

## Sero-Prevalence of Celiac Disease Among Symptom-Free Type 1 Diabetes Mellitus In Al-Baha Region, Saudi Arabia

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**Abstract : Introduction:** Celiac disease (CD) is a unique autoimmune disorder which is common among patients with type 1 diabetes mellitus (T1DM), but a majority of patients are asymptomatic and still undiagnosed.

**Aim:** For early diagnosis and treatment of celiac disease among patients with T1DM we estimate the prevalence of asymptomatic celiac disease among T1DM in Al-Baha region, southwestern of Saudi Arabia.

**Subjects and methods:** The clinical and laboratory data of 268 T1DM received medical care in Al-Baha Diabetic Center were retrospectively analyzed based on the records.

**Results:** Of the 268 T1DM screened, 131 were females (11 were seropositive for CD) and 137 were males (8 were positive for CD); age ranged between 2 years and 23 years (Mean  $12.14 \pm 4.33$  years). Elevated Anti-tTG levels were found in the sera of 19 patients (7.1%). All of our patients were asymptomatic for CD, Thus, the estimated serology-positive prevalence was 7.1%.

**Conclusions:** The prevalence of asymptomatic CD among patient with T1DM was (7.1%) is relatively high in our region based on the serology based assay. To avoid the co-morbidity of CD, regular screening of patients with T1DM for CD is recommended for early diagnosis and treatment especially among symptom-free patients.

**Keywords:** Prevalence, Type 1 diabetes mellitus, celiac disease, Saudi Arabia, tissue transglutaminase antibody

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### I. Introduction

Celiac disease (CD) is characterized by immune-mediated inflammatory lesions of the intestinal mucosa. Most of cases are asymptomatic and owing to its variable manifestations and age at onset, the CD has emerged as a worldwide public health problem (1).

The prevalence of CD among patients with type 1 diabetes mellitus (T1DM) is higher than in the general population, with almost 60% of cases being already present at the onset of diabetes, but mostly undetected and 40% of patients develop CD after few years of T1DM diagnosis (2). T1DM and CD both are associated with human leukocyte antigen (HLA) class II molecules, and presence of DQ8 and DQ2 have the major genetic association with T1DM and CD (3). HLA association was found to be present in the general population and it is expensive and not available in every institute (4). Studies done on different populations showed that CD occur in patient with T1DM varies from 4.4 to 11.1% (5).

The Presence of CD in T1DM patients is considered to be an additional chronic disease affect the clinical management of such cases such as predisposition to nutritional deficiencies, metabolic bone disease and growth retardation in most of cases (6). In T1DM, undiagnosed CD may be associated with unstable blood glucose levels, a greater risk of hypoglycemia (7) and increased risk of retinopathy (8). In those with confirmed CD and T1D, nonadherence to a gluten-free diet (GFD) is associated with early elevation of albumin excretion rate (9), whereas CD duration >10 years, irrespective of GFD adherence, is a risk factor for the development of diabetic retinopathy. Few studies from Saudi Arabia showed the prevalence varies from 4.9 to 11.3% (10-12). Till date, no previous study for the prevalence of CD among T1DM was done in our region, so the aim of this study was to determine the prevalence of asymptomatic CD in patients with T1DM for early diagnosis and treatment of CD to avoid this co-morbidity.

### II. Subjects And Methods

This is a retrospective record-based study, that included 268 patients who were diagnosed as T1DM and followed in the Diabetic Center Clinic at the King Fahd Hospital, Al-Baha, Saudi Arabia. Al-Baha region is located in the southwestern of Saudi Arabia, having an area of 9,921 km<sup>2</sup>, and a population of 466,384 (376,204

Saudi and 90,180 non Saudi). A retrospective data collection was conducted on diabetic patients from the follow up sheets, including patients demographic data (age, sex, nationality, residence, clinical presentation, date of onset and duration of diabetes) and laboratory data, including the serological screening for CD {anti-tissue transglutaminase IgA (IgA-tTG) and IgG antibodies (IgG-tTG)}.

Blood for determination of Anti-tTG antibodies were obtained during routine clinic visits and antibody positive patients were encouraged to undergo duodenal biopsy to confirm the diagnosis, however, none of our patients accepted the upper gastrointestinal endoscopy and biopsy.

