Original Article

Prevalence of celiac disease in patients with type 1 diabetes mellitus: a single-center cross-sectional cohort study

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Type 1 diabetes mellitus (T1DM) may be associated with other autoimmune diseases. Celiac disease (CD), another autoimmune disorder that mainly affects the small intestine, is caused by intolerance to gluten ingestion. CD has a higher prevalence in patients with T1DM than in the general population. However, the prevalence of CD in patients with T1DM in Japan is unknown. This study investigated the prevalence of CD in Japanese patients with T1DM. We included 115 patients with T1DM treated at Hyogo Brain and Heart Center from December 2020 to April 2021. A questionnaire survey about dietary habits and abdominal symptoms was administered, and serum anti-tissue transglutaminase (TTG) antibody titers were determined for all participants. A CD (CD-seropositive) diagnosis was based on TTG levels >10 U/ml. Fifty-eight patients (50.4%) had some abdominal symptoms (such as constipation, diarrhea, and abdominal pain). The average TTG-IgA antibody titer was 0.75 ± 0.49 U/ml and negative (<10 U/ml) in all patients. In conclusion, the prevalence of CD among patients with T1DM at our hospital was 0%. Thus, the prevalence of CD in Japan is low compared to that in other countries, even among patients with T1DM, who are considered to have high comorbidity rates.

***Key Words*:** **type 1 diabetes mellitus, celiac disease, human leukocyte antigen, zonulin**

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder, and patients with T1DM have an increased risk of developing other autoimmune diseases.(1) The co-occurrence of at least two autoimmune-induced endocrine gland insufficiencies is defined as autoimmune polyglandular syndrome.(2) Celiac disease (CD) is another autoimmune disease involving the small intestine, which is triggered by an immune response to gliadin present in gluten, resulting in the destruction of the villi of the small intestine and malabsorption of various nutrients. In recent years, the incidence of CD has been increasing globally in children and adults. Due to the changes in dietary habits, wheat intake has been increasing in Japan compared to the traditional rice-based diet. This is considered to be the reason for the increase in CD in Japan.(3) In addition, as the number of adult-onset cases increases, the number of mild, non-classic symptomatic, and latent types of disease is also increasing.(4)

The prevalence of CD is higher in patients with T1DM than in the general population having no T1DM,(5,6) but this varies widely between countries.(7,8) The comorbidity rate of T1DM and CD in Japan has not been reported yet. This study aimed to determine the prevalence of CD in patients with T1DM undergoing outpatient treatment at our hospital.

Materials and Methods

In this study, we included 115 Japanese outpatients with T1DM who visited Hyogo Brain and Heart Center (Himeji, Hyogo, Japan) from December 2020 to April 2021. The diagnosis of T1DM was made by the attending physician based on the patient's medical history, endogenous insulin secretion capacity, and presence of pancreatic autoantibodies. All patients with T1DM were eligible to participate in this study, and no specific exclusion criteria were established.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Hyogo Brain and Heart Center (approval no. 2-18). All included patients gave written informed consent for this study.

At the time of the regular visit, a questionnaire was administered to the patients regarding childhood eating habits (wheat- or rice-based diet), the number of wheat meals consumed per week, and abdominal symptoms (such as diarrhea, constipation, and abdominal pain) experienced within the last 3 weeks.

Approximately 1–2 ml of the serum collected for routine medical tests was used for serology testing of CD in this study by measuring anti-tissue transglutaminase (TTG) IgA antibodies. Measurement of the concentration of TTG-IgA antibodies is considered a screening test for CD because of its high sensitivity and negative predictive values (90.9% and 99.6%, respectively). Serum samples were stored at −30°C and assayed for the presence of anti-TTG antibody with the ELISA kit (ORG540A Anti-Tissue-Transglutaminase IgA, ORGENTEC Diagnostika GmbH, Mainz, Germany). An anti-TTG-IgA antibody level of >10 U/ml was considered to be positive for CD. We planned to recommend a confirmatory small bowel biopsy to TTG-positive patients.

Results

The study participants' characteristics are shown in Table 1. Approximately 90% of the patients reported eating a rice-based diet during childhood. For each meal of the day, nine patients (7.8%) reported not consuming a wheat meal at breakfast, 18 patients (15.6%) at lunch, and 46 patients (40.0%) at dinner, with

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Table 1. Clinical characteristics of the study participants

Number of patients	115
Sex (male/female, *n*)	45/70
Age (years)	48.7 ± 18.3
Age of diabetes diagnosis (years)	35.3 ± 19.3
Duration of T1DM (years)	13.4 ± 11.0
BMI (kg/m^2)	22.0 ± 3.6
Plasma glucose level (mg/dl)	171.0 ± 76.4
HbA1c (%)	7.9 ± 1.1
eGFR (ml/min/1.73 m^2)	85.0 ± 30.7
Childhood eating habits	
Wheat-based diet, *n* (%)	8 (6.9)
Rice-based diet, *n* (%)	104 (90.4)
Number of patients without eating wheat products	
Morning, *n* (%)	9 (7.8)
Lunch, *n* (%)	18 (15.6)
Dinner, *n* (%)	46 (40)
Symptoms, *n* (%)	
Abdominal distension	16 (13.9)
Abdominal pain	18 (15.6)
Diarrhea	16 (13.9)
Loose stools	16 (13.9)
Constipation	35 (30.4)
Anorexia	2 (1.7)
Nausea/vomiting	4 (3.5)

Data are presented as the mean ± SD. T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate.

