Review Article: coeliac disease in later life – not to be missed R3

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SUMMARY

Background

The presenting symptoms of coeliac disease are often subtle and the diagnosis is frequently delayed or overlooked. Therefore, especially elderly patients may be denied the benefits conferred by gluten free diet which can be dramatically life-changing.

Aim

To review the occurrence, clinical features, diagnosis and management in coeliac patients detected later in life.

Methods

To review manuscripts concerned with coeliac disease in the elderly and to derive subgroups of elderly people from publications on the disorder.

Results

Approximately a quarter of all diagnoses are now made at the age of 60 years or more and a fifth at 65 years or over. About 4% are diagnosed at 80 years or above. Even so, 60% remain undetected, since their symptoms are often subtle: tiredness, indigestion, reduced appetite. Good compliance with

gluten free diet, resolution of symptoms and improvement in laboratory indices can be achieved in over 90% of patients.

Conclusions

Coeliac disease not uncommonly presents for the first time in older patients and is an important diagnosis to make.

INTRODUCTION

In past decades coeliac disease was thought to mainly affect children and young adults. Today we have learned that the disorder may be detected at any age, and is regarded as one of the commonest chronic disorders encountered worldwide with a serological prevalence of about 1-2 %. [1,2] The advent of an endoscopic technique to obtain duodenal biopsies quickly and the development of reliable serological screening tests have been responsible for this remarkable turnaround.

In a proportion of older people the symptoms go back to childhood but the diagnosis of coeliac disease is not made because they either do not present to health care workers or the diagnosis is missed only to be arrived at often many years later. [3] Compared to younger patients, the clinical picture may thus be different when the disease is diagnosed at advanced age. The diagnostic delay has probably been longer, and in any case these individuals will have been consuming gluten for many decades. This may expose them to long term consequences of malabsorption and to complications of coeliac disease. [4] Some might argue why the diagnosis of coeliac disease should be pursued in the elderly, especially when symptoms are only mild and adopting

-a gluten free diet demands considerable changes in life style. The evidence points to the value of making the diagnosis in this population. Mild symptoms do not necessarily equate to a satisfactory quality of life in elderly people with coeliac disease without gluten free diet. [3] The case for pursuing the diagnosis in the elderly is compelling but patients of course, will make the final decision about how they wish to proceed. In any event, older people are increasingly unwilling to put up with ill health that might indicate coeliac disease and are rightly demanding investigation. Old age itself should never be blamed for clinical features such as tiredness, indigestion, reduced appetite or anaemia which may be due to coeliac disease. [3,5]

REVIEW CRITERIA

We searched PubMed, Medline and Cochrane library for articles published in English until May 2017. We used the terms celiac disease, coeliac disease, age, aging, elderly and dermatitis herpetiformis. We utilized such articles where it was possible to distinguish clinical features, diagnosis or management of coeliac disease later in life.

PREVALENCE AND INCIDENCE

The overall prevalence of coeliac disease in the elderly is expected to rise because life expectancy generally is getting longer, and the mortality rate is not much different from the population in general. [6,7] Older people are increasingly unwilling to put up with ill health that might indicate coeliac disease and are rightly demanding investigation.

The published prevalence figures of coeliac disease vary widely, depending on the target population and the study design. Coeliac disease antibody testing, especially with IgA class endomysial antibodies and tissue transglutaminase antibodies, offers a powerful tool for screening, and most prevalence studies are therefore based on this approach [8-10]

Epidemiological studies of coeliac disease in elderly people are sparse. In Finland the overall prevalence of coeliac disease was 1.99%, and 1.2% in the patients over 75 years of age.[1] Casella et al found that in their cohort comprising 1,225 coeliac disease patients, 4.8% were over 65 years of age at the time of examination.[11] In a further series only 4.4% were over the age of

65 years at diagnosis. [12] Tortora et al [13] reported an even lower percentage; in their series only 2.5% were detected in individuals over 65 years of age. This series was collected in a tertiary referral centre and almost certainly referral bias was responsible for this low result. More realistic figures come from the coeliac disease clinic in Derby, UK, which is not a referral centre. Here 28% and 21% were diagnosed by small intestinal biopsy at the ages of 60 years or more or 65 years and over, respectively. [14] About 4% were diagnosed at or over the age of 80 years. Among the Asian population there is a dearth of diagnoses in later life. Only 5% of Asians were diagnosed in the Derby clinic at or over the age of 60 years which is far less than for whites. [14] In a series from New Delhi only 9% were diagnosed at the age of 50 years or more. [15] Whether coeliac disease is uncommon in elderly Asians or these individuals are not presenting for diagnosis remains to be determined.

