure period was comparable with the natural history of disease in young multiple auto-antibody positive relatives (22).



- *untreated CD is associated with other auto Ab or auto-immune diseases*

Ventura et al., Gastroenterology, 1999
Ventura et al., J Pediatr, 2000

Fig. 1

Clinical presentation

The spectrum of clinical and biological expressions of coeliac sprue was recently reviewed (1) and is beyond the scope of the present paper.

In patients with auto-immune thyroid diseases, features of (subclinical) CD are globally comparable to those observed in control populations.

In cohorts of type 1 diabetic patients, the presence of an increased frequency of (symptomatic) hypoglycaemia together with a progressive reduction of the insulin requirements (ranging from 30 to 60%), not apparently justified by less nutrient intake or more physical activity, also indicated a diagnosis of CD (23). On the contrary, Iafusco *et al.* showed that a gluten-free diet induced an increase in insulin requirement up to the doses usually administered in diabetic patients without CD, matched for age, sex and duration of diabetes (24). Overall improvement of brittleness after the introduction of a gluten-free diet was reported by Andreelli *et al.* (25) and others (26). Faced with vague gastrointestinal symptoms, it is also of importance to exclude a diabetic autonomic neuropathy (5) before considering the diagnosis of CD which can eventually be complicated by the development of a lymphoma (27).

Conclusions

Coeliac disease commonly occurs in type 1 diabetes. There is also a frequent association between coeliac disease and auto-immune thyroid disorders. It is recommended that screening for coeliac sprue should be part of the routine evaluation, in particular in type 1 diabetic patients and relatives. Recurrent hypoglycaemia seems to be a valid sign of active coeliac disease in type 1 diabetes.

