

## CLINICAL STUDY

# Prevalence of celiac disease among type 1 diabetic Egyptian patients and the association with autoimmune thyroid disease

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**Abstract:** *Background:* Celiac disease (CD) is a common genetically transmitted immune mediated disease. *Method:* Seventy three type 1 DM patients attending the Diabetes, Metabolic and Endocrinology outpatient clinic were recruited in the study. Thorough history taking and medical examination were done. They were screened for the prevalence of celiac disease by ELISA for coeliac disease antibodies against tTG. Anti-thyroglobulin antibodies, antithyroidperoxidase antibodies were analysed to estimate the prevalence of autoimmune thyroid disease.

*Results:* Four out of seventy three (5.48 %) type 1 diabetic children were seropositive for anti-tTG antibodies. They had symptoms of celiac disease such as chronic diarrhea (5.48 %), recurrent abdominal pain (2.7 %) and short stature (5.48 %). Six patients were diagnosed with autoimmune thyroid diseases as they were seropositive for antithyroglobulin antibodies and/or antithyroidperoxidase antibodies. None of them proved to be positive for anti-tTG antibodies.

*Conclusion:* The prevalence of CD among Type 1 DM patients by using tissue transglutaminase antibodies ELISA was (5.48 %) which supports the current practice of screening for celiac disease. Patients with autoimmune thyroid disease were negative for anti-tTG antibodies. HbA1c levels were adversely affected by malabsorption related to celiac disease in seropositive patients (Tab. 5, Ref. 27). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

Key words: celiac disease, type 1 diabetes, Egyptian patients, autoimmune thyroid disease.

Celiac disease is a strongly heritable gastrointestinal illness that is an especially important model of the genetically complex multifactorial immune mediated disease, having a non-mendelian mode of inheritance (1). It develops as a result of an interaction between genetic, environmental and immunological factors (2). Nine gene regions were known to predispose people to develop celiac disease based on twin and family studies. Four regions of celiac disease also have genes that predispose to type 1 diabetes, suggesting common origins for the diseases (3). Celiac sprue is a chronic intestinal disorder caused by hypersensitivity to prolamins, the glutamine- and proline-rich gluten proteins contained in wheat, rye, and barley. Genetically predisposed subjects who ingest cereal proteins develop an inflammatory enteropathy characterized by proliferation of intraepithelial lymphocytes, crypt hyperplasia, and partial or complete atrophy of small intestinal villi. The inflammatory response is induced by cross-linking and transamidation of gluten peptides by tissue transglutaminase, an enzyme localized to the connective tissue (lamina propria or en-

domysium) underlying the epithelial cells of the small intestine. Posttranslational modification of gluten enhances its uptake by dendritic cells and its binding to HLA-DQ2 and DQ-8, which induce T-cell activation and cytokine release (4, 5). The resulting inflammation is accompanied by development of circulating antibodies to transglutaminase and to the endomysium. The only treatment at present is lifelong strict adherence to a gluten-free diet (GFD), which permits the recovery of the intestinal mucosa (6).

Celiac disease may present at any age after the introduction of gluten into the diet and the clinical presentation is variable, ranging from subclinical to severe. Although it is primarily a disorder affecting the small bowel, symptoms can range from classical gastrointestinal symptoms, as vomiting, chronic diarrhea, abdominal distension to non-specific symptoms and extraintestinal manifestations as growth failure, dental enamel defects, delayed puberty, arthritis, arthralgias, osteoporosis and neurological problems are common in young children (7,8). Insidious onset with non-specific symptoms as pallor, and fatigue and biochemical evidence of malabsorption as low serum folate, ferritin or calcium are typical of older age groups (9).

The iceberg concept has been used to draw attention to the fact that many cases are asymptomatic and therefore remain undiagnosed if screening tests are restricted to patients presenting with the classical signs and symptoms of the disease. Clinical

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CD is represented by the exposed tip of the iceberg, with silent and latent disease hidden below the waterline (9). Many children and adults with celiac disease have nonclassical forms of the illness. The so-called silent celiac disease refers to partial or complete villous atrophy in a seropositive patient who has no gastrointestinal or extra-intestinal complications.