It is possible to derive prevalence data from many publications focusing on the epidemiology of coeliac disease. Table 1 summarizes such screening studies, where the prevalence figures in the whole study population and in subgroups of older people can be estimated. The prevalence figures seem in general to be lower in older series than in the general population. As the

Table shows, the Finnish study seems to make an exception, reporting a higher prevalence of coeliac disease in elderly patients. [16] These differences may be due to patient selection; the Finnish study was population-based, and also included patients already diagnosed on clinical grounds prior to screening.

The prevalence figures in screening studies must be differentiated from those obtained in clinical practice. Figures for the occurrence of diagnosed coeliac disease are much lower than what have been reported in screening studies. Apart from study population and design, figures obtained depend on the diagnostic accuracy and the use of serologic screening in everyday clinics. Vilppula et al[17] reported that the frequency of clinically detected coeliac disease in patients over 50 years of age was 0.89%, while the overall population prevalence in same area was 0.5-0.7% over approximately the same period. [18]

As stated earlier, endomysial antibodies and tissue transglutaminase antibodies afford a high specificity for coeliac disease. Moreover, seropositive individuals with normal villous architecture often develop coeliac disease later in life. [19] Therefore the combined biopsy-proven and

seroprevalence is of interest. The Finnish series show that this was as high as 2.7% in individuals over 50 years of age (Table 1). [16]

Like the prevalence data (Table 1), some incidence data in the literature can be obtained separately for elderly people. The overall annual incidence figures vary quite markedly (Table 2). This variability can be attributed to different diagnostic strategies and efficacy, and due to the overall diagnostic delay. In adults of all ages, the annual incidence figures have been inconsistent, but are in general not lower in older than in younger coeliac patients, as shown in Figure 1.

Coeliac disease is more common in females than males with an overall female to male ration of 2:1 in white populations. [2,14,20] However, there was a paucity of diagnoses in young men < 20 years of age giving a ratio of 4:1. This difference in gender diminished in later years. For those aged 60 years or over at diagnosis, the female male ratio was found to be 1.4:1. [14] What could help to explain these gender differences? Women are more likely to develop autoimmune disorders than men [21] and women use health care facilities more than men so are more likely to be diagnosed with coeliac disease. Women are more symptomatic than men [22] and this may lead to earlier d--

iagnosis and men may delay presenting to healthcare professionals. [23] An interplay between sex hormones and the gastrointestinal microbiota may prevent men from developing coeliac disease. In rodents it has been shown that this interplay increases the prevalence of autoimmunity in females. [24] Increasing age might reduce this interplay as sex hormone levels decrease.

To conclude, coeliac disease, including undetected, is common in the elderly, the disorder may manifest at any age, seropositive individuals may later develop coeliac disease regardless of their age, and seropositivity may appear also later in life. [16]

CLINICAL MANIFESTATIONS

Symptoms and malabsorption

Classic symptoms of coeliac disease are weight loss, diarrhoea, and fatty stools indicative of malabsorption. When these are present making the diagnosis of coeliac disease is relatively straight forward although it can still

be overlooked. However, most patients now present with non-classical features such as fatigue; dyspepsia; vague abdominal pain suggestive of irritable bowel syndrome; [25] constipation; and characteristics such as poor growth, anaemia, mouth ulcers, osteoporosis and neuropathy. This clinical diversity often delays or obscures the diagnosis of coeliac disease and particularly so in the elderly when it is easy to dismiss such symptoms as due to "old age" and of no real consequence. This was illustrated by a series reported by Hankey and Holmes [3] who found a delay of 28 years in those diagnosed at the age of 60 years or over; the maximum delay was an astonishing 50 years. It has to be conceded that this was in an era when awareness of coeliac disease was not as prominent as it is now. In a more recent cohort of elderly patients [26] the duration of symptoms was 6.14 ± 12.6 years, similar to that in young adults at 5.8 ± 12 years but unacceptably long delays still occur. Even in those presenting with classical manifestations a diagnostic delay of 17 years can occur. [12]

In the study of Vivas et al, [27] typical symptoms were present in 62.5% children versus 31% in adults (P = 0.01). The average time to diagnosis after

the appearance of symptoms was 7.6 months for children and 90 months for adults ($P < 0.001$).

