ANITTA VILPPULA

Coeliac Disease in the Elderly Population

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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ABSTRACT

This dissertation addresses the prevalence, incidence and clinical picture of coeliac disease (CD) and the benefit of gluten-free diet (GFD) in a population-based sample of individuals aged 50 years or more in Päijät-Häme province in Finland.

The study comprised 2,815 randomly selected subjects 52–74 years of age. The subjects participated a follow-up research project on ageing and well-being entitled Good Ageing in Lahti Region (GOAL). Clinical cases of CD were recorded and all subjects were screened with immunoglobulin A (IgA) class tissue transglutaminase (tTGA) antibodies. Seropositive subjects underwent small bowel biopsy. A second screening in the same population was carried out three years later, now comprising 2,216 individuals. tTGA seroconversion cases were confirmed with small bowel biopsy. All new coeliac cases were placed on GFD, and a control biopsy was carried out after one year. Their family and disease history, symptoms and dietary compliance were elicited. CD patients adhering to GFD were followed up for three years. The effect of GFD was evaluated by laboratory parameters and bone density measurements, personal interview and questionnaires about gastrointestinal (GI) symptoms and quality of life (QoL).

In 2005 of the 2,815 GOAL -participants 26 reported clinically detected CD and the screening of the population found an additional 35 CD patients. In 2008 five new cases were found among previously seronegative individuals, giving an annual incidence of 75 /100 000 CD in this study population. The prevalence of biopsy-proven CD increased within three years from 2.13% to 2.34%, and the overall prevalence of biopsy-proven and seropositive cases from 2.45% to 2.70%. Twenty-eight per cent of clinically detected and screen-detected CD patients had classic and 35% subtle symptoms, 38% were symptom-free at the time of diagnosis. Five (8%) had malignant disease, two of them small bowel T cell lymphoma. Fourteen (20%) had an autoimmune condition known to be associated with CD. Twenty-seven (39%) had low bone mineral density (BMD).

Dietary compliance was good; only three out of 66 patients did not adhere to GFD. At the time of diagnosis of CD the mean serum ferritin values were in general low, indicating subclinical or manifest iron deficiency, which was restored on GFD. The diet also significantly increased vitamin B12, vitamin D and

erythrocyte folic acid levels and improved BMD. The alleviation of GI symptoms was evident and QoL remained unchanged.

The study showed that positive serology and CD may appear later in life. The prevalence of CD was higher in patients 50 years of age or more than that reported in younger individuals. Like younger patients, many had only subtle symptoms or were even asymptomatic. However, in retrospect the majority of screen-detected patients had signs, symptoms or conditions associated with CD, which would suggest an increased risk of CD. Regardless of age those at risk are first-degree relatives of CD patients, patients with autoimmune diseases, osteoporosis or osteopenia, low-energy fractures, anaemia or vitamin malabsorptions or subtle abdominal symptoms. Abdominal complaints were alleviated on GFD, and signs of malabsorption when present improved, but QoL did not deteriorate, so ageing CD patients benefit from GFD. Active case-finding by serological screening in at-risk groups is encouraged, since ageing does not protect against CD.

TIIVISTELMÄ

Tämä tutkimus selvitti keliakian esiintyvyyttä ja ilmaantuvuutta, kliinisiä oireita ja gluteenittoman dieetin hyötyä yli 50 -vuotiailla. Tutkimusaineisto koostui Päijät-Hämeen maakunnassa asuvasta 2815 satunnaisesti valitusta 52-74 -vuotiaasta henkilöstä, jotka osallistuivat ikääntymistä, hyvinvointia, terveyttä ja palvelutarpeita koskevaan tutkimukseen (Ikihyvä Päijät-Häme). Aineistosta selvitettiin ensin osallistujien oman ilmoituksen perusteella keliakiaa sairastavat henkilöt, joiden keliakiaa oli diagnostisoitu ennen tutkimuksen aloittamista, ns. kliinisin oirein löydetyt -keliaakikot. Kaikilta tutkimukseen osallistuneilta seulottiin verestä immunoglobuliini A-luokan kudostransglutaminaasi vasta-aineet (tTGA). Henkilöille, joilla oli vasta-aineita (tTGA positiiviset), tarjottiin mahdollisuus ohutsuolen näytepalan ottoon keliakian toteamiseksi. Samanlainen seulonta tehtiin uudelleen kolmen vuoden kuluttua. Henkilöitä, jotka osallistuvat molempiin seulontoihin, oli 2216. Serokonvertoituneille henkilöille tarjottiin mahdollisuus ohutsuolen koepalan ottoon. Gluteenitonta dieettiä suositeltiin kaikille uusille keliaakikoille. Sekä aiemmin että seulonnalla todetuilta keliakiaa sairastavilta potilailta selvitettiin sairaudet, suolistovaivat ja oireet ennen keliakian toteamista, sukuhistoria, elämänlaatu sekä gluteenittoman dieetin noudattaminen. Ensimmäisestä seulonnasta löytyneitä keliakiaa sairastavia pyydettiin seurantaan. Dieetin tehoa arvioitiin ottamalla uusi koepala ohutsuolesta noin vuoden kuluttua. Gluteenittoman ruokavaliohoidon hyötyä arvioitiin myös laboratoriotutkimuksilla ja luuntiheysmittauksella ennen dieettiä ja 2-3 vuoden kuluttua dieetin aloituksen jälkeen sekä henkilökohtaisella haastattelulla. Potilaat täyttivät lisäksi vatsaoireita ja elämänlaatua selvittävät kyselylomakkeet.

Aineistosta löytyi 26 kliinisin oirein löydettyä keliaakikkoa ja seulomalla löydettiin 35. Kolmen vuoden kuluttua uusitussa seulonnassa tutkimusaineistosta löytyi viisi serokonvertoitunutta keliakiaa sairastavaa henkilöä, joten keliakian vuosittainen ilmaantuvuus (insidenssi) oli 75/100 000. Keliakian koepalalla varmistettu esiintyvyys (prevalenssi) lisääntyi kolmen vuoden seurantajakson aikana 2.13%:sta 2.34%:iin, ja keliakiaa sairastavien ja tTGA seropositiivisten yhteenlaskettu esiintyvyys 2.45%:stä 2.70%:iin.

Aineiston keliaakikoista kolmasosalla (28%) oli toteamishetkellä keliakiaan liitetyt klassiset oireet, 35%:lla vähäisiä oireita, ja täysin oireettomia oli 38%. Viidellä potilaalla (8%) oli pahanlaatuinen tauti, ja heistä kahdella ohutsuolilymfooma. Neljällätoista (20%) oli keliakiaan liitetty autoimmuunitauti, 27:llä (39%) alentunut luustontiheys.

Myöntyvyys dieettihoitoon oli hyvä: vain kolme potilasta ei aloittanut gluteiinitonta ruokavaliota. Heillä, jotka suostuivat seurantaryhmään, oli ennen ruokavaliohoitoa subkliininen raudanpuute, sillä seerumin keskimääräinen ferritiinitaso oli matala. Gluteeniton dieetti korjasi ferritiiniarvot normaalitasolle ja nosti merkittävästi keskimääräisiä vitamiini B12, D25 ja foolihappoarvoja sekä paransi luuntiheyttä. Vatsaoireet helpottuivat, mutta elämänlaatu ei keskimäärin muuttunut.

Tämä tutkimus osoitti, että keliakia vasta-aineet ja keliakia voivat ilmetä vasta myöhemmällä iällä. Keliakian esiintyvyys tässä aineistossa oli korkeampi yli 50 -vuotiailla kuin on raportoitu nuoremmassa ikäryhmässä. Kuten nuoremmassa ikäryhmässä monilla yli 50 -vuotiailla oli ennen keliakiadiagnoosia vain vähäisiä oireita tai he olivat jopa oireettomia. Kuitenkin retrospektiivisesti tarkastellen valtaosalla seulomalla löydetyistä keliakiapotilaista voitiin todeta keliakiaan liitetty sairaus, oire tai löydös, josta keliakiaa olisi voinut epäillä. Riskiryhmässä sairastua keliakiaan ovat, ikään katsomatta, keliakiaa sairastavien ensimmäisen asteen sukulaiset, autoimmuunisairautta, osteopeniaa tai osteoporoosia sairastavat, vähä-energisen murtuman saaneet, anemiasta tai vitamiinin puutteista tai lievistä vatsaoireista kärsivät henkilöt. Gluteeniton dieetti paransi lievät oireet, korjasi imeytymishäiriöt ja paransi luuntiheyttä muttei huonontanut elämänlaatua, joten myös vanhempi ikäryhmä hyötyy dieetistä. Yli 50 –vuotiaiden keliakian aktiivinen seulonta riskiryhmissä on suositeltavaa, koska ikä ei suojaa keliakian puhkeamiselta.

CONTENTS

ABBREVIATIONS

AGA	anti-gliadin antibody A
BMI	body mass index
BMD	bone mineral density
CD	coeliac disease
CI	confidence interval
DGP	deamidated gliadin peptides
DH	dermatitis herpetiformis
EMA	endomysial antibodies
EATL	enteropathy-associated T cell lymphoma
GFD	gluten-free diet
GI	gastrointestinal
GOAL	Good Ageing in Lahti Region research project
GSRS	Gastrointestinal Symptom Rating Scale
HLA	human leukocyte antigen
IgA	immunoglobulin A
IgG	immunoglobulin G
IEL	intraepithelial lymphocyte
NHL	Non-Hodgkin lymphoma
PGWB	Psychological General Well-Being
RCD	refractory coeliac disease
SD	standard deviation
TG2	tissue transglutaminase
tTGA	IgA-class tissue transglutaminase antibody
QoL	Quality of Life

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications referred to in the text by Roman numerals I-III:

I Vilppula A, Collin P, Mäki M, Valve R, Luostarinen M, Krekelä I, Patrikainen H, Kaukinen K, Luostarinen L: Undetected coeliac disease in the elderly. A biopsy-proven population-based study. Dig Liver Dis 2008;40:809-813. (Reprinted with permission of the copyright holder)

II Vilppula A, Kaukinen K, Luostarinen L, Krekelä I, Patrikainen H, Valve R, Mäki M, Collin P: Increasing prevalence and high incidence of celiac disease in elderly people: A population-based study. BMC Gastroenterology 2009;9:49. (Open access)

III Vilppula A, Kaukinen K, Luostarinen L, Krekelä I, Patrikainen H, Valve R, Luostarinen M, Laurila K, Mäki M, Collin P: Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. BMC Gastroenterology 2011 11:136. (Open access)

INTRODUCTION

In the first century AD a famous Greco-Roman physician Aretaeus the Cappadocian, described "the Coeliac Affection" so giving the name to an abdominal disease i.e. CD. In the early 19th century Dr. Mathew Baillie published his observations of a chronic diarrhoeal disorder in adults and even proposed a treatment; diet (Losowsky 2008). In 1888 an English authority on paediatrics, Samuel Gee, presented the classic symptoms of CD, diarrhoea and wasting (Gee 1888). About 60 years later a Dutch paediatrician W.K. Dicke published that wheat was the cause of CD and that GFD would relieve the symptoms (Dicke et al. 1953). A year later Paulley reported that villous atrophy of the small intestine mucosa was present in CD (Paulley 1954). After the development of gastroscopy apparatus by Crosby and Shiner in the mid-1950's and the discovery of first anti-gliadin antibodies (AGA) in blood by Berger in the 1960's, the tools to identify, diagnose and treat CD were available to modern physicians (Losowsky 2008).

CD is a life-long disease where the ingestion of dietary gluten results in small bowel mucosal inflammation, crypt hyperplasia and villous atrophy (Maki et al. 1997). It was for a long time considered to be a childhood disease, and it was assumed that the disease would manifest due to the symptoms, whereas clinically silent or undiagnosed disease was uncommon. These assumptions turned out to be incorrect. The prevalence of CD in children is about 1.0% and higher later in adulthood, 1.5% (Collin et al. 2002b, Maki et al. 2003, Roginsky et al. 2010). It is also known that most patients remain undiagnosed due to mild or no symptoms (Maki et al. 1997, Rostami Nejad et al. 2009).

The prevalence of CD in the elderly is not known. One might hypothesize that the disease would become symptomatic overtime and would therefore be more easily detected in older than in younger individuals. On the other hand, if the disease has remained symptomless for decades, while patients have ingested gluten-containing cereals all their lives, it is uncertain whether dietary treatment would be of any benefit. On the contrary, changing the dietary habits might even impair such people's QoL. It is moreover unknown whether older people may develop CD. The GOAL project made it feasible to investigate these issues in a Finnish

population aged 50 years or more. The aim was to ascertain the risk of CD, the effect of GFD, and the incidence of new cases.

REVIEW OF THE LITERATURE

1. DEFINITIONS AND DIAGNOSIS

1.1. Definitions

According the recent Oslo definitions CD is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals (Ludvigsson et al. 2013b). Gluten-related disorders is a term to describe all conditions related to gluten such as gluten ataxia, dermatitis herpetiformis (DH), non-coeliac gluten sensitivity and CD (Ludvigsson et al. 2013b).

Classic CD presents with signs and symptoms of malabsorption syndrome in adults and children. These patients are usually clinically detected. Patients with subtle symptoms - but no signs or symptoms of malabsorption have non-classic CD. CD is considered to be subclinical when patients have clinical or laboratory signs like iron deficiency anaemia, incidental endoscopic features or osteoporosis, but no symptoms. CD with clinically evident GI or extraintestinal symptoms like DH is symptomatic (Ludvigsson et al. 2013b).

In refractory CD (RCD) despite strict GFD, villous atrophy with malabsorptive symptoms and signs persist for over a year. It is divided into two categories: type I has normal intraepithelial lymphocytes (IEL) and type II has a clonal expansion of an aberrant IEL population (Ludvigsson et al. 2013b, Ilus et al. 2014a). Both are associated with high mortality, especially RCD II, for developing enteropathy-associated T cell lymphoma (EATL). The prevalence of RCD in Finland is 0.31% among CD patients (Ilus et al. 2014a).

The family members of CD patients who have CD-related human leukocyte antigen (HLA) -DQ2 and/or -DQ8 are genetically at risk of CD. When tissue transglutaminase (TG2) or endomysial antibodies (EMA) have been increased on at

least two occasions and the intestinal biopsy is not known the patient has CD autoimmunity. If tTGA or EMA has been tested only once, patients should to be referred to as tTG+ or EMA+. CD is likely when small intestinal mucosa is normal, but CD serology is positive. These individuals are at risk of developing CD, but are not CD patients. The Oslo definition for CD related terms also defines non-coeliac gluten sensitivity (NCGS) as one or more of a variety of immunological, morphological, or symptomatic manifestations that are precipitated by the ingestion of gluten in individuals in whom CD has been excluded (Ludvigsson et al. 2013b).

1.2. Pathogenesis

Gluten is a complex of water insoluble proteins from wheat, rye and barley that are harmful to CD patients (Ludvigsson et al. 2013b). Gluten consists of a broad group of prolamins (gliadins and glutens) found in wheat. Other prolamins (hordenin in barley and secalin in rye) have properties, which are immunogenetically similar to those of gluten (Platt et al. 1971, Rostom et al. 2006). Daily gluten consumption is normally 10 to 20 g.

Gastric enzymes cannot degrade gluten peptides, so they have to be transported across the epithelium of the small bowel mucosa. It has been hypothesized that viral infection or genetic changes could cause the increased permeability (Fasano et al. 2000, Koskinen et al. 2008, Wolters et al. 2008). The peptides use both paracellular and transepithelial passages to reach the lamina propria (Fasano et al. 2000, Koskinen et al. 2008, Wolters et al. 2008). The toxic gluten peptides promote upregulation of interleukin 15 of epithelial and dendritic cells. Interleukin 15 in turn induces proliferation of IELs, which play a part in enterocyte apoptosis and villous atrophy (Nilsen et al. 1998, Maiuri et al. 2000). In the submucosal layer the gluten peptides also react with TG2. They are deamidated by the enzyme and autoantigen TG2 to glutamic acid residue and presented to T cells on the surface of antigen presenting cells (APC) of people with HLA types DQ2 or DQ8, thereby stimulating gluten-specific T cells (Lundin et al. 1993, Lundin et al. 1994). The activated T cells in the lamina propria and within the epithelium are cytotoxic (producing cytokine interferon), capable of apoptosis of enterocytes, to remodel the mucosa (fibroblasts) towards atrophy and cause malabsorption (Deem et al. 1991, Bajaj-Elliott et al. 1998, Schuppan et al. 2013). Through the crosslinking

activity of TG2 and gliadin and the formation of gliadin-TG2 immunogenic complexes IgA class anti-TG2 antibodies are produced by plasma cells as well as IgA and immunoglobulin G (IgG) class deamidated gliadin peptides (DGP). This is believed to cause antibody mediated inhibition of TG2 functions, and lead to mucosal damage (Di Sabatino et al. 2012).

1.3. Genetics

The genetics of CD is closely related to HLA class II molecules HLA B8 and HLA DR3, which are located on the short arm of chromosome 6 (Falchuk et al. 1972, Keuning et al. 1976, Mearin et al. 1983). These genes encode DQ molecules on the surface of the immune system cells. More than 99% of CD patients have HLA DQ2 or DQ8 encoded alleles DGA1*0501 and DGB1*0201 or and DQA1*0301 and DQB1*0302 respectively (Sollid et al. 1989, Polvi et al. 1996, Polvi et al. 1998). Less than 1% of CD patients are negative for both of these alleles (Polvi et al. 1998, Karell et al. 2002, Karell et al. 2003). These uncommon gene types are not yet fully known. About 20 to 35% of Finnish general population have HLA DQ2 or DQ8 types, so the HLA -type as such is not very specific to determining coeliac disease (Sollid et al. 1989, Holm 1993, Polvi et al. 1996). However, if a person does not have this HLA genotype, he is very unlikely to have CD (Karell et al. 2003).

1.4. Symptoms

In adults the typical symptoms of CD are GI symptoms like diarrhoea, statorrhoea, bloating, nausea and stomach pain, and malabsorption signs like weight loss and oedema (Cooke et al. 1984, Ludvigsson et al. 2013b). In further investigations more signs of malabsorption - anaemia due to iron or folic acid deficiency, B-vitamin or D-vitamin deficiencies, hypoalbumenia and osteoporosis can be detected. In children failure to thrive and wasting and poor appetite are typical of CD in addition to GI symptoms and malabsorption syndromes (Visakorpi et al. 1967, Visakorpi et al. 1970). Recently the clinical picture has altered towards more subtle, non-classic GI symptoms (abdominal distension, occasional diarrhoea, bloating, vague stomach pain, constipation) and incidental malabsorption signs (low

haemoglobin values, iron, D-vitamin, B12–vitamin or folic acid deficiency, abnormalities in liver function tests, osteopenia or osteoporosis, low-energy fractures, enamel defects and secondary lactose intolerance) or even to be symptomless (Reilly et al. 2012). The symptoms may be atypical and general and easily be confused with many other GI diseases like irritable bowel syndrome, a common condition in general population with a global prevalence of 11% (Canavan et al. 2014).

DH is the classic extraintestinal manifestation of CD (Reunala 1998). About 5% of CD patients present with DH during their lifetime (Kotze 2013). DH is a blistering cutaneous disease. It has a typical presentation: pruritic papulovesicular rash on extensor surfaces and buttock, but may also present in the mucous membrane. The presence of granular deposits of IgA along the epidermal junction in biopsy of uninvolved skin in the perilesional area is immunologically diagnostic to DH (Zone et al. 1996, Kotze 2013). Villous damage in duodenal biopsy is often less obvious than in CD and is present in about 70-80% of HD patients. A further 25% have normal villous architecture with increased IELs (Fry et al. 1974, Gawkrodger et al. 1984, Reunala 1998). DH is a typical example of CD without villous atrophy. Today it is well recognized that CD may indeed occur in the absence of atrophy (Collin et al. 1994a, Salmi et al. 2010). DH and CD have identical HLA DQ and both may occur separately in identical twins (Hervonen et al. 2000). Autoimmune conditions in DH are similar to those in CD (Collin et al. 1994a).

1.5. Diagnosis

1.5.1. Serology

The serological diagnosis of CD is based on blood antibody testing. Elevated CD antibodies in blood indicate a possibility of CD and often lead to small bowel biopsy.

Taylor et al. discovered the first serological marker for CD AGA in 1961 (Taylor et al. 1961, Ludvigsson et al. 2013b). AGA is a direct antibody produced against consumed gliadin, the prolamin of wheat. Its sensitivity for CD is 50-80% and specificity 70-80 % (Volta et al. 1984, Maki et al. 1991b, Bode et al. 1994). It was widely used in the diagnostics of CD before tTGA and EMA (Roginsky et al.

