ANNIINA UKKOLA

The Burden of Coeliac Disease

The Perspectives of Patients, Health Care System and Society

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ACADEMIC DISSERTATION
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To my family

ABSTRACT

Coeliac disease is heavily underdiagnosed and delay in diagnosis is typically several years. Untreated symptomatic disease is associated with increased morbidity, much of which can be prevented or reversed by treatment with a gluten-free diet in symptomatic patients. Whether a similar health gain can be achieved in screen-detected patients remains unclear. It has been suggested that undiagnosed coeliac disease causes an increased burden on the health care system as consumption of health care services might be increased among undiagnosed patients but be reduced on treatment. The aims of this study were to gain a comprehensive understanding of the burden of illness related to coeliac disease from the standpoint of affected individuals, the health care system and society, and to ascertain the impact of treatment with a gluten-free diet on this burden.

This dissertation comprised four prospective studies. In study **I**, health-related quality of life was evaluated with the Psychological General Well-Being (PGWB) questionnaire and the results compared to those of 110 adult non-coeliac controls at diagnosis and in the follow-up. The patients were asked to grade their subjective health status and concern about their heath in general. Study **II** assessed patients' thoughts of coeliac disease, how the diagnosis was established, and treatment with a gluten-free diet. In addition, they indicated their special wishes or needs related to the disease. Initial body mass index (BMI) and the impact of a gluten-free diet on it, in addition to items explaining favourable or poor BMI outcome were assessed in study **III**. BMI values at diagnosis and on dietary treatment were compared to those of a random sample of the general population during the same periods. Study **IV** measured use of health care services, consumption of pharmaceutical agents and number of days of sickness absence from work in the years prior to and following the diagnosis to establish the possible effect of dietary treatment on these parameters. The number of consultations with a physician and days of sickness absence were compared to those in a sample of the general

population.

The study involved 698 newly-detected adult coeliac disease patients, who were divided into three study groups according to clinical presentation: i) gastrointestinal symptoms and signs, ii) extraintestinal symptoms, and iii) screen-detected patients among whom a sub-group of asymptomatic patients was also analysed separately (**I-III**). Participants completed paired study questionnaires at diagnosis and after one year from the initial appointment.

The results of studies **I-III** showed that quality of life was reduced in untreated patients but improved on a gluten-free diet and did not differ from that among the controls after one year. Dietary treatment resulted in similar health gain in all study groups irrespective of clinical presentation. Perceptions of health improved correspondingly and patients in all groups reported a positive general attitude towards the disease and dietary treatment. Only screen-detected asymptomatic patients reported no such positive effect. Their PGWB scores were comparable to those of the controls both at diagnosis and on a gluten-free diet, but concern for health increased after being diagnosed. Study **III** showed that even though 39% of coeliac disease patients were overweight at diagnosis, BMI in the coeliac group was lower than that in the general population both at diagnosis and after one year on treatment. Treatment with a gluten-free diet induced favourable changes in BMI equally in all study groups and also in asymptomatic patients. Prior to diagnosis, consumption of health care services and on-demand medication was increased, but was reduced during one year on treatment (**IV**). Compared to the general population, patients made more visits to a physician prior to but not post diagnosis. No excess in sickness absence was noted.

This study demonstrated that the burden of illness related to coeliac disease affects similarly both symptom- and screen-detected patients. Improved quality of life and health status and changes towards normal BMI can be achieved by dietary treatment. However, screen-detected asymptomatic patients show no such beneficial effects of treatment. Additionally, the burden to the health care system caused by undetected coeliac disease was diminished after implementation of a gluten-free diet. The results indicate that patients, health care system and, indirectly, society benefit from the early detection and treatment of coeliac disease. Further studies are needed to promote earlier diagnosis and to establish optimal strategies in the management of coeliac disease.

TIIVISTELMÄ

Keliakia on huomattavan alidiagnosoitu sairaus, ja viive oireiden alun ja diagnoosin välillä on tyypillisesti useita vuosia. Hoitamattomaan keliakiaan liittyy lisääntynyttä sairastuvuutta, jonka on oireisilla potilailla osoitettu vähenevän tai estyvän gluteenittomalla ruokavaliohoidolla. Ruokavaliohoidon vaikutukset seulonnalla todettujen potilaiden terveyteen ja elämänlaatuun ovat kuitenkin ristiriitaisia. Lisäksi on esitetty, että diagnosoimaton keliakia aiheuttaisi ylimääräistä terveydenhuollon kuormitusta, koska diagnosoimattomat keliakiapotilaat saattavat käyttää enemmän terveydenhuollon palveluita, ja että kuormitus voisi vähentyä ruokavaliohoidon aloittamisen myötä.