Tortora et al [13] found no differences in the malabsorption values between young and elderly people. However, elderly coeliac patients were more likely than younger ones to be diagnosed due to malabsorption symptoms, whereas non-classic symptoms were less common in the elderly. This suggests that elderly coeliac patients with subtle or atypical symptoms may go undetected by the health care staff.

Table 3 summarizes some reports on symptoms or malabsorption in elderly people with coeliac disease. It is noteworthy that many patients had not suffered from any obvious symptoms.

Dermatitis herpetiformis

Dermatitis herpetiformis is the classic cutaneous manifestation of extraintestinal coeliac disease. This is a blistering itching skin disease typically affecting elbows, knees, buttocks and scalp. Granular IgA deposits of the uninvolved skin are diagnostic. The disease affects up to 12% of adult coeliac

patients. [28] In contrast to coeliac disease, the incidence of dermatitis herpetiformis is decreasing. [20,29] It was suggested that an early diagnosis and treatment of coeliac disease might lead to less dermatitis herpetiformis. [28] The mean age at diagnosis of dermatitis herpetiformis in our series was 39 years, which was not much different from that in coeliac disease (44 years). [30] However, dermatitis herpetiformis is fairly uncommon in children, in our series only 4% of 476 patients were less than 17 years of age. [28]

B-cell lymphoma in dermatitis herpetiformis may develop more likely than in those with coeliac disease, who develop typically enteropathy-associated T-cell lymphoma. In our series 11 out of 1104 patients with dermatitis herpetiformis had non-Hodgkin lymphoma; 8 B-cell lymphoma, 2 enteropathy-associated T-cell lymphoma, and one was unclassified. Six of the 11 were over 50 years of age (median 50, range 32-79 years). [31]

In general, the clinical course of dermatitis herpetiformis does not differ between young and elderly patients. A decreased mortality rate in dermatitis herpetiformis is an intriguing feature. Hervonen et al. [32] found the relative risk in mortality to be 0.7; 95% confidence intervals (CI) 0.55-0.87. A similar trend has been shown in smaller series, though not statistically significantly.

[7,33] The risk of lymphoma in the elderly should be borne in mind, including the B-cell type, although it may appear in younger people. [31]

Bone mineral density and fractures

Adult coeliac patients have more osteoporosis or osteopenia and altogether lower bone mineral density than the reference population [34,35] Osteoporosis, as would be expected, is much more prevalent in elderly coeliacs. In one series of patients 65 years or older at the diagnosis of coeliac disease by biopsy, 67% of males had osteoporosis compared with 14% in younger participants, while the corresponding figures for females were 70% and 9%. [11] Importantly, it has been found that reduced bone mineral density can affect those who have no symptoms of coeliac disease and are discovered by screening, [5,34] or are children who have returned to a normal diet but have remained symptom free in adult life.[35] Meta-analysis showed that there is a moderate reduction of bone mineral density in untreated coeliac disease with weighted T-scores at the lumbar spine and hip of -1.7 and -1.4 (osteopenia defined as T-score 1 to -2.4 an osteoporosis ≤-2.5 standard deviations). [36]As expected, the same seems

to be true in the elderly, in whom osteopenia and osteoporosis are common. [11,37,38]

The fracture risk was higher in coeliac disease patients (8.7%) than in a control population (6.1%) according to a meta-analysis of Olmos et al.[39] In another study, a modest increase in risk of fracture was evident (risk ratio 1.38; 95% CI 1.14-1.68). [36]West et al. [38] in their population based study reported small increase in fractures in patients with coeliac disease (hazard ratio 1.30 ; 95% CI 1.16-1.46) but considered that undue concern was unwarranted. In some other small series the fracture risk was also elevated. [5]