2010). The problem with AGA is that it has been found, for example, in food allergy or chronic inflammatory bowel disease patients or even in healthy individuals without coeliac associated genetics (Lindberg et al. 1985, Maki et al. 1991b, Kull et al. 1999, Ruuskanen et al. 2011). The DGP are produced by TG2 of the gliadin that has entered the lamina propria. B cells then produce antibodies against DGP, and these antibodies are measurable in serum and are more sensitive to CD than gliadin itself (Schwertz et al. 2004, Kaukinen et al. 2007, Volta et al. 2008). However, the sensitivity or the specificity is not as high as tTGA or EMA (Niveloni et al. 2007, Sakly et al. 2012, Wang et al. 2014). In 1983 Chorzelski et al. introduced EMA, an indirect antibody test against endomysium of small intestine. It is highly specific and sensitive to CD (Chorzelski et al. 1983, Maki et al. 1991b, Volta et al. 1995). Its downside is that the immunofluorescence is a rather laborious and laboratory dependent method. The most widely used immunological test of CD is tTGA, a direct IgA class antibody test (ELISA). It is a calcium dependent enzyme produced by the mucosa of small intestine during consumption of gluten. It has very good sensitivity and specificity for CD (Table 1) (Sulkanen et al. 1998b). Another application of the TG2 antibody test is the promising whole-blood self-TG2-based point-of-care test, which is available "over the counter" for quick testing (Korponay-Szabo et al. 2005, Raivio et al. 2006).

IgA deficiency in CD patients is rather common; 2% of American and 3.6% of Finnish CD patients have IgA deficiency (Collin et al. 1992b, Chow et al. 2012). In general IgA deficiency in Finnish blood donors is 0.25% (Koistinen 1975). For IgA deficient patients there are IgG class tTGA, EMA and DPG tests with good sensitivity and specificity for CD (Table 1) (Korponay-Szabo et al. 2003, Niveloni et al. 2007, Wang et al. 2014). Both tTGA and EMA are nowadays standardized and validated tests when screening for CD. In recent years and in various studies tTGA has been used for screening for CD and EMA to verify the findings (Kapuscinska et al. 1987, Sulkanen et al. 1998b, Stern 2000, Raivio et al. 2006). The prevalence of seronegative CD varies a lot; it is 6-22% of all diagnosed cases (Dickey et al. 2000, Collin et al. 2005, Hopper et al. 2007, Rashtak et al. 2008).

Table 1. Sensitivity and specificity of endomysial antibodies (EMA), tissue trasglutaminase antibodies (tTGA) and deamidated gliadin peptide antibodies (DGP) in diagnostics of coeliac disease

Author, year	Study population - CD patients	Controls	tTGA		EMA		IgA DGP		IgG DGP	
	n	n	Sensitivity %	Specificity %	Sensitivity %	Specificity %	Sensitivity %	Specificity %	Sensitivity %	Specificity %
Sulkanen et al. 1998a,b	136	207	95	94	93	100	nd	nd	nd	nd
Tesei et al. 2003	250	176	90	95	86	100	nd	nd	nd	nd
Collin et al. 2005	126	106	94	99	89	98	nd	nd	nd	nd
Kaukinen et al. 2007	44	46	89	98	80	100	91	98	nd	nd
Niveloni et al. 2007	60	81	95	98	nd	nd	98	94	97	100
Hopper et al. 2008	77	1923	91	91	87	98	nd	nd	nd	nd
Raivio et al. 2008	139	103	99	99	99	100	nd	nd	nd	nd
Rashtak et al. 2008	216	124	78	98	nd	nd	74	95	65	98
Volta et al. 2008	128	134	97	91	94	100	nd	nd	nd	nd
Volta et al. 2010	48	89	94	97	92	100	84	80	82	99
Sakly et al. 2012	103	274	96	100	96	100	97	92	94	93

nd = no data

1.5.2. Histology

The diagnosis of CD has traditionally been based on the histology. Small bowel mucosal inflammation, villous atrophy and crypt hyperplasia are typical for the condition (Maki et al. 1997). When cereals wheat, rye and barley are excluded from the daily diet, the small bowel mucosa will be restored (Collin et al. 2004).

The British Society of Gastroenterology published the first guidelines on adult CD in 1996 (Ludvigsson et al. 2014a). These criteria were established at the United European Gastroenterology Week in Amsterdam in 2001 (United European 2001). The diagnosis entailed the demonstration of small intestinal villous atrophy and histological or clinical response to GFD. Just recently the British Society of Gastroenterology updated the guidelines for adult CD (Ludvigsson et al. 2014a). The diagnosis requires a small intestinal biopsy, taken when the patient is still on gluten-containing diet, and a positive serology. Biopsy is essential for diagnosis, and serological tests cannot replace it. Follow-up should aim at strict adherence to GFD (Ludvigsson et al. 2014a). Because the serologic tests EMA and tTGA are highly specific for CD, the renewed European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria in 2012 allow the diagnosis in selected cases to be based on serology only in symptomatic (i.e. classic) CD patients. In asymptomatic children at risk the diagnosis is based on positive serology and histology; in addition the HLA –DQ2 and –DQ8 testing is valuable for excluding CD (Husby et al. 2012). In adult patients who are unable or unwilling to undergo endoscopy, the similar serological guidelines are followed; tTGA 10 times higher the upper limit of normal, and a positive EMA or DGP (Ludvigsson et al. 2014a). Capsule endoscopy combined with biopsies is an alternative to endoscopy. It has specificity to CD similar to that of endoscopy and is less invasive (Atlas et al. 2011, Tennyson et al. 2012).

For the histological definition the Marsh-Oberhuber classification is frequently applied (Table 2). It demonstrates that the severity of mucosal atrophy is variable in CD (Marsh 1992, Oberhuber et al. 1999). The biopsies must be properly oriented as the correct orientation is necessary for the assessment of villous height crypt depth ratio (Villanacci et al. 2011). Types 0 and 1 are normal non-coeliac findings and types 2 and 3(a to c) typical for CD (Villanacci et al. 2011, Ludvigsson et al. 2014a). There are numerous other non-coeliac causes of lymphocytic duodenosis and villus atrophy, which must be kept in mind: immune disorders (e.g.

common variable immunodeficiency syndrome, glomerulonephritis), autoimmune disease (these may co-occur with CD; like Grave's disease, rheumatoid arthritis), infectious causes (parasites, viral, mycobacterial, Whipple's disease etc.), deficiency syndromes (nutrient deficiencies like vitamin B12, folic acid and Kwashikor; immunodeficiency syndromes like AIDS; intestinal lymphangiectasia), drugs (e.g. chemotherapy), neoplasia (EATL), other diseases (like Crohn's disease, collagenous colitis) (Freeman 2009, Ludvigsson et al. 2014a). If the patient is seronegative for CD, but has villus atrophy, he/she should be considered in an appropriate clinical context to determine whether the patient has CD or some other disease (Ludvigsson et al. 2014a).

Table 2. Marsh-Oberhuber classification

Classification	Morphology of duodenal mucosal biopsy
Type 0	Normal architecture and increased intraepithelial lymphocytes ≥ 25/100 enterocytes
Type I	Normal architecture and increased intraepithelial lymphocytes ≥ 40/100 enterocytes (villous crypt ratio > 3:1)
Type 2	Normal architecture and increased intraepithelial lymphocytes ≥ 40/100 enterocytes with crypt hyperplasia (villous crypt ratio < 3:1)
Type 3 a	Partial villous atrophy; villi blunt and shortened with a villous crypt ratio 1:1
Type 3 b	Subtotal villous atrophy; villi atrophic but still separate and recognizable
Type 3 c	Total villous atrophy; villi rudimentary or absent; mucosal resembles colonic mucosa
Type 4	Atrophic hypoplastic lesion: flat mucosa, normal crypt height, no inflammation with normal intraepitheal lymphocyte counts

1.5.3. Associated conditions

The association between CD and autoimmune conditions such as type I diabetes mellitus, autoimmune thyroid disorders, Sjögren's syndrome and other associated conditions like infertility has been demonstrated in several studies (Table 3 and Table 4) (Collin et al. 1989, Collin et al. 1994b, Iltanen et al. 1999, Picarelli et al. 2005). Children with diabetes mellitus type I, autoimmune liver disease, Down's, Turner's and Willam's syndrome carry an increased risk of CD – the prevalence of

CD being from 5 up to 16% (George et al. 1996, Carlsson et al. 1999, Giannotti et al. 2001, Bonamico et al. 2002, Caprai et al. 2008, Vajro et al. 2013, Atherton et al. 2014, Bybrant et al. 2014, Roizen et al. 2014). Similar genetic background and predisposition to autoimmune conditions may explain the association (Collin et al. 2002a).

It has been shown that GFD is necessary to prevent complications such as anaemia or osteoporosis (Collin et al. 2002a). The diet may have a protective effect against developing autoimmune diseases but did not prevent progression of thyroid disease in newly diagnosed CD patients (Cosnes et al. 2008, Metso et al. 2012, Reilly et al. 2012).

Table 3. Prevalence of associated conditions in coeliac disease patients

Condition and reference	Study population (n)	Prevalence %
Diabetes mellitus type I		
Collin 1994	335 adults	5
Autoimmune thyroid disease		
Collin 1994	335 adults	5
Sategna-Guidetti et al. 1998	185 adults	21
Sategna-Guidetti et al. 2001	285 adults	16
Mukherjee et al. 2010	125 ≥65 year	14
	149 18-30 years	7
IgA deficiency		
Collin 1994	355 adults	3
Chow et al. 2012	317 children, 1498 adults	2
Sjögren's syndrome		
Collin 1994	355 adults	3
Addison's disease		
Collin 1994	355 adults	0.6
Sarcoidosis		
Collin 1994	355 adults	1
Primary hyperparathyroidism		
Maida et al. 2006	309 women, 1 man	2
Ludvigsson et al. 2012	17121 adults	0.4
Epilepsy		
Chapman et al. 1978	165 adults	6
Peripheral neuropathy		
Luostarinen et al. 2003	26 adults	23
Inflammatory bowel disease		
Collin 1994	355 adults	0.3
Pascual et al. 2014	not specified	0.03-0.2
Psoriasis		
Collin 1994	355 adults	1
Infertility		
Fortunato et al. 2014	91 women	1

Table 4. Prevalence of coeliac disease in subjects with associate conditions

Condition and reference	Study population (n)	Prevalence %
Diabetes mellitus type I		
Collin et al. 1989	195 adults	4
Page et al. 1994	1798 adults	2
Picarelli 2005	194 adults	6
Gerco et al. 2013	492 adults	4
Autoimmune thyroid disease		
Collin et al. 1994b	83 adults	5
Sategna-Guidetti et al. 1998	152 adults	3
Hakanen et al. 2001	79 adults	24
Spadaccino et al. 2008	276	4
IgA deficiency		
Ludvigsson et al. 2014b	2100 children and adults	7
Sjögren's syndrome		
Collin et al. 1992a	63 adults	10
Iltanen et al. 1999	34 adults	15
Szoroday et al. 2004	111 adults	5
Addison's disease		
Myhre et al. 2003	75 children and adults	8
Betterle et al. 2006	5 children, 104 adults	3
Primary biliary cirrhosis		
Gillett et al. 2000	378 adults	1
Volta et al. 2002	47 adults	4
Autoimmune hepatitis		
Volta et al. 1998	181 children and adults	3
Villalta et al. 2005	47 adults	6
IgA nephropathy		
Collin et al. 2002c	223 adults	4
Autoimmune myocarditis		
Frustaci et al. 2002	187 adults	4
Sarcoidosis		
Rutherford et al. 2004	102 adults	4
Epilepsy		
Cronin et al.1998	117 children and adults	2
Luostarinen et al. 2001a	199 adults	3
Ataxia		
Luostarinen et al. 2001b	36 adults	17
Atopy		
Zauli et al. 2000	401 children and adults	1
Enroth et al. 2013	1068 children and adults	1
Psoriasis		
Brickefeld et al. 2009	12502 adults	0.3
Lindqvist et al. 2002	114 adults	4
Down's syndrome		
Cerqueira et al. 2010	98 children and adults	10
Turner's syndrome		
Frost et al. 2009	265 adults	5
Infertility		
Meloni et al. 1999	99 women	8
Choi et al. 2011	188 women	6

1.6. Treatment

The only treatment for CD and DH so far is GFD. GFD entails avoiding wheat, barley and rye in daily diet (Maki et al. 1991a). Originally oat was also included in the avoidance list, but nowadays it is a generally accepted that oat does not cause histological deterioration of the small intestine mucosa (Janatuinen et al. 1995, Janatuinen et al. 2000, Janatuinen et al. 2002). It may cause some CD patients symptoms or even mucosal atrophy due to cross-contamination with wheat or they may be sensitive to oat (Lundin et al. 2003, Arentz-Hansen et al. 2004, Comino et al. 2011). The European Commission legislated for the determination of gluten-free foodstuffs: They should contain $\leq$ 20 parts per million of gluten being safe for coeliac disease patients (Official Journal of the European Union 2009).

Newly diagnosed patients should be referred to a dietician to learn and discuss GFD. Such follow-up improves the adherence to GFD up to 97.5% compared to CD patients no so followed-up (Hall et al. 2009). In follow-up studies histological mucosal recovery varies widely, being 57-76% (Ciacci et al. 2002, Rubio-Tapia et al. 2010, Lebwohl et al. 2014). Most gastroenterologists favour a control intestinal biopsy after one year on GFD. However the new guidelines do not deem this to be necessary for patients with no risk of complications or symptoms while on GFD (Ludvigsson et al. 2014a). Patients with non-responsive CD should always be examined thoroughly and undergo follow-up biopsy to determine whether it is a case of RCD.

There are some novel treatments for CD under development, such as immunotherapy with subcutaneous injections of dominant immunotoxic gliadin peptides or TG2 inhibitors, but none of these are so far available or recommended for treatment (Ludvigsson et al. 2014a).

2. PREVALENCE

The reported prevalence figures for CD vary widely depending on the population and the study design. Most studies are based on serologic screening. Differences are also to be found in serologic screening; in general, earlier studies were based on EMA or AGA, and later on tTGA or nowadays, especially in IgA deficiency, on IgG DGP. In some studies the first screening method has been tTGA, and positive cases have been confirmed with EMA (Cellier et al. 2005, Katz et al. 2011). Either the prevalence of biopsy-proven disease or seroprevalence has been reported. The prevalence of CD worldwide has ranged from 0 to 1.87% when screening was based on EMA, 0 to 1.87% on tTGA and 0.02 to 1.24% with histological confirmation (Kang et al. 2013). A combined prevalence of 0.3-2.0% of screen-detected and biopsy-proven CD has been reported in European countries (Mustalahti et al. 2010). In children the worldwide clinically detected prevalence of CD varied from 0.0047% to 0.55% (Kang et al. 2013). For comparison, the screened biopsy-proven prevalence of CD in Finnish schoolchildren was 1.0% (Maki et al. 2003). The screened prevalence of CD in different parts of the world in general population is summarized in Table 5, and derived prevalence in the elderly in Table 6.

There are fewer studies on the prevalence of clinically detected CD. Logan et al. (1986) reported the prevalence of CD to be 0.061% in Scotland. In Sweden, Hallert et al. (1981) and Midhagen et al. (1988) found prevalences of 0.058% and 0.096% respectively. In the USA, Talley et al. (1994) estimated a prevalence of 0.022% of documented CD. In Finland, the latest clinical biopsy-proven prevalence of CD was extracted from the database of the National Social Insurance Institution, being 0.55% in the entire population, and 0.7% in the highest prevalence area (Virta et al. 2009).

The diagnostic delay of CD in adults is known to be long, for example in Sweden 9.7 years, and in the UK 13 years from the first symptoms (Norstrom et al. 2011, Aziz et al. 2012). In a recent study by Ukkola et al. (2011) the mean delay in Finland was only one to three years, but in individual cases could reach up to 50 years. The incidence of CD has risen since the 1970's (Hurley et al. 2012). This is due in part to better recognition of the condition. In adults, there was a threefold

increase in the number of newly detected CD cases from 1960 to 1979 in Scotland (Logan et al. 1986). In Finland, the annual incidence of clinically detected cases increased from 20 in 1997 to 31 per 100,000 in 2007 (Collin et al. 2007, Virta et al. 2009). In a recent study by Ludvigsson et al. (2013a) the incidence in the USA increased from 11.1 in 2000-20011 to 17.3 per 100,000 person-years in 2008-2010. However the incidence levelled off after 2004. The incidence of CD in different parts of world in general population (children and adults) is summarized in Table 7.

Hallert et al. reported in two of their studies in 1981 and 1983 the clinical biopsy-proven age-adjusted prevalence in patients aged 55-64 years to be 0.06-0.07%, in those 65-74 years old 0.04% and in those over 75 years old 0.02% (Hallert et al. 1981, Hallert et al. 1983). Midhagen et al. (1988) reported that the highest clinical prevalence was in the age group 65 to 74 years old, namely 0.18. In 1994 Hankey and Holmes found that 19% of all CD patients were over 60 years of age by the time when CD was diagnosed (Hankey et al. 1994). Gasbarrini et al. (2001) reported that 4.4% (60 out of 1353) patients were over 65 years of age at the time of diagnosis of CD. Again, a trend towards increasing occurrence by ageing was detected in Finland (Lohi et al. 2007). In Spain Marine and co-workers (2011) showed the opposite: the prevalence of CD was higher in children, and lower in older age groups, but still found a slight increase in CD prevalence in individuals older than 80 years.

DH manifests in about 12% of CD patients. The prevalence of DH in adults and children has been between 0.011% in the USA and 0.075% in Finland. The overall incidence of DH in Finland was high, but a significant decrease occurred in the 1990s (Smith et al. 1992, Salmi et al. 2011). Only few reports have been presented on DH in elderly CD patients. Hankey and Holmes (1994) described that seven out of 42 (16%) CD patients over 60 years old had DH. In the study by Godfrey et al. (2010) five (4%) of screened CD patients reported DH. The retrospective study by Casella et al. (2012) reported that 11.9 % of all CD patients over 65 years had DH.

Family history and occurrence of autoimmune conditions increase the likelihood of CD. The prevalence of CD in first-degree relatives varies between 10 and 20% (Maki et al. 1991b, Greco et al. 2002). In monozygotic twins the concordance of CD is 70-75% (Greco et al. 2002). The prevalence of CD (EMA based) in second-degree relatives was 2.6% and in first cousins 5.5% (Korponay-Szabo et al. 1998, Book et al. 2003).

In general, epidemiological studies on the prevalence of CD in elderly population are sparse. Prevalence figures in elderly derived from clinical screening

studies are summarized in Table 6 and incidence figures in Table 8, which suggest that the figures are extremely variable.

