Prevalence of celiac disease in children with type 1 diabetes mellitus screened by anti-tissue transglutaminase antibody from Western Saudi Arabia

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ABSTRACT

الأهداف: تحديد مدى انتشار الداء الزلاقي لدى الأطفال والمراهقين المصابين بالسكري من النوع الأول وذلك باستخدام فحص أضداد الترانسجلوتاميناز.

الطريقة: أجريت هذه الدراسة الإسترجاعية التي شملت الأطفال والمراهقين المصابين بمرض السكري من النوع الأول في مستشفى جامعة الملك عبدا لعزيز، جدة، المملكة العربية السعودية، واستمرت خلال الفترة من أكتوبر 2002م إلى يونيو 2011م. ولقد قمنا بمراجعة نتائج المسح الأولية لفحص أضداد الترانسجلوتاميناز لمعرفة المرضى المصابين بالداء الزلاقي. ثم قمنا بجمع المعلومات السريرية والديموغرافية والمخبرية من سجلات المرضى.

النتائج: شملت الدراسة 430 طفل مصاب بمرض السكري من النوع الأول ممن أُجري لهم فحص أضداد الترانسجلوتاميناز حيث كان متوسط الأعمار 10.7 سنوات (1.1–18) عند إجراء الفحص. وتشكلت العينة من 232 من السعوديين (54%)، وبلغت نسبة الإناث 58.8% من العدد الإجمالي. كانت نتيجة الفحص إيجابية لدى 91 مريضا (21.2%). كما بلغ عدد المصابين بالداء الزلاقي 48 مريضا (11.2%) من العدد الكلي. ولم يكن هناك شكوى من أعراض باطنية عند 42 مريضا (87.5%) من المصابين بالداء الزلاقي. وعند مقارنة مرضى الداء الزلاقي بمن ليس لديه الداء الزلاقي تبين أن مرضى الداء الزلاقي يعانون من أوزان قليلة بالنسبة للعمر (p=0.007)، كما يعانون من طول تحت المعدل الطبيعي بالنسبة للعمر (p=0.03)، وأن نسبة حدوث فقر الدم (p<0.001) وانخفاض نسبة البومين الدم (p<0.001)، وحدوث أمراض الغدة الدرقية المناعية (p=0.002) أكثر حدوثاً لدى مرضى الداء الزلاقي مقارنة بغيرهم من المرضى. كما أنه لم يظهر هناك تفاوت في مستوى الخضاب التركمي (p=0.38) أو نسبة الاحتياج اليومي للأنسولين (p=0.74) بين المجموعتين.

خاتمة: أثبتت الدراسة أن نسبة انتشار الداء الزلاقي لدى الأطفال والمراهقين المصابين بمرض السكري من النوع الأول تعد مرتفعة مقارنةً بدراسات مشابهة أجريت في مراكز أخرى من العالم مما يستدعي توصية فريق البحث بإجراء فحص الأضداد لجميع الأطفال المصابين بمرض السكري من النوع الأول.

Objectives: To determine the prevalence of celiac disease (CD) in children and adolescents with type 1 diabetes mellitus (T1DM) using anti-tissue transglutaminase (anti-tTG) antibodies.

Methods: A retrospective hospital record-based study of all children and adolescents with T1DM who were screened for CD was conducted at the Pediatric Diabetes Clinic of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia (KSA) between October 2002 and June 2011.

Results: A total of 430 children with T1DM were screened by anti-tTG antibody. The median age at screening was 10.7 years (range; 1.1-18). The study cohort included 232 (54%) Saudi patients, and females constituted 58.8% of the total number. Anti-tTG antibody screening was positive in 91 (21.2%) patients. Forty-eight (11.2%) out of 430 children screened had biopsy-proven CD. Forty-two patients with CD (87.5%) were asymptomatic. Patients with CD had less weight for age (p=0.007), and height for age (p=0.03) z-scores than non-CD patients. They showed more association with anemia (p<0.001), low albumin level (p<0.001), and autoimmune thyroid disease (p=0.002). There was no difference in the mean glycosylated hemoglobin level (p=0.38), or insulin requirements (p=0.74) between the 2 groups.

Conclusion: The prevalence of CD in patients with T1DM from the Western region of KSA is considered among the highest reported. Therefore, routine screening through proper serological testing is recommended.

Saudi Med J 2012; Vol. 33 (5): 541-546

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Received 19th December 2011. Accepted 14th April 2012.