Osteoporosis can be reliable assessed by measurement of bone mineral density using non-invasive dual-energy X-ray absorptiometry (DEXA) but the issue in practice is identifying which coeliac patients are at most risk of reduced bone mineral density so that investigations can be rationalised. High risk factors include age over 70 years, previous osteoporotic fracture, weight loss greater than 10%, and low body weight. [40] A case can therefore be made for limiting DEXA screening for osteoporosis to new patients with these features, to those with symptoms despite treatment with a gluten free diet for one year and to those who do not adhere strictly to the diet. The fracture

risk assessment tool (FRAX) has been devised to limit the need for DEXA scans. [41] The score is based in 10 variables. It appears to have a high negative predictive value of 94% but further evaluation of this test is required.

Osteoporosis is just one of many factors predisposing to fracture and the risk doubles with each standard deviation decrease in bone mineral density. [42] Advice to the elderly about wearing good shoes and slippers and avoiding hazards that might lead to falls is particularly important to avoid fracture. Apart from dietary advice, this is especially important for coeliac disease patients.

Among patients with osteoporosis, the prevalence of coeliac disease has been up to 3.4 %; [43] only slightly higher than the contemporary knowledge of the frequency of coeliac disease in the general population. Nevertheless, the possibility of coeliac disease should be considered in all subjects with osteoporosis or osteopenia, regardless of their age, since gluten free diet increases bone mineral density even in asymptomatic coeliac disease patients. [34,35]

Elevated alkaline phosphatase is a marker of osteomalacia in coeliac disease as in the general population. Normalisation of results with gluten free diet,

vitamin D and calcium will remove the need for further investigation including bone biopsy. [4]

Autoimmune diseases and morbidity

Screening studies have demonstrated an increased prevalence of autoimmune disorders including type 1 diabetes mellitus, thyroid disease and liver disorders. Of these diabetes is the best researched and in about 90% of patients diabetes precedes the diagnosis of coeliac disease. Apart from diabetes, hypothyroidism and hyperthyroidism, autoimmune liver disease and primary biliary cirrhosis deserve special mention. Isolated hypertransaminasemia is the most common hepatic injury and if this reverses on gluten free diet no further investigation is required. Primary Sjögren's syndrome must be remembered also in elderly coeliac disease patients. [44] These associations have recently been reviewed in detail. [4]

In elderly people, the concomitant occurrence of autoimmune conditions in coeliac disease does not differ from that in adults in general. [13,45] In particular, hypothyroidism is often associated with coeliac disease in the

elderly, [17,37] although highest risk estimates for thyroid disease have been obtained in coeliac children. [46] It is uncertain whether gluten free diet can alleviate or prevent the development of autoimmune disease, especially in adults. [47,48]

Heart disease and neurological disturbances

Apart from the burden of associated autoimmune diseases in coeliac patients, an increased risk of ischemic heart disease has been reported. [49] The overall risk of ischemic heart disease in coeliac disease is still debatable, which may be due to differences in smoking patterns or socioeconomic factors. [4] Recent studies have found no association between gluten intake and the risk of subsequent overall coronary heart disease. [50,51] Nevertheless, gluten free diet may result in reduced consumption of beneficial whole grains, which may affect cardiovascular risk, and coeliac patients should be informed about the potential risks of ischaemic heart disease. [51]

Various neurological problems have been encountered in coeliac disease. Many of these associations are still debatable. Patients with these

disturbances should be actively screened serologically for coeliac disease. Neuropathy, memory disturbances, ataxia of non-alcoholic origin and brain atrophy are conditions where coeliac disease may be associated. [52,53] The mean onset of gluten neuropathy and gluten ataxia occurs at the mean age of 55 years. [53,54] It seems that elderly patients with coeliac disease are overall not at increased risk for dementia compared to population in general. [55] Unfortunately, neurological conditions are often irreversible in spite of the introduction of a gluten-free diet. [56,57]

