



## Alimentary Tract

**Undetected coeliac disease in the elderly  
A biopsy-proven population-based study**A. Vilppula<sup>a</sup>, P. Collin<sup>b,c,\*</sup>, M. Mäki<sup>b,d</sup>, R. Valve<sup>e</sup>, M. Luostarinen<sup>f</sup>, I. Krekelä<sup>g</sup>,  
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**Abstract**

**Background.** Up to 1% of the population suffer from coeliac disease. Data on the prevalence in elderly people is scant. We hypothesized that they would over time have developed obvious symptoms. Clinically silent or undiagnosed disease would thus be relatively uncommon.

**Aims.** To evaluate the prevalence of coeliac disease in elderly people.

**Methods.** The study comprised 2815 individuals aged 52–74 years. Clinical cases of coeliac disease were recorded. Sera from all subjects were screened by IgA class tissue transglutaminase antibodies, and seropositive underwent small bowel biopsy.

**Results.** Coeliac disease was detected in altogether 60 individuals, in 25 (0.89%) on clinical grounds, and screening found in 35 (1.24%) new biopsy-proven cases. Thus, a total prevalence of 2.13% (95% confidence intervals 1.60–2.67%) was reached. Of the screen-detected cases, 15 had symptoms, albeit mostly mild. Two out of the 60 had small bowel T-cell lymphoma and two had gastric cancer. The total frequency of biopsy-proven coeliac disease and seropositive cases without histological confirmation was 2.45% (1.88–3.02%).

**Conclusion.** The prevalence of coeliac disease in elderly people was higher than what has been reported in the population in general. Active case finding by serologic screening is encouraged, since undetected cases may be prone to increased morbidity and mortality.

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**Keywords:** Ageing; Coeliac disease; Dermatitis herpetiformis; EATL; Gluten; Lymphoma; Tissue transglutaminase

**1. Introduction**

The classical symptoms of coeliac disease comprise diarrhoea, steatorrhoea, weight loss and malabsorption syndrome. Because of better recognition of the disease, the clinical pattern has changed. Patients may have mild abdominal discomfort, occasional diarrhoea, or isolated, subclinical malabsorption [1]. Many, if not most, patients do not have sig-

nificant gastrointestinal symptoms or any at all. Symptoms may also occur outside the gastrointestinal tract, dermatitis herpetiformis being the best-known condition. Without obvious symptoms coeliac disease often remains unrecognized. Serologic screening studies have shown that the prevalence of the disease in the population is 0.3–1% [2–4], but the number of detected cases is much lower.

The delay in diagnosis of coeliac disease in elderly patients is evidently long, and elderly people may often suffer from classical symptoms [5]. Consequently, the clinical diagnosis should be easier and undetected cases less common than in young people. However, data on the frequency of detected and undiagnosed coeliac disease in the elderly are sparse.

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This was investigated in a population-based cohort aged 52 years or more, as a part of a research and development project among ageing people in a well-defined area.

## 2. Methods

### 2.1. Subjects and methods

The study population comprised 4272 randomly selected individuals born in the years 1946–1950, 1936–1940 and 1926–1930 and living in the Päijät-Häme Hospital district; the study sample was representative of the general population in the respective age groups. The data were collected for a research project on Ageing and well-being (Good Ageing in the Lahti region = GOAL). Its primary target was to improve health and well-being in the ageing population. Patient recruitment and serum sampling took place in 2002, and the survey of established coeliac disease and serologic screening for undetected cases in 2004. The subjects attended a personal interview including past disease history and dietary habits. In coeliac disease, the criteria established at the United European Gastroenterology Week in 2001 were applied, including the demonstration of small intestinal villous atrophy and clinical or histological response to a gluten-free diet [6]; the diagnosis of dermatitis herpetiformis had to be based on typical rash and a finding of granular IgA deposits in the uninvolved skin [7]. Apart from the clinical history, it was also verified from patient files that the diagnostic criteria were met.

The sera were tested for IgA class tissue transglutaminase antibodies (tTGA); positive samples were further tested for IgA class endomysium antibodies (EMA). All tTGA-positive patients were offered upper gastrointestinal endoscopy (irrespective of the EMA titre); small intestinal biopsies were taken from the distal part of the duodenum and stained by haematoxylin–eosin. The diagnosis of coeliac disease was based on small intestinal villous atrophy and crypt hyperplasia. All participants underwent serologic screening, but since known coeliac disease patients usually adhered to a gluten-free diet, they remained seronegative. Thus, the total prevalence was the sum of previously diagnosed and new screen-detected cases.