Tutkimuksen tarkoituksena oli saada kokonaisvaltainen käsitys keliakian aiheuttamasta kuormituksesta keliakiapotilaiden, terveydenhuollon ja yhteiskunnan kannalta ja arvioida gluteenittoman ruokavaliohoidon vaikutuksia kuormitukseen. Tutkimus koostui neljästä prospektiivisesta osatyöstä. Osatyössä **I** arvioitiin terveyteen liittyvää elämänlaatua Psychological General Well-Being (PGWB) -kyselyllä ja tuloksia verrattiin 110:n keliakiaa sairastamattoman aikuisen tuloksiin. Lisäksi potilaita pyydettiin arvioimaan, millainen heidän terveydentilansa on ja kuinka huolissaan he ovat terveydestään. Osatyössä **II** arvioitiin potilaiden käsityksiä ja kokemuksia keliakiasta, diagnosoinnista ja ruokavaliohoidosta. Lisäksi tiedusteltiin erityisiä toiveita tai tarpeita keliakiaan liittyen. Osatyössä **III** tutkittiin potilaiden painoindeksiä ja gluteenittoman ruokavalion vaikutuksia siihen sekä suotuisaa tai epäedullista painonkehitystä selittäviä tekijöitä. Potilaiden painoindeksejä diagnoosihetkellä ja vuoden ruokavaliohoidon jälkeen verrattiin tuloksiin, jotka oli saatu väestön satunnaisotoksesta samoina vuosina. Osatyössä **IV** tutkittiin terveyspalvelujen käyttöä, lääkeaineiden kulutusta ja poissaolopäiviä työstä vuoden aikana ennen keliakiadiagnoosia ja sen jälkeen ja arvioitiin ruokavaliohoidon vaikutuksia niihin. Lääkärikäyntien ja sairauspoissaolopäivien määrää verrattiin väestöotoksen tuloksiin samoilta vuosilta.

Tutkimuksessa seurattiin 698:aa äskettäin diagnosoitua aikuista keliakiapotilasta. Potilaat jaettiin diagnoosiin johtaneiden syiden perusteella kolmeen ryhmään: i) ruuansulatusjärjestelmästä peräisin olevat oireet tai löydökset, ii) suoliston ulkopuoliset oireet ja iii) seulonnalla todetut potilaat, joiden joukosta tarkasteltiin erikseen täysin oireettomien potilaiden alaryhmää (**I-III**). Potilaat täyttivät samankaltaiset tutkimuskyselyt diagnoosihetkellä ja vuosi sen jälkeen.

Osatöiden **I-III** tulokset osoittivat, että potilaiden elämänlaatu oli alentunut ennen diagnoosia mutta korjaantui ruokavaliohoidolla vuodessa samalle tasolle kuin keliakiaa sairastamattomilla kontrolleilla. Ruokavaliohoito sai aikaan samanlaisia terveyshyötyjä kaikissa tutkimusryhmissä potilaiden alkuperäisestä oirekuvasta riippumatta. Potilaat ilmoittivat terveydentilansa parantuneen ja suhtautuivat myönteisesti keliakiaan ja gluteenittomaan ruokavalioon. Vastaavaa positiivista vaikutusta ei kuitenkaan havaittu täysin oireettomilla potilailla. Heidän PGWB-pisteensä eivät eronneet kontrolleista ennen diagnoosia eivätkä vuoden hoidon jälkeen, mutta he olivat enemmän huolissaan terveydestään vuoden kuluttua. Osatyö **III** näytti, että vaikka 39% keliakiapotilaista oli diagnosoitaessa ylipainoisia, sairastuneiden painoindeksi oli diagnoosihetkellä ja vuoden hoidon jälkeen alhaisempi kuin kontrolliväestöllä. Gluteeniton ruokavalio sai aikaan suotuisia muutoksia painoindeksissä kaikissa tutkimusryhmissä ja täysin oireettomilla potilailla. Terveyspalvelujen ja käsikauppalääkkeiden käyttö oli lisääntynyt diagnoosia edeltävän vuoden aikana mutta väheni hoidon aloittamista seuraavan vuoden aikana (**IV**). Kontrolliväestöön verrattuna potilailla oli enemmän lääkärikäyntejä ennen diagnoosia mutta ei sen jälkeen. Sairauspoissaoloissa ei havaittu muutosta.