Malignancy and mortality

According to a recent meta-analysis coeliac disease patients, including screen-detected cases, were at an increased risk of non-Hodgkin lymphoma and of all-cause mortality, but not of malignancy in general. [58] In clinically milder forms the risk may be lower [6,59] The increase was due especially to enteropathy-associated T-cell lymphoma, and with poor dietary compliance. [7,60] Lymphoma in young coeliac patients is uncommon [11] so the development of malignancy is mainly a concern in the elderly. In the review by Ludvigsson,

the overall survival of coeliac patients with lymphoproliferative malignancy was the same as that of controls. [61]

In 2009 Freeman[62] stated in his review that when coeliac disease is diagnosed initially in elderly individuals or late in the clinical course, the risk of developing lymphoma and other malignancies was increased. By contrast, Godfrey et al. [37] observed that in coeliac patients over 50 years of age there was no significantly greater risk of cancer or mortality in the undiagnosed coeliac patients than in the controls.

In contrast to coeliac disease, the risk of B- cell lymphoma was increased in dermatitis herpetiformis patients. Similarly to coeliac disease patients, the risk was associated with poor compliance to gluten-free diet, but as stated earlier, surprisingly the mortality rate was decreased in dermatitis herpetiformis. [31,63]

Refractory coeliac disease is a rare premalignant condition mainly affecting elderly coeliac disease patients. [64,65] The symptoms and mucosal lesions do not alleviate on a strict gluten free diet. In refractory coeliac disease type I the mucosal intraepithelial cell population is normal, whereas in type II a monoclonal cell population is typical, which clearly increases the risk of

enteropathy-associated T-cell lymphoma. [66] Refractory coeliac disease should be managed in special clinics. [67]

To conclude, increased risk of lymphoma clusters mainly in elderly coeliac patients. However, the risk is lower than previously thought, less than twofold in one recent series compared to that of the population in general. [68] However, the malignant development should be rigorously investigated in refractory coeliac disease, and in cases where the patient experiences alarming symptoms, or gluten-free diet is no longer effective.

Recently, Ilus et al [68] reported that patients with coeliac disease carry an increased risk of colon cancer. This has to be borne in mind in elderly coeliac patients, because this cancer is very common, and its overall incidence is increasing in the older age groups. In those with coeliac disease who present with or develop iron deficiency anaemia, especially in later life, the possibility of concurrent colon cancer should always be considered. If iron deficiency anaemia is not reversed by a gluten free diet and supplements, the presence of a colon cancer should be suspected.

In the same study, [68] the risk of breast cancer in females and lung cancer were lower than in the population in general; these reductions may explain

why the overall risk of cancer was not increased. [68] A similar finding has also been observed non-significantly in smaller series [7]

How children differ in terms of symptoms

In children, failure to thrive, anaemia and tiredness are typical symptoms. Lymphoma and is uncommon, but not absent, [69]other malignancies occurring in children have not been connected to coeliac disease. As stated earlier, dermatitis herpetiformis is uncommon. Also in children, many remain undetected and have subtle if no symptoms at all. [70]

The effect of gluten-free diet

Adopting a gluten free diet demands considerable changes in life style. Should the diagnosis of coeliac disease be pursued in the elderly, especially when symptoms are only mild? Several methods have been applied to measure quality of life in coeliac disease, these methods being mainly general and not disease-specific. Studies focusing on elderly coeliac patients are sparse.

The amelioration of the condition by gluten free diet is obvious when elderly coeliac patients suffer from classic symptoms or malabsorption. The issue

becomes more complicated when there are only subtle, if any, symptoms or signs of malabsorption. Vilppula et al showed that the diet improves quality of life even in elderly screen detected coeliac disease patients, also in seemingly asymptomatic ones. [5] This was particularly evident when quality of life was evaluated: in a series of 35 screen detected coeliac patients over 50 years of, 28 (77%) maintained a strict gluten free diet while 5 others ingested gluten less than once per month. [5] Compliance seems not to be a major problem as the majority of elderly coeliac patients, even apparently asymptomatic ones, adhere to a strict gluten free diet, which again improved their quality of life. Mucosal recovery is also expected to be good when the diet is strict, [5] although it may occur more slowly than in younger patients. [71] Hankey and Holmes found that compliance with gluten free diet in the elderly was good: in a study of 42 patients diagnosed at the age of 60 years or more, 38 (90%) complied strictly with the diet. [3] All of these reported a considerable improvement in well-being and resolution of symptoms after commencing diet. Weight increased by an average of 5.2 kg; blood haemoglobin, albumin, calcium and alkaline phosphatase levels all improved significantly to within the normal range after one year on diet.

