

# Prevalence of Celiac Disease in an Adult Jewish Population in Israel

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**ABSTRACT:** **Background:** In the last decade the frequency of celiac disease diagnosis has increased in adults.

**Objectives:** To determine disease prevalence (including silent and potential disease) in this population group.

**Methods:** We performed serologic screening of celiac disease in a representative and homogenous sample of a young adult general population in Israel, namely, 18 year old military conscripts, in 2003. Serologic screening was performed on serum samples randomly obtained from 850 healthy recruits (male/female = 1.1). Immunoglobulin A anti-tissue transglutaminase was determined by enzyme-linked immunosorbent assay. In cases of IgA deficiency, IgG anti-endomysial antibodies were determined. A small intestinal biopsy was offered to all patients with positive serology.

**Results:** The prevalence of overt CD diagnosed prior to recruitment was 0.12% (0.1% in men and 0.14% in women). The overall prevalence based on positive serology was 1.1%. Six of nine subjects with positive serology agreed to undergo endoscopy and intestinal biopsies. In all cases, biopsies were compatible with celiac disease (five biopsies were graded as Marsh 3a and one as Marsh 3b). One subject previously reporting irritable bowel-like symptoms was diagnosed with overt atypical CD. The prevalence of overt CD diagnosed by screening was 0.12%. The ratio of overt to silent CD was 1:8. No cases of potential CD were encountered.

**Conclusions:** Our findings suggest that CD is highly prevalent in the young adult population in Israel. Serologic screening for CD is a reliable and simple method for diagnosing this disease before symptoms or complications develop.

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**KEY WORDS:** celiac disease, prevalence, screening, young adult population

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Celiac disease is a permanent intolerance to dietary gluten characterized by an immune-mediated inflammatory lesion of the intestinal mucosa; a gluten-free diet assures full recovery. Due to its variable manifestations and age at onset, CD has emerged as a worldwide public health problem [1].

Although the 'classical' malabsorption syndrome characterized by diarrhea, steatorrhea, weight loss and fatigue may occur in severe cases, nowadays most patients present with a milder constellation of symptoms, such as abdominal discomfort and bloating mimicking irritable bowel syndrome, non-gastrointestinal symptoms (such as anemia and osteoporosis), or no symptoms at all. Due to this 'atypical' presentation, which is particularly frequent in the adult population, many patients are not diagnosed early. Prompt diagnosis and treatment of CD is associated with symptomatic improvement, reduction of potential complications (including malignancy), and decreased mortality [2,3]. It is therefore necessary to increase the awareness of medical professionals to the variable manifestations of CD; detection can be achieved by active screening.

The prevalence of CD varies greatly across different countries. This variability reflects population differences in the risk of CD, as well as differences in study design (e.g., serologic screening vs. symptom-based diagnosis, screening of general vs. high risk group populations). With these limitations in mind, the prevalence of CD in western populations (based on serologic screening) appears to be approximately 1%, with a reasonable range of 0.71%–1.25% [4]. However, the prevalence of CD is lower in other parts of the world such as South America [5] and Asia [6], whereas the disease rarely affects people of purely Chinese or Japanese origin. Since the origin of the Jewish population in Israel is diverse, we conducted a population-based study to determine the prevalence of CD including symptomatic and silent disease. The aim of this study was twofold: a) to determine the prevalence of symptomatic CD that was previously diagnosed, and b) to determine the prevalence of silent CD in the young adult population (aged 18 years) in Israel by active serologic screening.

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Ig = immunoglobulin  
CD = celiac disease

**PATIENTS AND METHODS**

The prevalence of previously diagnosed CD was determined in the 18 year old population of military recruits during 2003 through the medical database of the Israel Defense Forces. Since military service is mandatory in Israel, the survey provides a representative sample of the young adult Jewish population. This population as a whole undergoes medical evaluation prior to recruitment to military service, independent of previously established medical diagnoses. Excluded from the survey are ultra-Orthodox Jews and Arabs, who are largely exempted from service and are thus under-represented.

Serologic screening was performed on serum samples from a representative sample of 850 healthy recruits. These samples were drawn from an ongoing, large-scale prospective survey on medical status, health behavior and attitudes routinely carried out among a fixed proportion of IDF recruits upon induction, 95% of whom are aged 18. The selection process for the survey is systematic and includes both male and female recruits based on a code calculated from the subjects' serial numbers. The selected serum samples were drawn from our serum bank for laboratory testing, and subjects' prerecorded demographic data were accessed from our computerized database. The study was approved by the IDF Institutional Review Board, and written informed consent was obtained from all selected recruits prior to entry into the survey.