Studies in Western Europe, North America, and Australia indicate that the prevalence of celiac disease among children and adults with type 1 diabetes (mean 4.1 %, range 0–10.4) greatly exceeds the prevalence of the condition in the general population (0.3–0.5 %) (10, 11). An association between CD and type 1 DM has been recognized. CD is believed to have an adverse effect on Type 1DM, particularly with regards to glycaemic control. In addition, CD carries with it an increased risk of long term complications, including decreased bone density and gastrointestinal malignancies. Adherence to a gluten-free diet is difficult but appears to reduce the risk of malignancy. However, its effect on diabetes remains controversial (9). Thyroiditis, Addison's disease and systemic lupus erythematosus have also been shown to be associated with silent CD. In addition chronic thyroiditis or anti-thyroid antibodies were observed among patients with CD (12).

When a patient has symptoms suggestive of CD, a range of laboratory tests can be performed to support the diagnosis. These include hematological tests to reveal anemia or abnormal red cell morphology; biochemical tests for identification of thyroid disease or diabetes mellitus; and tests which may be indicative of malabsorption, such as serum folate, ferritin, calcium or alkaline phosphatase (6).

The identification of the enzyme tissue transglutaminase (tTG) has led to the development of assays that include a quantitative enzyme-linked immunosorbent assay (ELISA) that measures IgA antibodies to tTG (anti-tTG) (6).

It is well accepted that much CD remains undiagnosed in the community. Therefore, a strategy of case finding among high-risk populations, such as people with type 1 diabetes, may be an effective way to identify unrecognized CD (13).

The aim of the study is to:

Investigate the genetic background and phenotype characteristics of celiac disease and estimate the prevalence of celiac disease among a population of children and adolescents with Type 1DM using anti-tTG antibody as a marker in the diagnosis and screening of the disease in high risk individuals.

Investigate the mode of presentation among children and adolescents with type 1DM

Study the possible association of other autoimmune disorder like autoimmune thyroid disease with celiac disease and type 1DM.

## Patients and methods

Seventy three patients diagnosed as type 1 DM currently attending the Diabetes, Metabolic and Endocrinology outpatient clinic, Pediatric Hospital Cairo University, in the period from January to June 2007 were recruited in the study. The patients were compared to 30 age and sex matched controls. The duration of treatment with insulin is more than 1 year.

Informed consent was obtained from the children's parents.

All patients were subjected to:

- Full history taking and family pedigree analysis for the three disorders.
- Thorough clinical examination
- Laboratory investigations including
- Full blood count, Hemoglobin A1c, screening for celiac disease using tissue transglutaminase antibodies ELISA
- Screening for autoimmune thyroid disorder using Anti-thyroglobulin antibodies, antithyroidperoxidase antibodies

## Specimen Collection

Ten cc venous blood was withdrawn from the anticubital vein and was divided into two parts:

Two ml was collected in a tube containing ethylenediamine tetraacetate (EDTA) as an anticoagulant for determination of Hb A1c.

Eight cc was collected in a clean dry centrifuge tube. Blood was allowed to clot at 37 °C water bath. Clot was separated and centrifuged for 10 minutes at 3000 g. Serum was divided into aliquots and stored at -20 °C until analyzed. Samples were assayed for measurements of free T3, free T4, TSH, Antithyroid peroxidase antibodies (TPO ab), antithyroglobulin antibody (TG ab) and antitissue transglutaminase antibody (tTG ab).

## Methods

Hb A1C was measured with a cation exchange chromatography method assessed glycaemic control. The procedure is a microchromatographic methodology for the quantitation of glycosylated hemoglobin (non-diabetic reference 5.5-7.7 %) (GLYCO Hb Quick column procedure) (Helena) (14).

Serum TSH was determined by an immulite rapid TSH which is a solid phase two site chemiluminescent enzyme immunometric assay detected by immulite automated analyzer (15).

Serum fT3 (16) and fT4 (17) were assayed by commercial RIA which is a solid phase I 125 radioimmunoassay (Coat A-count, CA, USA).