In the elderly, visual impairment that might impede the reading of food labels and the reliance on a partner to help with the gluten free diet. Where possible, partners should be involved in dietary and management discussions. Elderly patients, especially those who live alone might easily feel daunted by the thought of changing dietary habits of a life-time and fearful of the cost implications and how products might be obtained. For all of these reasons patients should be introduced to sympathetic dieticians skilled in the gluten free diet, so that optimal management can be achieved. [72] The risk of overweight is present after commencing gluten-free diet, and weight maintenance counselling should be an integral part of coeliac dietary education. [73] Altogether, current limited evidence suggests adherence to a gluten-free diet and mucosal healing prevents or ameliorates complications. [73]

Before the diagnosis is pursued it should be established that patients are taking a full normal diet, because some will begin eliminating gluten as soon as the diagnosis of coeliac disease is mentioned, sometimes on the advice of their physicians. This should be strongly discouraged as it can make subsequent tests difficult to interpret.

DIAGNOSTIC WORK-UP OF COELIAC DISEASE IN ELDERLY PATIENTS

Population-based screening for coeliac disease is not supported by the current evidence. [74] The level of suspicion of coeliac disease should be as high in older people as in younger ones. Old age itself should never be blamed for clinical features such as tiredness, indigestion, reduced appetite or anaemia which may be due to coeliac disease. Individuals found to have coeliac disease through screening programmes, may have considered themselves as 'well' and it is the physician or healthcare system that is identifying them as potentially ill. A strategy of case-finding from groups at particular risk is preferable. [36] Individuals with a family history of coeliac disease have about a five-fold risk of having coeliac disease. [75] An active case finding strategy increases the detection of coeliac disease, [76] so health care workers should test patients with suggestive clinical features or because the belong to an at-risk group, e.g. have a family history or autoimmune diseases, and where necessary, perform small intestinal biopsy to confirm or refute the diagnosis. Testing for coeliac disease in patients with suspected irritable

bowel syndrome is likely to be cost-effective even at a relatively low coeliac disease prevalence. [25]

In the series of 40 patients found by serologic screening in the studies of Vilppula et al, [16,17] diagnostic clues were present in almost every patient's history, and should alert physicians to consider coeliac disease. Patients with clinical features indicative of coeliac disease may be seronegative, and in these cases obtaining a small bowel biopsy is mandatory to clarify the situation. Especially elderly coeliac patients may remain seronegative, [77] or tissue transglutaminase antibodies titres may be lower than in younger ones. [70] In such symptomatic individuals endoscopic examination will also establish whether other pathology is present in the upper gastrointestinal tract. In frail, elderly patients or those with co-morbidities that preclude performing an endoscopy to obtain small bowel biopsies, serological tests will usually help to establish the diagnosis [78,79]

There is a role for establishing the HLA-status of patients which can rule out coeliac disease, as virtually all coeliac patients have DQ2 or DQ8. However, this is not helpful in the diagnostics of coeliac disease, because up to 35 % of the population share DQ2 or DQ8. [80]

CONCLUSIONS

Coeliac disease is often undetected in elderly people. The lack of obvious symptoms does not exclude the possibility of the condition. High index of suspicion and active serological screening in at-risk groups help to identify elderly patients who evidently benefit from gluten free diet. The diagnosis may prevent severe complications such as low-energy bone fractures and enteropathy-associated T-cell lymphoma.

AUTHORSHIP

Guarantor of the article: PC

PC planned the first draft of the manuscript. All authors contributed to study design and writing of the manuscript.

All authors approved the final version of the manuscript.

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Table 1. The prevalence of coeliac disease; the figures in different age groups have been derived from the Results of the original publication. EMA endomysial antibodies; AGA gliadin antibodies; TTGA tissue transglutaminase antibodies.