Tutkimuksen tulokset osoittivat, että keliakia kuormittaa samalla tavoin sekä oireiden perusteella että seulonnalla todettuja potilaita. Ruokavaliohoidolla voidaan parantaa potilaiden elämänlaatua ja terveydentilaa sekä edistää painon muutoksia kohti normaalia painoindeksiä. Seulonnalla todetut oireettomat potilaat eivät kuitenkaan hyötyneet samoin hoidosta. Diagnosoimattoman keliakian terveydenhuollolle aiheuttama kuormitus väheni, kun potilaat ohjattiin aloittamaan gluteeniton ruokavalio. Tulosten perusteella sekä potilaat että terveydenhuolto ja epäsuorasti yhteiskuntakin hyötyvät keliakian varhaisesta toteamisesta ja hoidon aloittamisesta. Jatkossa tarvitaan lisää tutkimuksia varhaisemman diagnoosin mahdollistamiseksi ja ihanteellisten hoitokäytäntöjen löytämiseksi.

CONTENTS

ABBREVIATIONS

AGA	antigliadin antibodies
ARA	antireticulin antibodies
BMI	body mass index
CI	confidence interval
CD	Cluster design
ELISA	enzyme-linked immunosorbent assay
EmA	endomysium antibodies
ESPHGAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GFD	gluten-free diet
HLA	human leukocyte antigen
IEL	intraepithelial lymphocyte
Ig	immunoglobulin
IL	interleukin
ND	not defined
OR	odds ratio
PGWB	Psychological General Well-Being
QoL	quality of life
SF-36	Short-Form Health Survey
TAPQOL	TNO-AZL Preschool Children Quality of Life Questionnaire for Parents
TG2	transglutaminase 2
TG2A	transglutaminase 2 antibody
Th	helper T lymphocyte
TNF	tumour necrosis factor
WHO	World Health Organisation

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by the Roman numerals **I-IV**:

I Ukkola A, Mäki M, Kurppa K, Collin P, Huhtala H, Kekkonen L, Kaukinen K (2011): Diet improves perception of health and well-being among only symptomatic patients with celiac disease. Clin Gastroenterol Hepatol 9:118-23.

II Ukkola A, Mäki M, Kurppa K, Collin P, Huhtala H, Kekkonen L, Kaukinen K (2012): Patients' experiences and perceptions of living with coeliac disease - implications for optimizing care. J Gastrointestin Liver Dis 21:17-22.

III Ukkola A, Mäki M, Kurppa K, Collin P, Huhtala H, Kekkonen L, Kaukinen K (2012): Changes in body mass index on a gluten-free diet in coeliac disease: a nationwide study. Eur J Intern Med 23:384-8.

IV Ukkola A, Kurppa K, Collin P, Huhtala H, Forma L, Kekkonen L, Mäki M, Kaukinen K: Use of health care services and pharmaceutical agents in coeliac disease: a prospective nationwide study. Submitted.

INTRODUCTION

Coeliac disease is one of the most common chronic gastrointestinal disorders, characterised by small-bowel villous atrophy and crypt hyperplasia. The disease develops gradually in genetically predisposed individuals after ingestion of gluten-containing cereals, wheat, barley and rye. Classical gastrointestinal symptoms and signs comprise chronic diarrhoea, malabsorption and weight loss (Visakorpi et al. 1970, Young and Pringle 1971). Nowadays, an increasing proportion of coeliac disease patients are diagnosed due to mild abdominal or extraintestinal symptoms such as decreased bone mineral density, neurological disorders and dermatologic symptoms (Logan et al. 1983, Mäki et al. 1988). Patients detected by screening in at-risk groups may be asymptomatic at diagnosis (Collin et al. 1997, Kurppa et al. 2010). Symptom-detected and untreated coeliac disease is associated with an increased risk of malignancy and osteoporosis (Holmes et al. 1989, Mora et al. 1993). Persistent symptoms may lead to impaired health and decreased health-related quality of life (Usai et al. 2002, Johnston et al. 2004). Even though accurate serological tests are available in screening for coeliac disease, the delay between the onset of symptoms and diagnosis is usually several years (Lo et al. 2003, Green et al. 2001, Häuser et al. 2007, Gray et al. 2010). In addition, it has been suggested that undiagnosed coeliac disease is associated with increased medical costs (Long et al. 2010).