Table 5. Prevalence of coeliac disease (CD) in different studies

Study, year	Country	Population	n	Age, years	Screening method[a]	Biopsy-proven prevalence %	Sero-prevalence %
Hed et al. 1986	Sweden	Blood donors	1866	adults	AGA	0.38	
Corazza et al. 1997	San Marino	Random sample of general population	2237	20-87	EMA	0.18	
Kolho et al. 1998	Finland	Voluntary personnel of Helsinki University Hospital	1070	18-65	EMA	0.77	
Ivarsson et al. 1999	Sweden	Randomly selected adults from Northern Sweden population register	1894	25-74	AGA, EMA	0.53	
Cook et al. 2000	New Zeeland	Randomly selected individuals from electoral rolls	1064	adults	EMA	1.2	1.1
Riestra et al. 2000	Spain	Random sample of general population of North Spain	1170	adults	AGA, EMA	0.17	0.17
Volta et al. 2001	Italy	General Population	3483	12-65	EMA	0.49	0.57
Fasano et al. 2003	USA	At-risk: relatives of CD patient or had symptoms for CD	5686	19-71	AGA, EMA		1.47-4.70
		Not-at-risk: Blood donors, patients of outpatient clinics	2845				0.95
Mäki et al. 2003	Finland	Schoolchildren	3654	7-16	EMA, tTGA		
West et al. 2003b	England	General practitioner patients invited for health survey	7527	45-76	EMA		1.2

[a] tissue transglutaminase antibodies = tTGA, endomysial antibodies = EMA, antigliadin antibodies = AGA

Table 5. Prevalence of coeliac disease in different studies (continued)

Study, year	Country	Population	n	Age, years	Screening method[a]	Biopsy-proven prevalence %	Sero-prevalence %
Menardo et al. 2006	Italy	Blood donors, school pupils, primary care patients	1002	13-90	tTGA, EMA	1.0	1.3
Catassi et al. 2007	USA	Multi-centre, primary care at-risk patients	976	≥18	tTGA, EMA		3.07
Roka et al. 2007	Greece	Systematic random invited participants of the population registry	2230	18-80	tTGA, EMA	0.18	0.54
Lohi et al. 2007	Finland	Two health surveys, population based, years 1978-1980 and years 2000-2001	8000 8028	≥30	tTGA, EMA 1968-1980 2000-2001	0.03 0.52	1.03 2.02
Chin et al. 2009	Australia	Busselton Health Study participants, general population survey	3011	adults	tTGA	0.56	1.56
Marine et al. 2009	Spain	Occupational Health Department workers	1868	adults	tTGA, EMA	0.4	1.4
Katz et al 2011	USA	Volunteer health care participants	3850	≥18	tTGA		0.8
Rubio-Tapia et al. 2012	USA	Participants of Nutritional Health and Nutrition survey in 2009-2010	5830	20-80	tTGA, EMA	0.76	
Alencar et al. 2012	Brazil	Blood donors	4000	adults	tTGA, EMA	0.35	8

[a] tissue transglutaminase antibodies = tTGA, endomysial antibodies = EMA, antigliadin antibodies = AGA

Table 6. Derived prevalence of coeliac disease in older population

Study, year	Country	Population	n	Age, years	Screening method[a]	Biopsy-proven prevalence %	Sero-prevalence %	Overall prevalence %
Kolho et al. 1998	Finland	Voluntary personnel of Helsinki University Hospital	1070	58-65	EMA	0.09	0.18	
Ivarsson et al. 1999	Sweden	General population	1894	57-68	AGA, EMA	0.37	0.32	0.37
Volta et al. 2001	Italy	General population	632	56-65	EMA	0.32		
West et al. 2003b	UK	General practitioners' patients invited for health survey	4696	55-76	EMA		1.0	
Catassi et al. 2007	USA	Primary care at-risk patients	366	≥ 60	tTGA, EMA		1.37	
Lohi et al. 2007	Finland	Health Survey, population based 2000-2001	8028	55-64 65-74 ≥ 75	tTGA, EMA			2.20 1.68 1.21
Godfrey et al. 2010	USA	Participants of Monoclonal Gammopathy Study	16847	≥ 50	tTGA, EMA	0.2	0.8	0.92
Katz et al. 2011	USA	Volunteer health care participants	2727	≥ 50	tTGA, EMA		0.7	
Almeida et al. 2013	Brazil	Unselected outpatients	946	60-92	tTGA, EMA			0.1

[a] tissue transglutaminase antibodies = tTGA, endomysial antibodies = EMA, antigliadin antibodies = AGA

Table 7. Incidence of coeliac disease (CD) in different studies

Study, year	Country	Population based series	Age group, years of age	Time period, years	Overall annual incidence /100 000
Talley et al. 1994	USA	Retrospective survey of CD cases 1960-1990 in Olmsted County	children and adults	30	1.2
Bode et al. 1996	Denmark	Retrospective survey of CD cases 1976-1991 in Copenhagen	16-81	15	1.3
Collin et al. 1997	Finland	Retrospective survey of CD cases 1975-1994 in Tampere region	≥ 15	5	17
Murray et al. 2003	USA	Retrospective survey of CD cases 1950-2001 of Olmsted County	children and adults	50	2.1
Cook et al. 2004	New Zeeland	Retrospective CD cases 1970-1999 in Canterbury region	children and adults	30	2.2
Fowell et al. 2006	UK	Prospective survey of CD 1993-2002 in Pope Hospital in East Dorset	adults	10	8.7
Virta et al. 2009	Finland	Prospective survey on CD 1993-2002 on a National Social Insurance Institution database	children and adults	3	39
Hawkes et al. 2000	UK	Retrospective survey of CD 1981-1995 and	16-88	15	3.08
Hurley et al. 2012		1996-2005 in Cardiff & Vale of Glamorgan area		10	11.13
Riddle et al. 2012	USA	US military personnel on active duty 1999-2008	adults	10	3.55
Ludvigsson et al. 2013a	USA	Prospective survey of CD 2000-2010 in Olmsted County	0-85	10	17.4

Table 8. Derived incidence of coeliac disease (CD) in older population

Study, year	Country	Population based series	Time period years	Age group, years	Over all annual incidence /100 000 All or Female / Male
Murray et al. 2003	USA	Retrospective survey of CD cases 1950-2001 of Olmsted County	50	≥65	3.2
Fowell et al. 2006	UK	Prospective survey of CD 1993-2002 in Pope Hospital in East Dorset	10	60-74	16.8
Virta et al. 2009	Finland	CD patients from the database of the National Social Insurance Institution 2004-2006	3	55-64 65-74 ≥75	49 / 36 53 / 47 24 / 22
Godfrey et al. 2010	USA	Stored sera, CD patients 2001-2011 in Olmsted County	10	≥50	11.8
Angeli et al. 2012	Italy	Prospective survey of CD 2001-2011 in a Local Health Unit database in Terni	8	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. 2013a	USA	Prospective survey of CD 2000-2010 in Olmsted County	3	45-64 65-85	19.0 21.7

3. CLINICAL MANIFESTATIONS IN THE ELDERLY

3.1. Symptoms

The symptoms are not evident and the diagnostic delay may be long even in elderly people. Hankey and Holmes (1994) reported an average diagnostic delay of 28 years when CD was diagnosed at the age of 60 or over. In their series, 19 out of 42 subjects had classic symptoms and ten had non-specific symptoms such as lassitude. Mukherjee et al. reported that the duration of symptoms prior to diagnosis was similar in an elderly cohort ≥65 years of age and in young adults (18 to 30 years) (Mukherjee et al. 2010). The CD patients were diagnosed mostly because they had symptoms, only 13% of younger and 7% of elderly CD patients were screened; 3% of younger and 9% of elderly patients had incidental finding of CD, or had symptomless subclinical CD. Table 9 shows that the symptom profile in untreated CD in older subjects is by and large similar to that in younger subjects.

3.2. Autoimmune-associated conditions

There are no large studies on the occurrence of autoimmune conditions, especially in the elderly. In one study with clinically detected classic CD patients, the prevalence of autoimmune diseases was similar to that in younger adults (Mukherjee et al. 2010). Hypothyroidism may occur concomitantly with CD in the elderly, suggesting that the association between CD and autoimmune conditions does not differ from that in adults in general (Freeman 1995, Godfrey et al. 2010).

3.3. Bone mineral density and fractures

Adult CD patients have more osteoporosis or osteopenia and altogether lower BMD than reference population (Kemppainen et al. 1999, Mustalahti et al. 1999, Cellier et al. 2000, Meyer et al. 2001). The fracture risk was higher in CD patients (8.7%) than in control population (6.1%) according the meta-analysis by Olmos et al. (2008). West et al. (2003a) reported in their population based study that there was no increased fracture risk in patients with CD in general. Casella et al. (2012) noted that the BMD in the lumbosacral spine and femoral neck of elderly CD patients was lower, and that they had considerably more osteoporosis and osteopenia than did younger subjects (Table 9). Among patients with osteoporosis, the prevalence of CD was up to 3.4% (Stenson et al. 2005). Mukherjee et al. (Mukherjee et al. 2010) found no significant difference in the prevalence of bone disease comparing younger (18-30 years) and elderly (over 65 years of age) population with mostly classic or symptomatic CD.

3.4. Malabsorption

Gluten damages the mucous membrane of the small intestine in CD patients and malabsorption may occur. Anaemia due to iron deficiency is especially common in untreated CD patients (Harper et al. 2007). CD is one of the causes of malabsorption in the elderly (Montgomery et al. 1986). Several studies in adult population have showed that folic acid, vitamin B12 and D deficiency and low ferritin values are often seen at the time of diagnosis of CD, and these are alleviated or cured on GFD (Kemppainen et al. 1998, Dickey 2002, Katz et al. 2011). In a few studies on elderly CD patients, similar findings have been reported (Table 9) (Hankey et al. 1994, Meyer et al. 2001, Godfrey et al. 2010, Casella et al. 2012).

In general about 20% of women and 10% of men of 65 years of age are anaemic (Busti et al. 2014). Anaemia can cause several symptoms:

tiredness, weakness, breathless, dizziness, or even cognitive problems. The most common cause of anaemia is iron deficiency. Ferritin deficiency causes subclinical iron deficiency anaemia. Vitamin B12 deficiency may cause anaemia, but also neurological complications like polyneuropathy or even dementia (Hammond et al. 2013, Berrut et al. 2014). Folic acid deficiency can cause cognitive impairment in all ages, and miscarriage in young women (Reynolds 2014). Vitamin D deficiency is well known to cause osteoporosis or osteopenia, which in turn increase the risk of low energy fractures (Hill et al. 2013).

3.5. Malignancy and mortality

According a recent meta-analysis CD patients, including those screen-detected, were at an increased risk of non-Hodgkin's lymphoma (NHL) and all-cause mortality, but not of malignancy in general (Tio et al. 2012). The precise risk of malignancy or lymphoma in CD has been difficult to determine. According to Freeman, in adult CD patients with malignant biopsy findings in the proximal small intestine the overall lymphoma risk was 8-10% (Freeman 2009). With clinically milder forms the risk may be lower (Corrao et al. 2001, Catassi et al. 2005). The risk is associated particularly with EATL, and with poor compliance with GFD (Holmes et al. 1989, Howdle et al. 2003, Viljamaa et al. 2006). However, Olen et al. (2012) reported the opposite; poor compliance with GFD was not significantly associated with the risk of overall lymphoma or its subtypes. In some studies the screen-detected CD patients did not have an increased risk of malignancy or NHL (Corrao et al. 2001, Mearin et al. 2006, Lohi et al. 2009, Elli et al. 2012). Lymphoma in young patients was uncommon (Casella et al. 2012). In a more recent study by Ludvigsson et al. (2013a) the overall survival of CD patients with lymphoproliferative malignancy was the same as that of controls. In general several studies have confirmed the association between CD and B cell lymphoma and CD and small intestinal

adenocarcinoma (Moertel et al. 1961, Green et al. 2003, Card et al. 2004, West et al. 2004, Smedby et al. 2005, Olen et al. 2011)

In DH patients the risk of B and T cell lymphomas was increased, likewise in CD patients with poor compliance with GFD, but the general mortality was lower than the standardized expected mortality rate in Finland (Collin et al. 1996, Hervonen et al. 2005, Viljamaa et al. 2006).

In 2009 Freeman stated in a review that if CD is diagnosed initially in elderly subjects or late in the clinical course, the risk of developing lymphoma and other malignancies is greater than if CD is detected earlier (Freeman 2009). However, Godfrey et al. (2010) claimed that in patients over 50 years old there is no significantly increased risk of cancer or mortality in undiagnosed CD patients than in controls.

Table 9. Derived symptoms and signs of malabsorption in older patients with coeliac disease

Reference	n	Age, range, years	Symptoms n patients (%)	Malabsorption n patients (%)	Bone disease n patients (%)
Hankey and Holmes 1994 UK	42	> 60	19 classic GI symptoms 6 subtle GI symptoms	3 iron deficiency anaemia 4 folic acid deficiency anaemia 3 iron & folic acid deficiency anaemia	No data
Freeman et al. 1995 Canada	30	> 60	23 (77) classic GI symptom	20 (61) anaemia 12 (40) iron deficiency 11 (37) low vitamin B12 9 (30) low serum folic acid	No data
Ivarsson et al. 1999 Sweden	7	> 56	3 classic GI symptoms 3 subtle GI symptoms 1 no symptoms	2 cases of anaemia	No data
Gasbarrini et al. 2001 Italy	60	> 65	46 (77) classic GI symptoms 2 (3) no symptoms	35 (58) anaemia	15 (25)
West et al. 2003b UK	87	45-76	Not described	haemoglobin was lower than control group Mild anaemia	Increased risk of osteoporosis

classic symptoms: diarrhoea, weight loss, malabsorption, anaemia, dermatitis herpetiformis;
subtle symptoms: irritable bowel symptoms; GI, gastrointestinal

Table 9. Derived symptoms and signs of malabsorption in older patients with coeliac disease (continued)

Reference	n	Age, range, years	Symptoms n patients (%)	Malabsorption n patients (%)	Bone disease n patients (%)
Lurie et al. 2008 Israel	7	> 60	5 classic GI symptoms	5 iron deficiency 3 folic acid deficiency	2 osteoporosis
Catassi et al. 2007 USA	10	> 51	1 classic symptoms 6 subtle symptoms 3 no symptoms	2 iron deficiency	No data
Godfrey et al. 2010 USA	127 20*	> 50	27 (21) classic symptoms 3 (15) classic symptoms* * subgroup of 127	23 (18) anaemia 9 (45) iron deficiency*	Average T-score -1.7
Casella et al. 2012 Italy	59	≥ 65	49 (83) symptoms (not specified) 2 (3) no symptoms (incidental)	24 (41) anaemia	Osteoporosis: 10 (67) males 30 (70) females Osteopenia: 0 males 14 (32) females T –score lumbar-sacral spine -3.00 T –score femoral neck -2.39

classic symptoms: diarrhoea, weight loss, malabsorption, anaemia, dermatitis herpetiformis;
subtle symptoms: irritable bowel symptoms, GI, gastrointestinal

4. DIETARY COMPLIANCE AND QUALITY OF LIFE

4.1. Compliance with gluten-free diet

A strict lifelong GFD is the only treatment for coeliac disease. The symptoms diminish on GFD in both clinically detected and screened patients. Compliance varied across areas and countries (Table 10). It is good in Finland, even in asymptomatic patients, whereas in some countries dietary transgressions are common (Viljamaa et al. 2005a). In the recent study by Kurppa et al. (2012) adherence to GFD in patients over 65 years of age was good (91%) and there was no difference between children and adults; only teenagers were likely to be non-adherent. In the systematic review by Hall et al. (2009) the rates of strict adherence ranged from 42% to 91%. Adherence was associated with cognitive, emotional and socio-cultural influences, likewise membership of an advocacy and regular dietetic follow-up.

In a few patients GFD does not relieve symptoms and heal the small bowel mucosa. These non-responsive patients have refractory sprue, which may have several different causes, but the most common is incomplete GFD (Mooney et al. 2012). After carefully excluding all other causes, non-responsive CD patients are considered to be RCD patients (Abdulkarim et al. 2002, Ludvigsson et al. 2014a).

Table 10. Compliance with gluten-free diet (GFD) among adults

Author, year		Country	n	GFD duration, years	Compliance to GFD %		
					good	fair	poor
Hallert et al.	1998	Sweden	89	10	78	12	10
Lohiniemi et al.	2000	Finland	58	10	94	6	
Kaukinen et al.	2002	Finland	87	1	87	13	
Usai et al.	2002	Italy	68	>2	59	38	3
Ciacci et al.	2003	Italy	581	8	74	22	4
Fera et al.	2003	Italy	100	9	49	48	3
Högberg et al.	2003	Sweden	29	20	59	41	
Hervonen et al.	2005	Finland	1104	32	88-94		
Viljamaa et al.	2005a	Finland	97	14	93-96		
Hopman et al.	2009	Netherlands	53	>10	62	15	23
Whitaker et al.	2009	UK	147	>1	67	32	5
Barratt et al.	2011	UK	255	>0.5	65	31	4
Norström et al.	2012	Sweden	1025	1	96		4

4.2. Quality of life

QoL is an all-encompassing perception of health and well-being, influenced by and impacting on all aspects of our lives. The domains of QoL include social, religious, emotional, economic and physical well-being (Spilker 2009).

Several methods have been applied to measure QoL in CD; most of these are general (Table 11). The Gastrointestinal Symptom Rating Scale (GSRS) has been widely used. The Psychological General Well-Being (PGWB) evaluates QoL in general and the Short Form Health Survey 36 (SF-36) a person's functional status and well-being.

Disease-specific self-administered questionnaires for CD are less common. In Sweden Hallert et al. (2002) used the Burden of Illness (BI) protocol with more emphasis on non-cost aspects of CD; social functioning, emotional distress, attitudes and expectations. They noted that good compliance with GFD was important for both men and women. Perceived burden of disease, after being on GFD for a mean ten years, was similar to that in the control group. However middle-aged women with CD expressed less satisfaction with the outcome of the GFD treatment than men. In the USA Lee et al. (2012) used a self-administered survey including the Short Form Health Survey 12 (SF-12), and noted that the negative impact of GFD decreased over time, but CD patients had less positive health perceptions than the control population. The disease-specific questions revealed a negative impact on QoL in social settings (Lee et al. 2012).

In the Finnish adult CD population QoL on GFD did not differ from that in the control group, as shown in several studies (Lohiniemi et al. 2000, Mustalahti et al. 2002b, Viljamaa et al. 2005a, Kurppa et al. 2010). However, Ukkola et al. (2011) observed that even though GFD improved self-perceived health and alleviated anxiety in both symptom and screen-detected CD patients, in the asymptomatic patients perception of health deteriorated and concerns about health increased on GFD. The effect of GFD in QoL in adults is summarized in Table 12.

There are so far no QoL studies focusing specifically on elderly people with CD. In the UK, however, Hankey and Holmes (1994) observed that 90% (38 out of 42) of elderly people maintained a strict GFD and that the diet considerably improved their well-being.

Table 11. Different methods used to study Quality of Life (QoL) in coeliac disease (CD)

Abbreviation	Name of survey	Questions	Subscore	Evaluation target
GSRS	Gastrointestinal Symptom Rating Scale	15 questions 7 point Likert scale	indigestion diarrhoea constipation abdominal pain reflux	Common gastrointestinal symptoms Validated
PGWB	Psychological General Well-Being	22 questions 6 point Likert scale	anxiety positive wellbeing self-control depression general health vitality	Emotional states reflecting a sense of subjective wellbeing Validated
SF-36	36 –Item Short Form Health Survey	36 questions Likert scale	vitality physical functioning bodily pain general health perceptions physical role functioning emotional role functioning social role functioning mental health	Generic measure of functional status and wellbeing Validated
SF-12	12-item Short Form Health Survey	12 questions Likert scale	As in SF-36	Derived from SF-36 Validated
CD specific QoL	CD specific quality of life plot study	19 additional CD specific questions	travel family life health perception social activities dining out dietary compliance	Diet compliance Impact of dietary compliance to social implications Self-administered disease specific
BI	Burden of Illness protocol	9 questions 6 point Likert scale	As in SF-36	Access relevant non-cost aspects of perceived burden of illness On clinical experience based self-administered disease specific

Table 12. Quality of Life (QoL) in treated adult coeliac disease (CD) patients compared to non-coeliac controls

Authors, year, country	Treated CD patients, n	Non-coeliac controls, n	Method	Outcome
Hallert et al. 1998 Sweden	89	5277	SF-36	Worse
Lohiniemi et al. 2000 Finland	58	110	PGWB GSRS	No difference No difference
Usai et al. 2002 Italy	68	136	SF-36	Worse
Hallert et al. 2002 Sweden	68	68	Burden of illness protocol	No difference in total score Worse in general heath, vitality, social functioning
Mustalahti et al. 2002a Finland	40	105	PGWB GSRS	Improved Improved
Midhagen and Hallert 2003 Sweden	51	182	GSRS	Worse in females No difference in males
Viljamaa et al. 2005a Finland	97	110	PGWB GSRS SF-36	No difference No difference No difference
Hopman et al. 2009 Netherlands	53	1742	SF-36 GSRS	No difference No difference
Kurppa et al. 2010 Finland	46	110	PGWB	No difference
Barratt et al. 2011 UK	225	348	SF-36	Worse
Lee et al. 2012 USA	1743	1179	SF-12 + CD-specific QoL plot study	No difference Negative impact on social domain

THE PRESENT STUDY

1. AIMS OF THE STUDY

The aims of the present study were to evaluate the prevalence of CD in individuals over 50 years of age, and to assess whether active serological screening and subsequent placement on GFD would be justified.

The specific aims were to evaluate

1. The prevalence and incidence of CD
2. The clinical characteristics of CD
3. The effect of the introduction of GFD on health and well-being

2. STUDY SUBJECTS AND DESIGN

2.1. Study subjects

The original study population consisted of 4,272 randomly selected individuals born in the years 1946-1950, 1936-1940 and 1926-1930. Half of them were male and half female; all were living in the catchment area of Päijät-Häme hospital district in Finland. The study series were randomly selected at The Finnish National Institute for Health and Welfare, and were representative of general population in the respective age groups. The data was collected for a 10-year follow-up research project entitled GOAL and intended to improve health and well-being in the ageing population.

