

# Prevalence of coeliac disease among adult patients with autoimmune hypothyroidism in Jordan

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## معدل انتشار الداء البطني بين المرضى البالغين ممن يعانون من قصور الدرقية المناعي الذاتي في الأردن

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الخلاصة: لم تتم من قبل دراسة معدل انتشار الداء البطني بين المرضى ممن يعانون من قصور الدرقية المناعي الذاتي سواء في الأردن أو سائر البلدان العربية. وقد تم إجراء مراجعة مستعرضة بالاعتماد على السجلات، لجميع المرضى البالغين ممن يعانون من قصور الدرقية المناعي الذاتي، وممن حضروا إلى مركز الإحالة في الأردن خلال ثمانية أشهر. وقد تم تشخيص الداء البطني لدى هؤلاء المرضى من خلال الطبيب المشرف على الحالة بالاعتماد على الاختبارات المصلية الإيجابية المضادة لغمد الليف العضلي للغلوبولين المناعي A والغلوبولين المناعي G، على أن يعقبها إجراء خزعة للاثناعشري للتحقق من تشخيص الداء البطني. ووجد أن 117 مريضاً من بين 914 مريضاً هم إيجابيو المصل للداء البطني بنسبة 12.8٪، ومن بين 87 مريضاً إيجابيو المصل والذين أجروا خزعة الاثناعشري، هنالك 39 مريضاً لديهم نتائج هيستولوجية إيجابية للداء البطني (44.8٪). وبالاستقراء من هذه النتائج نجد أن المعدل العام للداء البطني لدى المرضى المصابين بقصور الدرقية المناعي الذاتي يقدر بنحو 5.7٪. ولقد ثبت من خلال التحوف اللوجستي المتعدد المتغيرات أن الداء البطني غالباً ما يصاحبه التقدم في العمر، (فوق سن الأربعين)، ووجود أمراض مناعية ذاتية أخرى، وعَوَز الفيتامين B12، وفقر الدم.

ABSTRACT The prevalence of coeliac disease among patients with autoimmune hypothyroidism has not been studied before in Jordan and other Arab countries. A cross-sectional record-based review was made of all adult autoimmune hypothyroidism patients who attended a referral centre in Jordan, during an 8-month period. Coeliac disease in these patients was diagnosed by the attending physician based on positive serological tests for anti-endomysial antibodies IgA and IgG followed by duodenal biopsy to confirm the diagnosis of coeliac disease. Of 914 patients recruited, 117 (12.8%) were seropositive for coeliac disease. Of 87 seropositive patients who underwent duodenal biopsy, 39 had positive histological findings of coeliac disease (44.8%). Extrapolating from these findings the overall rate of coeliac disease among autoimmune hypothyroidism patients was estimated to be 5.7%. In multivariate logistic regression coeliac disease was significantly associated with older age (> 40 years), presence of other autoimmune diseases, vitamin B12 deficiency and anaemia.

## Prévalence de la maladie cœliaque chez des patients adultes atteints d'hypothyroïdie auto-immune en Jordanie

RÉSUMÉ La prévalence de la maladie cœliaque chez des patients atteints d'hypothyroïdie auto-immune n'a pas été étudiée auparavant en Jordanie, ni dans d'autres pays arabes. Un examen transversal à partir des dossiers de tous les patients adultes atteints d'hypothyroïdie auto-immune qui avaient consulté un centre d'orientation en Jordanie au cours d'une période de huit mois a été mené. Le diagnostic de maladie cœliaque de ces patients a été posé par le médecin traitant à partir des analyses sérologiques positives pour les anticorps anti-endomysium de classe IgA et IgG, puis d'une biopsie duodénale à visée de confirmation du diagnostic de maladie cœliaque. Sur 914 patients recrutés, 117 (12,8 %) étaient séropositifs pour la maladie cœliaque. Sur 87 patients séropositifs chez qui une biopsie duodénale a été réalisée, 39 ont eu des résultats histologiques positifs pour la maladie cœliaque (44,8 %). En extrapolant à partir de ces résultats, le taux global de maladie cœliaque chez les patients atteints d'hypothyroïdie auto-immune a été estimé à 5,7 %. Dans une analyse de régression logistique multivariée, la maladie cœliaque était significativement associée à un âge plus avancé (plus de 40 ans), à la présence concomitante d'autres maladies auto-immunes, à une carence en vitamine B12 et à une anémie.