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Celiac disease (CD) is an immune related enteropathy triggered by gluten exposure in genetically susceptible individuals.[1] High prevalence of CD has been observed in patients with type 1 diabetes mellitus (T1DM). Many authors reported a prevalence ranging from 0.6-10.4% of CD in children with T1DM across different European countries.[2-4] Both conditions are associated with the human leukocyte antigen (HLA) class II gene on chromosome 6p21, and share common non-HLA alleles that probably contribute to this coexistence.[5] Published studies on the prevalence of CD in T1DM from the Arab world, including Saudi Arabia are scant.[6-9] Type 1 DM is common among Saudi children and adolescents. This was reflected through a cross-sectional nationwide study that reported a prevalence of 109.5 per 100,000 population in children and adolescents in Saudi Arabia.[10] Unfortunately, studies of CD prevalence in children with T1DM was limited only to one study[6] that reported the occurrence of CD in 4.9% of 123 children with T1DM screened by anti-gliadin (AGA) and anti-reticulin antibodies (ARA). The aim of this study was to determine the prevalence of CD in a large cohort of children and adolescents with T1DM seen at King Abdulaziz University Hospital, utilizing anti-tissue transglutaminase (anti-tTG) antibodies as being more sensitive and specific serological test.

Methods. This is a retrospective study of all patients with T1DM diagnosis who were followed up at the Pediatric Diabetes Clinic of King Abdulaziz University Hospital between October 2002 and June 2011. Selective screening for CD was started in January 2000 in this hospital. Different serological tests such as AGA and anti-endomysial (EMA) antibodies were used inconsistently for screening. In October 2002, anti-tTG was first introduced for routine screening of children with T1DM in this hospital. In this study, we only included children and adolescents less than 18 years of age with the diagnosis of T1DM. The results and type of serological screening test used were retrieved from the hospital database information system and the diagnostic immunology laboratory records. Exclusion criteria included patients who were screened with serological tests other than anti-tTG, and patients with DM other than type 1. Data were extracted from the medical records including demographic data, clinical symptoms, growth parameters, and laboratory investigations. The z scores for weight and height, and body mass index (BMI) were calculated using anthropometric software (Epi-Info, Centers for Disease Control and Prevention, Atlanta, GA, USA). This study was approved by the Bioethical and Research Committee of Faculty of Medicine of King Abdulaziz University, and the study was conducted according to the principles of Helsinki Declaration.

Antibody analysis. Enzyme linked immunosorbent assay (ELISA) based anti-tTG (immunoglobulin [Ig]A) was carried out by Quanta Lit tTG ELISA kit (INOVA Diagnostics Inc, San Diego, CA, USA). Blood samples were separated and the serum was pre-diluted with horseradish peroxidase (HRP) washing buffer. Then, the HRP-IgA conjugate was added to each of the ELISA wells and after incubation and washing, the 3,3',5'5-tetramethylbenzidine (TMB) chromogen substrate was added to stop the reaction. Results were read at 450 nm within one hour of stopping the reaction. Final results were calculated and interpreted according to the high positive cutoff. The cutoff was 20 unit/ml. Total serum IgA was measured for all patients using the nephelometry system (Siemens AG, Munich, Germany).

Diagnosis of celiac disease. Patients who had an elevated level of anti-tTG underwent upper endoscopy. Multiple biopsy specimens were obtained by an upper gastrointestinal endoscope from the distal duodenum, and these were sent for histopathology. The severity of small bowel mucosal damage was reviewed by an experienced gastrointestinal pathologist, and graded according to the Marsh classification from I to III.[11] The diagnosis of CD was based on compatible serologic tests, small bowel pathology results, and response to gluten free diet (GFD). Throughout the article, the working definition of CD will only include the biopsy positive cases.