Antithyroglobulin (Tg) antibody and antithyroid peroxidase (TPO) (18) antibody were quantified by enzyme linked immunosorbent assay (ELISA) for the detection and quantitation of autoantibodies against thyroglobulin and thyroid peroxidase respectively to aid in the diagnosis of certain thyroid disorders (IMMCO diagnostics). Anti TPO values  $\leq 20$  IU/ml were negative and  $> 20$  IU/ml were positive. Anti Tg  $\leq 80$  IU/ml were negative and  $> 80$  IU/ml were positive.

Anti-tTg IgA testing was undertaken with a commercially obtained ELISA kit (21) for the detection and semiquantitation of anti-human tissue transglutaminase IgG antibodies in human serum to aid in the diagnosis of IgA deficient patients with celiac disease (IMMCO Diagnostics). An ELISA of  $< 20$  IU/ml was negative, 20 to 25 IU/ml was border line and  $> 25$  IU/ml was positive.

Data handling and statistical analysis:

A statistical software package (SPSS version 10.0) was used for tabulation and statistical analysis. Data was subjected to the Kolmogorov-Smirnov test to determine its distribution and method

**Tab. 1. Demographic characteristics of type 1 diabetic subjects and the control group.**

	Control (n=30)	Type1DM (n=73)
Age (years)	10.12±2.57	9.18±4.09
Sex		
Males	11 (36.67%)	26 (35.62%)
Females	19 (63.33%)	47 (64.38%)

**Tab. 2. Clinical characteristics of type 1 diabetic patients.**

Clinical Characteristics	Type 1 diabetic patients (n=73)
Duration of diabetes (years)	3.23±3.97
Symptoms:	
Recurrent abdominal pain	2 (2.74 %)
Diarrhea	4 (5.48 %)
Vomiting	1 (1.37 %)
Abdominal distension	3 (4.11 %)
Short stature	4 (5.48 %)

**Tab. 3. Laboratory data of the control group and type 1 diabetic patients.**

Laboratory Data	Control (n=30)	Type1DM (n=73)	P value
fT3 (pg/ml)	3.52±0.72	2.65±0.69	<0.001
fT4 (ng/dl)	1.60±0.28	1.45±0.33	<0.05
TSH(uIU/ml)	2.30±1.12	2.62±1.80	<0.05
Calcium (mg/dl)	9.43±0.30	9.75±2.32	>0.05
Phosphorus (mg/dl)	3.77±0.70	5.82±1.70	<0.001
Alkaline phosphatase (IU/L)	163.73±42.91	428.54±192.06	<0.001
Anti Tgab (IU/ml)	–	6 positive	
Anti TPO ab (IU/ml)	–	6 positive	
Anti tTg ab (IU/ml)	–	4 positive	

HbA1c = glycosylated hemoglobin, Anti Tg ab = anti thyroglobulin antibody, Anti TPO ab = anti thyroid peroxidase antibody, Anti tTg ab = anti tissue transglutaminase antibody

of analysis. The measures were parametrically distributed and therefore were presented as mean±SD. Comparisons between cases and controls were performed using the student's t test. All tests were two-tailed and considered statistically significant when p was <0.05.

**Results**

Demographic characteristics of Type 1 diabetes mellitus and controls are listed in Table 1. Seventy three patients were included in the study (26 males and 47 females). The mean age of the patient group was 9.18±4.09 years. The control group included 30 children (11 males and 19 females). The mean for age was 10.12±2.57 years.

The patients group was age and sex matched compared to the control group. Sex ratio of the study participants was similar

**Tab. 4. Demographic and clinical characteristics of celiac disease patients.**

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	6.58	14	7	12
Gender	Female	Female	Male	Female
Duration of diabetes (years)	3	5	1	8
Symptoms:				
Recurrent abdominal pain	+	–	–	+
Diarrhea	+	+	+	+
Vomiting	–	+	–	–
Abdominal distension	+	+	+	+
Short stature	+	+	+	+

**Tab. 5. Laboratory data of Celiac disease patients.**

CD patients	Patient 1	Patient 2	Patient 3	Patient 4
fT3 (pg/ml)	2	2.8	3	2.7
fT4 (ng/dl)	1.1	1.2	1.5	1.2
TSH(uIU/ml)	1.7	1.3	2.5	3.5
HbA1C (%)	5.9	6.1	5.0	5.4
Calcium (mg/dl)	6.4	8.7	7.1	6.7
Phosphorus ((mg/dl)	2.2	5.4	3.8	4.6
Alkaline phosphatase (IU/L)	781	614	697	739
Anti Tgab (IU/ml)	Negative	negative	negative	Negative
Anti TPO ab (IU/ml)	Negative	negative	negative	Negative
Anti tTg ab (IU/ml)	Positive	positive	positive	Positive