The only treatment for coeliac disease is a permanent gluten-free diet, which typically results in clinical and histological improvement and a reduced risk of complications (Holmes et al. 1989, Murray et al. 2004, Olmos et al. 2008). Moreover, quality of life has been reported to improve on dietary treatment (Lohiniemi et al. 2000). However, it has remained obscure whether screen-detected patients also benefit from treatment with a gluten-free diet (Mustalahti et al. 1999, Mustalahti et al. 2002, Lohi et al. 2009a, van Koppen et al. 2009). In addition, there has been concern over increased body mass index (BMI) on dietary treatment (Dickey et al. 2006). A gluten-free diet is restrictive, expensive and difficult to

maintain (Lee et al. 2007, Niewinski 2008) and may thus be less acceptable to screen-detected and especially asymptomatic patients. These issues have raised the question whether early detection and treatment of coeliac disease would be beneficial for all affected individuals.

As noted above, untreated coeliac disease may itself be burdensome, but also the treatment is complicated and the benefits debatable. The purpose of the present study was to assess the burden of illness related to coeliac disease from the standpoint of coeliac disease patients, the health care system and society in a large cohort of newly detected adult patients. Further, the impact of treatment with a gluten-free diet was evaluated. Special interest focused on quality of life, patients' experiences of the disease and dietary treatment, body mass index, consumption of health care services and pharmaceutical agents, and sickness absence from work during the year prior to and following the diagnosis of coeliac disease.

REVIEW OF THE LITERATURE

1. DEFINITION AND CLINICAL FEATURES OF COELIAC DISEASE

By classical definition, coeliac disease is a chronic autoimmune-mediated disorder in which gluten peptides from wheat, barley and rye cause villous atrophy with crypt hyperplasia in the small intestine in genetically susceptible individuals. Mucosal injury recovers after removal of gluten peptides from the diet and develops again if consumption of gluten is resumed (Walker-Smith et al. 1990).

Coeliac disease may manifest as an active disease with presenting symptoms ranging from grave to mild, or as clinically silent, that is asymptomatic. Subjects with latent coeliac disease may have a normal mucosal structure while on a gluten-containing diet, but after some time will develop the typical mucosal lesion (Weinstein 1974, Ferguson et al.1993). A recent study found that the presentation of coeliac disease depends on age: presenting symptom among the youngest children being chronic diarrhoea and, among older children, abdominal pain (Savilahti et al. 2010).

1.1 Classical gastrointestinal coeliac disease

Coeliac disease has been classically considered to manifest as a malabsorption syndrome in small children, characterised by chronic diarrhoea, steatorrhoea, malnutrition, failure to thrive and abdominal distension and pain (Visakorpi et al. 1970, Young and Pringle 1971). Children have also been reported to suffer from short stature and rickets (Visakorpi et al. 1970, Young and Pringle 1971, Verkasalo et al. 1978, Groll et al. 1980). Malabsorption may lead to deficiencies in vitamins

and micronutrients, resulting, for example, in iron deficiency or megaloblastic anaemia and bone disturbances (Melvin et al. 1970, Young and Pringle 1971). Nutritional deficiencies have been reported to be common also among screen-detected patients (Tikkakoski et al. 2007). Over the last few decades there have been reports of the changing nature of coeliac disease. Fewer patients with severe gastrointestinal symptoms are detected and an increasing number are diagnosed due to mild or extraintestinal symptoms (Logan et al. 1983, Mäki et al. 1988). In addition, the disease may be totally asymptomatic at diagnosis (Collin et al. 1997). As in the case of other autoimmune diseases, most coeliac disease patients are female (Mäki et al. 1997).

1.2 Extraintestinal manifestations and complications

Contrary to what has previously been thought, coeliac disease cannot be regarded solely as a gastrointestinal disease, since symptoms may also derive from other than gastrointestinal origin. Dermatitis herpetiformis is the skin form of coeliac disease and almost all such patients betray mucosal changes in the small bowel (Marks et al. 1966). Dermatitis herpetiformis is more common among males than females and is associated with complications similar to those in gastrointestinal coeliac disease (Collin et al. 1996a).

Coeliac disease has been associated with numerous neurological disorders, for example migraine, peripheral neuropathy, ataxia, encephalopathy, myopathy and epilepsy with occipital calcifications (Gobbi et al. 1992, Hadjivassiliou et al. 1996, Luostarinen et al. 1999, Gabrielli et al. 2003, Peltola et al. 2009, Hadjivassiliou et al. 2010). In addition, early-onset dementia has been associated with the disease (Collin et al. 1991). Psychiatric disturbances reported to be related to coeliac disease include depression and anxiety (Hallert and Aström 1982, Addolorato et al. 2001). Patients have also been suggested to suffer from sleeping disorders (Zingone et al. 2010).