IgA class tTGA were detected by enzyme-linked immunosorbent assay (Celikey, Phadia, Freiburg, Germany) and the limit of positivity was five arbitrary units; EMA

were detected by an indirect immunofluorescence method using human umbilical cord as antigen; a dilution of 1:≥5 was considered positive [2]. To further strengthen the specificity of positive serology, blood samples for coeliac-type genetic involvement, that is HLA DQ2 and DQ8, were analysed by the polymerase chain reaction/restriction fragment length polymorphism method [8].

Patients with newly detected coeliac disease or dermatitis herpetiformis were referred for clinical examination. Symptoms were classified into three groups: classic symptoms (diarrhoea, weight loss, anaemia, malabsorption, dermatitis herpetiformis), subtle symptoms (abdominal pain, distended abdomen, occasional diarrhoea or loose stools, flatulence, fatigue), and no obvious symptoms (asymptomatic). The patients were placed on a gluten-free diet, and the control biopsy and serologic assay took place after one year.

The study was accepted by the Ethical committee of Päijät-Häme Central Hospital, and written informed consent was obtained from all participants.

### 2.2. Statistical analysis

Frequency data are expressed as mean and 95% confidence intervals.

## 3. Results

### 3.1. The prevalence of coeliac disease

Altogether 2815 (66%) out of 4242 individuals consented to participate in the original GOAL study (Table 1). Coeliac disease had previously been established on clinical grounds in 25 (0.89%) out of the 2815 subjects, six of them also having dermatitis herpetiformis. Four of the 25 had been detected due to symptoms between sampling (in 2002) and analysis (in 2004) of sera, and had thus been on a normal diet when the sera were drawn. All fulfilled the current diagnostic criteria. It was possible to evaluate the extended Marsh classification [6] in 19 cases: two had Marsh IIIa, 11 IIIb and six IIIc.

Forty-nine out of 2815 serum samples were positive for IgA class tTGA, and 44 of these also for EMA. These 49 included the four patients detected clinically in 2002–2004, and one patient with previously diagnosed disease. Of the remaining 44, 39 underwent endoscopy and small intestinal

Table 1  
Number of subjects and the occurrence of coeliac disease in different age groups

Year of birth	No. of subjects invited to the original study project (female, %)	No. of subjects participating (female, %)	Clinically detected coeliac disease (female, <i>n</i> )	Screen-detected coeliac disease (female, <i>n</i> )	Total prevalence of coeliac disease, (95% confidence intervals)
1946–1950	1424 (50)	910 (55)	6 (5)	17 (10)	2.53% (1.55–3.55)
1936–1940	1424 (50)	1024 (51)	13 (5)	11 (8)	2.34% (1.34–3.16)
1926–1930	1424 (50)	881 (51)	6 (2)	7 (2)	1.48% (0.68–2.27)
Total	4272 (50)	2815 (52)	25 (12)	35 (20)	2.13% (1.60–2.67)

Table 2  
Symptoms of patients with clinically detected and screen-detected coeliac disease at time of diagnosis

	Clinically detected (n = 25) <sup>a</sup>	Screen detected (n = 35)
Classic symptoms <sup>b</sup>	17	1
Diarrhoea <sup>c</sup>	14	1
Weight loss <sup>c</sup>	9	1
Anaemia or malabsorption <sup>c</sup>	10	4
Dermatitis herpetiformis <sup>c</sup>	6	
Subtle symptoms <sup>b</sup>	5	14
Abdominal pain, distention, flatulence <sup>c</sup>	5	14
Occasional diarrhoea or loose stools <sup>c</sup>	4	9
Fatigue <sup>c</sup>	2	3
Blisters in mouth <sup>c</sup>		2
No symptoms <sup>b</sup>	0	20

<sup>a</sup> Data missing in three.

<sup>b</sup> Number of subjects.