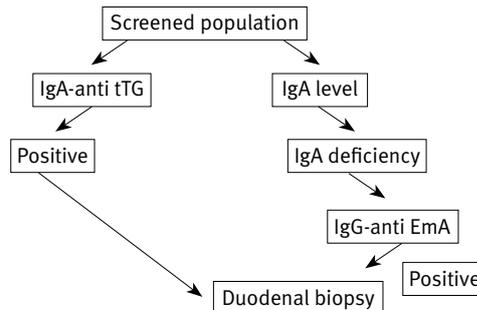
The medical history of all the subjects with a positive serology was assessed based on medical records, and the subjects were questioned with special focus on gastrointestinal symptoms and autoimmune diseases. A complete physical examination including body weight and height measurement was performed.

**STUDY DESIGN**

Blood samples were drawn from the antecubital veins of study participants on the day of recruitment and were stored at room temperature for up to 1 hour. Samples were then refrigerated for up to 2 hours at 4–8°C and were centrifuged for serum separation. Serum was then frozen at -20°C and stored at the IDF Health Surveillance Serum Bank until analysis. The screening algorithm is illustrated in Figure 1.

All samples were tested in parallel for IgA anti-tissue transglutaminase and total serum IgA level. IgA anti-tTG was determined by using a quantitative automated enzyme-linked immunosorbent assay method based on recombinant human tissue transglutaminase as antigen (EurospitalSpa, Trieste, Italy). Serum values of IgA anti-tTG higher than 7 AU/ml were considered positive. Total serum IgA level was determined by a radial immunodiffusion test. In cases of IgA deficiency, IgG anti-endomysial antibodies were determined

**Figure 1.** Flow chart of the study



by an immunofluorescence method on primate esophagus substrate (IMMCO Diagnostics, Buffalo, New York).

Additional laboratory workup was done for serologically positive subjects, including a complete blood count, liver enzymes, serum albumin, ferritin, iron saturation, calcium and folic acid.

A small intestinal biopsy was offered to all subjects who were serologically positive. Four endoscopic biopsies from the second and third duodenal portions were obtained, fixed in 4% formaldehyde and embedded in paraffin. Specimens were stained with hematoxylin-eosin for morphologic assessment. The biopsies were assessed by two independent expert gastrointestinal pathologists and were staged according to the Marsh criteria as revised by Oberhuber et al. [7]. The diagnosis of intraepithelial lymphocytosis was made when more than 25 intraepithelial lymphocytes per 100 epithelial cells were observed.

**RESULTS**

The prevalence of overt CD diagnosed prior to recruitment in the entire population of military conscripts in Israel during 2003 was 0.12% (0.1% in men and 0.14% in women).

**SCREENING OF ASYMPTOMATIC SUBJECTS [FIGURE 2]**

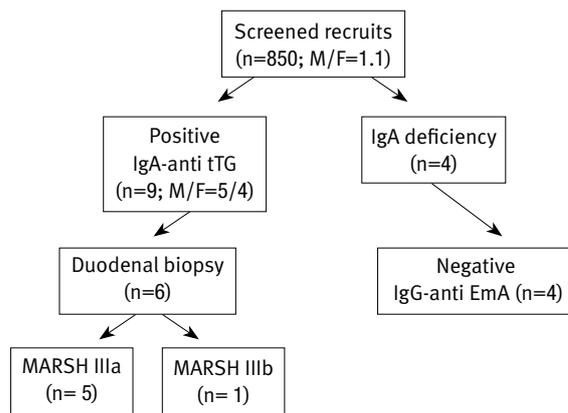
Positive IgA anti-tTG was found in 1.1% (95% confidence interval 0.46–1.74%) of our study cohort (male/female ratio 1.25). Four patients had IgA deficiency. All these patients tested negative for IgG anti-EmA.

Six of nine subjects with positive serology agreed to undergo endoscopy with small bowel biopsies. All of these biopsies demonstrated duodenal villous atrophy. Five patients had partial villous atrophy (compatible with Marsh 3a) and one had subtotal villous atrophy (compatible with Marsh 3b). Based on these data, the prevalence of CD in our population was at least 0.7% (95% CI 0.44–0.96%).

Eight patients with positive serology were clinically asymptomatic and had normal laboratory results. One addi-

IDF = Israel Defense Force  
Anti-tTG = anti-tissue transglutaminase

IgG anti-EmA = IgG anti-endomysial antibodies  
CI = confidence interval

**Figure 2.** Flow chart of diagnostic steps according to the study design

tional patient was underweight and reported symptoms of abdominal pain and loose stools. This patient had Marsh 3b histologic grading and a normal laboratory workup. This subject had a previous diagnosis of inflammatory bowel syndrome, and the diagnosis of overt atypical CD was established by screening. Serologic screening established the diagnosis of overt CD in 0.12% of our cohort.