Coeliac disease may manifest with gynaecological or obstetric problems. It is reported to be associated with delayed menarche, intrauterine growth retardation, miscarriages and infertility (Ferguson et al. 1982, Sher and Mayberry 1994, Smecuol et al. 1996, Ciacci et al. 1996). However, such findings have not been

consistent (Kolho et al. 1999, Greco et al. 2004). Further, some studies have reported that males may suffer from infertility caused by coeliac disease, whereas others have found no indication of such a risk (Baker and Read 1975, Meloni et al. 1999, Zugna et al. 2011).

Osteomalasia, impaired bone metabolism, osteopenia and osteoporosis have been reported in untreated coeliac disease patients (Hajjar et al. 1974, Caraceni et al. 1988, Mora et al. 1993, Valdimarsson et al. 1994). Bone disturbances have been held to be a separate autoimmune process in addition to calcium malabsorption (Corrazza et al. 2005). In some studies, the disease has been associated with an increased risk of fractures while in some the risk was comparable to that among controls (Weast et al. 2003, Thomason et al. 2003, Moreno et al. 2004, Olmos et al. 2008, Sánchez et al. 2011). There are, however, qualitative and quantitative differences among the relevant studies. Untreated coeliac disease has also been thought to lead to hyposplenism and to expose patients to infections (Di O'Donoghue 1986, Sabatino et al. 2006, Ludvigsson et al. 2008). Further, coeliac disease has been associated with other disorders such as dental enamel defects (Aine et al. 1990), aphthous ulcerations (Ferguson et al. 1980), joint pain and arthritis (Bourne et al. 1985, Collin et al. 1992) and elevated liver enzymes or liver dysfunction (Hagander et al. 1977, Volta et al. 1998, Kaukinen et al. 2002). Prolonged gluten exposure has been suggested to predispose coeliac disease patients to the development of other autoimmune disorders (See section 1.3), but results are controversial (Ventura et al. 1999, Sategna Guidetti et al. 2001, Viljamaa et al. 2005b).

The most severe complications related to coeliac disease are certain malignancies. Patients have been reported to carry an increased risk especially of non-Hodgkin lymphomas, but also of cancers of the gastrointestinal tract (Holmes et al. 1989, Green et al. 2003, Viljamaa et al. 2006). The excess risk of lymphomas seems, however, to have decreased during recent decades (Gao et al. 2009). The disease has also been associated with increased mortality, mainly due to malignancies (Corrao et al. 2001, West et al. 2004a, Solaymani-Dodaran et al. 2007). In contrast, the risk of malignant diseases and mortality among diagnosed coeliac disease patients following a gluten-free diet has been reported to be comparable with that in the general population (Collin et al. 1994a). However, results indicative of an increased risk of malignancies have been obtained in

Table 1. The prevalence of biopsy-proven coeliac disease among patients with associated conditions.

Condition and reference	Population	Antibody positivity (%)	Coeliac disease (%)
Type 1 diabetes mellitus			
Mäki et al. 1984a	215 children	ARA 4.2	2.3
Picarelli et al. 2005	94 adults	EmA 13.8	13.8
Autoimmune thyroid diseases			
Collin et al. 1994b	83 adults	EmA, ARA, AGA 4.8	4.8
Sattar et al. 2011	302 children and adolescents	TG2A 4.6	2.3
Sjögren's syndrome			
Iltanen et al. 1999	34 adults	AGA 38.2, EmA 8.8	14.7
Szodoray et al. 2004	111 adults	AGA, EmA, TG2A 5.4	4.5
Autoimmune hepatitis			
Volta et al. 1998b	181 children and adults	AGA 13.8, EmA 4.4	2.8
Villalta et al. 2005	47 children and adults	EmA, TG2A 6.4	6.4
Primary biliary cirrhosis			
Dickey et al. 1997	57 adults	EmA 10.5	7.0
Gillett et al. 2000	378 adults	EmA 2.6, TG2A 14.3	1.3
Addison's disease			
O'Leary et al. 2002	44 children and adults	EmA 4.5	12.2
Betterle et a. 2006	109 children and adults	TG2A 3.7	2.7
IgA-nephropathy			
Fornasieri et al. 1987	121 children and adults	AGA 3.3	1.7
Collin et al. 2002	168 adults	EmA 1.8, TG2A 3.6	3.6
Selective IgA deficiency			
Meini et al. 1996	65 children	AGA 24.6	7.7
Lenhardt et al. 2004	126 children	AGA 21.4, TG2A 14.3	8.7
Down's syndrome			
Carlsson et al. 1998	43 children and adolescents	AGA 37.2, EmA 16.3	18.6
Cerqueira et al. 2010	98 children and adults	EmA 19.4, TG2A 12.2	9.2
Turner's syndrome			
Ivarsson et al. 1999	87 children and adolescents	AGA 14.9, EmA 4.6	4.6
Bonamico et al. 2002	389 children and adults	ND	6.4