<sup>c</sup> Number of diseases or symptoms.

biopsy. Thirty-five had small bowel mucosal villous atrophy and crypt hyperplasia consistent with coeliac disease: five with Marsh IIIa, seven IIIb and 23 IIIc. The total frequency of coeliac disease in the elderly population was thus 60/2815 (2.13%, 95% confidence intervals 1.60–2.67%). Mucosal villous architecture was normal in four (three had Marsh 0 and one Marsh I); two were positive for tTGA and EMA and two for tTGA only. Of the five seropositives who did not consent to endoscopy, three were positive for tTGA and EMA, and two for tTGA only. The pooled frequency of biopsy-proven and seropositive cases was 69/2815 (2.45%, 95% confidence intervals 1.88–3.02%). All 38 seropositives tested had either HLA DQ2 or DQ8.

### 3.2. Clinical characteristics and follow-up

The presenting symptoms of patients with coeliac disease are depicted in Table 2. Most of those clinically detected had had classic symptoms at the time of diagnosis. Of the screen-detected subjects, most had at most subtle symptoms, but one female had suffered from diarrhoea for over 20 years. In the clinically detected patients, anaemia was normocytic in five, and the type was unknown in five; of the screen-detected, two had iron deficiency and two normocytic anaemia.

Two out of 60 coeliac disease patients had small bowel lymphoma of T-cell origin (enteropathy associated T-cell lymphoma, EATL), and both appeared without preceding refractory sprue. In one, lymphoma and coeliac disease were found simultaneously in 2003 when the patient underwent endoscopy due to abdominal pain; he died in 2006. The other had had coeliac disease for 27 years, lymphoma was detected in 2006 and he died in 2007. Two coeliac patients had carcinoma of the stomach. One had suffered from coeliac symptoms, failure to thrive, diarrhoea and abdominal pain, since early childhood; cancer and coeliac disease were found

Table 3  
Associated conditions in patients with coeliac diseases

	Clinically detected (n = 25)	Screen detected (n = 35)
Malignant diseases <sup>a</sup>	3	2
Lymphoma <sup>a</sup>	2	
Carcinoma of stomach <sup>a</sup>	1	1
Ovarian cancer <sup>a</sup>		1
Autoimmune conditions <sup>a</sup>	3	10
Autoimmune thyroid disease <sup>b</sup>	1	7
Sjögren's syndrome <sup>b</sup>	1	0
Pernicious anaemia <sup>b</sup>	1	1
Type I diabetes mellitus <sup>b</sup>		1
Psoriasis <sup>b</sup>		3

<sup>a</sup> Number of subjects.

<sup>b</sup> Number of diseases.

in endoscopy carried out on clinical grounds in 2004. The other had no symptoms, but she turned out to be seropositive and gastric cancer was detected, together with coeliac disease, upon subsequent endoscopy. In the whole series of 2815 individuals, there were in addition three lymphomas and one adenocancer of the stomach; 14 had colorectal cancer. Thirteen (22%) out of 60 coeliac disease patients had one or more autoimmune conditions (Table 3), autoimmune hypothyroidism being the most common.

All 25 clinically detected coeliac disease patients were following a gluten-free diet but, as stated above, only one was antibody-positive in screening indicating dietary lapses. Of the 35 new screen-detected patients, 32 were willing to adhere to a gluten-free diet and three declined. The control biopsy was carried out in 30 patients adhering to the diet. Twenty-six patients had no signs of villous atrophy: 12 of them Marsh 0, seven Marsh I, and seven Marsh II. Villous atrophy was seen in four, comprising two Marsh IIIa and two Marsh IIIb; nobody had Marsh IIIc. Serologic tests became negative in 29 out of 31 tested individuals. Twenty-eight patients reported subjective amelioration of their symptoms; six of them told spontaneously an incredible improvement in quality of life.

## 4. Discussion

The frequency of biopsy-proven coeliac disease in patients over 50 years of age was 2.1%, the corresponding percentages in Finnish and Estonia children being 1.0% and 0.34%, respectively [2,9]. The prevalence of clinically detected cases in our series was 0.89%. This is almost two times higher than that (0.45%) in our adult population [10], and comparable to the percentages achieved in serologic screening studies [2–4].