Study, year	Country	Population	Screening method	n total n subpop.	Population age Subpopulation age, years	Biopsy-proven prevalence %	Sero-prevalence %
Kolho et al. 1998 [81]	Finland	Voluntary personnel	EMA	1070	18-65 58-65	0.77 0.09	1.03 0.18
Ivarsson et al. 1999 [82]	Sweden	General population	AGA, EMA	1894	25-74 57-68	0.53 0.37	 0.32
Volta et al. 2001 [83]	Italy	General population	EMA	3483 632	12-65 56-65	0.49 0.32	0.57
West et al. 2003 [2]	UK	Health survey	EMA	7527 4696	45-76 55-76		1.2 1.0
Catassi et al. 2007 [76]	USA	Primary care at-risk patients	TTGA,EMA	976 366	≥ 18 ≥ 60		3.07 1.37

Lohi et al. 2007 [1]	Finland	Heath survey, population based	TTGA, EMA	8028 1095 812 747	≥ 30 55-64 65-74 ≥ 75	0.52	2.02 1.68 1.21
Vilppula et al. 2009 [16]	Finland	General population	TTGA, EMA	2815	≥ 55	2.34	2.70
Godfrey et al. 2010 [37]	USA	Monoclonal gammopathy study	TTGA, EMA	16847	≥ 50	0.2	0.8
Katz et al. 2011 [84]	USA	Volunteer health care participants	TTGA, EMA	3850 2727	≥ 18 ≥ 50		0.8 0.7
Almeida et al. 2013 [85]	Brazil	Unselected outpatients	TTGA, EMA	946	≥ 60	0.1	

Table 2. The annual coeliac disease incidence per 100,000 in different age groups; derived from the original publications.

Study, year	Country	Population	Population age Subpopulation age, years	Incidence All or female/male %
Murray et al. 2003[86]o	USA	Retrospective survey of cases 1950-2001	Children and adults ≥65	2.1 3.2
Fowell et al. 2006[87]	UK	Prospective survey 1993-2002	Adults 60-74	8.7 16.8
Virta et al. 2009[18]	Finland	Database of the National Social Insurance Institution 2004-2006	Children and adults 55-64 65-74 ≥75	39 49 / 36 53 / 47 24 / 22
Vilppula et al. 2009[16]	Finland	General population 2002-2005	≥55	75

Godfrey et al. 2010[16]	USA	Stored sera, 2001-2011	≥50	11.8
Angeli et al. 2012[88]	Italy	Prospective survey 2001-2011 in a local health unit	50-54 55-59 60-64 65-69 70-74 75-79	92 / 28 89 / 0 79 / 56 40 / 14 27 /17 14 / 20
Ludvigsson et al. 2013[89]	USA	Prospective survey 2000-2010	0-85 45-64 65-85	17.4 19.0 21.7

Table 3. Symptoms and signs of malabsorption in older patients with coeliac disease. Derived from the original publications

Reference	n	Age, years	Symptoms	Malabsorption
Hankey and-Holmes 1994 UK [3]	42	> 60	45% classic symptoms 14% subtle symptoms	80% anaemia (male) 75 % anaemia (female)
Freeman et al. Canada 1995[90]	30	> 60	77% weight loss	61% anaemia 40% iron deficiency 37% low vitamin B12 30% low serum folate
Gasbarrini et al. Italy 2001[12]	60	> 65	77% classic symptoms 3% no symptoms	58 % anaemia
West et al. UK 2003 UK[2]	87	45-76	Not described	Blood haemoglobin was lower than in control group

Vilppula et al Finland[17]	60	>55	31% classic symptoms 36% subtle symptoms 33% no symptoms	50% anaemia or malabsorption

Subtle symptoms: Abdominal distention, occasional loose stools or diarrhoea, bloating.

Classic symptoms: Chronic diarrhoea, malabsorption (iron, vitamin B12, folic acid), abnormal loss of weight

Figure legend: The annual incidence of coeliac disease per 100,000 in the whole population and in the elderly (65 years or older in different studies). The respective references are shown in parentheses. Population: Murray and Ludvigsson all ages, Fowell 15 years and Virta 16 years or older.