ARA antireticulin antibody; EmA antiendomysium antibody; ND not defined; TG2A transglutaminase 2 antibody; AGA antigliadin antibody

cohorts comprising symptom-detected patients who might have suffered from the disease for several years. Recently, no excess in mortality or malignancy was observed among undetected coeliac disease patients identified by screening (Lohi et al. 2009a, Lohi et al. 2009b, Godfrey et al. 2010).

1.3 Associated conditions and risk groups

Coeliac disease has been associated with a number of conditions among which the disease is more common than in the general population. This increased risk is partly attributable to shared genetics. One well-known at-risk group are first-degree relatives of coeliac disease patients, among whom about 10% have been suggested to be affected (Stokes et al. 1976, Mäki et al. 1991, Fasano et al. 2003). Associated conditions include other autoimmune disorders such as type 1 diabetes mellitus (Mäki et al. 1984a) and autoimmune thyroidal diseases (Collin et al. 1994a). In addition, subjects with Down's syndrome (Zubillaga et al. 1993), Turner's syndrome (Ivarsson et al. 1999) and selective immunoglobulin A deficiency (Meini et al. 1996) are at risk of developing coeliac disease. The prevalence of coeliac disease among some of the associated conditions is shown in Table 1.

1.4 Body mass index in coeliac disease

BMI is defined as body weight divided by body height squared (kg/m^2). According to the World Health Organisation (WHO) criteria, BMI <18.5 kg/m^2 is considered to be underweight, 18.5-24.9 kg/m^2 normal weight, 25-29.9 kg/m^2 overweight and ≥30 kg/m^2 obese (WHO 2000).

Since the classical presentation of coeliac disease is diarrhoea and weight loss, patients are traditionally assumed to be underweight at diagnosis (Visakorpi et al. 1970, Young and Pringle 1971). Even though the clinical presentation has been shown to be changing (Logan et al. 1983, Lo et al. 2003), it has only in the last decade been noted that coeliac disease patients may be overweight or even obese at diagnosis (Murray et al. 2004, Viljamaa et al. 2005, Dickey et al. 2006, Olén et al. 2009, Cheng et al. 2010) in line with patterns in the general population (Table 2).

Consequently, concern for initially overweight patients gaining further weight on a gluten-free diet has increased, whereas weight gain is desired in underweight patients (Dickey et al. 2006). Reports of the impact of a gluten-free diet on the BMI of patients in recent conditions have been contradictory. Treatment with a gluten-free diet has been reported to induce beneficial changes in BMI (i.e. underweight patients gaining and overweight losing weight) (Murray et al. 2004, Cheng et al. 2010). In contrast, in a study by Dickey and associates (2006), 81% of all patients, including 82% of initially overweight patients, gained weight on a gluten-free diet. Concern over weight gain has applied especially to screen-detected patients, since this may counter the possible benefits of diagnosis (Mearin et al. 2005).

Excessive weight gain and elevated BMI have been associated with an increased risk of morbidities such as type II diabetes mellitus and metabolic syndrome, and a higher risk of vascular disease (Adams et al 2006, Guh et al. 2009). In addition, overweight, obesity and possibly also underweight have recently been found to be associated with increased all-cause mortality (de Gonzalez et al. 2010). On the other hand, coeliac disease patients have been held to have a reduced risk of cardiovascular diseases, but the impact of a gluten-free diet on this risk profile has remained obscure (West et al. 2004b).

Detailed dietary counselling and follow-up in special clinics with expertise in coeliac disease have been suggested to be a major factor in the effort to achieve favourable BMI outcome on a gluten-free diet (Butterworth et al. 2004, Cheng et al. 2010).