Anti-tTG (IgA and IgG) samples were analyzed using Fluorescent Enzyme Immunoassay method and values more than 20U/ml is considered positive.

The diagnosis of T1DM was made according to the World Health Organization (WHO) criteria (13). Any patient with Type 2diabetes mellitus, diabetes secondary to cystic fibrosis, or steroid therapy or any symptomatic patients for the CD were excluded from the study. The study was approved by the Hospital Research and Ethics Committee.

### Statistical Analysis

Statistical analyses carried out using the Statistical Package for Social Sciences (SPSS; Student version 21). Data were expressed as frequencies [n (%)], whereas means and standard deviation were used for continuous variables. Chi-square statistics was used to compare between categorical variables. The Independent T-test was applied to compare two quantitative variances. A p-value smaller than 0.05 was accepted as statistically significant

### III. Results

Of the 268 T1DM patients screened, 131 were females (11 were seropositive for CD) and 137 were males (8 were positive for CD); age ranged between 2 years and 23 years (Mean  $12.14 \pm 4.33$  years). 254 of them were Saudi (18 of them were seropositive for CD) and 12 were non Saudi (1 of them was seropositive for CD) as shown in table 1. Mean age at diagnosis of T1D was  $7.3 \pm 2.6$  years. Mean time of duration of T1DM was  $3.44 \pm 1.7$  years (range 0 – 10 years). There was none significant difference between the prevalence of CD among males and females ( $p=0.28$ ).

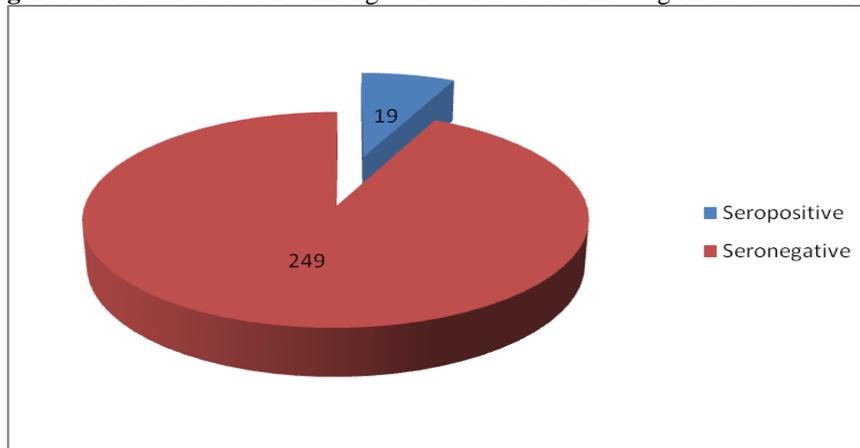
Elevated Anti-tTG antibodies levels were found in the sera of 19 (7.1%) of 268 T1DM patients (figure 1). Clinical description and laboratory results in these patient were shown in table 2.

### IV. Figures And Tables

**Table 1:** Clinical And Laboratory Data Of Patients With And Without Celiac Disease

Parameter	Celiac disease screening		P
	Positive	Negative	
Age (years)	12.8±3.2	12.1±4.4	0.5
<b>Gender</b>			
Females	11	120	0.28
Males	8	129	
<b>Nationality</b>			
Saudi	18	236	0.9
Non Saudi	1	13	
Duration of DM (years)	3.39±1.5	3.45±1.7	0.89
HbA1c	9.8±1.71	10.1±1.98	0.5

**Figure 1:** Prevalence Of CD Among T1DM Based On Anti-Ttg Antibodies Serology



**Table 2:** Clinical Characteristics And Laboratory Test Results In Patients With Celiac Disease

Number	Gender	Age (years)	Duration of diabetes (years)	Nationality	A1c levels	Retinopathy
1	Female	11	2	Saudi	11	Absent
2	Female	12	2	Saudi	11	Absent
3	Female	11	1	Saudi	8	Absent
4	Male	9	2	Saudi	8	Absent
5	Female	12	5	Saudi	9	Absent
6	Female	13	2	Saudi	12	Absent
7	Female	7	5	Saudi	8	Absent
8	Male	13	4	Saudi	9	Absent
9	Female	13	4	Non Saudi	8	Absent
10	Female	15	3	Saudi	9	Absent
11	Male	13	2	Saudi	8	Absent
12	Male	17	5	Saudi	9	Absent
13	Male	13	2	Saudi	8	Absent
14	Male	18	5	Saudi	10	Non proliferative
15	Male	9	3	Saudi	12	Absent
16	Female	16	3	Saudi	12	Absent
17	Female	9	6	Saudi	11	Non proliferative
18	Male	19	4	Saudi	13	Absent
19	Female	13	5	Saudi	11	Absent

## V. Discussion

Celiac disease (CD) is a unique autoimmune disorder which is common among patients with T1DM, but a majority of patients are asymptomatic and still undiagnosed.