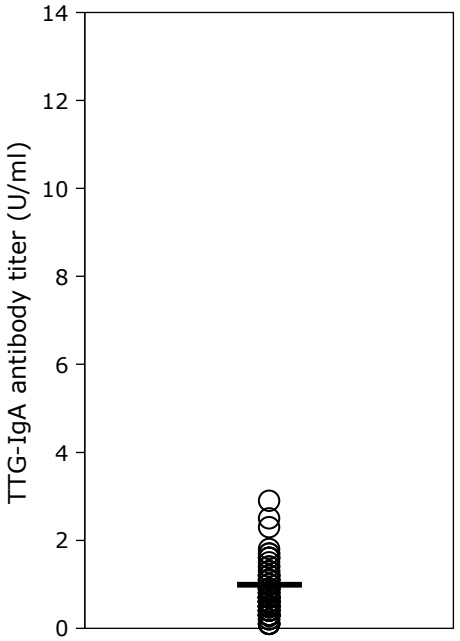

Fig. 1. TTG-IgA antibody titer results in patients with type 1 diabetes mellitus. Scatter plot of the TTG-IgA antibody titers in patients with type 1 diabetes (*n* = 115) showing all the data points and the mean. TTG, tissue transglutaminase; Ig, immunoglobulin.

only one patient not consuming wheat at any of the three meals. Overall, 58 patients (50.4%) had some abdominal symptoms (such as constipation, diarrhea, and abdominal pain). Constipation was the most common (35 patients, 30.4%), followed by abdominal pain (18 patients, 15.6%) and abdominal distension or diarrhea (16 patients, 13.9%) (Table 1).

The average anti-TTG antibody level was 0.75 ± 0.49 U/ml (0.1–2.9 U/ml), and all patients were found to be CD negative as the level was less than 10 U/ml. This result shows a 0% prevalence of CD in patients with T1DM included in this study (Fig. 1). No patient underwent gastrointestinal endoscopic examination as a confirmatory examination.

Discussion

T1DM is considered to be mainly an autoimmune disease, which can be complicated by various other autoimmune disorders.[1] T1DM is caused by the interaction between genetic and environmental factors; the human leukocyte antigen (HLA) region is most strongly associated with T1DM, with class II *DR* and *DQ* genes reported to be strongly associated with an increased risk of the disease.[9] There is national and racial diversity in the incidence of T1DM, and HLA haplotypes, associated with T1DM susceptibility, have been found to vary by race. The haplotypes associated with genetic susceptibility to T1DM in the Japanese population are *DRB1*04:05-DQB1*04:01*, *DRB1*09:01-DQB1*03:03*, and *DRB1*08:02-DRB1*03:02*,[10,11] while the representative haplotypes are *DRB1*03:01-DQB1*02:01* and *DRB1*04:01-DQB1*03:02* in Caucasians,[12] and are known to differ from each other.

CD is likewise an autoimmune disease, in which the immune response in the small intestine to gluten results in the malabsorption of various nutrients.[13] It can be further complicated by various non-gastrointestinal symptoms (dermatitis herpetiformis, fatigue, iron deficiency anemia, arthritis, osteoporosis, among others.) as well as gastrointestinal symptoms such as diarrhea, weight loss, and abdominal pain.[14] CD is also a multifactorial disease caused by specific allelic mutations in *HLA-DQ2* (approximately 95%) or *HLA-DQ8*. In addition to the interaction of environmental factors, these allelic mutations are known to be associated with disease susceptibility.[15,16] In general, the prevalence of CD is higher in countries with high wheat consumption. While the prevalence of CD is approximately 1% in Western countries,[17,18] it is 0.05% in Japan, indicating that the disease is extremely rare in the Japanese population.[19] In Europeans and Americans, approximately 25–40% of the population has *HLA-DQ2* or *HLA-DQ8*, which in addition to the high wheat consumption, is considered to responsible for the high prevalence of CD in these countries.[16]

Patients with T1DM are at increased risk for developing CD. The prevalence of CD in patients with T1DM varies among countries (2.4–16.4%),[5–8] while the risk for CD in the general population is about 1%. Therefore, it has been suggested that all pediatric patients with T1DM should be screened for CD. However, the comorbidity of CD in Japanese patients with T1DM has not been reported previously. In the present study, all 115 patients with T1DM had anti-TTG antibodies <10 U/ml. The sensitivity of anti-TTG antibody measurement was very high and based on this result, we concluded that 0% (0/115) of the patients with T1DM evaluated in this study had coexisting CD.