Table 2. Body mass index among untreated coeliac disease patients and control subjects in different studies according to World Health Organisation (WHO) criteria for body mass index

Study	Country	n	Study period	Body mass index, (%)			
				Underweight	Normal	Overweight	Obese
Untreated coeliac disease							
Murray et al. 2004	USA	215	1984-1998*	33	32	14	12
Dickey et al. 2006	UK	371	1995-2005	5	57	26	13
Olén et al. 2009	Sweden	244	1983-2000	16	73	11	ND
Cheng et al. 2010	USA	369	1981-2007	17	61	15	7
Kurppa et al. 2010	Finland	46	2003-2008	2	55	24	19
Control population							
West et al. 2004	UK	17925	1987-2002	2	49	34	15
Helakorpi et al. 2008	Finland	3186	2007	8	43	34	15
Sundquist et al. 2010	Sweden	10000	2004-2005	ND	ND	40	11
Ogden et al. 2010 and Fryar et al. 2010	USA	4881	2007-2008	2	30	34	34

ND not defined

*retrospective study, data missing in 9%; different from the WHO definition, underweight is categorised as body mass index less than 20 kg/m^2

1.5 Coeliac disease and quality of life

Health-related quality of life can be defined as an individual's overall satisfaction with life in the context of the culture in which he lives and sense of general personal well-being comprising physical, social and psychological aspects and also somatic sensations affected by one's health status (WHO 1997, Usai et al. 2002). Health-related quality of life has appeared as an emerging outcome in the management of chronic diseases, as assessments also measure health status and the impact of a chronic disorder and its treatment from the patient's perspective (Guyatt et al. 1993). Disease-specific instruments assess the impact of a particular condition, whereas generic instruments can be used in general in many populations (Naughton and Shumaker 2003). Health-related quality of life scores can be used to measure quality-adjusted life years (QALY; a year of life lived at an optimal state of health) which assesses the quality and quantity of life (Raisch 2000). In coeliac disease research, frequently used validated and reliable generic questionnaires include Psychological General Well-Being (PGWB) (Dupuy et al. 1984) and the 36-item short-form (SF-36) (Ware and Sherbourne 1992; Table 3). Most studies assessing quality of life in coeliac disease patients have been cross-sectional and have involved mainly adults with gastrointestinal symptoms (Hallert et al. 1998, Lohiniemi et al. 2000, Häuser et al. 2006, Nachman et al. 2009). There have, however, been a few prospective studies covering both symptom- and screen-detected patients (Table 4).

Untreated coeliac disease is mainly associated with reduced quality of life as compared with healthy controls or the general population (Johnston et al. 2004, Viljamaa et al. 2005, Nachman et al. 2010). In untreated patients, female gender and the presence of symptoms have been reported to explain impaired quality of life (Usai et al. 2002, Hallert et al. 2002a, Johnston et al. 2004). However, the results in question have mostly been obtained among symptom-detected patients.

Table 3. Some generic health-related quality of life instruments used in coeliac disease.

HRQoL instrument	Measured domains	Scale	Score
Psychological General Well-Being questionnaire (PGWB) (Dupuy et al. 1984)	Anxiety Depressed mood Positive well-being Self-control General Health Vitality	6-point Likert scale	22 questions. Total score from 22 to 132; higher scores indicating greater well-being.
Short Form 36 Health Survey (SF-36) (Ware and Sherbourne 1992)	Physical functioning Role limitations because of physical health problems Bodily pain Social functioning General mental health Role limitations because of emotional problems Vitality General health perceptions	Yes/No; 4- to 6-point Likert scale	36 questions. Separated scores for each domain; higher scores indicating greater well-being.
Child health questionnaire (CHQ) (Orban et al. 2001)	Global general health Physical functioning Role-social limitations, behavioural Role-social limitations, physical Bodily pain Behaviour Mental health Self esteem General health perceptions Parental impact, emotional Parental impact, time Family activities Family cohesion	4- to 6-point Likert scale	50 or 28 questions. Scores from 0 to 100 for each domain; higher scores indicating greater health.
TNO-AZL Preschool Children Quality of Life Questionnaire for Parents (TAPQOL) (Fekkes et al. 2000)	Sleeping Appetite Lung problems Stomach problems Skin problems Motor function Problem behaviour Social functioning Communication Positive mood Anxiety Liveliness	5-point scale	43 questions. Scores from 0 to 100 for each domain, higher scores indicate a better quality of life.

Table 4. Prospective studies assessing the quality of life (QoL) of coeliac disease patients at diagnosis and after one year on a gluten-free diet.