## DISCUSSION

All military conscripts to the IDF undergo medical inquiry and screening prior to their recruitment; they represent the vast majority of the Jewish population of Israel. The process of recruitment is unique to the IDF; it provides the opportunity to examine the prevalence of a particular disease that was diagnosed before recruitment. The IDF sera database was utilized to screen a representative and homogenous sample of the young adult general population in Israel for the same disease.

We chose IgA anti-tTG as the preferred screening test, based on recommendations from a recently published National Institutes of Health consensus [8]. This test has a high sensitivity and specificity (similar to IgA anti-EmA), is easier to perform, is less observer-dependent and less costly than the anti-EmA test and is therefore more suitable for large screening programs [9].

In our study the prevalence of previously diagnosed subjects with overt CD was 0.12% and is similar to that found in a regional study previously carried out in the southwestern region of Israel (0.17%) [10]. This prevalence is in accordance with the literature data from both the United States and Europe (0.02% to 0.27%) and is much lower than the prevalence of asymptomatic disease [11,12].

Clinical CD represents the tip of the iceberg [13-15]. According to our findings, the prevalence of biopsy-proven CD diagnosed by screening is at least 0.7%. We calculated a

positive predictive value of 29% for positive serologic testing based on the prevalence determined by our study (0.7%) and the sensitivity and specificity of the IgA anti-tTG [4]. Based on this figure one of the three subjects who refused endoscopy would likely have had an abnormal biopsy categorizing him as silent CD. Thus, the true prevalence of CD (including overt and silent CD) detected by screening is likely to be even higher, approximated as 0.9%.

The present study demonstrated that the prevalence of serologically diagnosed CD is higher than previously found in healthy blood donors in Israel (0.6%) [16], but similar to its prevalence worldwide [17-19]. Several reasons for the higher prevalence in our study compared to the study of Shamir et al. [16] are plausible. First, CD is more common in women, who were under-represented among the blood donor cohort. Second, CD subjects with anemia may not have been allowed to donate blood.

In our study we did not detect any subject with potential CD. All antibody-positive subjects who underwent small bowel biopsy were found to have mucosal atrophy. One possible explanation for this finding is the adult age of our cohort. Since exposure to dietary gluten usually begins in early childhood, it is plausible that continuous exposure to gluten will trigger the histologic changes of CD in an accumulating number of subjects until adulthood. Previous studies have demonstrated that children with positive serologic testing and morphologically normal mucosa will become symptomatic at an annual rate of 2.8% [19].

Since selective IgA deficiency is 10–15 times more common in patients with CD than in the general population (1.7%–3%) [20], we elected to measure IgA serum levels in all screened patients. We found a 0.4% prevalence of IgA deficiency; however, all these patients tested negative for IgG anti-tTG. The absence of patients with CD among IgA-deficient subjects is probably related to the small size of the screened cohort.

Theoretically, there are many factors favoring mass screening for CD – a common disorder for which there is an effective and available treatment that leads to symptomatic relief and also prevents the complications of the disease. The crucial question is whether population-based screening should be considered outside of research programs. Most of the CD patients diagnosed by screening are asymptomatic. In our young adult population 88.9% of serologically positive subjects were clinically silent. Nonetheless, the question whether treatment in fact benefits clinically silent CD should be thoroughly assessed. Undetected CD increases the risk of complications, some of them life-threatening, like intestinal lymphoma [21]. On the other hand, the lifelong need to follow a strict gluten-free diet may be burdensome, especially when the patient is asymptomatic [22]. The natural history of undiagnosed CD remains unclear. Published studies have

been limited to patients who have received a clinical diagnosis, an approach that ultimately leads to a biased estimate of the risks [23]. The positive predictive value of serologic tests for CD (despite their high sensitivity) decreases when they are used in the general population rather than in groups at increased risk [24]. Further studies of the outcome of asymptomatic CD, including cost-effectiveness evaluations, are needed before population-based screening studies can be recommended.

In summary, we found that CD is highly prevalent in the young adult population in Israel. All subjects with a positive serology had duodenal mucosal atrophy, and therefore a gluten-free diet was indicated in all cases that were diagnosed by screening. Serologic screening for CD is a reliable and simple method for diagnosing this disease before symptoms or other complications develop.

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