T1DM and CD share several common gene loci, including *HLA-DR3* and *HLA-DQ2*. Patients with these diseases are susceptible to tissue damage and intolerance to dietary antigens through autoimmune mechanisms.[20] In addition, increased permeability of the intestinal mucosa and disruption of the intestinal epithelial barrier caused by environmental factors may activate the intestinal immune response to antigen exposure. These changes might be involved in the development of autoimmune diseases. Zonulin is known to be a key modulator of the intestinal barrier; it is a protein produced in the gastrointestinal tract and

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liver that reversibly regulates intestinal permeability by inducing degradation of the intestinal mucosal tight junctions.[21] In humans, an increase in the serum zonulin levels has been shown in patients with insulin-dependent diabetes mellitus and CD, which is considered as one of the common pathogenic mechanisms of both diseases.[22] Gliadin, a significant component of gluten found in wheat and other grains, promotes zonulin production and secretion, and is considered to be involved in the pathogenesis of CD. It may also contribute to the development of other autoimmune diseases, including T1DM.[23]

The meager co-morbidity rate of CD in Japanese patients with T1DM may be related mainly to the low *HLA-DQ2* prevalence, which is only 0.3% among patients with T1DM in Japan.[24,25] In addition, wheat consumption is lower in Japan than in Western countries, especially in childhood, and there may be differences in the activation of intestinal immunity by zonulin. Furthermore, this study differs from many previous reports on pediatric patients with T1DM in that it included many patients with adult-onset T1DM. A younger onset age and longer duration of T1DM are risk factors for the development of CD in children;[26] therefore, the difference in the age of onset of T1DM in this study may have resulted in a lower co-morbidity rate of CD. However, there are reports of cases in which the diagnosis of CD was delayed in adult patients with T1DM because of the absence of symptoms or misdiagnosis of abdominal symptoms due to diabetic neuropathy. In this study, approximately 50% of the T1DM patients had some abdominal symptoms. We should be aware of the relationship between T1DM and CD to ensure optimal care for not only the symptomatic but also asymptomatic patients with T1DM.

The treatment of CD is based on a gluten-free diet. Whether a gluten-free diet improves the glycemic control in patients with both CD and T1DM is unclear.[27] Some reports indicate that postprandial blood glucose levels increased by improvement in nutrient absorption after gluten-free diet.[28] On the other hand, it is also thought that an initiation of gluten-free diet can be low in carbohydrates depending on how the diet is taken, and patients may have to reduce the insulin dose. In fact, with regard to the use of a sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are presumed to have similar pathophysiology to a low-carbohydrate diet, the importance of preventing hypoglycemia and avoiding the risk of ketosis by appropriately adjusting the insulin dose when using SGLT2 inhibitors in the combination therapy for T1DM patients has been noted.[29] When treating the patient with both T1DM and CD on a gluten-free diet, it is essential to carefully determine the insulin dose while monitoring the dietary management and the trends of blood glucose.

This is the first study to investigate the co-occurrence of CD and T1DM in Japan. However, a major limitation of our study is the small number of participants evaluated at a single center. It is difficult to confirm that the prevalence of CD in Japanese patients with T1DM is 0%, but we expect that the prevalence rate is lower than that in other countries based on the results of our study. For further confirmation, multi-center study may be required.

In conclusion, the prevalence of CD among patients with T1DM visiting our hospital was 0%. Although the prevalence of CD is expected to increase in Japan as wheat consumption increases, this result suggests that the prevalence of CD in Japan may be extremely low compared to that in other countries, even among patients with T1DM, in whom the CD prevalence is considered higher than in the general population in other countries.

Author Contributions

YN primarily contributed to all parts of the study. NK, AI, and TT contributed to the analyses and interpretation. NH contributed to the study conceptualization, study design, interpretation, and review of the manuscript. MT and SI contributed to the interpretation and the review of the manuscript. YK and TO contributed to the study conceptualization, analyses interpretation, review, and editing the manuscript.

Compliance with Ethical Standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethical Committee of Hyogo Brain and Heart Center, approval number: 2-18, date of approval: 14/07/2020) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before being included in the study.

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Abbreviations

CD	celiac disease
HLA	human leukocyte antigen
T1DM	type 1 diabetes mellitus
TTG	anti-tissue transglutaminase

Conflict of Interest

No potential conflicts of interest were disclosed.

Data Availability Statement

Data are available from the corresponding author on reasonable request.

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