

IgA Anti-transglutaminase Autoantibodies at Type 1 Diabetes Onset Are Less Frequent in Adult Patients and Are Associated With a General Celiac-Specific Lower Immune Response in Comparison With Nondiabetic Celiac Patients at Diagnosis

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OBJECTIVE—To evaluate the celiac-associated humoral autoimmunity in child, adolescent, and adult patients at type 1 diabetes (DM1) onset and to determine whether DM1 celiac-specific humoral immunoreactivity occurs similarly to that in nondiabetic patients at celiac disease (CD) diagnosis.

RESEARCH DESIGN AND METHODS—IgA anti-transglutaminase autoantibody (IgA-tTGAb) was detected in 654 new-onset DM1 sera. IgA-tTGAb⁺ DM1 sera were subsequently analyzed for IgG-tTG, deamidated gliadin (DGP), and actin antibodies, and results were compared with those found in 83 screen-detected nondiabetic patients at CD diagnosis.

RESULTS—A total of 12.8% DM1 sera were IgA-tTGAb⁺, with a lower autoantibody frequency in adult patients aged >18 years (6.8 vs. 15.1%, aged ≤18 years; $P = 0.005$). IgA-tTGAb titers, IgG-tTGAb, and DGPAb frequency/titers and mean number of celiac-autoantibody positivities per patient were significantly lower in IgA-tTGAb⁺ DM1 compared with nondiabetic CD patients.

CONCLUSIONS—Age of diabetes onset is negatively associated with risk of CD. The celiac-specific humoral immunoreactivity at DM1 onset is significantly lower compared with that found in nondiabetic patients at CD diagnosis.

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Type 1a diabetes (DM1) is associated with an increased risk of celiac disease (CD) (1). Usually DM1 precedes the onset of CD, which, in diabetic patients, often occurs in a silent or asymptomatic form and may only be detected by serological autoantibody screening, in particular measuring IgA anti-transglutaminase autoantibodies (IgA-tTGAb) (2,3). Literature

reports several studies aimed at evaluating the IgA-tTGAb frequency in DM1. Most of them were, however, targeted to analyze child, adolescent, and adult patients with long-standing DM1 (4,5), but rarely at disease onset, in which only young patients were investigated (6,7). In addition, it is not known whether the celiac-specific humoral immunoreactivity found at DM1

onset occurs with the same characteristics shown by screen-detected nondiabetic patients at CD diagnosis. On this basis, our aims were 1) to establish the IgA-tTGAb frequency and titer in a large cohort of Caucasian patients at DM1 onset; 2) to evaluate in the IgA-tTGAb⁺ DM1 sera the IgG-tTG, deamidated gliadin IgA/IgG (DGPAb) (8), and IgA-actin (ActA) (9) antibody levels; and 3) to compare the celiac-specific humoral immune response shown by screen-detected DM1 patients at onset and nondiabetic CD patients at diagnosis.

RESEARCH DESIGN AND METHODS

Sera from 654 DM1 patients diagnosed according to American Diabetes Association criteria (10) from 1990 to 2010 at University of Rome “Sapienza” (282 females; median and age range: 11.8 and 1.0–69.2 years, respectively) were tested for presence of IgA-tTGAb. These samples, collected within 1 week from DM1 diagnosis, were subdivided into group 1 (≤18 years, $n = 478$, 283 females, median age 9.5 years) and group 2 (>18 years, $n = 176$, 73 females, median age 27.9 years) sera. Subsequently, only IgA-tTGAb⁺ DM1 sera were analyzed for presence of IgG-tTGAb, DGPAb, and ActA and the results compared with those found in 83 nondiabetic, biopsy-proved IgA-tTGAb⁺ patient sera at CD diagnosis (56 females; median and age range: 7.2 and 3.1–45.0 years, respectively). The 83 CD patients were identified in screening programs on school children and CD first-degree relatives. Serum IgA- and IgG-tTGAb were detected by a fluid-phase radioimmunoprecipitation method, which was the most sensitive (93%) and specific (100%) assay among the 20 laboratories participating in the First International

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Transglutaminase Autoantibody Workshop for Celiac Disease (11). Serum DGPAb and ActA were detected by ELISA kits (Inova). SAS 9.2 software (SAS Institute) was used for statistical analyses.