References

1. FARRELL R., KELLY C. Current concepts : celiac sprue. *New Engl. J. Med.*, 2002, **346** : 180-188.
2. SADOUL J.L. Manifestations endocrines de la maladie coeliaque. Mises au point cliniques d'Endocrinologie, Paris, 2001 : 145-158.
3. LIU E., EISENBARTH G.S. Type 1A diabetes mellitus-associated autoimmunity. *Endocrinol. Metab. Clin. N.A.*, 2002, **31** : 391-410.
4. BUYSSCHAERT M. Diabétologie Clinique. De Boeck Université, Paris et Louvain-la-Neuve, 2nd Edition, 2001 : 19-28.
5. HOLMES G. Coeliac disease and type 1 diabetes mellitus – the case for screening. *Diabetic Med.*, 2001 : **18** : 164-177.
6. BARERA G., BONFANTI R., VISCARDI M., BAZZIGALUPPI E., CALORI G., MESCHI F., BIANCHI C., CHIUMELLO G. Occurrence of celiac disease after onset of type 1 diabetes : a 6-year prospective longitudinal study. *Pediatrics*, 2002, **109** : 833-838.
7. NOT T., TOMMASINI A., TONINI G., BURATTI E., POCECCO M., TORTUL C., VALUSSI M., CRICHIUTTI G., BERTI I., TREVISIOL C., AZZONI E., NERI E., TORRE G., MARTELOSSI S., SOBAN M., LENHARDT A., CATTIN L., VENTURA A. Undiagnosed coeliac disease and risk of auto-immune disorders in subjects with type 1 diabetes mellitus. *Diabetologia*, 2001, **44** : 151-155.
8. BUYSSCHAERT M., DECERF J. A., HERMANS M.P. Prevalence and clinical correlates of immune markers for celiac disease in adult subjects with type 1 diabetes. *Diabetologia*, 2003, **46** : A 233.
9. GALLI-TSINOPOULOU A., NOUSIA-ARVANITAKIS S., DRACOULACOS D., XEFTERI M., KARAMOUZIS M. Auto-antibodies predicting diabetes mellitus type 1 in coeliac disease. *Horm. Res.*, 1999, **52** : 119-129.
10. VITORIA J., CASTANO L., RICA J., BILBAO R., ARRIETA A., GARCIA-MASDEVALL M. Association of insulin-dependent diabetes mellitus and celiac disease : a study based on serological markers. *J. Pediatr. Gastroenterol. Nutr.*, 1998, **27** : 47-52.
11. HUMMEL M., BONIFACIO E., STERN M., DITTLER J., SCHIMMEL A., ZIEGLER A. Development of celiac disease-associated antibodies in offspring of parents with type 1 diabetes. *Diabetologia*, 2000, **43** : 1005-1011.
12. JAEGER C., HATZIAGELAKI E., PETZOLDT R., BRETZEL R. Comparative analysis of organ-specific antibodies in type 1 diabetic patients, their first-degree relatives and healthy control subjects. *Diabetes Care*, 2001, **24** : 27-32.
13. CRONIN C. Insulin-dependent diabetes mellitus and coeliac disease. *Lancet*, 1997, **349** : 1096-1097.
14. BERTI I., TREVISIOL C., TOMMASINI A., CITTA A., NERI E., GEATTI O., GIAMMARINI A., VENTURA A., NOT T. Usefulness of screening program for celiac disease in auto-immune thyroiditis. *Digestive Diseases and Sciences*, 2000, **45** : 403-406.
15. COLLIN P., SALMI J., HALLSTRÖM O., REUNALA T., PASTERNACK A. Autoimmune thyroid disorders and coeliac disease. *Eur. J. Endocrinol.*, 1994, **130** : 137-140.
16. VOLTA U., RAVAGLIA G., GRANITO A., FORTI P., MAIOLI F., PETROLINI N., ZOLI M., BIANCHI F. Coeliac disease in patients with auto-immune thyroiditis. *Digestion*, 2001, **64** : 61-65.
17. LI VOON CHONG J., LEONG K., WALLYMAHMED M., STURGESS R., MACFARLANE I.A. Is coeliac disease more prevalent in young adults with coexisting type 1 diabetes mellitus and auto-immune thyroid disease compared with those with type 1 diabetes mellitus alone ? *Diabetic Med.*, 2002, **19** : 334-337.
18. LANCASTER-SMITH M.J., PERRIN J., SWARBRUCK E.T., WRIGHT J.T. Coeliac disease and autoimmunity. *Postgrad. Med. J.*, 1974, **5°** : 45-48.
19. POCECCO M., VENTURA A. Coeliac disease and insulin-dependent diabetes mellitus : a causal association. *Acta Paediatr.*, 1995, **84** : 1432-1433.
20. VENTURA A., MAGAZZU G., GRECO L. for the SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. *Gastroenterology*, 1999, **117** : 297-303.
21. VENTURA A., NERI E., UGHI C., LEOPALDI A., CITTA A., NOT T. Gluten-dependent diabetes-related and thyroid-related auto-antibodies in patients with celiac disease. *J. Pediatr.*, 2000, **137** : 263-265.
22. HUMMEL M., BONIFACIO E., NAZERKE H., ZIEGLER A. Elimination of dietary gluten does not reduce titers of type 1 diabetes-associated autoantibodies in high risk subjects. *Diabetes Care*, 2002 : 1111-1116.

23. MOHN A., CERRUTO M., IAFUSCO D., PRISCO F., TUMINI S., STOPPOLONI O., CHIARELLI F. Celiac disease in children and adolescents with type 1 diabetes : importance of hypoglycemia. *J. Pediatr. Gastroenterol. Nutr.*, 2001, **32** : 37-40.
24. IAFUSCO D., REA F., PRISCO F. Hypoglycemic and reduction of the insulin requirement as a sign of celiac disease in children with IDDM. *Diabetes Care*, 1998, **21** : 1379-1380.
25. ANDREELLI F., PLOTTON J., RIOU J.P., THIVOLET C. Diabetic instability and celiac disease : a frequent association to keep in mind. *Diabetes Care*, 1998, **21** : 2192-2193.
26. KATUTA K.P., BUYSSCHAERT M. Association d'un diabète de type 1 et d'une maladie coeliaque. *Louv. Méd.*, 2002, **121** : 26-30.
27. O'CONNOR T.M., CRONIN C., LOANE J.F., O'MEARA N.M., FIRTH R., SHANAHAN F., O'HALLORAN D. Type 1 diabetes mellitus, celiac disease and lymphoma : a report of four cases. *Diabetic Med.*, 1999, **16** : 614-617.