Earlier coeliac disease was regarded as a condition affecting mainly children and young adults. Our results support active serologic screening for the disease also in elderly people. Most undetected cases here in fact suffered from mild or no symptoms (Table 2), but it is nonetheless important to recognize the condition in the elderly, since

they may be especially prone to malignant conditions, as was seen in the present study: two small intestinal lymphomas and two gastric cancers were recently detected. The association between coeliac disease and small bowel lymphoma, and the protective effect of a gluten-free diet, are well recognized [11–13]. The risk of small bowel adenocarcinoma is increased in coeliac disease [14], but there was no such a case in these series. The prevalence of small bowel cancer in Finland is approximately 1 per 10000 ([http://www.cancerregistry.fi/WWW\\_sr\\_1207.pdf](http://www.cancerregistry.fi/WWW_sr_1207.pdf)), and that of EATL even smaller, its annual incidence in Finland being approximately 0.0046 per 1000. The occurrence of carcinoma of the stomach is probably coincidental, but in a separate study, one of our 13 histologically non-responsive coeliac disease cases also developed gastric malignancy [15]. The frequency of autoimmune conditions (in 21%) was not different from that observed among Finnish coeliac patients in general (22%) [16]. Thyroid disease was the most common autoimmune condition, which association is well recognized [17].

The occurrence of coeliac disease seemed to be lower in the eldest as against the youngest cohort (Table 1). This may well be coincidental. Other alternatives are that mortality due to coeliac disease in the former group had been higher, or that the prevalence of coeliac disease is increasing over time; it was not possible to evaluate these issues in the present study. It is also possible that elderly coeliac patients more often remain seronegative than younger [15], and the actual prevalence may thus be even higher.

By comparison, in a study by Hankey and Holmes [18] 42 (19%) out of 228 patients with adult coeliac disease were diagnosed at the age of 60 years or over. Of these 42, 15 had attended family doctors and hospital outpatient departments for an average of 28 years suffering from symptoms or signs of coeliac disease, but the diagnosis had been overlooked. In a recent study by Gasbarrini and co-workers [5], severe symptoms were more frequent in elderly than in young untreated coeliac disease patients. However, their study comprised only patients detected on clinical grounds.

The combined frequency of biopsy-proven coeliac disease patients and seropositive cases was 2.5%. This percentage helps us to understand the occurrence of potential coeliac disease in the elderly, since the serologic tests, IgA tTG and EMA, are highly specific. False positive findings are uncommon, and the individuals in question often develop manifest coeliac disease later [19,20]. Seropositive individuals had HLA DQ2 or DQ8, which further supports the conception of genetic gluten intolerance. Again, the frequency of seropositivity in children (1.5%) [2] and in adults [21] living in the same country was lower than in this study (2.5%), whilst the screening study designs were similar. This suggests that seropositivity and coeliac disease may appear later in life.

Sixty-six per cent of the randomly selected subjects consented to participate in the original GOAL study. It may be

argued that there would thus be a selection bias: those suffering from symptoms might be more willing to participate. However, the project was not originally planned for coeliac disease case finding, or even for evaluation of any gastrointestinal disorder; its primary target was to improve health and well-being in the ageing population and to find innovations for more effective health care. There is thus no reason to suppose that coeliac disease patients would be over-represented in the participation rate.

Coeliac disease is not a condition affecting only children, adolescents or middle-aged people. Clinicians should maintain increased alertness to coeliac disease also in the elderly, where the prevalence of the condition seems to be even higher than in younger people. Because of the subtle symptoms and an increased risk of complications, serology should be widely applied for case-finding of coeliac disease in the elderly.

### Practice points

- Up to 2.1% of the elderly people suffered from coeliac disease. Most of the patients had remained undiagnosed due to subtle symptoms.
- In elderly people, the frequency of coeliac disease was higher than what has been reported in the population in general.
- Active case finding by serologic screening is encouraged, since undetected cases may be prone to increased morbidity and mortality.
- IgA tissue transglutaminase antibody test is the recommended screening method.

### Research agenda

- To estimate the cancer risk in elderly people with undetected coeliac disease.
- To study whether screen-detected elderly coeliac disease patients have an increased risk of osteoporosis and bone fractures.
- To investigate whether new seropositive cases will appear in the future among those who remained seronegative.
- To investigate quality of life in screen-detected elderly coeliac disease patients.

### Conflict of interest statement

None declared

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## ANNOUNCEMENT

### NEW EDITOR-IN-CHIEF

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