RESULTS—Of 654 DM1 patients investigated, 84 (12.8%) were serum IgA-tTGAb⁺, with a significantly higher frequency in group 1 (≤18 years) compared with group 2 (>18 years) patients (15.1%, 72 of 478 vs. 6.8%, 12 of 176; *P* = 0.005). Most DM1 patients found to be IgA-tTGAb⁺ were females (16.7%, 47 of 282 vs. males 9.9%, 37 of 372; *P* = 0.013). Most of these females were aged ≤18 years (19.1%, 40 of 209 vs. 9.6%, 7 of 73 females aged >18 years; *P* = 0.001). No IgA-tTGAb frequency differences were found between males aged ≤18 and >18 years. Of 84 DM1 sera identified as IgA-tTGAb⁺ (median age 10 years, 60% females), 33.3, 40.5, and 36.9% were IgG-tTGAb, DGPAb, and ActA positive, respectively. Thirty-four of 84 IgA-tTGAb⁺ DM1 patients were biopsied, and

33 of 34 (18 females) had CD. The comparison of celiac-specific humoral autoimmunity shown by nonbiopsied DM1 (DM1_A), biopsied DM1 (DM1_B), and nondiabetic CD patients at diagnosis is shown in Fig. 1. Multivariate logistic regression analysis demonstrated that age and gender of DM1_A, DM1_B, and nondiabetic CD patients do not affect the frequency and titer of the antibodies investigated.

CONCLUSIONS—CD is a well-documented comorbidity of DM1. In this study, we demonstrated that the IgA-tTGAb frequency at DM1 onset is significantly higher in patients aged ≤18 years, 2.2 times more than in adult patients. This result reinforces previous findings that showed a lower age of DM1 onset is associated with a higher risk of developing CD (12). It is possible that distinct genetic susceptibility might contribute to the differences between the two age-groups. Gender biases in the susceptibility and severity of autoimmune diseases are well recognized, and a female prevalence of CD was

demonstrated in long-standing diabetes (13). We found that also at DM1 diagnosis, celiac-specific IgA-tTG immunoreactivity is prevalent in females, especially when aged ≤18 years. The absence of other gender associations in this study may be explained by the limited number of adult patients found autoantibody-positive. The comparison of celiac-specific humoral immunoreactivities shown by IgA-tTGAb⁺ DM1 (biopsied or not) and screen-detected nondiabetic CD patients at diagnosis provided additional interesting data. We found that the concomitant presence of DM1 and CD strongly influences the quantitative and qualitative expression of the celiac-specific humoral immunoreactivity that, at DM1 onset, is significantly lower in comparison with nondiabetic patients at CD diagnosis. Only anti-actin autoantibody immunoreactivity, marker of CD intestinal damage severity, did not differ between DM1 and CD patients. The impact of CD on the clinical characteristics of DM1 patients is controversial, probably because of the variable