The patient recruitment for the GOAL study took place in 2002, when 2,815 individuals agreed to participate in the study. The second call to attend the GOAL study was in 2005, when 3,996 individuals were invited and 2,415 consented, 199 of who were new subjects. In total 2,216 individuals responded to both the 2002 and 2005 calls (GOAL 2012).

The first serum sampling took place in 2002. The serologic testing for CD and the survey of confirmed CD from the GOAL population took place in 2004. The patients with IgA class tTGA > 5 units (U) were further tested for IgA class EMA. tTGA positive patients and those whose CD was clinically diagnosed before the GOAL study attended a personal interview. The diagnoses of clinically detected coeliac patients were verified from the histological biopsy information in their case records. tTGA positive patients were invited to GI endoscopy including small bowel biopsy, which took place in 2004-2005

All screen-detected patients were placed on GFD, and were subject to further follow-up. In 2006, small bowel histology upon endoscopy was repeated after maintaining GFD. Laboratory studies to detect malabsorption, BMD measurements for detecting osteopenia or osteoporosis and QoL studies were conducted before and after commencing GFD.

The second serum sampling of the GOAL study population took place in 2005, in other words three years after the first one. There were individuals in the GOAL study who did not participate in 2002, but who did in 2005 (new participants presented in Figure 2). All the sera were again tested for tTGA. tTGA positive patients were tested for EMA, and all tTGA positive subjects were invited to small intestine endoscopy to confirm CD histologically. Clinical CD cases detected 2002-2005 were scrutinized.

The study design is illustrated in Figures 1 and 2 on pages 57-58. All the study tests and measurements are listed by subgroup and the year of implementation in Table 13.

2.2. Control subjects

The control group of 110 subjects for the GI symptom rating and QoL tests (GSRS and PGWB) was collected from Finnish general population. The controls were neighbours of coeliac members of the Finnish Coeliac Society. Society members were asked to select an individual living in their neighbourhood and not suffering from CD. These neighbours formed the controls, who were matched for age and gender with the study subjects. CD was not systematically excluded in the controls, but they did not report such symptoms and had no relatives with CD.

The reference group for bone fractures and body mass index (BMI) consisted of participants of the GOAL study who were not tTGA or EMA positive and had no treated CD, and were on normal gluten-containing diet.

3. METHODS

3.1. Definitions

In this study clinically detected CD refers to patients whose CD was diagnosed before the start of the GOAL study in 2002 or between the years 2002 and 2004 and not by screening; most of them had classic or symptomatic CD, a few had non-classic CD. Screen-detected CD patients were diagnosed after screening with tTGA and EMA in 2004 or in 2006. Most of them had subclinical CD (Table 16). Biopsy-proven CD patients were either clinically detected or screen-detected with definite CD findings in their small intestine biopsies. These patients are included in the documented biopsy-proven prevalence. The follow-up group consisted of the screen-detected CD patients (n=35), who were followed up for three years after the diagnosis of CD. Those who declined endoscopy, but were tTGA positive, are called tTGA positive and were included in seroprevalence.

The GOAL study population is the participants of GOAL study (n=2,815 in 2002 and n=2,415 in 2005).

3.2. Serologic tests for coeliac disease

The analysis of IgA class tTGA was carried out by enzyme-linked immunosorbent assay according to manufacturer's instructions (Celikey, Phadia, Freiburg, Germany) and values above the limit of five arbitrary units (U) were considered elevated. The positive sera were further analysed for IgA class EMA; detected by an indirect immunofluorescence using human umbilical cord as antigen; a dilution of 1:≥5 was considered positive (Sulkanen et al. 1998a, Maki et al. 2003).

3.3. Small bowel biopsy and diagnostic criteria for coeliac disease

The small bowel mucosal biopsy was taken from the distal part of the duodenum upon upper GI endoscopy. Three samples were paraffin embedded, processed, stained with haematoxylin-eosin and studied under light microscopy for signs of CD. The modified Marsh classification was used to evaluate the degree of villus damage: Marsh 0 indicates normal small intestine mucosa, Marsh 1 indicates normal villous architecture with increased (IELs≥25/100 enterocytes) intra-epithelial lymphocytes (IELs), Marsh 2 includes increased IELs with findings of crypt hypertrophy, Marsh 3a partial villous atrophy, Marsh 3b subtotal, and Marsh 3c total villous atrophy (Table 2) (Oberhuber et al. 1999). In this study March 0 and 1 were considered normal findings.

The villous height/crypt depth ratio (Vh/CrD) was calculated from well-orientated specimens. A ratio < 2 was considered abnormal and indicative of active CD. The density of IELs was counted from randomly selected surface epithelium and expressed as IELs per 100 epithelial cells (Kuitunen et al. 1982).

The criteria for CD, established at the United European Gastroenterology Week in Amsterdam in 2001 were applied (United European 2001) since this study was conducted before the publication of the renewed guidelines from the British Society of Gastroenterology. The diagnosis of DH was based on typical rash and a finding of granular IgA deposits in the uninvolved skin (van der Meer 1969, Reunala 1998, Reunala et al. 1998).

Small intestine biopsy on screened tTGA positive patients was performed in 2004-2005 in Päijät-Häme Central Hospital. The control biopsy took place ether in Päijät-Häme Central Hospital (most of the patients) or at the other local hospital in Päijät-Häme in 2006. After the second screening the seroconversion patients were invited to small intestine biopsy to Päijät-Häme Central Hospital in 2007-2008 (Table 13).

3.4. Coeliac genetics

The tTGA positive patients were analysed for HLA according to manufacturer's instructions (Celikey; Phadia, Freiburg, Germany) (Ota et al. 1991). They were genotyped for HLA-DQB1*02 and DQB1*0302 and DQA1*05 alleles using the

DELFIA Coeliac Disease Hybridization Assay (Perin-Elmer Life and Analytic Sciences, Wallac Oy, Turku, Finland) according to the manufacturer's instructions. HLA-DQB1*02 and DQA1*05 corresponded to associated alleles for HLA DQ2 and DQB1*0302 for HLA DQ8.

3.5. The interview

A personal interview with a self-administered questionnaire was conducted to collect information on GI and other symptoms related to CD, family history of CD, autoimmune and other diseases, malignant diseases, bone fractures, dietary habits and medication. The symptoms were classified into three groups: classic symptoms (diarrhoea, weight loss, anaemia, malabsorption, DH), subtle symptoms (abdominal pain, distended abdomen, occasional diarrhoea or loose stools, flatulence, fatigue, blisters in mouth) and no obvious symptoms (asymptomatic).

For subjects who consented to participate in the study, but did not want to be interviewed, the information was collected from the patient history as accurately as possible. At follow-up, adherence to GFD, symptoms and medication were elicited (Table 13).

The number of low-energy fractures and BMI in the GOAL study population was extracted from the GOAL study questionnaires (n= 2,815).

3.6. Gastrointestinal symptoms and quality of life

The Finnish translation of the GSRS was used to evaluate abdominal complaints. The total score is derived from five GI symptoms: diarrhoea, indigestion, constipation, abdominal pain and gastro-oesophageal reflux; applying a Likert scale where higher score indicates more severe symptoms (Svedlund et al. 1988, Mustalahti et al. 2002a). One question on the Likert scale ranges integers from 0 (no symptoms) to 6 (most symptoms).

The non-validated Finnish translation of the PGWB questionnaire was used to evaluate QoL. This is a 22-item questionnaire measuring components of psychological well-being; anxiety, positive wellbeing, self-control, depression, and general health and vitality (Dupuy 1984, Mustalahti et al. 2002a). On this Likert

scale a higher score indicates better QoL. One question on the Likert scale ranges integers from 0 (most negative option) to 5 (most positive option).

The patients completed the GSRS and PGWB questionnaires for the first time in 2005, at the time of the small bowel biopsy. The second time the questionnaires were posted to them in 2007 and they returned them by mail (Table 13).

3.7. Assessment of nutritional condition

BMI was computed as weight/height^2 (kg/m^2). The baseline height and weight were derived from the GOAL study-questionnaires in 2005, when the patients were on gluten-containing diet. The second BMI was derived from the BMD measurement form in 2007 when the study patients had been on GFD for about two years.

BMI was categorized according to the WHO criteria: values below 18.5 kg/m^2 being underweight, from 18.5 to 24.9 kg/m^2 normal weight, from 25.0 to 29.9 kg/m^2 overweight, from 30.0 to 39.9 kg/m^2 obese and over 40.0 kg/m^2 morbidly obese.

Blood haemoglobin (Hb, reference values: male 13.4-16.7 g/dl, female 11.7-15.5 g/dl; EDTA blood sample, automated cell-counting), erythrocyte folic acid levels (folic acid, 180-845 nmol/l; to specific binding proteins based chemi-luminometric method, fist determine B-folate, which is applied to calculate E-folate using the haematocrit), serum iron (Fe, 10.34 umol/l; photometric method), serum ferritin (male 20-275 ug/l, female 7-205 ug/l; immuno-chemi-luminometric method), serum ionized calcium (Ca^{2+}, 1.15-1.30 mmol/l; ion specific electrode, automated measurement), plasma phosphorous (Pi, 0.71-1.53 mmol/l; photometric method) and serum vitamin A (1.0-3.0 umol/l; liquid-chromatographic method, HPLC)), B12 (150-740 pmol/l; immuno-chemi-luminometric method, LOCI), D25 (22-103 nmol/l; immuno-chemi-luminometric method, measures both ergocalciferol and cholecalciferol content) and E (12-48 umol/l; HPLC method) concentrations were measured by routine laboratory methods in Päijät-Häme Central Hospital, Lahti, Finland. The laboratory measurements were done twice; in 2004-2005 and in 2006-2007, for the screen-detected follow-up group (Table 13).

3.8. Bone mineral density

BMD was measured by dual-energy X-ray absorptiometry (GE Medical Systems, LUNAR, UK) in spine (L1 to L4) and right femoral neck; values were expressed as standard deviation (SD) scores. T-score compares individual values to the mean BMD of sex-matched young adults and Z-score SD to age and sex-matched population. T-score above -1.0 SD indicates normal BMD, score -1.0 SD to -2.4 SD osteopenia and score equal or below -2.5 SD osteoporosis.

3.9. Ethical considerations

The study was approved by the Ethics Committee of Päijät-Häme Central Hospital and written consent was obtained from all patients. The research was in compliance with the World Medical Association Declaration of Helsinki (WMA 2004).

3.10. Statistical analysis

The prevalence of CD was calculated by dividing the number of CD patients by the number of study participants and multiplying the quotient by 100%. The number of all new CD patients (the seroconverted patients) in the study between 2005 and 2008 was divided by the number of patients who participated in both the 2002 and 2005 surveys and the quotient further divided by the years between the surveys gave the annual incidence. Then the quotient was multiplied by 100% or given as x/100 000. The data were given as means with 95% confidence intervals (CI) or medians with lower and upper quartiles and range when appropriate. Chi-square or Fisher's test were used in cross-tabulations and Wilcoxon signed or paired rank tests to compare changes within the study group. A p value < 0.05 was considered statistically significant. It was also estimated that differences of >0.5 in the Vh/CrD and of 0.5 in GSRS were clinically significant (Svedlund et al. 1988, Kaukinen et al. 2005, Kaukinen et al. 2008).

Table 13. Study tests and measurements by subgroup and year of implementation

Clinically detected coeliac disease (CD) patients n= 26	year	year
Serum sampling	2002	2005
tTGA measurement	2004	2006
Personal interview, patient history retrieval, clinical examination	2004	
Screen-detected CD patients - The follow-up group n = 35		
Serum sampling	2002	2005
tTGA measurement	2004	2006
EMA measurement	2004	2006
Small intestinal biopsy	2004-05	2006
Personal interview, patient history retrieval	2005	2007
Clinical examination	2005	
GSRS	2005	2007
PGWB	2005	2007
Bone mass density (BMD)	2004-05	2007
Body mass index (BMI)	2002	2007
Human leukocyte antigen (HLA)	2004	
Laboratory measurements	2004-05	2006-07
Hb, Fe, Ferritin, Pi, Ca^{2+}, folic acid, vitamin B12, D25, A and E		
Screen-detected seroconversion CD patients n = 6		
Serum sampling	2002	2005
tTGA measurement	2004	2006
EMA measurement		2006
Patient history retrieval		2007-08
Small intestinal biopsy		2007-08
HLA		2007-08
Screen-detected CD patients who participated GOAL only in 2005 – new patients n=5		
Serum sampling		2005
tTGA		2006
EMA		2006
Patient history retrieval		2007-08
Small intestinal biopsy		2007-08
HLA		2007-08

4. RESULTS

4.1. Prevalence and incidence of coeliac disease (I,II)

Altogether 2,518 (66%) out of 4,272 individuals invited consented to participate in the GOAL study in 2002, 52% of them female. CD was clinically detected in 25 before 2002 or between 2002 and 2004. One subject with clinically detected CD did not consent to participate in this study in 2002, but did so in 2005, raising the number to 26. All 26 fulfilled the criteria for CD (Figure 1). Three GOAL participants had reported that they were on GFD because it had cured their symptoms: one had blistering eczema, but the skin biopsy was negative for CD and two had GI symptoms but the small intestinal biopsy was normal. Perhaps they were gluten-intolerant or their biopsies were poorly done, however they no longer wished to return to a gluten-containing diet.

Serological screening in 2004 found 49 tTGA positive subjects, who were further analysed for EMA, which was positive in 44. Five out of these 49 had earlier diagnosis of CD: one was unable to adhere to GFD even though her CD diagnosis was made fifteen years earlier and four were diagnosed between 2002 and 2004. Five did not agree to endoscopy. Of the 39 who consented to endoscopy, 35 had biopsy-proven CD, four had normal small bowel mucosa: three with Marsh classification 0 and one with 1. Of these four, two were positive for tTGA and EMA, two for tTGA only, three had HLA DQ2 and one did not have CD type HLA. Of the five who declined endoscopy, three were positive for tTGA and EMA, two for tTGA only.

In 2005, 3,996 individuals were invited to the first follow-up of the GOAL study, and 2,415 consented. These included 2,216 individuals who participated in both the 2002 and 2005 studies and were retested for coeliac serology; 199 were tested for the first time (Figure 2). Of the 199 new participants five were positive for tTGA and four also for EMA. Three agreed to biopsy and all had atrophy (two Marsh 3a and one Marsh 3c) and HLA DQ2 genotype. One patient declined due to her severe heart condition and one had moved away from the hospital district.

Figure 1. The flow chart of the study in 2002-2005

Good Ageing in Lahti region (GOAL) Coeliac disease (CD)

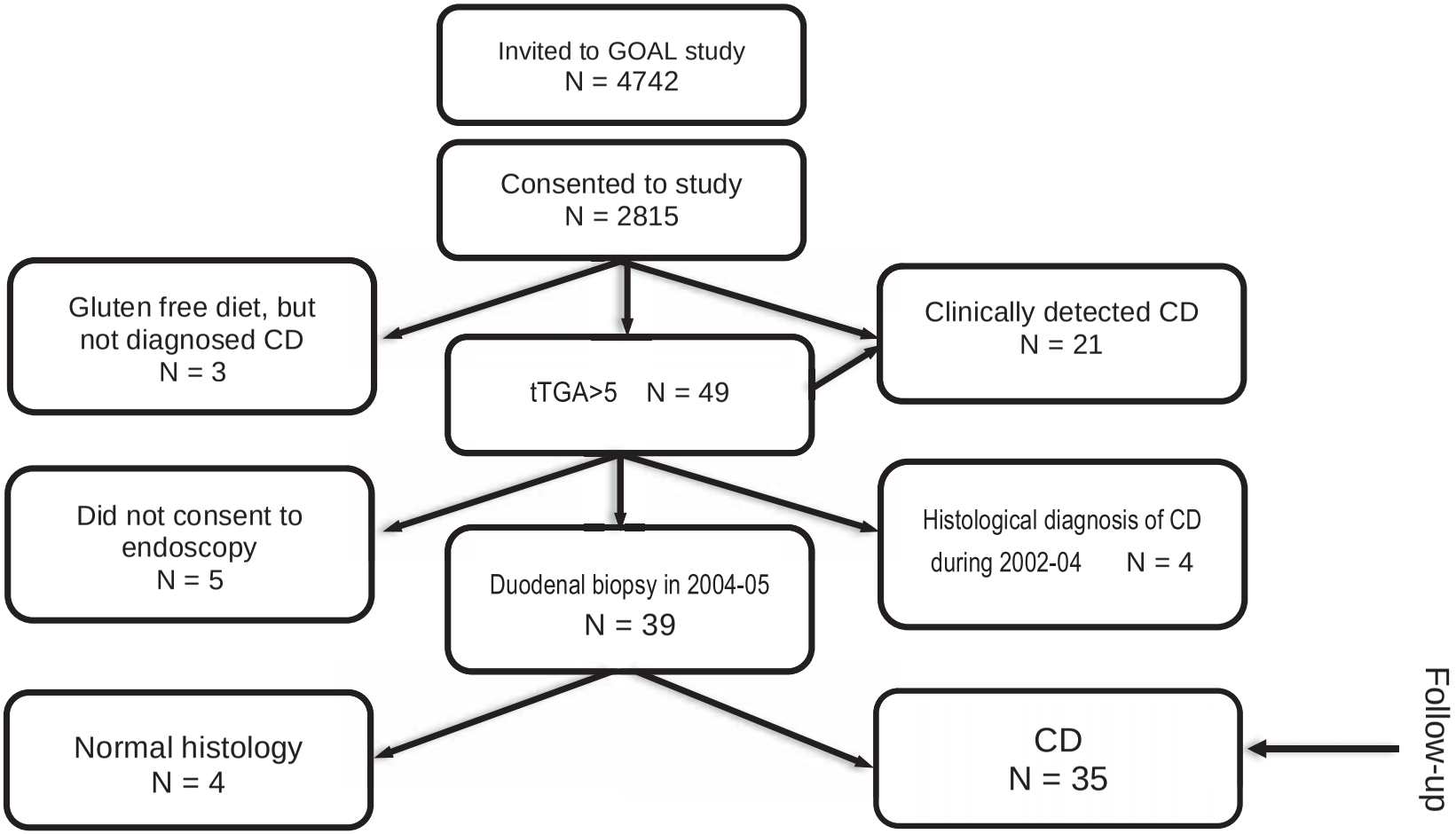
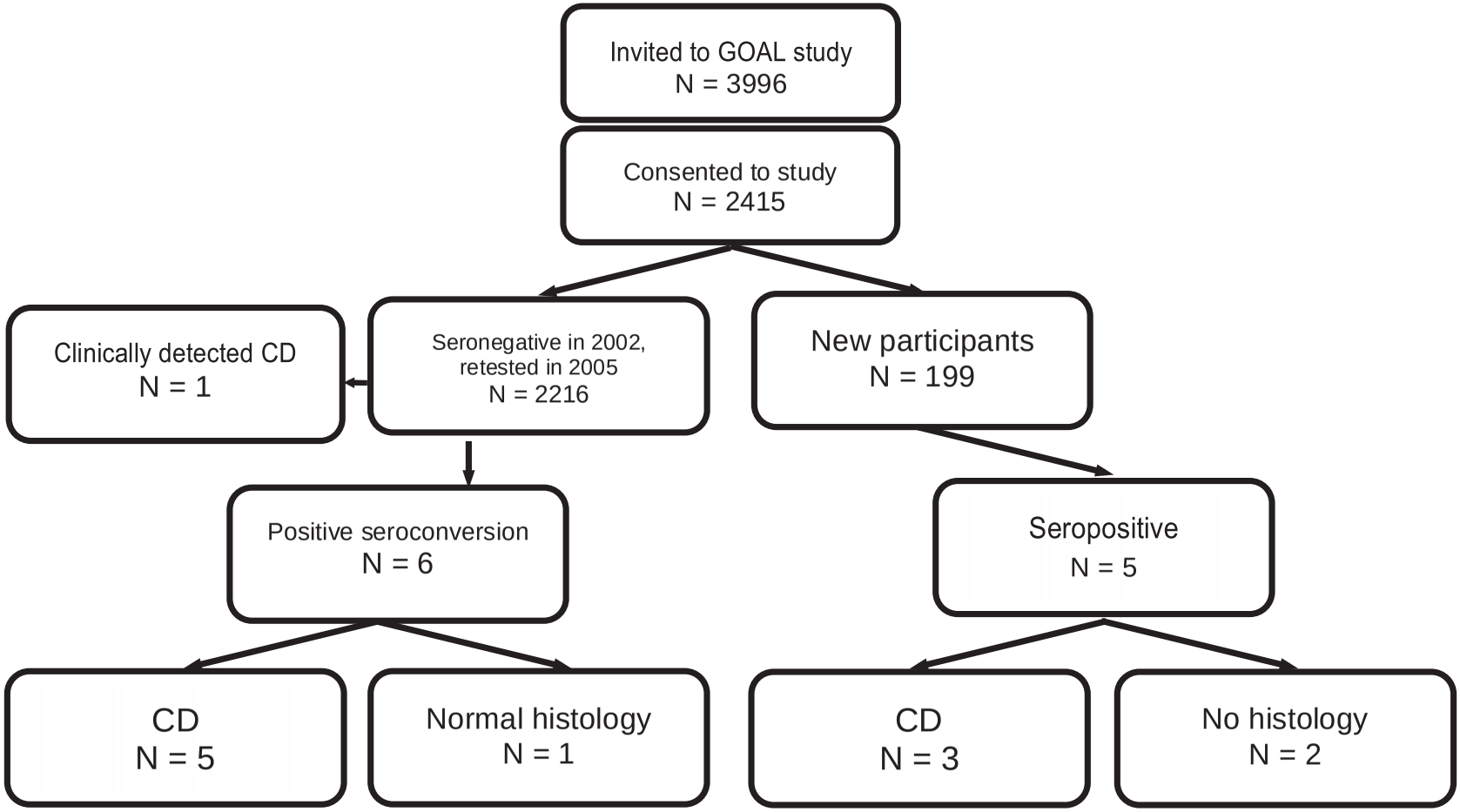


Figure 2. The flow chart of the study in 2005-2008
Good Ageing in Lahti region (GOAL)
Coeliac disease (CD)



The seroconversion for tTGA had occurred in six out of the 2,216 initially seronegative subjects (Figure 2); four were positive and two negative for EMA. All six agreed to endoscopy and biopsy. One had Marsh 2, two Marsh 3a and two Marsh 3c small bowel mucosal atrophy. Four had HLA DQ2. One did not have DQ2 or DQ8, but he had typical crypt hyperplasia and villous atrophy (See Article II Figure 2 in appendix). The one whose small bowel biopsy was normal did not have coeliac type HLA and was EMA negative (Table 15).