HbA1c = glycosylated hemoglobin, Anti Tg ab = anti thyroglobulin antibody, Anti TPO ab = anti thyroid peroxidase antibody, Anti tTg ab = anti tissue transglutaminase antibody

as the proportion of boys to girls in the control group. The results of patients group with type 1 diabetes mellitus being evaluated prospectively for recurrent abdominal pain, diarrhea, short stature, vomiting and abdominal distension are shown in (Tab. 2).

Table 3 demonstrates mean±SD of the laboratory findings for Type 1 diabetic patients. Four out of the 73 children with Type 1 DM (5.48 %) were found to be positive for tTG Abs.

There were 6 patients (6/73) (8.21 %) positive for antibodies directed to thyroperoxidase and/or thyroglobulin and were diagnosed as autoimmune thyroid disease. None of them were positive for tTG Abs.

Clinical characteristics of CD patients are listed in Table 4.

Table 5 demonstrates the laboratory findings of CD patients.

Mean height standard deviation (SDs) for all patients was calculated from data collected. Mean height SDs did not deviate significantly from expected values (1.98±0.1).

**Discussion**

Our study evaluated seventy three diabetic children, for the prevalence of CD.

Four seropositive cases (5.48 %) out of the total of 73 patients with type 1 diabetes in our cohort were detected. This is in accordance with a previous study (9) which estimated prevalence

of celiac disease among children and adolescents with diabetes in their clinical setting is at least 4.4 %. This prevalence rate is consistent with previously estimated values and is reflective of the association between the two diseases. The prevalence of celiac disease in high risk populations is up to 20 % in first degree relatives, 3–6 % with type 1 DM (2). The relatively high prevalence rate supports the practice of screening patients with Type 1DM for celiac disease.

The overall prevalence of CD in patients of all ages with type 1 diabetes with similar rates for pediatric and adult groups in the community-based study was 7.0 % (14). Comparable North American studies have focused on selected patients seen at referral centers and observed a prevalence of CD in type 1 diabetes that ranged from 1.4 % to 5.1 % in pediatric patients and from 3.5 % to 6.0 % in adults (19, 20) Two European studies (18, 19) had evaluated a combined pediatric and adult type 1 diabetic cohort and observed a biopsy proven prevalence of CD of 3.6 % and 5.7 %, respectively.

Seroconversion of celiac autoantibodies in patients previously negative for autoantibodies suggests that screening must be carried out regularly and repeatedly this was proven in another study (9). Even if a patient has tested negative for celiac antibodies in the past this does not mean he will not develop the disease in the future.

There has been controversy about whether or not it is worth diagnosing and treating sub clinical celiac disease but it appears that the risk of developing complications exists regardless of the severity of symptoms. Malignancy may be the first presentation of sub clinical celiac disease and osteoporosis is a well recognized complication, regardless of symptoms (9). Thus it is important to find diagnostic-prognostic markers identification of celiac disease.

Erratic absorption of nutrients in symptomatic celiac disease may increase the risk of severe hypoglycemia in diabetic patients (10, 11). This may be due to coexistence of celiac disease and diabetes, although more likely to suffer from poor control of their diabetes (raising HbA1c). Untreated subclinical celiac disease in diabetic children may increase the risk of hypoglycemia, while early identification and treatment may reduce hypoglycemic risk. This can therefore result in lower HbA1c levels than that might be expected and a non significant difference between subjects and controls. The result of our study agrees with other studies (9). Although our study confirms the high prevalence of CD in type 1 DM (5.48 %). The observed low HbA1c among those patients may reflect the problem of malabsorption. Only a few studies (21, 22) have reported that treatment of CD improves glycaemic control.