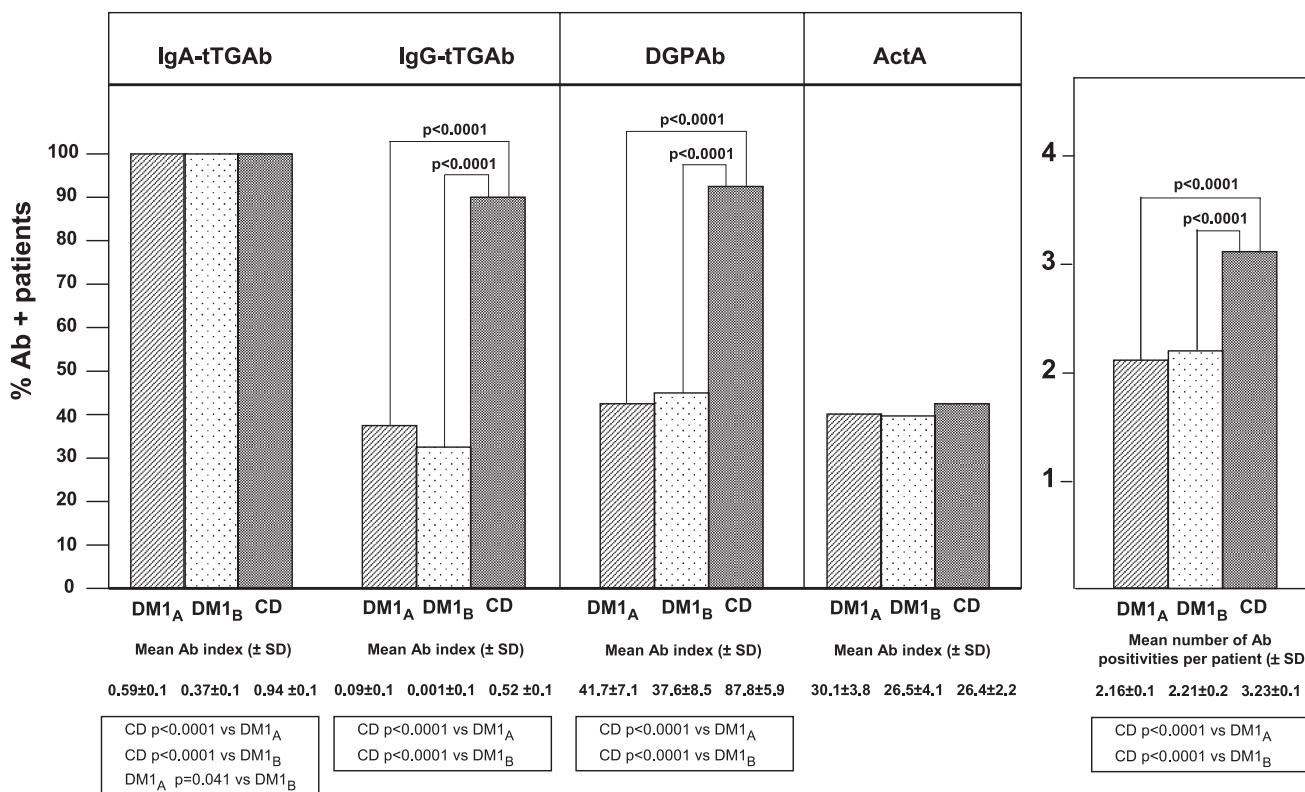


Figure 1—Comparison of celiac-specific autoantibody frequency, titers, and mean number of autoantibody positivities per patient in newly diagnosed DM1 and nondiabetic CD patients at diagnosis. The y-axis indicates the percent of serum IgA-tTG, IgG-tTG, DGP, and actin autoantibody-positive patients at diagnosis. The x-axis reports the groups of patients analyzed for each single celiac-specific autoantibody. Apart, on the right of the figure, y-axis indicates, for the same set of patients, the mean number of autoantibody positivities found in each group. At the bottom of the figure for DM1_A, DM1_B, and CD patients, the mean Ab indexes relative to each celiac-specific autoantibody investigated and their eventual statistical significances were reported. CD, biopsy-confirmed celiac patients; DM1_A, nonbiopsied IgA-tTGAb⁺ DM1 patients; DM1_B, IgA-tTGAb⁺ DM1 patients confirmed as celiac by intestinal biopsy.

severity of the disease process (14). However, most DM1 patients tend to develop an asymptomatic, subclinical form of CD. Even if they show the pathological changes of the small bowel villi, they do not show the classical CD symptoms (2,13). On this basis, we suggest that a general lower celiac-specific humoral immune response reflects a slower CD process development in DM1 patients, characterized by subtle, if any, gastrointestinal symptoms. To support this hypothesis, the results of a study on autoimmune diabetes show a direct correlation between intensity of the humoral immune response and more prominent characteristics of insulin deficiency (15).

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References

1. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab* 2006;91:1210–1217
2. Hoffenberg EJ, Liu E. Screening-identified celiac disease: who needs treatment and when? *Clin Gastroenterol Hepatol* 2011;9:284–285
3. Silverstein J, Klingensmith G, Copeland K, et al.; American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005;28:186–212
4. Babiker A, Morris MA, Datta V. Coeliac disease and type 1 diabetes: 7 years experience versus NICE guidance 2009. *Arch Dis Child* 2010;95:1068–1069
5. Franzese A, Iafusco D, Spadaro R, et al.; Study-Group on Diabetes of Italian Society of Pediatric Endocrinology and Diabetology. Potential celiac disease in type 1 diabetes: a multicenter study. *Diabetes Res Clin Pract* 2011;92:53–56
6. Jaeger C, Hatzigelaki E, Petzoldt R, Bretzel RG. Comparative analysis of organ-specific autoantibodies and celiac disease—associated antibodies in type 1 diabetic patients, their first-degree relatives, and healthy control subjects. *Diabetes Care* 2001;24:27–32
7. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213
8. Mubarak A, Gmelig-Meyling FHJ, Wolters VM, Ten Kate FJ, Houwen RH. Immunoglobulin G antibodies against deamidated-gliadin-peptides outperform anti-endomysium and tissue transglutaminase antibodies in children <2 years age. *APMIS* 2011;119:894–900
9. Carroccio A, Brusca I, Iacono G, et al. IgA anti-actin antibodies ELISA in coeliac disease: a multicentre study. *Dig Liver Dis* 2007;39:818–823
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006;29(Suppl. 1):S43–S48
11. Li M, Yu L, Tiberti C, et al. A report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. *Am J Gastroenterol* 2009;104:154–163
12. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C; Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care* 2004;27:1294–1298
13. Collin P, Kaukinen K, Välimäki M, Salmi J. Endocrinological disorders and celiac disease. *Endocr Rev* 2002;23:464–483
14. Fröhlich-Reiterer EE, Kaspers S, Hofer S, Schober E, Kordonouri O, Bechtold-Dalla Pozza S, Holl RW; Diabetes Patientent Verlaufsdokumentationssystem-Wiss Study Group. Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy-proven celiac disease. *J Pediatr* 2011;158:589–593
15. Buzzetti R, Di Pietro S, Giaccari A, et al.; Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 2007;30:932–938