The prevalences of CD are shown in Table 14. At the first evaluation all coeliac patients were alive in 2005 and thus included in the new prevalence data. The detection of five new cases among the 2,216 originally seronegative subjects gave an annual incidence of CD of 75:100 000 (Figure 2).

Table 14. Total prevalence of coeliac disease and seropositivity for IgA-class tissue transglutaminase antibody (tTGA) in patients over 50 years

	Biopsy-proven	Biopsy-proven + tTGA positive
Number of patients	66[a]	76[b]
Overall prevalence	2.34%	2.70%
95% confidence intervals	1.78-2.90%	2.10-3.30%

[a] all clinically detected CD (25+1) and screen-detected CD (35+5), see Figures 1 and 2 (no new participants)
[b] point [a] and all tTGA seropositive (9+1), see Figure 1 and 2 (no new participants)

4.2. Characteristics of coeliac disease patients (I, II, III)

4.2.1. Clinically detected patients

The 26 patients whose CD had been clinically detected by classic or non-classic symptoms were at the time of their diagnosis 53 years of age on average (range 36-77 years, 50% women). Six of those 26 patients had DH and their diagnosis was made on average at the age of 42 years (range 36-67). All DH patients had had a skin biopsy taken according to the method at the time of diagnosis, and none of

them had had endoscopy at that time. Nevertheless they all had abdominal symptoms at the same time as papulovesicular rash.

Symptoms at the time of diagnosis were classic in 18 patients, seven had subtle non-classic and one patient did not want to participate in the interview (Table 16). Five had a relative with CD.

Adherence to GFD was good; 19 out of 26 kept strictly to GFD, four reported occasional lapses. The information was not available on three: one had terminal EATL and two did not want to participate.

At the time of the interview the mean BMI of the clinically detected CD patients maintaining GFD for several years was 25; none were underweight, 12 patients had normal BMI and 11 were overweight; the data were missing for three.

Four CD patients had died 2006 – 2007, at the age of 70 - 80 years. Two died of small bowel lymphoma (EATL) and the cause of death remained unknown in two. Of the patients with lymphoma, one had been diagnosed with DH 30 years earlier, and the other with CD two years ago (Table 17).

4.2.2. Screen-detected patients – baseline findings

All 35 CD patients detected at the first screening had CD type villous atrophy and crypt hyperplasia: five had Marsh 3a, seven Marsh 3b and 23 Marsh 3c. Twenty-seven had HLA DQ2, three HLA DQ8, and five had both. At the time of the diagnosis 20 had no symptoms, 14 reported subtle symptoms like abdominal pain, distension, flatulence, occasional diarrhoea, loose stools, fatigue or blisters in the mouth; one had suffered from diarrhoea for more than 20 years (Table 16). Ten (29%) out of the 35 had a family member with CD.

At the time of diagnosis, 20 (57%) patients were found to have signs of malabsorption. None were underweight at the time of diagnosis, 12 patients had normal weight, and 17 were overweight and six obese.

The total baseline scores of GSRS and PGWB did not differ from those of the non-coeliac controls (Figure 3 and 4). In GSRS, none of the subscores differed significantly from those of the non-coeliac controls (Figure 3); in PGWB general heath was significantly poorer than in non-coeliac controls (Figure 4.).

4.2.3. Seroconversion and new participants

Six subjects had undergone seroconversion in 2006, and five were subsequently found to have CD. Two of them suffered from subtle abdominal symptoms and three had no symptoms (Table 15). One had a family member with CD.
Of the 199 new participants in the GOAL study, five (2.5%) were seropositive. One had only subtle symptoms, and had a family member with CD. The other two were symptom-free and had no family history of CD. One had a CD-related autoimmune condition, pernicious anaemia (Table 17). For two the data was not available..

Table 15. Antibody levels, human leukocyte antigen (HLA), histological Marsh classification and symptoms in seroconversion patients and one non-coeliac patient (No 6)

Gender, age (years) in 2005	Serum sampling I in 2002[a]	Serum sampling II in 2005				
	tTGA Units	tTGA Units	EMA Titre	HLA DQ2/DQ8	Marsh	Symptoms
1. Male 67	0.1	54.6	500	DQ2	3c	None
2. Female, 55	1.1	9.1	200	DQ2	3a	None
3. Male, 65	0.8	9.5	100	DQ2	3a	Subtle
4. Female, 75	2.7	6	5	DQ2	2	None
5. Male, 66	0	7.1	<5		3c	Subtle
6. Male, 75	2.2	8.7	<5	no	0	None

[a] Endomysial antibodies (EMA) not indicated in sample I
tTGA, IgA-class tissue transglutaminase antibody

4.2.4. Associated conditions and bone disease

Concomitant diseases, osteoporosis or osteopenia and patient's history of fractures are summarized for all patients in Table 17. Screen-detected CD patients seemed to have more autoimmune disorders than clinically detected patients but the number of fractures did not differ between the groups.

In this CD study population 13 (19%) patients had had low-energy fractures, whereas the GOAL study subjects reported 123 (4%) fractures.

Table 16. Symptoms of patients with clinically and screen-detected biopsy-proven coeliac disease at the time of diagnosis

	Clinically detected n = 26	All screen-detected[b] n = 43	All patients n = 69
Classic symptoms[a]	18 (69%)	1 (2%)	19 (28%)
Diarrhoea	15	1	16
Weight loss	10	1	11
Anaemia or malabsorption	10	1	11
Dermatitis herpetiformis	6		6
Subtle non-classic symptoms[a]	7 (27 %)	17 (39%)	24 (35%)
Abdominal pain, distension, flatulence	7	17	25
Occasional diarrhoea or loose stools	6	10	16
Fatigue	3	3	6
Blisters in mouth		2	2
No symptoms		25 (58%)	25 (36%)
Data missing	1 (4%)		1 (2%)

[a] One subject could have more than one symptom
[b] Includes the seroconversion patients

Table 17. Associated conditions, malignant and bone diseases in patients with clinically and screen-detected biopsy-proven coeliac disease at the time of diagnosis

	Clinically detected n = 26	Screen-detected in 2004 n = 35	Screen-detected in 2006 n = 8	All patients n = 69
Malignant disease[a]	3	2		5 (8%)
Lymphoma	2[†]			2
Stomach Carcinoma	1	1		2
Ovarian cancer		1		1
Autoimmune conditions[a]	3	10	1	14 (20%)
Autoimmune thyroid disease	1	7		8
Sjögren's syndrome	1			1
Pernicious anaemia	1	1	1	3
Type I diabetes mellitus		1		1
Psoriasis		3		3
Bone diseases and conditions[a]	5	22		27 (39%)
Low-energy fractures	5	8		13
Osteoporosis		8		8
Osteopenia		14		14

[a] One subject could have more than one condition or disease
[†] Died of enteropathy- associated T cell lymphoma (EATL)

4.3. Effect of gluten-free diet (I, III)

4.3.1. Follow-up of screen-detected patients on gluten-free diet

Thirty-two (91%) of the 35 screen-detected CD patients consented to GFD. In 27 the adherence to the diet was strict, and five had only occasional lapses. Three patients did not start the diet during the follow-up time.

A follow-up small bowel biopsy was taken after 1.2 years on GFD on average. In 26 out of 32 CD patients the villous height crypt depth ratio increased and the densities of IELs decreased (III Figure 1). In one patient the control biopsy was taken after 1.7 years on strict GFD, and there was still a total atrophy although tTGA and EMA were normalized. He did not report any symptoms, but had osteoporosis and folic acid deficiency; 2.6 years after the diagnosis the small bowel mucosa had recovered, osteoporosis had alleviated to osteopenia level, and the folic acid level was normal. Five patients out of the 32 did not consent to follow-up endoscopy; in four the tTGA and EMA levels normalized and one did not consent to follow-up tTGA. I.e. tTGA normalized in 29 and EMA in 25 of the 32 patients; EMA was not tested in four. In two neither tTGA nor EMA was followed up, but in one the small bowel biopsy normalized even though he had occasional lapses on his GFD; in the other one biopsy showed mid atrophy after one year with strict GFD but biopsy was clearly better than at the time of diagnosis.

GI and CD associated symptoms disappeared in 14 out of the 15 patients who had reported some, mostly subtle symptoms, including the one who had suffered from diarrhoea for more than 20 years. One with initially subtle abdominal symptoms developed diarrhoea while on a strict diet, but her small bowel mucosa was normal in control biopsy. The reason for diarrhoea remained obscure as colonoscopy showed no abnormal findings or inflammation.

The alleviation of symptoms could also be verified by GSRS, where the total score and subscores (except constipation) were statistically significantly lower when the patients had been on GFD for about two years (Figure 3). QoL measured by PGWB did not change during the two years, although the well-being score improved significantly (Figure 4).

The mean serum ferritin increased significantly on GFD, and there was also improvement in many laboratory values (Table 19). Vitamin and bisphosphonate

substitution were started when considered necessary. After analysing separately patients not receiving any additional medical, iron or vitamin, substitution the beneficial effect was still significant in serum iron (12 patients excluded from analysis), serum ferritin (12 patients excluded), vitamin B12 (14 patients excluded) and vitamin D (21 patients excluded).

The mean femoral Z-score increased significantly on GFD; the increase in the lumbar spine Z-score did not reach statistical significance. In the patients with osteoporosis or osteopenia T-score improved significantly both in femoral neck and lumbar spine (Table 18). Three patients were treated with bisphosphonates; the increase remained significant in lumbar spine T-score after they were excluded from the analysis (p=0.021). The mean BMI before the diet was 26 kg/m^2 and on the diet 25 kg/m^2. By comparison, the mean BMI in the GOAL study subjects, 28 kg/m^2, did not change in three years (2005 to 2008).

Table 18. Effect of gluten-free diet (GFD) on bone mineral density

	At diagnosis		After two years of GFD		p-value
	mean	95% CI	mean	95% CI	
All (n= 32)					
Lumbar spine Z-score	0.6	0.0 – 1.1	0.9	0.1 – 1.5	0.060
Femoral neck Z-score	-0.1	-0.5 – 0.2	0.1	-0.2 – 0.6	0.009
Lumbar spine T-score	-0.7	-1.2 – -0.1	-0.4	-1.2 – 0.1	0.241
Femoral neck T-score	-1.1	-1.5 – -0.6	-1.1	-1.5 – -0.5	0.670
Patients with osteoporosis or osteopenia (n=22)					
Lumbar spine T-score	-2.0	-2.3 – -1.7	-1.7	-2.1 – -1.3	0.030
Femoral neck T-score	-2.2	-2.5 – -1.9	-2.1	-2.4 – -1.8	0.020

CI, confidence interval

4.3.2. Follow-up of screen-detected patients on regular diet

Three patients did not start GFD, but consented to small bowel endoscopy and biopsy one year after the diagnosis of CD. Two had still Marsh 3a and 3c atrophy and one had normal duodenal mucosa. The tTGA and EMA levels were elevated in one, and normalized in two. All three had subtle symptoms at the time of the control endoscopy, even though they initially reported no symptoms. Initially two had had osteopenia and one normal bone density; after two years the osteopenia had become worse in two, and the only one with previously normal density had developed osteopenia.

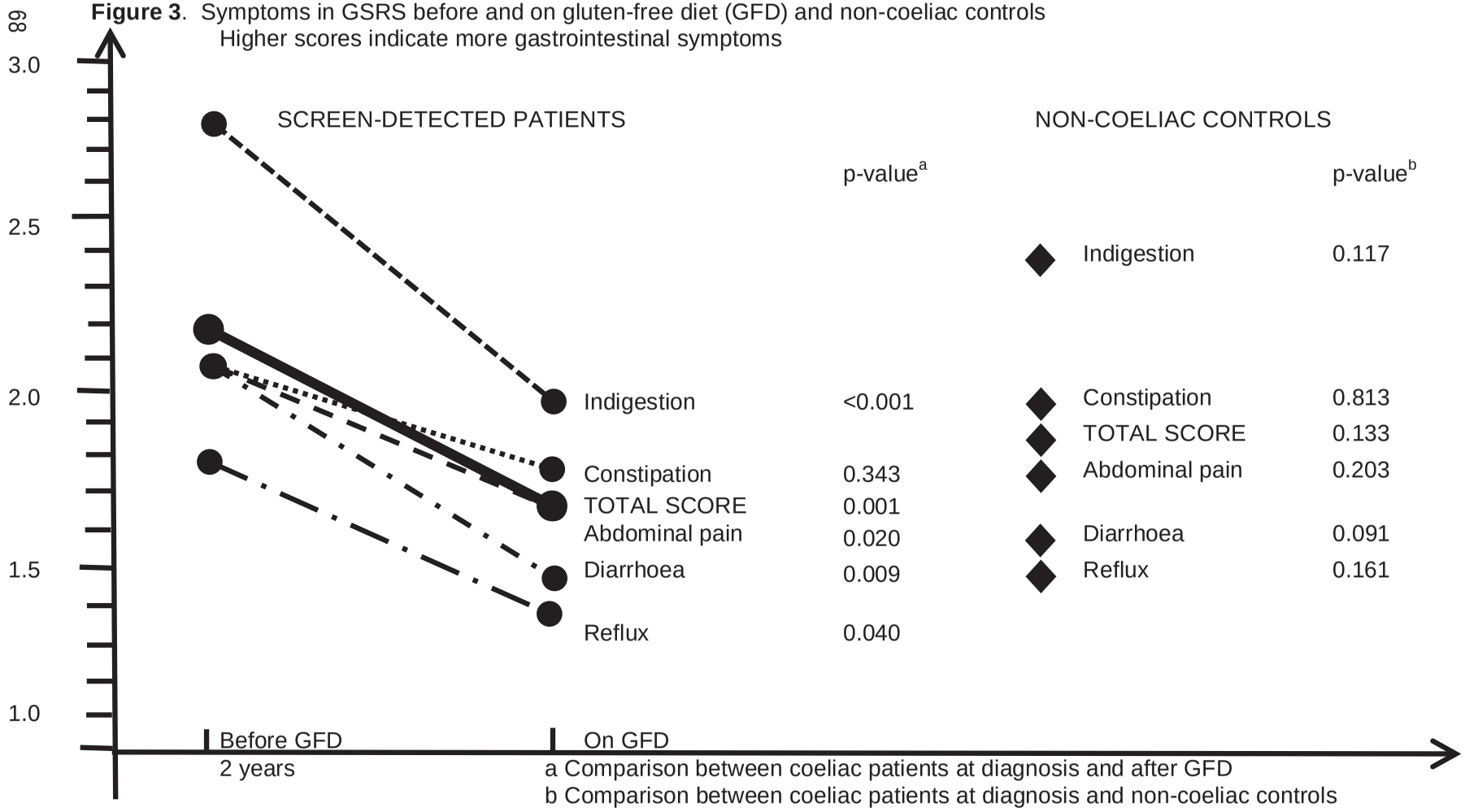
Two of the three patients had malabsorptions in their laboratory tests at the time of the CD diagnosis. One patient had an iron deficiency and anaemia as well as folic acid deficiency. He had been medicated for several years with hydroxycobalamin injections due to pernicious anaemia, but in the endoscopy the mucosa of stomach was normal. It was probable that the vitamin B12 deficiency was due to CD not atrophic gastritis. After the CD diagnosis he was medicated with multivitamin and folic acid in addition to hydroxycobalamin; in follow-up the iron deficiency anaemia resolved, however he still had subclinical ferritin deficiency and the folic acid deficiency did not improve. The other patient also had vitamin B12 and folic acid deficiencies for which he was put on medications; hydroxycobalamin injections and folate substitution. He did not have atrophic gastritis. In follow-up the medication resolved the vitamin B12 but not the folic acid deficiency. After the control biopsy and laboratory tests, two of the three patients on regular diet considered starting GFD because of the symptoms and laboratory findings.