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## Introduction

Coeliac disease (gluten-sensitive enteropathy) is a systemic autoimmune disorder characterized by inflammation of the small-bowel mucosa, villous atrophy and crypt hyperplasia due to exposure to gliadin fraction of wheat gluten, hordein in barley, secalin in rye and avenin in oats and others in genetically susceptible individuals [1,2]. Based on the presence of anti-endomysial antibody (EMA) and anti-tissue transglutaminase (anti-tTG) antibody, with sensitivity and specificity reaching above 95%, the prevalence of coeliac disease has increased in subclinical cases and several risk groups over the past 30 years [3]. Coeliac disease is associated with many autoimmune endocrine disorders, particularly type 1 diabetes mellitus, autoimmune thyroid diseases and others [4,5]. In previous studies, coeliac disease was found to be more prevalent in patients with autoimmune hypothyroidism (AIH) with a prevalence of 3.3%–4.8% [6] compared with 1% in the general population [7].

To the best of our knowledge, the prevalence of coeliac disease among patients with AIH has not been investigated before in Jordan or other Arab countries. The aim of this study was to assess the prevalence of coeliac disease in patients with AIH in Jordan and to identify patients at higher risk of the disease.

## Methods

### Study population

A cross-sectional study was conducted at the National Centre for Diabetes, Endocrinology and Genetics, Amman, Jordan. All adult patients (a total of 914) with AIH who attended the Centre during the period October 2009 through May 2010, were included in the study. Exclusion criteria were hypothyroidism post-thyroidectomy or post-radioactive ablation therapy, pregnancy and thyroid malignancy.

## Data collection

### Clinical data

The diagnosis of AIH was made by the attending physician based on elevated thyroid-stimulating hormone (TSH) levels with reduced thyroxine and positive thyroid antibodies (anti-thyroid peroxidase and/or anti-thyroglobulin auto-antibodies). The diagnosis of coeliac disease was also made by the attending physician based on seropositivity of anti-EMA immunoglobulin (Ig)A and IgG. Patients who were seropositive for coeliac disease were further subjected to duodenal biopsy to confirm the diagnosis [8]. An experienced pathologist evaluated the biopsy according to the Modified Marsh Classification [9]. All data were collected from the medical records.

### Laboratory measurement methods

Anti-EMA IgA and IgG levels were measured by generic assays (Dahlewitz GmbH), an enzyme immunoassay for the quantitative determination of IgA and IgG autoantibodies to human EMA. TSH, anti-thyroid peroxidase and anti-thyroglobulin levels were measured by 3rd-generation system (AxSYM, Abbot), a microparticle enzyme immunoassay for the quantitative determination of TSH in human serum or plasma. All other measurements were carried out using standard techniques.

### Ethical considerations

The study protocol was approved by the ethics committee of the National Centre for Diabetes, Endocrinology and Genetics. All data were kept strictly confidential and used for scientific purposes only. The study carried no harm to the patients as all data were obtained from routine medical records with no identifying information.

### Statistical analysis

The percentage of AIH patients with seropositivity to coeliac disease markers was obtained as well as the percentage of histologically confirmed coeliac disease. For the purpose of obtaining

the overall rate of histologically confirmed coeliac disease in AIH patients, seropositive AIH patients who were not subjected to duodenal biopsy were assumed to be similar to those who underwent biopsy with respect to the percentage of histologically confirmed coeliac disease. The chi-squared test was used to determine the association of coeliac disease seropositivity with different variables. Multivariate logistic regression analysis was used to determine factors associated with seropositivity after controlling for potential confounders. The magnitude of the associations were expressed as odds ratios (OR). A 2-tailed *P*-value of 0.05 was considered statistically significant.

## Results

### Participants' characteristics

This study included 914 patients with AIH (806 females and 108 males) aged 20–82 years with a mean age of 51.1 years [standard deviation (SD) 13.4]. The demographic, clinical and other relevant characteristics of the study population are presented in Table 1. The mean duration of AIH was 5.1 (SD 4.8) years, with almost 11% of patients having long-standing hypothyroidism of more than 10 years. The mean body mass index (BMI) was 32.2 (SD 6.7) kg/m<sup>2</sup>; 60.7% of the AIH patients were obese and 26.8% were overweight. Around 42.2% had type 2 diabetes mellitus, 1.6% type 1 diabetes mellitus, 28.4% anaemia, 22.1% vitamin B12 deficiency, 67.9% vitamin D deficiency and 3.7% other autoimmune diseases. The mean thyroxine dose was 723 (SD 389) µg/week (Table 1).