Statistical analysis was performed using Statistical Package for Social Sciences version 19 (SPSS, Inc, Chicago, IL, USA). Data were expressed as percentage of the total for categorical variables, as mean with standard deviation (SD) for normally distributed continuous variables, or as median with interquartile range for skewed distributed variables. Group comparison of variables was performed by independent sample t-test, or the non-parametric tests (Mann-Whitney) for continuous variables when appropriate, and Pearson Chi-square ($\chi 2$) test for categorical variables. Binary logistic regression analysis was performed to examine variables that independently predict the presence of CD. A $p<0.05$ was considered significant.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Results. A total cohort of 430 children with T1DM was initially screened utilizing anti-tTG. The baseline characteristics of the study cohort are shown in **Table 1**. Ninety-one patients were positive on anti-tTG serological testing, giving a seroprevalence of 21.2%. Out of the 83 patients whose parents agreed for upper endoscopy and small bowel biopsy, 48 showed histopathological changes compatible with the diagnosis of CD and 35 patients had normal small bowel histology. The histopathological grading that was performed according to Marsh classification is shown in **Table 2**. Out of the total number of children screened (n=430), 48 patients had CD giving a prevalence rate of 11.2% for biopsy proven CD in this cohort. In subgroup analysis, CD was found in 25 of 232 Saudi children screened (10.8%). Clinical symptoms were observed in only 6 (12.5 %) out of 48 CD patients and were as follows: abdominal pain (n=3); diarrhea (n=1); abdominal distension (n=1); and vomiting (n=1). However, all the remaining patients were asymptomatic. Growth parameters of CD patients were compared to the T1DM patients without CD (**Figures 1a and 1b**). The difference between the median weight for age z-scores (p=0.007), and the median height for age z-scores between the 2 groups was statistically significant (p=0.03). However, there was no difference observed in the BMI between both groups (p=0.15). This pattern of growth failure was more related to the patients with CD. In comparing different variables at the time of screening between DM patients with and without CD (**Table 3**), CD patients had longer duration of DM (p=0.01), and lower hemoglobin (p<0.001) and albumin levels (p=0.008) compared to non-CD patients. There was no difference at the time of screening between both groups in either insulin requirement as measured by the number of units per kg body weight (p=0.74), or the mean glycosylated hemoglobin (HbA1C) level (p=0.38). Autoimmune thyroid disease was found in 10 of 48 patients with CD, and in 25 of 357 patients with no CD (χ^2; p=0.002). The CD patients had more nutritional

Table 1 - The baseline characteristic of 430 patients with type-1 diabetes mellitus (DM).

Variable	Mean ± SD	Range
Females, n (%)	253 (58.8)	
Saudis, n (%)	232 (54.0)	
Age at screening, median (years)	10.7	(1.1 - 18)
Age at type-1 DM diagnosis, median (years)	7.7	(0.03 - 17)
Duration of type-1 DM (years)	2.5 ± 1.8	(0.17 - 12.68)
Autoimmune thyroid disease, n (%)	35 (8.0)	
Weight for age z-score	-0.39 ± 1.3	(-6.5 - 4.7)
Height for age z-score	-0.73 ± 1.46	(-7.8 - 6.1)
Body mass index, kg/m^2	17.9 ± 3.9	(11.6 - 42)
Hemoglobin (g/dl)	12.6 ± 1.3	(5.7 - 16)
Albumin (g/L)	37.7 ± 3.8	(23 - 48)
Glycosylated hemoglobin	9.7 ± 2.3	(4.8 - 18.6)
Anti-tissue transglutaminase	33 ± 59	(1 - 296)

Table 2 - The histopathological changes of small bowel biopsy according to Marsh classification[11] (n=48).

Classification	n	(%)
Marsh 1	8	(16.7)
Marsh 3a	7	(14.6)
Marsh 3b	19	(39.6)
Marsh 3c	14	(29.1)
Total	**48**	**(100)**