Table 19. Laboratory values before and after gluten-free diet (GFD) treatment

Test	Reference values	At diagnosis		After two years on GFD		p-value	p-value[a]
		Mean (range)	Below reference	Mean (range)	Below reference		
Blood haemoglobin	M: 13.4-16.7 g/dl	14.1 (11.6-16.4)	9%	14.3 (11.9-16.0)	9 %	0.225	
	F: 11.7-15.5 g/dl	13.8 (12.0-15.6)		13.3 (10.7-16.1)		0.019	
Serum iron	10-34 µmol/l	17 (5-28)	6%	19 (9-40)		0.280	0.042
Serum ferritin	M: 20-275 µg/l	46 (5-177)	16%	120 (7-351)	3%	0.004	< 0.001
	F: 7-205 µg/l	33 (5-78)		83 (7-351)	3%	0.001	
Serum vitamin B12	150-740 pmol/l	275 (110-542)	16%	355 (142-739)	3%	0.018	0.039
Erythrocyte folic acid	180-845 nmol/l	290 (88-662)	34%	403 (108-1292)	13%	0.058	
Serum vitamin D25	22-103 nmol/l	45 (15-77)	9%	64 (29-97)	3%	< 0.001	0.006
Plasma phosphorus	0.71-1.53 mmol/l	0.94 (0.59-1.19)	9%	0.93 (0.72-1.24)		0.382	
Serum vitamin A	1.0-3.0 µmol/l	2.2 (1.1-3.3)		2.0 (1.0-2.5)		0.025	
Serum vitamin E	12-48 µmol/l	30 (10-42)	3%	35 (25-65)		0.005	
Serum ionized calcium	1.15-1.30 mmol/l	1.23 (1.15-1.33)		1.22 (1.15-1.32)		0.049	

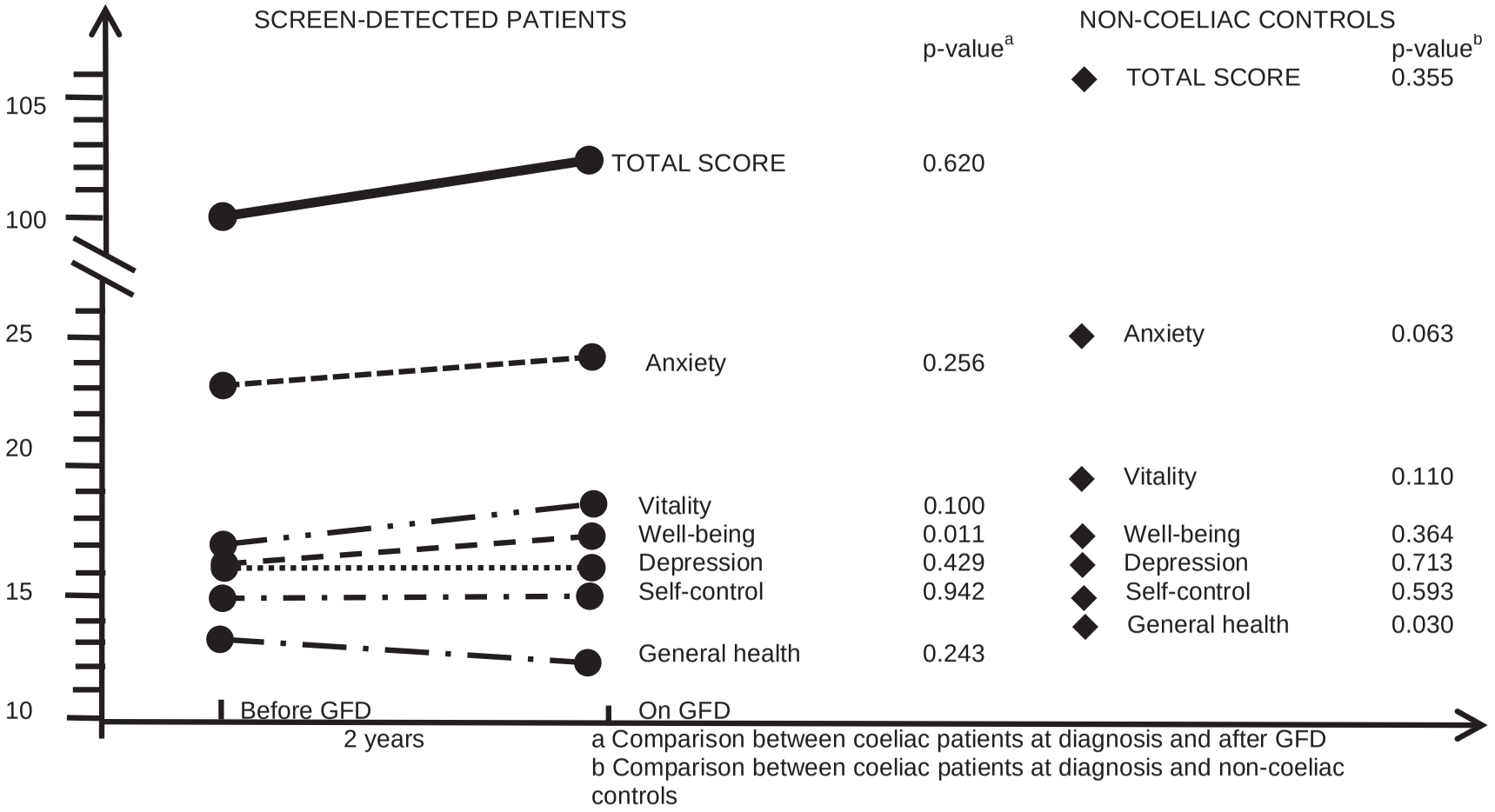
[a] p-value after exclusion of subjects with iron and vitamin supplements; M, male; F, female

Figure 3. Symptoms in GSRS before and on gluten-free diet (GFD) and non-coeliac controls
Higher scores indicate more gastrointestinal symptoms



a Comparison between coeliac patients at diagnosis and after GFD
b Comparison between coeliac patients at diagnosis and non-coeliac controls

Figure 4. Quality of Life (QoL) in PGWB before and during gluten-free diet (GFD) and non-coeliac controls. Higher score indicates better QoL



a Comparison between coeliac patients at diagnosis and after GFD
b Comparison between coeliac patients at diagnosis and non-coeliac controls

5. DISCUSSION

5.1. Epidemiological aspects

First of all, the present study showed that CD is common in elderly patients and the disorder often remains undetected, as is the case in younger patients with CD (Maki et al. 1997). The clinical course of the disease was surprisingly similar to that in younger adults. Severe malabsorption was not typical; on the contrary, many subjects had subtle symptoms, if any. The study further showed that seroconversion and the manifestation of CD may occur later in life. As a result, the prevalence of documented CD and seroprevalence in ageing people was shown to be higher than in younger people in Finland (Table 20). In the review of European studies on CD, the adult prevalence in overall sample was 1.6% but the variation was wide, ranging from 2.0% in Finland to 0.3% in Germany (Mustalahti et al. 2010). In the USA prevalence of CD in population over 50 years old was 0.8% (Godfrey et al. 2010).

Table 20. Prevalence and seroprevalence of coeliac disease in Finland

(range, years)	Reference, year	Prevalence	Documented and seroprevalence
Children (7-16)	Mäki et al. 2003	1.0%	1.5%
Adults (18-65)	Kolho et al. 1998	0.74%	1.0%
Elderly (52-79)	Current study 2008	2.34%	2.7%

In this study the prevalence of CD in population over 50 years increased in 2002-2005 from 2.13% to 2.34%, giving a crude annual incidence of 0.08%. In general the incidence of CD in adults has been increasing over time in Finland (Collin et al. 1997, Lohi et al. 2007). Whether this also applies to the elderly remains to be elucidated. Rashtak and Murray (2009) in their review stated that the

incidence rate was indeed increasing in people of 60 years of age or older. In another study by Murray and colleagues (2003) the incidence increased over 10 year period in clinically diagnosed symptomatic elderly CD patients. Angeli et al. (2012) reported that the incidence was lower in age group 60-64 years than in younger people, but in general the incidence was increasing.

It remains obscure why the prevalence figures are different and why the incidence is increasing, for instance in Finland. Environmental factors may contribute to this. The hygiene hypothesis suggests that microbial exposure in childhood gives protection against controlled autoimmune reactions. This theory is supported in that the prevalence of CD in children is much lower in North Karelia in Russia than across the border in Finland; the same phenomenon has been observed in type I diabetes and thyroid autoimmunity (Kondrashova et al. 2008a, Kondrashova et al. 2008b). It is unknown if this applies to adults or the elderly. However, it would explain the increasing prevalence over time, since in Finland the living environment has become more and more hygienic in recent decades. On the other hand, the triggering hypothesis suggests that specific microbes may trigger or facilitate the emergence of autoimmune diseases. Riddle et al. (2013) in a retrospective study on adults, showed that those adults with a Campylobacteria associated medical encounter had a 3.5-fold higher rate of CD compared to unexposed individuals or other pathogens. Given that older people have had more time to encounter possible triggering pathogens, the prevalence of CD would thus be proportionately higher.

Marine et al. (2011) suggested that CD cases appearing in childhood progress to latent form or to gluten tolerance. These patients would be seronegative to CD antibody-tests over time. In fact Simell et al. proved this in 2007 by monitoring children aged 3 months to 9 years carrying a genetic risk of CD and measuring at certain age intervals CD antibodies consecutively (Simell et al. 2007). There were patients who were permanently, transiently and fluctuatingly positive to CD antibodies on gluten-containing diet. The transient seropositivity together with few or no-symptoms would explain why the CD was not detected earlier. Our study has shown that seropositivity may emerge, and possibly re-emerge later in life. The reason for these findings is a subject for further study.

This study showed that both documented and undetected CD was common in ageing patients, and the diagnostic challenges were similar to those in younger patients. The lack of obvious symptoms or malabsorption in spite of a long challenging period for gluten-containing products was particularly conspicuous. Serologic screening will detect many patients with CD, including older individuals..

5.2. Associated diseases and mortality

Associated conditions in the elderly were by and large the same as among Finnish coeliac patients in general (Viljamaa et al. 2005b). This suggests that the prevalence of autoimmune conditions does not increase with age and along with long gluten exposure, although the number of patients was too small to permit firm conclusions. The number of patients was also too small to estimate the relative risk of small intestinal lymphoma in elderly people with CD; the risk exists, but was not especially high in these series. In a study by Godfrey et al. (2010) undiagnosed CD in patients over 50 was not found to be associated with increased risk of cancer-related mortality. Similarly, the meta-analysis by Tio et al. (2012) showed that although CD patients had an increased risk of T cell non-Hodgkin's lymphoma, they had no increased risk of malignancy in general. In the latest and largest study on the incidence of malignancies of Finnish CD patients the overall incidence of malignancies was not increased compared to that of general population, but five years after CD diagnosis it was. The risk for small intestinal cancer and NHL was increased, but to a lesser extent than in rest of the world (Ilus et al. 2014b).

Several studies and a recent meta-analysis have shown clinically and screen-detected CD patients to have increased mortality in most studies related to malignancies of the GI tract, and thus smaller prevalence of CD in the elderly (Metzger et al. 2006, Anderson et al. 2007, Rubio-Tapia et al. 2009, Tio et al. 2012). Contrary to this, in Finnish population the overall mortality risk was not increased in tTGA or EMA antibody positive subjects (Lohi et al. 2009). The study by Godfrey et al. (2010) on elderly subjects did not support this assumption. The extensive health care system in Finland may contribute to lower mortality risk by detecting and treating CD patients early. The active patient organization also contributes to good awareness of the disease and to the availability of gluten-free foodstuffs. The number of patients in this study was too small to estimate the relative risk of mortality.

5.3. Malabsorption and osteoporosis

The present study showed that the alleviation of malabsorption and the improvement in BMD can be achieved by dietary treatment. Screen-detected CD patients had at the time of diagnosis signs of malabsorption, which were often subclinical. Low mean serum ferritin and vitamin B12, D25 and E values were observed. All these deficiencies improved when the subjects had been on GFD for two years. Subclinical iron deficiency and its improvement through GFD has also been reported in diabetic children with CD (Hansen et al. 2006). The alleviation of absorption is beneficial even for patients with subclinical CD, because GFD can prevent or alleviate malabsorption, subsequent diseases and conditions like neuropathy, cognitive impairment or low-energy fractures.

The small decrease in serum ionized calcium and vitamin A on GFD may possibly be explained by ongoing bone restoration. There is a risk of low BMD in apparently asymptomatic CD patients (Mustalahti et al. 1999). In this study Z-scores were within the reference values, but a significant improvement in BMD was observed on GFD. There was no improvement in total T-scores, but the absolute T-score values typically decrease with age. At individual level, in patients with osteoporosis or osteopenia the T-scores improved significantly. Mautalen et al. (1997) showed that strict GFD promoted a significant increase in BMD, but calcium and vitamin D supplements did not provide additional benefit. Nevertheless, the positive effect in this study was sustained when the patients taking biphosphonates were excluded from the analysis.

Traditionally CD patients are thought to be underweight at the time of diagnosis, and underweight is associated with undetected CD (Olen et al. 2009). However, recent studies suggest that CD patients are more likely to be overweight than underweight (Dickey et al. 2006, Tucker et al. 2012). By commencing GFD it is suspected that patients increase their consumption of fat and sugar containing foods and therefore gain weight and become even more overweight (Dickey et al. 2006). In this study the BMI of screen-detected elderly CD patients did not differ from that of the GOAL study population. It is thus noteworthy that GFD together with the alleviation of malabsorption did not lead to weight increase. Another Finnish study also showed that the increase in BMI is not a problem when patients with newly-detected CD are placed on GFD (Ukkola et al. 2011). However, the BMI change in this study was not was statistically significant and was affected by regular dietary counselling on the GOAL study.

5.4. Gluten-free diet

Compliance with GFD is in general good in Finnish patients with CD, which may be due to the easy access to gluten-free food products, and to the awareness of the foodstuffs industry and restaurants of CD and its management. Serologic and histologic remission is possible in the majority of cases on GFD (Collin et al. 2004). This study showed that similar good compliance can be achieved in older patients with CD. Adherence to GFD was excellent, and resulted in alleviation of GI symptoms. This improvement was evident in both GSRS total score and subscores (with the exception of constipation). There are no earlier studies on dietary compliance or QoL in elderly population. Here, QoL did not differ in patients with newly detected CD from that in non-coeliac controls. QoL did not change on GFD, although a slight increase in the well-being score was seen. The same result has been achieved in other Finnish studies on adults (Mustalahti et al. 2002a). Altogether, GFD did not impair QoL in ageing CD patients, and the diet was well-tolerated and easily acceptable. As this study had no CD-specific questionnaire, it was not possible to evaluate elderly patients' social difficulties with GFD in more detail. The cost of the diet to CD patients was not measured, but it is known that GFD is more expensive than regular diet. This may cause difficulties in maintaining GFD.

5.5. Strengths and limitations of the present study

The strength of this study was the study design; it was a prospective follow-up survey in older population and based on randomly selected series. It is noteworthy that the aim of the GOAL study was not to investigate GI symptoms, malabsorptions or CD, but instead to improve the health and well-being of the ageing population. The study subjects were systematically interviewed and clinically studied before and after the commencement of GFD.

The limitations of this study were the relatively small number of cases, and there was no control group of matching age for the BMD and laboratory values. The costs of the screening could not be reliably assessed. Seronegative CD may be common in older patients with advanced disease (Salmi et al. 2006). Such cases would remain undetected with this study design. On the other hand, the study showed that CD may remain undetected for a long time, and a clinical suspicion of

and increased alertness to the condition are warranted. Serological tests are not 100% sensitive in detecting CD. In this study tTGA positive patients had normal bowel mucosa biopsy. These patients had either false positive tTGA test, or they might have early patchy or minor changes in the small intestine that cannot be detected by duodenal biopsy. There was no available follow-up on these potential CD patients, so it is not possible to know if they subsequently developed CD. CD patients with selective IgA deficiency went undetected in this study, where screening was done first only with tTGA, and then all tTGA positives were screened with EMA. It is possible that, if the screening had also been performed with EMA on all GOAL participants, the prevalence and incidence would have been higher. Thus the figures in this study on the elderly indicate minimum prevalence and incidence.

This study describes the prevalence and incidence of CD in the Päijät-Häme district with a total population of 200,000. The population is ageing as it is in general in Finland (Verkkotietokeskus 2013). The prevalence and incidence of diagnosed CD in different parts of Finland was described in the study by Virta et al. (Virta et al. 2009). Prevalence varied from 0.409 to 0.723% and incidence from 32.4 to 48.5/100 000. In Pirkanmaa Hospital District, to which Päijät-Häme province belongs, the prevalence was 0.661% and the annual incidence 43.6/100,000 (Virta et al. 2009). Virta claims that it is not likely that the prevalence or incidence differs in different regions of Finland; Finns are considered to be a fairly homogenous population. In this study the annual incidence in the elderly was 75/100,000 and the prevalence of clinically detected CD was 0.92%. Incidence and prevalence were higher than reported by Virta et al.. However, in that study the highest prevalence was in the elderly population aged 65-74 years, thereby supporting the finding of the present study.

5.6. Future aspects and how to detect coeliac disease in the elderly

Screening elderly patients in other countries, especially those where the CD diagnostic rate and compliance with GFD in general are low, would be of interest. A long-term prospective follow-up study of elderly CD patients would determine better the risk of fractures, improvement of malabsorptions and adherence to GFD. A study on the QoL in the long run and with a disease-specific QoL questionnaire would also be necessary.

There is a need to study malignancy and mortality in CD patients diagnosed at an advanced age. Another important aspect is to evaluate the risk of low-energy fractures in larger series. Provided that detecting and treating CD earlier can reduce the risk of fractures in elderly people, it would be economically sound and also improve the health and well-being of ageing patients.

It has been stated that symptoms do not predict who has coeliac disease and therefore case-finding is ineffective (Katz et al. 2011). The prevalence of CD in non-constipated irritable bowel syndrome was similar in adult and ageing population to that of controls, but the CD-associated antibodies were more common than in the control group (Godfrey et al. 2010, Cash et al. 2011). This may indicate the direction of non-coeliac gluten sensitivity, which is already under vigorous research.

In this study it was intriguing to see that there were many clinical clues to find CD among ageing patients (Table 21). Those at risk of CD were relatives of CD patients, patients with autoimmune diseases, osteoporosis or osteopenia, low-energy fractures, anaemia or vitamin malabsorptions or subtle abdominal symptoms. Serological tests for CD are not expensive and are easily available to general practitioners, even in primary health care. Testing the effect of screening for CD in elderly people in these at-risk groups might result in a high diagnostic rate with lower costs than in screening the population in general.

Table 21. Clinical features of screen-detected elderly patients – Diagnostic clues for coeliac disease (CD) in the present series

	Number of cases n = 40[a]	%
Subtle symptoms	16	40
Family history	11	28
Malabsorption	22	55
Autoimmune disease	11	28
Osteoporosis (+osteopenia)	8 (22)	20 (55)
Fractures	8	20
No diagnostic clues for CD	2	5

[a] I screening n=35 + II screening n=5

6. SUMMARY AND CONCLUSIONS

This study showed that CD is common in ageing people; it may appear later in life, and as in younger patients, most go undetected. Older CD patients often only suffer from subtle non-classic or symptomless subclinical symptoms, if any. They often have low BMD, osteopenia or osteoporosis, and an increased risk of fractures. Associated diseases are similar to those in younger CD population. In general, GFD is well tolerated and results in clinical improvement of malabsorption without impairing well-being.

CD in the elderly is not only common, but it is also detectable, treatable and dietary treatment is well-tolerated. Serologic screening should be targeted at the same group of at-risk people regardless of the patient's age. Ageing does not protect against CD.

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Alimentary Tract

Undetected coeliac disease in the elderly
A biopsy-proven population-based study

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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.

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 significant 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 form 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, *n*)	Screen-detected coeliac disease (female, *n*)	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 ($n = 25$)[a]	Screen detected ($n = 35$)
Classic symptoms[b]	17	1
Diarrhoea[c]	14	1
Weight loss[c]	9	1
Anaemia or malabsorption[c]	10	4
Dermatitis herpetiformis[c]	6	
Subtle symptoms[b]	5	14
Abdominal pain, distention, flatulence[c]	5	14
Occasional diarrhoea or loose stools[c]	4	9
Fatigue[c]	2	3
Blisters in mouth[c]		2
No symptoms[b]	0	20

[a] Data missing in three.
[b] Number of subjects.
[c] Number of diseases or symptoms.

Table 3
Associated conditions in patients with coeliac diseases

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

[a] Number of subjects.
[b] Number of diseases.

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 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 adenocancer 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), 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 coworkers [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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Research article

Increasing prevalence and high incidence of celiac disease in elderly people: A population-based study

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Abstract

Background: Celiac disease may emerge at any age, but little is known of its appearance in elderly people. We evaluated the prevalence of the condition in individuals over 55 years of age, and determined the incidence of biopsy-proven celiac disease (CDb) and celiac disease including seropositive subjects for anti-tissue transglutaminase antibodies (CDb+s).

Methods: The study based on prevalence figures in 2815 randomly selected subjects who had undergone a clinical examination and serologic screening for celiac disease in 2002. A second screening in the same population was carried out in 2005, comprising now 2216 individuals. Positive tissue transglutaminase antibodies were confirmed with small bowel biopsy.

Results: Within three years the prevalence of CDb increased from 2.13 to 2.34%, and that of CDb+s from 2.45 to 2.70%. Five new cases were found among patients previously seronegative; two had minor abdominal symptoms and three were asymptomatic. The incidence of celiac disease in 2002–2005 was 0.23%, giving an annual incidence of 0.08% in this population.

Conclusion: The prevalence of celiac disease was high in elderly people, but the symptoms were subtle. Repeated screening detected five biopsy-proven cases in three years, indicating that the disorder may develop even in the elderly. Increased alertness to the disorder is therefore warranted.

Background

Celiac disease is a common disorder affecting more than one percent of the population in the Western world [1]. Serologic screening enables detection of individuals with atypical or subtle symptoms, or even symptomless cases [2]. The condition is often assumed to involve children and young adults. On the contrary, we recently revealed a high number of both diagnosed and undetected celiac disease among elderly people [3]. It remains obscure whether the number of undetected cases in the elderly is due to diagnostic delay, or to the development of celiac disease at an advanced age, or both. The question is important in

contemplating whether celiac disease should be actively sought in elderly people, and whether seronegativity could exclude celiac disease once and for all. The aim of this study was to show the current prevalence and incidence of biopsy-proven celiac disease in individuals over 55 years of age. Given the high specificity of serum endomysial (EmA) and tissue transglutaminase antibodies (tTGA) for overt or forthcoming celiac disease, the frequency of seropositivity was likewise investigated.