### Prevalence of coeliac disease among adult patients with AIH

The seroprevalence of coeliac disease was 12.8% (117 out of 914 patients).

Only 87 seropositive patients underwent duodenal biopsy, and of these 39 had positive histological findings

**Table 1 Sociodemographic, clinical and other relevant characteristics of study participants with autoimmune hypothyroidism (AIH) (n = 914)**

Variable	No.	%
<b>Age (years)</b>		
20–40	199	21.8
41–60	472	51.6
61–82	243	26.6
<b>Sex</b>		
Female	806	88.2
Male	108	11.8
<b>BMI (kg/m<sup>2</sup>)</b>		
Normal (< 27)	114	12.5
Overweight (27–29)	245	26.8
Obese (30+)	555	60.7
<b>Duration of AIH (years)</b>		
≤ 5	597	65.3
6–10	210	23.0
> 10	107	11.7
<b>Anaemia</b>		
Yes <sup>a</sup>	260	28.4
No	654	71.6
<b>Thyroxine dose (µg/week)</b>		
350–650	311	34.0
651–1000	504	55.1
> 1000	99	10.8
<b>Diabetes</b>		
Yes	386	42.2
No	528	57.8
<b>Vitamin B12</b>		
Deficiency <sup>b</sup>	202	22.1
Normal	712	77.9
<b>Vitamin D deficiency</b>		
Yes <sup>c</sup>	621	67.9
No	293	32.1
<b>Other autoimmune diseases</b>		
Present	34	3.7
Absent	880	96.3

<sup>a</sup>Haemoglobin level < 13 g/dL for males and < 12 g/dL for females [16]; <sup>b</sup>Vitamin B12 level < 208 pg/mL; <sup>c</sup>25-hydroxy vitamin D level < 30 ng/mL.

of coeliac disease (44.8%). The histological findings of coeliac disease were consistent with Marsh I in 5 (12.8%) patients, Marsh II in 8 patients (20.8%), Marsh IIIa in 12 patients (30.8%), Marsh IIIb in 10 patients (25.6%), and Marsh IIIc in 4 (10.3%) patients with AIH.

Assuming that the remaining 30 seropositive AIH patients who were

not subjected to duodenal biopsy had the same rate of coeliac disease as those who underwent duodenal biopsy, the overall rate of coeliac disease among AIH patients was estimated to be 5.7% (Table 2).

### Regression analysis

Using multivariate logistic regression analysis it was found that anaemia

(adjusted OR = 3.7,  $P = 0.04$ ), vitamin B12 deficiency (adjusted OR = 3.0,  $P = 0.01$ ), and presence of other autoimmune diseases (adjusted OR = 3.1,  $P = 0.04$ ) were significantly associated with coeliac disease (Table 2). In addition, older patients (> 40 years) were significantly 4.3 times more likely to have coeliac disease as compared with patients aged 20–40 years ( $P = 0.02$ ). Each of these 4 variables were adjusted simultaneously for the other 3 variables. All other variables shown in Table 1, namely sex, BMI, duration of AIH, thyroid dose, presence of diabetes and vitamin D deficiency were not independently related to coeliac disease seropositivity and were therefore removed from the logistic regression model.

### Autoimmune diseases in the study population

A total of 34 patients had other associated autoimmune disorders, such as type 1 diabetes mellitus, Addison disease and vitiligo as shown in Table 3.

## Discussion

The present study was the first in Jordan to assess the prevalence of coeliac disease in patients with AIH. The sample size we used was relatively large as compared with many previous studies conducted outside Jordan. Recent population screening studies have found that the prevalence of coeliac disease in Western countries approaches 1% [10]. The present study showed that the prevalence of histologically confirmed coeliac disease among patients with AIH was 5.7%. This figure is slightly higher than the estimated range of global prevalence of coeliac disease among adult patients with AIH (3.3%–4.8%) [4]. The prevalences reported by Guilter et al. in a Turkish population [10], Berti et al. in Italians [11] and Hadithi et al. in Dutch patients [11] were 5.4%, 3.4% and 4.8% respectively.