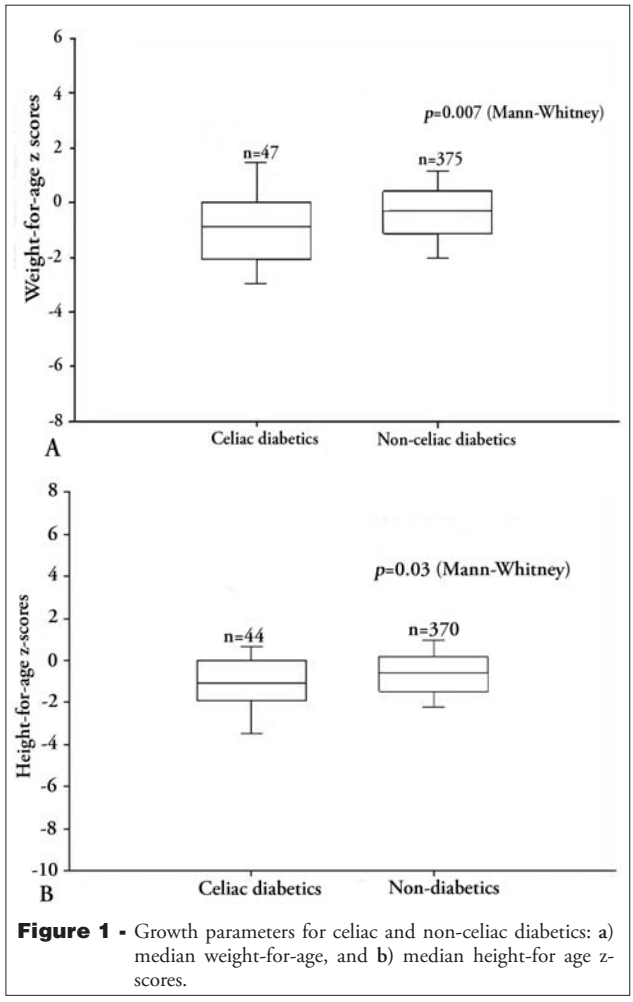

Figure 1 - Growth parameters for celiac and non-celiac diabetics: **a)** median weight-for-age, and **b)** median height-for age z-scores.

Table 3 - Comparison between celiac and non-celiac diabetic children.

Variables	Mean ± SD	95% CI	Mean ± SD	95% CI	*P*-value
	Celiac (n=48)		Non-celiac (n=382)		
Age at screening, years	10.2 ± 3.8	9.1 - 11.3	10.2 ± 3.6	9.7 - 10.5	0.98
Age at diabetes mellitus (DM) diagnosis, years	8.2 ± 4.3	7.1 - 9.4	7.6 ± 3.8	7.2 - 7.9	0.32
Duration of DM, years	2.6 ± 1.8	2.4 - 2.8	2.0 ± 1.4	1.7 - 2.4	0.01
Insulin requirement (u/kg)	1.0 ± 0.5	0.8-1.1	1.1 ± 2.2	0.9 - 1.3	0.74
Hemoglobin (g/dl)	11.8 ± 1.5	11.4 - 12.3	12.7 ± 1.2	12.6 - 12.9	<0.001
Albumin (g/L)	35.8 ± 4.6	34.4 - 37.2	37.8 ± 3.7	37.4 - 38.2	0.008
Glycosylated hemoglobin	9.4 ± 2.2	8.8 - 10.1	9.7 ± 2.3	9.5 - 9.97	0.38
Anti-tissue transglutaminase	152.6 ± 85.9	128.2 - 177.4	18.7 ± 34.1	15.5 - 22.5	<0.001

problems as evidenced by the presence of anemia and hypoalbuminemia. Anemia (hemoglobin <12 g/dl) was found in 21 out of 48 CD patients, and 62 of 316 non-CD patients (χ^2; p<0.001) and hypoalbuminemia (albumin <30 g/L) in 17 of 46 CD patients, and 56 of 340 non-CD patients (χ^2; p<0.001). Logistic regression analysis of multiple variables includes: age at screening; age at T1DM diagnosis; duration of DM; insulin requirement at diagnosis; HbA1C level; and association with autoimmune thyroid disease. The presence of anemia and hypoalbuminemia demonstrated that the following variables were independently associated with the diagnosis of biopsy proven CD: autoimmune thyroid disease (odds ratio [OR]: 1.9; 95% confidence interval [CI] 1.9-11.4; p=0.001), anemia (OR: 3.6; 95% CI: 1.8-7.2; p<0.001), hypoalbuminemia (OR: 2.9; 95% CI: 1.4-5.9; p=0.003), and duration of DM (OR: 1.3; 95% CI: 1.0-1.7; p=0.03).

Discussion. In Saudi Arabia, there are no valuable population based studies, indicating the prevalence of CD in children and adolescents generally. However, there are scant reports of case series describing the existence of CD in children community,[12,13] and in adults.[14] A study of screening of another high risk population of Down syndrome patients for CD has also been published.[15]