Methods

The original study population comprised 4272 randomly selected individuals born in the years 1946–50, 1936–40 and 1926–30; the study sample was representative of the general population in the respective age groups. Altogether 2815 (66%) consented to participate in the original study. Their data were collected for a 10-year research project on Ageing and well-being (Good Ageing in the Lahti region = GOAL) [4]. Sera were collected in 2002, and tested for celiac disease antibodies in 2004. At that time, the number of clinically detected celiac disease cases was evaluated, and new seropositive cases underwent small intestinal biopsy for confirmation of celiac disease. The Amsterdam criteria were applied in the diagnosis of the condition [5]. In the first population screening in 2002 the frequency of diagnosed celiac disease cases was 0.89%, that of screen-detected 1.24% and that of biopsy-proven cases together with cases seropositive without histological confirmation of the disorder 2.45%; these data have been published elsewhere [3].

In 2005, all eligible patients were asked to undergo a new serologic testing. Of the previously tested 2815 patients, 2216 consented. Again, clinically detected celiac disease cases were scrutinized. All sera were tested for IgA class tTGA; positive samples were further tested for IgA class EmA. IgA class tTGA were detected by enzyme-linked immunosorbent assay (Celikey, Phadia, Freiburg, Germany) and the limit of positivity was 5 arbitrary units; IgA class EmA were detected by an indirect immunofluorescence method using human umbilical cord as antigen; a dilution of 1:≥5 was considered positive [6].

All tTGA-positive patients without previous diagnosis of celiac disease were offered upper gastrointestinal endoscopy (irrespective of the EmA titre); four small intestinal biopsies were taken form the distal part of the duodenum and stained with hematoxylin-eosin. The diagnosis of celiac disease was based on typical lesion in small intestinal mucosa.

In the prevalence estimations, subjects with previously detected celiac disease and new biopsy-proven cases found by clinically or screening were included; they are defined in this report as biopsy-proven celiac disease (CDb). The combined prevalence of biopsy-proven and seropositive cases included in addition individuals with positive tTGA but no histological verification of celiac disease (CDb+s).

The incidence of biopsy-proven celiac disease (CDb) was calculated in the 2216 subjects who were tested both in 2002 and 2005, and those seropositive without histological confirmation were added in the combined incidence figures (CDb+s), as defined in the prevalence figures.

Screening of New Cases

In the original on Ageing and well-being project, there were 199 individuals whose sera were not available in 2002, but consented to screening in 2005. The prevalence of CDb and CDb+s in this group was estimated separately.

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

Statistical Analysis

Prevalence figures were calculated with 95% confidence intervals.

Results

In the first evaluation, 61 had had been diagnosed with celiac disease (one additional case was found upon re-examination of the case records after the first publication) [3]. All 61 were alive in 2005, and were thus included in the new prevalence data.

Of the 2216 individuals proving seronegative in the first examination, six had undergone positive seroconversion and five had biopsy-proven celiac disease (Marsh III); of these five new cases two reported minor abdominal complaints and three were asymptomatic. Thus, within three years, 0.23% developed celiac disease (CDb) and 0.24% underwent seroconversion (CDb+s). The values of IgA tTGA antibodies and EmA in the five patients with newly detected celiac disease are depicted in Table 1. The small bowel biopsy findings in patients with the lowest positive tTGA antibodies are shown in Figures 1 and 2. One of the five subjects (patient 4, Table 1) had immunosuppressive treatment (corticosteroids) upon the first and second screening. In 2005 the prevalence of celiac disease (CDb) was 2.34% in subjects aged 55 or more, and the frequency of biopsy-proven and seropositive individuals (CDb+s) 2.70% (Table 2).

Of the 199 who underwent serologic screening for the first time in 2005, five had positive IgA tTGA antibodies and four positive EmA; three had villous atrophy compatible with celiac disease; biopsy was not possible in one who had moved away, and another subject declined due to

Table 1: Serum Tissue Transglutaminase (tTGA) and Endomysial Antibody (EmA) Levels in the Five New Cases Who Underwent Positive Seroconversion and Were Found to Have Biopsy-Proven Celiac disease.

Gender, age (years), (by the time of diagnosis)	Screening in 2002		Screening in 2005	
	tTGA (Units)	EmA (titre)	tTGA (Units)	EmA (titre)
1: Male, 67	0.1	Not done	54.6	1:500
2: Female, 55	1.1	Not done	9.1	1:200
3: Male, 65	0.8	Not done	9.5	1:100
4: Female, 75	2.7	Not done	6.0	1:5[a]
5: Male, 66	0	Not done	7.1	0[b]

Reference Values for tTGA ≥ 5 Units and for EmA 1:≥5.
[a] Small bowel mucosal villous morphology is shown in Figures 1 and [b] 2

serious heart disease. Thus the frequency of celiac disease was 1.5% (3/199), and when seropositives were included, 2.5% (5/199).

Discussion

We have previously shown that the prevalence of celiac disease was higher in the elderly than what has been reported in the Finnish population among adolescents (1.5%)[7] or adults (2.0%) [8]. This difference might be due to diagnostic delay, which would increase the prevalence of the disease by time; the mortality of patients is low and comparable to that in the general population in Finland [9]. Nevertheless, from 2002 to 2005, the prevalence of biopsy-proven celiac disease (CDb) in this age group increased from 2.13% to 2.34%, and the combined prevalence of disease and seropositivity (CDb+s) from 2.45% to 2.70%. Such a combination makes sense: seropositivity for these specific antibodies in the absence of villous atrophy often indicates early developing celiac disease [10], and seropositive without villous atrophy may even benefit of dietary treatment [11].

There was a significant increase in the tTGA values in the five subjects who underwent seroconversion and were subsequently found to have biopsy proven coeliac disease (Table 1). This implies that there occurred a true seroconversion, though we did not have the opportunity to test again the original sera. It was also notable that the biopsy showed unequivocal villous atrophy and crypt hyperplasia even in the two patients with the lowest positive tTGA levels, shown in Figure 1 and 2.

It is not excluded that some of the five patients had had seronegative celiac disease and became seropositive later. On the other hand, there is some evidence that elderly people with newly detected celiac disease rather become

Table 2: Prevalence and Incidence of Celiac Disease (CD) and Seropositivity for IgA Class Tissue Transglutaminase (tTGA) and Endomysial (EmA) Antibodies in Patients Aged Over 55 Years.

Year, total population	Procedure	Number clinically detected	tTGA positive in screening	EmA positive in screening	Biopsy-proven cases in screening	Overall frequency of biopsy proven CD	Patients with CD and tTGA seropositive individuals
2002, 2815	Serum sampling						
2004, 2815	Recording of detected CD. First serologic analysis	25	48	43	35	60	69[a]
2005, 2216	Recording of detected CD. Second serologic screening	1	6	4	5[b]	6	7
Overall prevalence, N = 2815		0.92% (26/2815)	1.92% (54/2815)	1.70% (47/2815)	1.42% (40/2815)	2.34% (66/2815)	2.70% (76/2815)
95% confidence intervals		0.57–1.27%	1.41–2.43%	1.22–2.18%	0.98–1.86%	1.78–2.90%	2.10–3.30%

[a] Four seropositive were found to have celiac disease between 2002–2004
[b]The incidence of celiac disease 2002–2005 was 0.23% (5/2216)

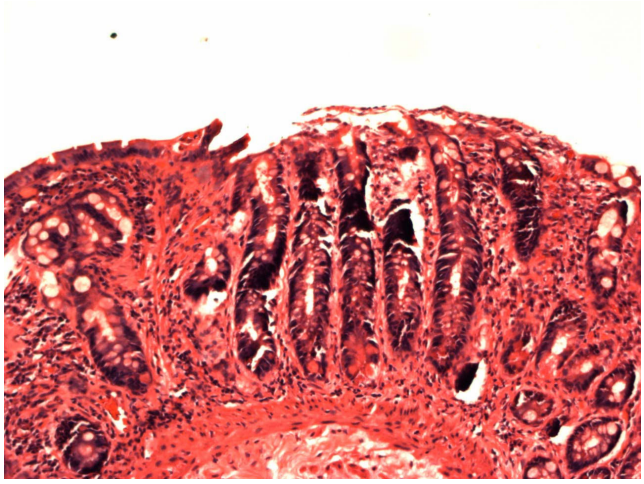

Figure 1
Small-bowel biopsy sample of the patient who underwent positive seroconversion (Patient 4 in Table 1).

seronegative by time [12]. This also means that the true frequency of celiac disease may be even higher than reported here.

Murray et al. [13] found that the incidence rates of celiac disease increased with age. A low index of suspicion by a physician may lead to diagnostic delay in recognition or to a distraction to other disorders. Apart from better diagnostics, a true increase in incidence may also occur [14]. We showed for the first time that the frequency of celiac disease was indeed increasing in elderly people, where clinically detected cases were recorded, and serologic screening has been carried out twice. The increase was thus not due to better diagnostics. Finland is considered genetically homogeneous, and there is no reason to believe that the frequency of celiac disease would be higher in Lahti region than in Finland in general.

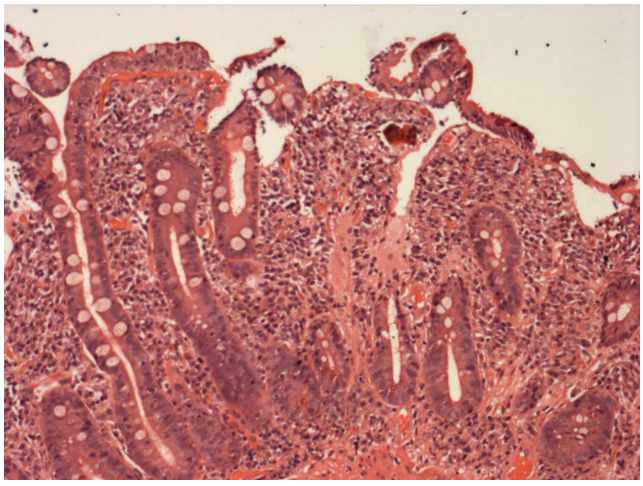

Figure 2
Small-bowel biopsy sample of the patient who underwent positive seroconversion (Patient 5 in Table 1).

The incidence of 0.23% during the study period implies that celiac disease may develop even at an advanced age. This again would imply that serologic testing should be repeated. Admittedly, the number of new cases was to low for any far-reaching conclusions. On the other hand, the annual incidence of about 0.1% indicates that the number of new cases may be 1% in 10 years. This percentage has in fact been achieved in many population screening studies. We would further emphasize that this incidence figure has been found in the general population with no suspicion of celiac disease, and with originally a high number of detected cases. The frequency of detected celiac disease in our general population is as high as 0.45% [15]. It is subject for further studies to establish whether the prevalence and incidence figures for celiac disease are even higher in elderly people belonging to the risk groups for the disease. For comparison, in relatives with celiac disease the incidence of new cases has been 1.7–4.5% within 7–12 years [16-18].

In those 199 screened for the first time, the prevalence of biopsy-proven celiac disease (CDb) was 1.5% (3/199), and when tTGA seroposives are included (CDb+s), 2.5%. These percentages are comparable to those detected in the main prospective study, supporting its results.

Earlier studies indicate that undiagnosed celiac disease may generate significant problems in the elderly. Freeman observed in his series of 30 celiac disease patients diagnosed over age 60 that they had suffered from many symptoms and had altogether 14 malignant conditions [19]. Hankey and Holmes [20] showed the diagnostic delay in the elderly to be considerable: 15 out the 35 aged 60 years or over had attended physicians for an average of 28 years with different complaints before the diagnosis. Their patients evinced good compliance with a gluten-free diet, and subsequently a significant improvement in their symptoms and signs. Similarly, Lurie et al. [21] found a significant lack in diagnosis, and a varied spectrum of manifestations in celiac patients diagnosed after the age of 60.

Conclusion

In conclusion, the prevalence of celiac disease proved to be high in elderly people. Increased alertness and the free employment of serologic screening tests are warranted. One seronegative test result does not exclude forthcoming celiac disease. Our serial screening in the same population indicated that seropositivity and the disease may also

appear later in life. This should be taken into account when considering celiac disease case finding and screening studies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AV participated in the study design, carried out the clinical studies, statistical analysis and drafted the manuscript. KK, MM and PC participated in the original study design and planning of the protocol, in the analysis of the data, and in writing and revising the manuscript. IK and HP carried out the endoscopy examinations and participated in the clinical examination of the patients. LL participated in the study planning, study protocol and drafted the manuscript. RV collected the data and sera, and participated in the study design. All authors have read and approved the final manuscript.

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RESEARCH ARTICLE Open Access

Clinical benefit of gluten-free diet in screen-detected older celiac disease patients

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Abstract

Background: The utility of serologic screening for celiac disease is still debatable. Evidence suggests that the disorder remains undetected even in the older population. It remains obscure whether screening makes good or harm in subjects with long-standing gluten ingestion. We evaluated whether older subjects benefit from active detection and subsequent gluten free dietary treatment of celiac disease.

Methods: Thirty-five biopsy-proven patients aged over 50 years had been detected by serologic mass screening. We examined the disease history, dietary compliance, symptoms, quality of life and bone mineral density at baseline and 1-2 years after the commencement of a gluten-free diet. Symptoms were evaluated by gastrointestinal symptom rating scale and quality of life by psychological general well-being questionnaires. Small bowel biopsy, serology, laboratory parameters assessing malabsorption, and bone mineral density were investigated.

Results: Dietary compliance was good. The patients had initially low mean serum ferritin values indicating subclinical iron deficiency, which was restored by a gluten-free diet. Vitamin B12, vitamin D and erythrocyte folic acid levels increased significantly on diet. Celiac patients had a history of low-energy fractures more often than the background population, and the diet had a beneficial effect on bone mineral density. Alleviation in gastrointestinal symptoms was observed, even though the patients reported no or only subtle symptoms at diagnosis. Quality of life remained unchanged. Of all the cases, two thirds would have been diagnosed even without screening if the family history, fractures or concomitant autoimmune diseases had been taken carefully into account.

Conclusions: Screen-detected patients benefited from a gluten-free diet. We encourage a high index of suspicion and active case-finding in celiac disease as an alternative to mass screening in older patients.

Background

Evidence suggests that the incidence of celiac disease increases with age [1,2]. Physicians' lack of alertness in the older people may result in a significant delay in diagnosis, as celiac disease is widely deemed to be a condition affecting younger subjects. Indeed, the majority of older celiac disease patients have remained undetected, often due to the absence of symptoms [3,4]. It is reasonable to assume that, due to long gluten exposure, older patients with untreated celiac disease may be disposed to severe nutritional deficiencies, even when they are seemingly asymptomatic. In particular, the rate of bone loss is accelerated in women after the menopause, likewise in men at the same age. We know that even young and asymptomatic patients with celiac disease may have reduced bone mineral density while untreated [5], and the condition might be even more evident in older [6].

On the other hand, a lifelong gluten-free diet is restrictive and may also increase the burden of illness and impairs quality of life [7,8]. Especially in the older subjects the diet may not be well tolerated, as patients will have adopted lifetime dietary habits which may be hard to break. Moreover, if a gluten-free diet does not necessarily produce any clinical improvement, screen-detected cases may not be motivated to adhere strictly to it. Therefore, to clarify the benefit of serologic screening for celiac disease in older population, a follow-up of

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the previously undiagnosed patients identified by screening is required [6].

In this prospective study we evaluated the benefits of active serologic population-based mass screening for celiac disease and subsequent dietary treatment in subjects over 50 years of age. The aim was to establish whether celiac disease should be rigorously searched for in the older people.

Methods

Patients and study design

We identified screen-detected new celiac disease patients enrolled from a cohort representing the older Finnish population. The original study population comprised 4272 randomly selected individuals born in the years 1946-50, 1936-40 and 1926-30, and was defined for a 10-year research project on ageing and well-being (Good Ageing in the Lahti region = GOAL) http://www.palmenia.helsinki.fi/ikihyva/InEnglish.html. In 2002, altogether 2815 subjects (66%) consented to participate and serum samples were drawn and stored at -20°C until used. Anti-tissue transglutaminase antibodies were tested from the stored sera in 2004, and 48 new seropositive cases were identified; their diagnostic work-up has been published elsewhere [2]. Four had started a gluten-free diet before enrolment, 39 of the remainder consented to a small bowel biopsy, and villous atrophy with crypt hyperplasia compatible with celiac disease was found in 35. These 35 comprised the current study group; their median age was 61 years (range 52-76) and 57% were female.

At baseline the patients were interviewed for their family history, associated disorders and symptoms of celiac disease. Nutritional condition and quality of life were evaluated. The patients were advised to start a gluten-free diet, and dietary counseling was carried out by a gastroenterologist and a dietician. To ensure dietary response and adherence to a gluten-free diet, an interview by the dietitian, small bowel biopsies and celiac disease antibodies were investigated after a median of one year; nutritional condition and quality of life were assessed after a median of two years on a gluten-free diet. The diet was considered strict when there were no signs of dietary transgressions upon the interview. Occasional gluten-free diet was defined as a gluten intake occurring less often than once in the month.

Small bowel mucosal biopsy

Small bowel mucosal biopsy samples were taken by upper gastrointestinal endoscopy from the distal part of the duodenum. Three samples were paraffin-embedded, processed, stained with hematoxylin-eosin and studied under light microscopy. The villous height/crypt depth ratio (Vh/CrD) was calculated from well orientated biopsy specimens as previously described [9]; a ratio < 2 was considered abnormal and indicative of active celiac disease. The densities of intraepithelial lymphocytes (IELs) were counted from randomly selected surface epithelium and expressed as IELs per 100 epithelial cells [9].

Celiac serology and HLA

IgA-class tissue transglutaminase antibodies (TGA) were investigated by enzyme-linked immunosorbent assay (Celikey; Phadia, Freiburg, Germany) according to manufacturer's instructions; values ≥5.0 arbitrary units (U) were considered elevated. TGA-positive sera were further analyzed for IgA-class endomysial antibodies (EMA) by an indirect immunofluorescence method using human umbilical cord as substrate; a dilution of 1:5 or more was considered positive [10].

The study patients were genotyped for HLA-DQB1*02, DQB1*0302 and DQA1*05 alleles using the DELFIA Coeliac Disease Hybridization Assay (Perkin-Elmer Life and Analytic Sciences, Wallac Oy, Turku, Finland) according to manufacturer's instructions; DQB1*02 and DQA1*05 corresponding to associated alleles for HLA DQ2 and DQB1*0302 for HLA DQ8.

Clinical symptoms

The clinical symptoms were classified into three different subgroups: (i) no symptoms, (ii) subtle symptoms with occasionally one or more of the following: abdominal pain, flatulence, belching, loose stools, tiredness, joint pain or oral blisters, and (iii) classical symptoms with constant abdominal complaints, diarrhea or excessive weight loss. Abdominal complaints were additionally evaluated by the Gastrointestinal Symptom Rating Scale (GSRS), which denotes the total score derived from five different gastrointestinal symptoms; diarrhea, indigestion, constipation, abdominal pain and gastroesophageal reflux; a higher score indicates more severe symptoms [11]. Quality of life was appraised by the Psychological General Well Being (PGWB) questionnaire [12]. This is a 22-item questionnaire including both negative and positive affective states divided into six parts: anxiety, depressed mood, positive well-being, self-control, health and vitality; here a higher score denotes better quality of life. Both questionnaires have been widely employed in celiac disease. A total of 110 subjects served as non-celiac controls for GSRS and PGWB. The controls for GSRS and PGWB were collected form the general population. We asked celiac members of the Finnish celiac society to recruit an individual living in their neighbourhood and not suffering from celiac disease. They had similar age and sex distribution as the study subjects. Celiac disease was not systematically excluded in controls, but the subjects reported no symptoms and had no relatives with celiac disease.

Assessment of nutritional condition

Body mass index was computed as weight/height^2 (kg/m^2). Blood hemoglobin, erythrocyte folic acid levels, serum iron, ferritin, ionized calcium, phosphate and vitamin A, B-12, D-25 and E concentrations were measured using routine laboratory methods.

Bone mineral density and history of fractures

Bone mineral density was measured by dual-energy X-ray absorptiometry (GE Medical Systems, LUNAR, UK) in the spine (L1 to L4) and right femoral neck. Values were expressed as standard deviation (SD) scores, which compare individual values to the mean bone mineral density of sex-matched young adults (T score) or of the age- and sex-matched population (Z score). T scores above -1.0 SD represented normal values, scores between -1.0 and -2.4 osteopenia and scores ≤ -2.5 SD osteoporosis. When indicated, bisphosphonate medication together with supplementary calcium and vitamin D were recommended, since it was considered unethical to postpone medical treatment and wait for the effect of a gluten-free diet.

The number of low-energy bone fractures was extracted from the questionnaires of the original GOAL study, equally in the total (n = 2815) series and in study subjects.

Ethical considerations

The study was accepted by the Ethical Committee of Päijät-Häme Central Hospital, and written informed consent was obtained from all participants. Research is in compliance with the Helsinki Declaration.

