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RESEARCH LETTER

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The prevalence of coeliac disease in adult Danish patients with type 1 diabetes with and without nephropathy

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To the Editor: Coeliac disease causes malabsorption due to small bowel villous atrophy, which normalises when gluten, which is found in wheat, rye and barley, is withdrawn from the diet. Coeliac patients should be treated with a gluten-free diet that corrects the intestinal malabsorption and protects against the development of osteoporosis and intestinal lymphoma.

As shown in several studies (review [1]), type 1 diabetes is associated with a high prevalence (2–10%) of coeliac disease. This has, in part, been explained by genetic factors, in particular by increased frequencies of *HLA-DR3* and *HLA-DQ2* [2]. Coeliac symptoms are often absent or atypical in type 1 diabetic patients and the diagnosis is therefore often delayed.

Diabetic nephropathy is the leading cause of end-stage renal disease and develops in approximately one-third of type 1 diabetic patients within the first 20 years of diabetes. The pathogenesis of diabetic nephropathy is only partially understood. In addition to genetic factors, haemodynamic, metabolic and growth factors are generally accepted to contribute [3]. As in diabetic nephropathy [4], reduced final height is a significant clinical manifestation of coeliac disease. In this study we investigated the prevalence of coeliac disease in adult Danish type 1 diabetes patients, with the specific aim of studying whether undiagnosed coeliac disease is more prevalent in type 1 diabetic patients with diabetic nephropathy than in type 1 diabetic patients without nephropathy.

We studied 967 type 1 diabetic patients [5]. The patient population comprised a group of 462 patients with overt diabetic nephropathy (defined as persistent macroalbuminuria [>300 mg/24 h], retinopathy and no signs of other kidney or urinary tract disease; 284 men, median age 41 [range: 17–78] years, median serum creatinine 103 [range: 52–706] μmol/l) and a group of 505 patients with long-standing (23 [range: 10–63] years) type 1 diabetes and persistent normoalbuminuria (275 men, age 46 [range: 20–81] years). Median age at onset of diabetes was 12 (range: 0–47) and 18 (range: 0–64) years in the nephropathy and normoalbuminuric groups respectively ($p<0.001$).

Total serum IgA concentration (in-house ELISA; Statens Serum Institute, Copenhagen, Denmark) and IgA anti-transglutaminase concentration (anti-tTG, commercial ELISA, Celikey; Pharmacia, Freiburg, Germany) were measured in a single random blood sample. The specificity and sensitivity values of the IgA anti-tTG assays were 99 and 96% respectively. The presence of IgA anti-tTG is highly indicative of coeliac disease even in asymptomatic cases [6]. Patients positive after screening were referred to their local hospital for a possible small bowel biopsy procedure and instructions for a gluten-free diet. Sera from five subjects with IgA deficiency (<0.1 mg/ml) were analysed for IgG anti-gliadin antibodies and IgG anti-tTG. We collected clinical data and laboratory results using a questionnaire including questions concerning possible earlier diagnosis of coeliac disease and possible previous gluten-free diet.

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Of the 967 type 1 diabetic patients, 16 patients (1.7%) had positive IgA anti-tTG. In addition, one patient with IgA deficiency had positive IgG anti-tTG, and two patients were on a gluten-free diet due to earlier diagnosed coeliac disease and were therefore negative for anti-tTG. The total coeliac disease prevalence in our type 1 diabetic population was thus 2%. Seventeen of the 19 patients had not been diagnosed previously.

Of the 462 patients with diabetic nephropathy, 12 (2.6%) had serological signs of active coeliac disease (including one patient earlier diagnosed with coeliac disease, but non-compliant with the gluten-free diet). In the group with normoalbuminuria, five patients (1%) had serological signs of active coeliac disease. Two patients with established coeliac disease, on a gluten-free diet with negative anti-tTG, were found in this group, which gives a total prevalence of 1.4%. The observed difference in prevalence of coeliac disease between type 1 diabetic patients with nephropathy and those without was not statistically significant (p=0.17).

The age at diagnosis of diabetes in the patients with coeliac disease was significantly lower (9 [range: 0–39] years) than in patients without coeliac disease (15 [range: 0–64] years; p=0.03). This finding is consistent with those of previous studies [7]. No differences in glycaemic control (HbA_1c) or in signs of malabsorption (haemoglobin and BMI) were found between the group with coeliac disease and the group without.

In a study of 106 Danish children with type 1 diabetes, the highest prevalence of coeliac disease in Europe (10.6%) was observed [7]. Since coeliac disease is a chronic disorder, the lower prevalence in Danish adult type 1 diabetic patients found in this study might point to the possibility that the incidence of coeliac disease is currently increasing in Danish children. An alternative explanation is survival bias leading to a lower prevalence estimate in our cross-sectional study of patients with long-standing type 1 diabetes. Our data are consistent with those of similar reports from other adult diabetic patient populations [1].

The reported effect of a gluten-free diet on glycaemic control in type 1 diabetic patients has been variable. However, the improvement in factors related to coeliac disease, such as growth, villous architecture and biochemical indices, also applies to patients with type 1 diabetes, and a trend towards increased BMI and tighter glycaemic control has been reported [8]. Another effect of the gluten-free diet is relief from non-specific symptoms such as tiredness and abdominal discomfort as well as a reduced risk of long-term complications such as infertility, osteoporosis and lymphomas of the small intestine.

Even though this study did not find a statistically significant association between coeliac disease and diabetic nephropathy, it is apparent that further long-term follow-up studies are needed to define more precisely the risk of nephropathy conferred by coeliac disease, and to evaluate the long-term effect of a gluten-free diet on the development of microalbuminuria. Considering the overall prevalence of coeliac disease in Danish type 1 diabetic patients, of whom many have silent disease or limited clinical symptoms, we highly recommend that screening for coeliac disease is undertaken in all patients with type 1 diabetes.

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