Recognized symptoms of celiac disease are chronic diarrhea and weight loss, and we might therefore expect to see impaired growth in subjects with celiac disease. In our study this was evidenced in only 4 subjects (4/73) (5.48 %) who were seropositive. This may be related to early diagnosis in the course of the disease, before the overt symptoms of weight loss and failure to thrive could be seen. In addition to the high index of suspicion for celiac disease in diabetic patients means that subjects who

present with weight loss are screened and treated before this weight loss had time to become significant and malabsorption could affect linear growth. Our result of impaired growth in the seropositive group agrees with other studies (20). In severe symptomatic celiac disease, chronic malabsorption of vitamin D and calcium may also lead to bone demineralization, osteoporosis, and rickets. The osteopenia may be exacerbated by reductions in plasma IGF-1 concentrations (23) and by sex steroid deficiencies in children with delayed puberty. A follow-up study (4) by the same investigative group found a 19 % decrease in total body bone mineral content (assessed by dual-energy X-ray absorptiometry) in a heterogeneous group of celiac children and adolescents that included patients with symptomatic disease. Thus, osteopenia in patients with subclinical disease can be reversed if detected at an early stage. On the other hand, bone mineralization may be more difficult to restore in patients with severe osteopenia due to symptomatic disease. The reduction in BMD in celiac patients may predispose to fractures (5).

The laboratory values of individual celiac patients regarding calcium, phosphorus and high alkaline phosphatase support intestinal malabsorption rickets.

It is worth to mention that the mean phosphorus and alkaline phosphatase level in the whole diabetic group were significantly elevated compared to the control group, this may be related to complex phenomenon in diabetic patients.

According to our results: There were 6 patients (6/73) (8.21 %) positive for antibodies directed to thyroperoxidase and/or thyroglobulin and were diagnosed as autoimmune thyroid disease. None of them were positive for tTG Abs.

Thyroglobulin is a 660 KD glycoprotein which functions as thyroid prohormone. Thyroid peroxidase is a membrane bound enzyme of 105 KD that catalyses thyroid hormone biosynthesis. Thyroxine and tri-iodothyronine are generated by the thyroid peroxidase catalysed iodination and coupling at specific homogenic tyrosines. Measurements of autoantibodies to thyroglobulin and thyroid peroxidase are important in the diagnosis of autoimmune thyroid diseases (26). Type 1 DM may accompanied by other autoimmune disorders, including autoimmune thyroid disease (AIT). The affected patient may be hyper, hypo or even euthyroid. Three thyroid diseases are considered to have autoimmune etiology: Hashimoto's thyroiditis, idiopathic myxedema, and Grave's disease.

Our results are in disagreement with a previous study (5) in which a significant proportion of patients with autoimmune thyroid disease presented with signs of potential CD. Celiac disease and autoimmune thyroid disorders share a common genetic predisposition. This common predisposing genetic background would explain the higher incidence of thyroid autoimmune disorders in CD than in the general population. Because of the varied clinical presentations of CD, serological methods have been found to be very useful for detecting its existence in patients with thyroid autoimmunity (27). This variation may reflect the ethnic, genetic and clinical heterogeneities between the two studies.

## Conclusion

Identification of the genes for celiac disease helps to understand the pathogenesis and heterogeneity of the disease, and enable the development of new treatment strategies and diagnostic procedures for the disease. The prevalence of CD among Type 1 DM patients by using anti tTG antibody ELISA supports the current practice of screening for celiac disease. The use of tissue transglutaminase ELISA may offer the capacity to analyze a large number of serum samples. The use of tTG antibodies will enable the laboratory to play a part in the diagnosis and monitoring of this disorder. Patients with proved autoimmune thyroid disease were negative for tissue transglutaminase antibodies. The level of HbA1c seems adversely affected by malabsorption related to celiac disease in tTG seropositive patients. Also short stature was observed in those children

Recommendation: The genetic background of celiac disease remains still partly unknown and needs further studies. Once genes have been shown to play a role in the disease, researchers can then begin to focus on developing therapies that target these genes. Our findings indicate that CD in type 1 diabetic populations is not rare and that clinicians caring for those with type 1 diabetes or investigating gastrointestinal symptoms should strongly suspect CD. Screening should be conducted at any time if a diabetic child or adolescent develops intestinal or extra-intestinal symptoms consistent with celiac disease. Screening will also identify patients needing careful monitoring because they have the potential for developing complications.

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Received October 20, 2008.

Accepted January 23, 2009.