The association between T1DM and CD is well documented, although reported rates vary. Prevalence rates from both cross-sectional and longitudinal studies range from 1.6% to 16.4% worldwide (12, 14-17). In contrast, CD prevalence is 0.3% to 1.0% in the general population of all ages (18). The prevalence of celiac disease is approximately 1–2% in the populations of North and South America, North Africa, the Middle East and India (19,20).

There is limited data on the prevalence of CD in Arab children with T1DM. Data from Arab countries in North Africa indicate the prevalence rate ranging from 5 to 16%, Egypt (11.2) (5.4), Libya (11%), Tunisia (5.3%) and Algeria (16.4%) (21-25).

The diagnosis of CD involves several serological tests, anti-gliadin antibodies (AGA) have been used as a first step, recognizing celiac autoimmunity, but currently it was replaced by the new effective and superior serology such as endomysial antibodies (EMA), tissue transglutaminase (tTG) antibodies (26). The EMA and anti-tTG are highly sensitive and specific in detecting individuals with celiac disease (27,28). Although the specificity of EMA is high enough, but inadequate sensitivity resulted in some false negative values, in addition to that the test is high cost, complex, and handler-dependent (29-31). Anti- tTG is the preferred first serological test to identify cases of CD because of its high sensitivity and accuracy (30).

Anti-gliadin antibodies- based screening study in Riyadh, the capital city of Saudi Arabia, revealed a 4.9% prevalence of CD in T1D children (10). Anti-gliadin antibodies-based screening is no longer recommended because of the poor sensitivity and specificity (32). In a large retrospective, anti-tissue transglutaminase (anti-tTG) antibodies based, screening study, the prevalence of CD among T1DM children in the Western region of Saudi Arabia was 11.2% (11).

In our study, elevated Anti-tTG antibodies levels were found in the sera of 19 (7.1%) of 268 T1DM patients screened at the Diabetic Center in Al-Baha region, southwestern of Saudi Arabia. Although Anti-tTG antibodies are very sensitive markers for the presence of clinical CD, it is possible that some patients were antibody positive, without having frank disease. These patients could have latent diseases and need to be closely followed up. This prevalence was matched with the Saudi study done by Alshareef et al (7.3%) (33).

The considerable variation in the prevalence of CD across the various studies in Saudi Arabia, Arab regions and worldwide may be related to the ethnic differences across the study populations, which is likely to reflect the greater risk of CD among individuals with high-risk HLA antigen genotypes (34), as well as the varying impact of environmental influences across different countries (35). The variation in prevalence rates may also be related to differences in study design, including retrospective versus prospective, the frequency of screening, and duration of follow-up and laboratory methods of screening.

Recommendations for screening frequency are variable and not evidence based. The International Society for Pediatric and Adolescent Diabetes recommends screening at the time of diagnosis and every 1-2 years thereafter, with more frequent assessment if clinically indicated or if there is a first-degree relative with CD(36), whereas the American Diabetes Association recommends CD screening should be at the time of diagnosis and repeated at 2 and then 5 years soon after diabetes diagnosis and in those with clinical symptoms suggestive of CD (37).

This study was limited by the absence of small intestinal biopsy to confirm the diagnosis of CD in our symptom free patients for CD but non of our patients accepted this invasive maneuver, however many studies have been done with the aim of identifying the serological screening methods with appropriate diagnostic accuracy that could be an alternative to small intestine biopsy for the diagnosis of CD (38,39).

## VI. Conclusion

The prevalence of asymptomatic CD among patient with T1DM was (7.1%) is relatively high in our region based on the serology assay. To avoid the co-morbidity of CD, regular screening of patients with T1DM for CD is recommended for early diagnosis and treatment especially among symptom- free patients. Larger prospective studies are needed for a newer non-invasive test to diagnose those patients.

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