**Table 2 Multivariate logistic regression analysis of factors associated with coeliac disease seropositivity among patients with autoimmune hypothyroidism**

Variable	OR	95% CI	P-value
<b>Anaemia</b>			
Yes	3.7	0.63–16.9	0.04
No <sup>a</sup>	1		
<b>Vitamin B12</b>			
Deficiency	3.0	0.91–17.1	0.01
Normal <sup>a</sup>	1		
<b>Other autoimmune diseases</b>			
Present	3.1	0.47–30.7	0.04
Absent <sup>a</sup>	1		
<b>Age years</b>			
20–40 <sup>a</sup>	1		0.02
> 40	4.3	1.04–28.1	

Each variable in the table was adjusted for all other variables in the table.

<sup>a</sup>Reference group.

OR = odds ratio; CI = confidence interval.

With respect to the seroprevalence of coeliac disease in patients with AIH, several studies reported higher figures than that for histologically confirmed coeliac disease [11–13]. Hadithi et al. reported a seroprevalence of coeliac disease of 15% in patients with Hashimoto thyroiditis using anti-gliadin, anti-EMA and anti-tTG [11], while Iuorio et al. reported a much higher coeliac disease seroprevalence of 27.4% using anti-EMA, both IgA and IgG [12]. Our data showed a much lower seroprevalence of coeliac disease (12.8%) than that reported by Iuorio et al. (27.5%) [13]. However, Iuorio et al.'s study was based on a much smaller sample size (113 AIH patients) than our study (914 AIH patients).

In the present study, age > 40 years, anaemia, vitamin B12 deficiency and

presence of other autoimmune diseases were independently associated with the seroprevalence of coeliac disease. Consistent with our findings, Ravaglia et al. reported significantly higher prevalence of coeliac disease in patients with AIH aged ≥ 65 years than in patients aged < 65 years ( $P = 0.02$ ) [14]. Our data showed that AIH patients aged > 40 years were 4.3 times more likely to have coeliac disease than patients aged ≤ 40 years ( $P = 0.02$ ).

With respect to anaemia, our findings of an association are consistent with the findings of Unsworth et al. who reported that 6% of 483 anaemic volunteers had coeliac disease [15], and Zamani et al. who reported that 14.6% of 206 anaemic patients had coeliac disease [16].

Vitamin B12 deficiency is common in Jordan (48.1%), as reported by Fora et al. [17], and this rate is higher than the reported global prevalence (ranging from 3% to 40% of the adult population) [18]. This difference is mainly related to ethnic variations and intestinal malabsorption problems [19]. To our knowledge, the association between vitamin B12 and coeliac disease had not been reported previously.

Our findings are consistent with a higher rate of coeliac disease in patients with other autoimmune diseases as had been previously reported by Kaukinen et al. [3]. Jiskra et al. found significantly higher serum levels of IgA anti-gliadin antibodies among 169 patients with autoimmune thyroid diseases, i.e. chronic thyroiditis and Graves' disease treated with a high replacement dosage of levothyroxine compared with patients treated with a lower dosage [14]. Our data, however, did not show an association between thyroxine replacement dosage and coeliac disease seroprevalence. This may be attributed to the use of anti-EMA antibodies in the present study, which have higher specificity and sensitivity than the IgA anti-gliadin antibodies used by Jiskra et al.

The present study had some limitations. First, it was a cross-sectional study, making it impossible to compare the prevalence of coeliac disease among patients with AIH and a control group. Secondly, we used only anti-EMA antibodies IgA and IgG as serological test for coeliac disease.

In conclusion, the prevalence of histologically-confirmed coeliac disease among patients with AIH in our study was estimated to be 5.7% compared with a seroprevalence of 12.8%. Age > 40 years, anaemia, vitamin B12 deficiency and the presence of other autoimmune disorders were significantly associated with a higher seroprevalence of coeliac disease. These findings may provide a basis for screening of patients with AIH for coeliac disease, particularly the higher risk groups identified in this study.

**Table 3 Autoimmune diseases in the study group of patients with autoimmune hypothyroidism (n = 914)**

Disease	No.	%
Vitiligo	7	0.8
Addison disease	8	0.9
Systemic lupus erythematosus	2	0.2
Type 1 diabetes mellitus	15	1.6
Turner syndrome	1	0.1
Psoriasis	1	0.1
Normal	880	96.3



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