In the present study, we investigated a total of 430 children and adolescents less than 18 years of age with T1DM seen at a tertiary referral center in Western KSA, in an area with relatively high prevalence of T1DM in this age group.[10] In this cohort, we found a prevalence of biopsy proven CD in 11.2%. The prevalence of CD might even be higher if we consider the 8 patients whose parents refused performing upper GI endoscopy on them to obtain small bowel biopsy for histopathological evaluation, while still having positive celiac serology. The prevalence in our study is higher than the prevalence reported from Germany (0.6%),[4] France (1.6%),[16] Italy (6.8%),[2] and Tunisia (5.3%),[7] and comparable to the prevalence reported from Denmark (10.4%),[3] Libya (10.3 %),[9] and Algeria (16.4%)[8]. Comparing the prevalence reported in this cohort with an earlier study from the Central region of Saudi Arabia,[6] the prevalence reported in the present study is higher than the 4.9% reported from the previous study[6]. This lower prevalence rate reported may be related to the choice of the screening test, in which the authors used AGA and ARA as the basic serology testing for screening. These tests were found to be less sensitive and specific, and is no longer recommended.[17] The anti-tTG antibody used as the screening test of choice in our study has been regarded as the most sensitive and specific test for initial screening, despite the development of several new tests.[18,19]

It is not clear why Saudi children with T1DM display a high prevalence rate of CD compared to other populations reported in the literature.[2,4,16] This may be related to the fact that wheat was considered the major staple food in our region for many centuries. In addition, the high rate of consanguinity in our region may have contributed to the high prevalence observed. In this study, in agreement with previous reports,[20,21] we did not find a significant difference in the onset of T1DM between CD and non-CD patients (**Table 3**). However, T1DM with CD had longer duration of DM compared to non-CD patients. Both groups did not differ in their diabetic control at baseline as measured by HbA1C and insulin requirements. This observation was in agreement with previous studies.[22,23] Most patients with CD identified through screening were either asymptomatic, or have non-specific symptoms of CD.[20,24] Few authors have reported that children with T1DM and CD identified during screening are not truly asymptomatic, and these subtle symptoms may not be

apparent except after direct questioning,[25] or recognized retrospectively after starting gluten-free diet (GFD)[26,27] In the present study, only 6 (12.5%) CD patients had gastrointestinal symptoms. This observation is in agreement with previous reports,[2,22] and supports the recommendation for screening all children with T1DM for CD regardless of symptoms.

Autoimmune thyroid disease (ATD) was described to be more prevalent in patients with T1DM.[28] Similarly, the association of ATD with CD is well-known in the medical literature.[29] All the 3 conditions are autoimmune related, and share the same mechanisms of immune mediated end organ damage. In the present study, we found a significant higher prevalence of thyroid disease in patients with T1DM and CD than patients without CD. Furthermore, the presence of ATD was found to be one of the independent predictors for the development of CD in this cohort of patients. We also found that T1DM patients with CD had affected growth parameters compared to patients without CD (**Figures 1a & 1b**). However, we did not include information regarding the long term effect of institution of GFD on growth parameters, because this was not among the objectives of the current study. This finding of growth impairment of CD patients at the time of screening is in agreement with previous studies.[26,27,30] Several published longitudinal studies of patients with T1DM following consumption of GFD showed improvement in growth parameters, such as Saadah et al[22] found an increase in weight for age z-scores, Sanchez-Albisua et al[31] showed an increase in height z-scores in patients with good adherence to GFD, and Amin et al[32] showed improvement in BMI z-scores after institution of GFD. Anemia and low albumin level were encountered more in T1DM patients with CD than non-CD patients in our study, both of which may reflect the underlying subclinical mucosal damage. Furthermore, the presence of anemia was identified by the logistic regression analysis to be one of the predictors for the diagnosis of CD. Harper et al[33] attributed the anemia observed in asymptomatic CD patients, identified by screening to the presence of chronic inflammation.

Asymptomatic children and adolescents with T1DM and CD identified by screening may not perceive any benefit from GFD, which may add to the dietary constrains, and decreased dietary compliance.[34,35] However, a recent study has demonstrated minimal impact of the double diagnosis on the quality of life of children with concomitant CD and T1DM.[36]

This study was limited by its retrospective nature. Further studies in our population are required to understand the impact of CD and GFD on the health of children identified through screening programs. Additionally, studies should focus in finding a reliable diagnostic tool that can spare the patients from undergoing upper endoscopy and small bowel biopsy. Recently published guidelines recommended the possibility of omitting the biopsy under strict conditions including: the presence of symptoms suggestive of CD, high anti-tTG levels more than 10 times the upper normal limit, verified by anti-endomysial antibody positivity, and positive result for HLA DQ2 and/or DQ8.

In conclusion, the prevalence of CD in hospital attendants with T1DM children from Western Saudi Arabia is considered among the highest reported. Therefore, proper identification through implementation of routine screening test with a high sensitivity and specificity is recommended.

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