Statistics

Data were given as means with 95% confidence intervals (CI) or medians with lower and upper quartiles and range when appropriate. Chi-square or Fisher's tests were used in cross tabulations Wilcoxon signed or paired rank test to compare changes within the study group. A p value < 0.05 was considered statistically significant. We calculated that, for the statistical power of 0.80 at a significance level of 0.05, 30 subjects would be sufficient. We estimated that the difference of > 0.5 in the Vh/CrD and that of 0.5 in GSRS were clinically significant [13,14].

Results

Baseline findings

All 35 new celiac disease patients identified by mass screening consented to participate (Table 1). Celiac disease-related genetic susceptibility markers were found in all. Ten (29%) out of 35 had a family history of celiac disease and 10 (29%) one or several autoimmune diseases. Table 1 displays subjects in whom clinical features would make case-finding by active screening possible. Fourteen were reported to suffer from subtle, one from classical symptoms, and 20 had no symptoms prior to the diagnosis of celiac disease. Blood hemoglobin levels were below reference values in four (13%), serum iron in two (6%), ferritin in nine (26%), vitamin B12 in six (17%), erythrocyte folic acid in 13 (37%), serum phosphate in three (9%) and vitamin E levels in one (3%). Iron or folic acid supplement were given when considered ethically justified. Osteopenia was found in 14 and osteoporosis in eight (altogether in 62%). Eight (23%) out of 35 had a history of low-energy fractures; for comparison, in the whole GOAL study, low-energy fractures were reported in 123 (4%) out of 2815 o subjects, the difference being statistically significant (p < 0.01). None of the new celiac disease patients was under-weight. At baseline, GSRS and PGWB scores did not differ from those in the control series (Table 2), although the GSRS scores were in general higher in celiac patients, indicating more gastrointestinal symptoms.

Gluten-free dietary treatment

Thirty-two (91%) of the 35 screen-detected older celiac disease patients consented to start a gluten-free diet. Twenty-seven maintained a strict diet, and five had occasional transgressions less often than once in the month; three patients did not commence gluten-free diet.

After one year on the diet, small bowel mucosal villous morphology improved and densities of IELs decreased statistically significantly in the 26 who agreed to undergo the follow-up biopsy (Figure 1). In parallel, serum TGA levels normalized.

Clinical symptoms resolved in 14 out of the 15 who reported symptoms at the time of diagnosis. One with initially subtle abdominal complaints developed diarrhea despite small bowel mucosal normalization on a strict gluten-free diet; colonoscopy showed no abnormal findings or inflammation. In accordance with the clinical history, alleviation in gastrointestinal symptoms was observed both by GSRS total score and by subscores, and was statistically significant, except in the case of constipation (Table 2).

Mean serum ferritin and vitamin B_{12}, D and E values improved significantly in those 32 who started the gluten-free diet (Table 3). By contrast, mean serum vitamin A and ionized calcium values decreased after commencement of diet, albeit remaining within normal reference range. There was also a small albeit statistically significant decrease in blood hemoglobin levels in females. To verify that the beneficial effects were due to gluten-free diet, we analyzed separately patients who did not receive any additional medical iron or vitamin substitution. The beneficial effect remained significant in

Table 1 Clinical features

Case	Gender Age (y)	tTGA[a]	EMA[b]	Symptoms	Mal-absorption	Diagnostic clues for detecting celiac disease
1	M 52	> 100	1:2000	Subtle		Vitamin B12 deficiency
2	M 52	29.2	1:2000	None	-	Fracture of hand
3	F 52	> 100	1:4000	None	+	Pernicious anemia, hypothyroidism
4	F 52	8.2	1:50	None	+	Blisters in mouth, family history
5	F 52	35.7	1:500	Subtle	-	
6	F 52	> 100	1:2000	Subtle	+	
7	M 53	29.7	1:200	Subtle	-	Sarcoidosis, family history
8	M 53	6.1	1:5	Subtle	-	Family history
9	F 53	6.2	0	Subtle	+	Fracture of vertebra, osteomalacia hypothyroidism
10	M 54	88.3	1:1000	None	+	Fracture of ankle, psoriasis
11	M 54	93.0	1:500	None	+	
12	F 55	> 100	1:500	Subtle	-	Sjögren's syndrome, psoriasis
13	F 55	43.4	1:500	None	-	Osteoporosis
14	M 55	24.5	1:200	Subtle	+	Psoriasis, osteoporosis
15	F 56	58.5	1:200	Classic	-	Family history
16	F 56	18.3	1:50	None	-	Family history
17	F 56	46.6	1:1000	None	-	Type I diabetes mellitus, hypothyroidism
18	M 62	97.4	1:500	None	+	Depression, vitamin B12 deficiency
19	F 63	5.8	1:5	None	+	
20	M 63	38.9	1:1000	Subtle	+	Sarcoidosis, osteoporosis
21	F 63	94.1	1:200	None	-	Hypothyroidism
22	F 63	16.5	1:100	None	+	Hyperthyroidism, family history
23	F 64	71.2	1:500	None	+	Fracture of ribs and sternum, osteoporosis
24	M 64	5.8	1:5	None	+	Fracture of wrist
25	F 64	10.5	1:5	None	-	
26	F 65	> 100	1:500	Subtle	+	Osteoporosis
27	F 65	64.3	1:200	Subtle	-	Hypothyroidism, family history
28	F 66	79.8	1:500	Subtle	+	Hypothyroidism, family history
29	M 72	> 100	1:200	Subtle	+	Fracture of foot, family history
30	M 73	27.4	1:50	Subtle	+	
31	M 73	20.2	1:200	None	+	Fracture of ribs, osteoporosis blisters in mouth
32	M 75	6.0	1:5	None	+	Osteoporosis
33	F 76	7.4	1:5	None	-	Osteoporosis
34	M 76	5.4	1:5	None	+	Fracture of ribs, family history
35	F 76	48.3	1:500	None	-	Stomach cancer

Clinical features of screen-detected celiac disease patients having small bowel mucosal villous atrophy at the time of diagnosis.

[A] Serum IgA-class tissue transglutaminase antibodies, values > 5.0 U/l abnormal

[B] Serum IgA-class endomysial antibodies, titers 1:≥5 abnormal

[C] Sarcoidosis treated with immunosuppressive medication

serum iron (12 excluded, p = 0.042), serum ferritin (12, p > 0.001), vitamin B_{12} (14, p = 0.039), and vitamin D (21, p = 0.006).

The mean femoral Z-score improved significantly when patients had adhered to the gluten-free diet for two years; in the lumbar spine the improvement did not reach statistical significance (Table 4). There were no significant changes in T-scores. In subjects with osteopenia or osteoporosis, the mean T-score increased in lumbar spine from -2.0 (95%CI -2.3 to -1.7) to -1.7 (95% CI -2.1 to-1.3), and in femoral neck from -2.2 (95%CI -2.5 to -1.9) to -2.1 (95%CI -2.4 to -1.8) (p-values 0.03 and 0.20, respectively). Bisphosphonates were prescribed for three patients with osteoporosis or osteopenia. When these patients were excluded from the analysis, the increase in lumbar spine T-score remained still statistically significant (p = 0.021). The diet had no obvious effect on BMI. Quality of life measured by PGWB did not change during the follow-up; apart from improvement in the well-being score (Table 2). The three patients who declined the diet initially reported no symptoms, but developed minor abdominal complaints

Table 2 Symptoms and quality of life

	Screen-detected celiac patients				
	At the diagnosis	After gluten-free diet	p-value[a]	Non-celiac controls	p-value [b]
GSRS [c]					
Diarrhea	2.1 (1.7-2.6)	1.5 (1.2-1.9)	0.009	1.6 (1.5-1.8)	0.091
Indigestion	2.8 (2.4-3.2)	2.0 (1.6-2.3)	< 0.001	2.4 (2.0-2.7)	0.117
Constipation	2.1 (1.7-2.5)	1.8 (1.5-2.1)	0.343	2.0 (1.6-2.3)	0.813
Abdominal pain	2.1 (1.7-2.4)	1.7 (1.4-2.0)	0.020	1.8 (1.5-2.1)	0.203
Reflux	1.8 (1.4-2.2)	1.4 (1.2-1.7)	0.040	1.5 (1.8-1.2)	0.161
Total score	2.2 (1.9-2.5)	1.7 (1.5-2.0)	0.001	1.9 (1.7-2.1)	0.133
PGWB[d]					
Anxiety	23 (21-24)	24 (22-25)	0.256	25 (24-26)	0.063
Depression	16 (15-17)	16 (15-17)	0.429	16 (16-17)	0.713
Well-being	16 (15-17)	17 (16-18)	0.011	17 (16-17)	0.364
Self-control	15 (14-16)	15 (14-16)	0.942	15 (15-16)	0.593
General health	13 (12-14)	12 (11-14)	0.243	14 (14-15)	0.030
Vitality	17 (16-18)	18 (16-19)	0.100	19 (18-19)	0.110
Total score	100 (93-106)	102 (95-109)	0.620	106 (104-108)	0.355

Gastrointestinal symptom score (GSRS) and psychological general well-being (PGWB) in older celiac disease patients before and after dietary treatment, compared to non-celiac controls

[a] Comparison between celiac patients at the diagnosis and after gluten-free diet

[b] Comparison between celiac patients at the diagnosis and non-celiac controls

[c] Gastrointestinal symptom rating scale; higher scores indicate more gastro-intestinal symptoms

[d] Psychological general well-being; higher scores indicate better quality of life

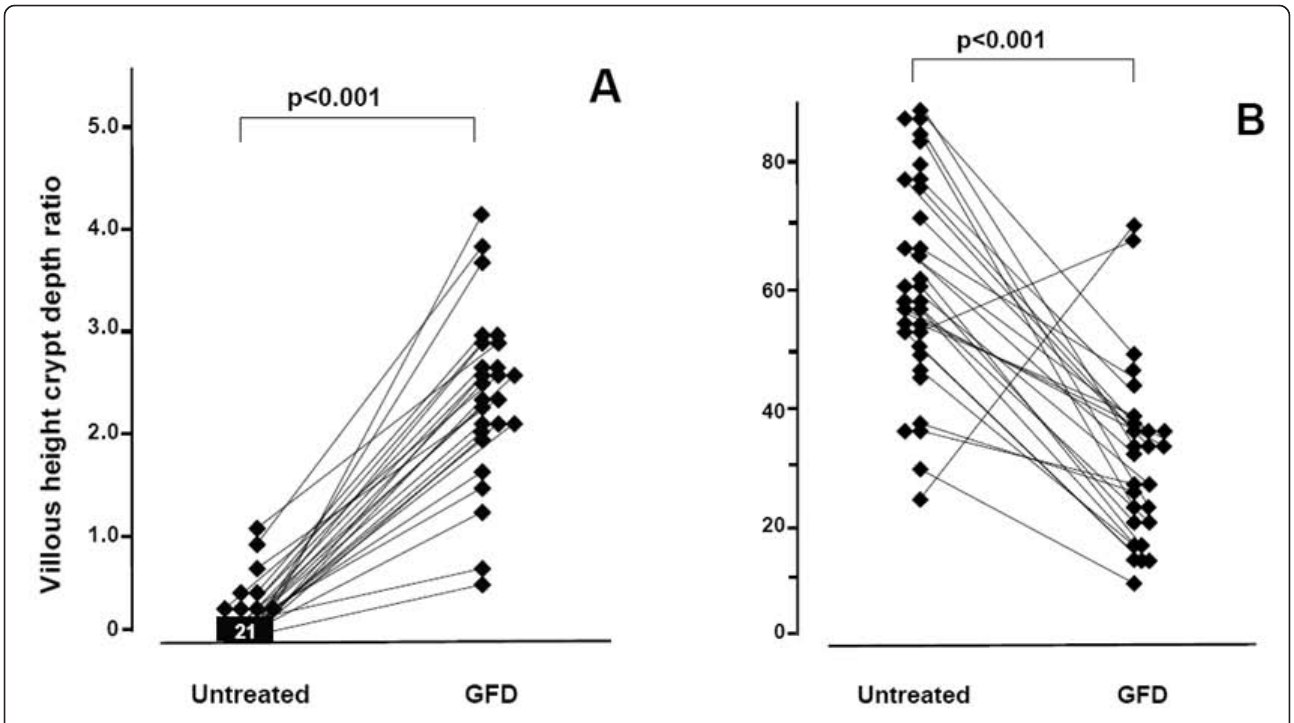

Figure 1 Small bowel mucosa before and after gluten-free diet. The villous height crypt depth ratio (A) and the densities of intraepithelial lymphocytes/100 enterocytes (B) at the time of diagnosis and after one year on a gluten free diet (GFD) in older celiac disease patients detected by mass-screening.

Table 3 Malabsorption

	Reference values	At the diagnosis		After gluten-free diet		p-value
		Mean	Range	Mean	Range	
Blood hemoglobin	M: 13.4-16.7 g/dl	14.1	11.6-16.4	14.3	11.9-16.0	0.225
	F: 11.7-15.5 g/dl	13.8	12.0-15.6	13.3	10.7-16.1	0.019
Serum iron	10-34 μmol/l	17	5-28	19	9-40	0.280
Serum ferritin	M: 20-275 μg/l	46	5-177	120	7-351	0.004
	F: 7-205 μg/l	33	5-78	83	7-351	0.001
Serum vitamin B12	150-740 pmol/l	275	110-542	355	142-739	0.018
Erythrocyte folic acid	180-845 nmol/l	290	88-662	403	108-1292	0.058
Serum vitamin D25	22-103 nmol/l	45	15-77	64	29-97	< 0.001
Plasma phosphorus	0.71-1.53 mmol/l	0.94	0.59-1.19	0.93	0.72-1.24	0.382
Serum vitamin A	1.0-3.0 μmol/l	2.2	1.1-3.3	2.0	1.0-2.5	0.025
Serum vitamin E	12-48 μmol/l	30	10-42	35	25-65	0.005
Serum ionized calcium	1.15-1.30 mmol/l	1.23	1.15-1.33	1.22	1.15-1.32	0.049

Malabsorption parameters at the diagnosis and after gluten-free diet in 32 screen-detected older celiac disease patients. Some of the patients received also vitamin or iron supplements, see the text.

after the follow-up; in two osteopenia and low folic acid levels remained.

Discussion

An increasing number of patients with celiac disease will be diagnosed among the older people [1-3]. The correct diagnosis may have been missed even when the patients had contacted their physicians for many years due to unexplained symptoms or abnormalities in blood tests [3]. Altogether, older patients may have more symptoms than younger ones [15], and may have an increased risk of malabsorption or enteropathy-associated T-cell lymphoma[16]. Anemia, iron, vitamin B12, folic acid, and calcium deficiency have been the major malnutrition findings in older celiac disease patients [3,16]. It would thus, appear desirable to detect the disease as early as possible.

On the other hand, it is of crucial importance to know what the overall implications of the diagnosis are in older people. Mortality has not increased among older undiagnosed celiac disease patients [6] and the effect of the diagnosis on well-being has not been investigated. In this prospective follow-up study we evaluated the consequences of dietary treatment in a definite celiac disease patient series obtained by population-based mass screening in the older [17]. Since neither celiac disease nor any abdominal disease was the target of the original GOAL project, there was no selection bias towards individuals suffering from gastrointestinal symptoms. Of note, the rate of detection of celiac disease in Finland is relatively high, and in the present series, 0.9% of individuals already had the diagnosis of celiac disease established before the screening program [17]. This notwithstanding, even here the majority of older celiac disease patients would have remained undiagnosed without active screening or case finding.

In these screen-detected patients an improvement in GSRS was evident under dietary treatment, both in total score and in virtually in all subscores, displaying an alleviation in gastrointestinal symptoms. The effect of the treatment on quality of life (PGWB) was not so evident, but it is of note that the diet did not worsen it. A comparable finding was obtained in our recent study where celiac patients detected by screening at risk groups were investigated [18]. An improvement in laboratory values was seen almost invariably. This was most evident in serum mean ferritin indicating the presence of subclinical iron deficiency, as the serum iron levels remained

Table 4 Bone density and body mass index

	At the diagnosis		After gluten-free diet		
	Mean; 95% confidence intervals		Mean; 95% confidence intervals		
Lumbar spine Z-score (SD)	0.6	0.0 - 1.1	0.9	0.1 - 1.5	0.060
Femoral Z-score (SD)	-0.1	-0.5 - 0.2	0.1	-0.2 - 0.6	0.009
Lumbar spine T-score (SD)	-0.7	-1.2 - -0.1	-0.4	-1.2 - 0.1	0.241
Femoral T-score (SD)	-1.1	-1.5 - -0.6	-1.1	-1.5 - -0.5	0.670
Body mass index (kg/m^2)	25.9	24.6-27.1	25.3	24.1-26.5	0.139

Bone mass density (T and Z -score) and body mass index (mean with 95% confidence intervals (CI)) at diagnosis and after gluten-free diet in 32 screen-detected older celiac disease patients

within normal range. A low ferritin level was similarly observed in a series from Godfrey and colleagues [6]. Apart from gluten-free diet, iron or vitamin supplementation was given to some of our patients, but the beneficial effect was evident also in those subjects, who did not receive any substitution. There was a slight but statistically significant decrease in blood hemoglobin levels in females (Table 3), but none of the patients suffered from severe anemia. A regular follow-up of hemoglobin values is in any case indicated in celiac patients.

A risk of low bone mineral density is possible in screen-detected apparently asymptomatic celiac disease patients [5]. In the present study, Z-scores, reflecting the values in the age- and sex-matched population, were within reference levels at baseline, but a significant improvement was observed on a gluten-free diet. As Z-score reference values usually decrease with age, we concluded that this process was slowed down by dietary treatment. Though no improvement was observed in T-scores in the total series, such an effect was seen in subjects with osteoporosis or osteopenia, even when subjects treated with bisphosphonates were excluded. The analysis would have been impossible if also subjects receiving vitamin D or calcium substitution were excluded. On the other hand, in the randomized study carried out by Mautalen et al. [19], strict gluten-free diet promoted a significant increase in bone mineral density, but calcium and vitamin D supplementation did not provide additional benefit. We will further point out, that the medical management for bone disease of malabsorption would not have been possible without our active screening. There was a small but significant decrease in serum calcium levels. This may be due to ongoing bone restoration, which implies that calcium substitution is indicated after the commencement of a gluten-free diet. Our results further suggest that low-energy fractures may be a risk in untreated celiac disease. Larger prospective studies are however needed to confirm this finding.

Compliance with a gluten-free diet does not seem to be a problem in older patients with celiac disease, as compliance rates have been more than 90% [3]. Accordingly, the histological or serological recovery in the 32 patients adhering to a gluten-free was virtually complete. However, our results cannot directly be applied in every country, as the availability of gluten-fee diet may not be as good as in Finland. Another limitation of the study was that we did not have laboratory or bone mineral density values for the control group. Nevertheless, we emphasize that a favorable outcome can be achieved by screening older population for celiac disease.

None of our celiac disease patients suffered from severe malabsorption syndrome, and they did not have refractory sprue or any other severe complications. Ten (29%) of these 35 screen-detected celiac patients had had relatives with celiac disease and 10 autoimmune diseases, which should both alert to celiac disease. Katz and associates [20] concluded that symptoms do not predict who will have celiac disease, making case-finding ineffective, and they therefore suggested that general population screening may be needed to find the disorder. To the contrary, we believe that in this older population case finding will be effective as long as symptoms and risk-groups are taken into account. Altogether, 29 out of 35 of our celiac patients would have been detected without serologic mass-screening if family history, bone fractures or concomitant diseases (Table 1) had alerted the physicians (in patient 35 routine duodenal biopsy would have detected celiac disease). We therefore recommend screening in groups, where the costs are lower than in mass-screening, and as shown here, the patients benefit from dietary treatment.

Conclusions

Screen-detected, apparently asymptomatic older celiac disease patients may suffer from subclinical malabsorption, gastrointestinal symptoms or bone disease, which are alleviated during gluten-free dietary treatment. No deterioration in quality of life was seen in our series, and dietary compliance was excellent. Despite this, we consider that there is still insufficient evidence to advocate mass screening, until the costs and benefits of the approach have been thoroughly evaluated. Instead, as the majority of patients had a family history or associated conditions known to occur with celiac disease, we recommend active case finding in older people belonging to at-risk groups.

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Authors' contributions

AV, KK, LL, MM and PC conceived the study participated in the patient enrolment, data collection and study design: IK, ML and HP participated in the data collection and study design. RV and KL carried out the immunological studies and participated in the study design. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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