Study	Population, n	QoL measured by	Results
Mustalahti et al. 2002	19 screen-detected and 21 symptom-detected adults; 105 non-coeliac controls	PGWB	QoL did not differ from that of controls at baseline among screen-detected patients and improved on a gluten-free diet exceeding that of controls; QoL was impaired at baseline and improved on diet among symptom-detected patients reaching the level of controls
Peräaho et al. 2002	7 screen-detected and 50 symptom-detected adults*	PGWB	QoL improved on a gluten-free diet among the combined group
Johnston et al. 2004	14 screen-detected and 17 symptom-detected adults; 23 and 26 healthy non-coeliac controls†	SF-36	QoL of symptom-detected patients was impaired at baseline but improved on treatment and was comparable with that of controls; QoL of screen-detected patients did not differ from that of controls at baseline or after follow-up
Korponay-Szabó et al. 2007	32 screen-detected children; 80 non-coeliac controls‡	Child health questionnaire	General health was impaired at baseline and improved on a gluten-free diet, bodily pain decreased on diet
Nachman et al. 2009	10 screen-detected and 122 symptom-detected adults; 70 healthy controls	SF-36	QoL improved among symptom-detected patients and was comparable with that of controls; QoL of screen-detected patients did not differ from that of controls at baseline or after follow-up
van Koppen et al. 2009	19 screen-detected children (12 symptomatic); 251 controls from the general population	TAPQOL	QoL of symptomatic children was impaired at baseline but improved on treatment and was comparable with that of controls; QoL of asymptomatic children did not differ from that of controls at baseline or after follow-up
Kurppa et al. 2010	5 screen-detected and 41 symptom-detected adults*; 110 non-coeliac controls	PGWB	QoL of the whole coeliac group was comparable with that of controls at baseline and improved on dietary treatment

QoL quality of life; PGWB Psychological General Well-Being questionnaire; SF-36 Short Form 36 Health Survey; TAPQOL TNO-AZL Preschool Children Quality of Life Questionnaire for Parents

*Screen-detected and symptom-detected patients were analysed together

†23 for screen-detected and 26 for symptom-detected patients

‡Follow-up time 6 months

Results on the effect of treatment with a gluten-free diet are still inconclusive especially in cases detected by screening. In many studies, quality of life among symptom-detected coeliac disease patients has improved on dietary treatment, being comparable to that among non-coeliac controls (Lohiniemi et al. 2000, Peräaho et al. 2003, Johnston et al. 2004, Nachman et al. 2009). In addition, screen-detected patients have been shown to benefit from a gluten-free diet (Mustalahti et al. 2002, van Koppen et al. 2009) and to enjoy a quality of life comparable to that among symptom-detected patients and non-coeliac controls after several years on treatment (Viljamaa et al. 2005) (Table 4). In contrast, beneficial effects of treatment (for example alleviation of symptoms, enhanced quality of life and better well-being) have been observed only in those with gastrointestinal symptoms (Whitaker et al. 2009). One recent study, however, found that experienced negative impact of diagnosis and treatmenton quality of life were not associated with the presence or absence of symptoms prior to diagnosis (Rosén et al. 2011). In the long term, coeliac disease patients have been reported to suffer from lowered quality of life when compared to the general population despite of being on a gluten-free diet (Hallert et al. 1998). Poorer quality of life on treatment has been associated with female gender (Hallert et al. 2002a), younger age at diagnosis (Ciacci et al. 2003, Häuser et al. 2007), physical and mental co-morbidities (Häuser et al. 2007) and dissatisfaction with doctor-patient communication (Häuser et al. 2007). In addition, some studies have shown a connection between poor dietary compliance and impaired quality of life (Usai et al. 2002, Häuser et al 2007, Nachman et al. 2010), whereas some studies have found no such connection (Fera et al. 2003, Hopman et al. 2009).

Being diagnosed with coeliac disease may induce a stigma of chronic disorder or the experience of being different from others mainly by reason of dietary restrictions (Hallert et al. 2002a, Lee and Newman 2003, Sverker et al. 2005, Olsson et al. 2009, Whitaker et al. 2009). According to these studies patients socialise less, avoid dining out and travelling and also report the diet to have a negative impact on family life. Experiences of being different comprise a major problem especially for adolescents, among whom they reflected negatively on dietary compliance (Olsson et al. 2009*).* Depression has been associated with both untreated and treated coeliac disease in adults (Hallert and Åström 1982, Ciacci et al. 1998, Addolorato et al. 2001), whereas anxiety has been shown to be reduced

on treatment (Addolorato et al 2001). Patients have indicated as issues promotive of their quality of life for example better labelling and availability of gluten-free products, earlier diagnosis and improved dietary counselling (Zarkadas et al. 2006, Bebb et al. 2006). Also the physician's attitude and the quality of doctor-patient communication have been pointed as important in increasing the patient's ability to adapt to coeliac disease (Ciacci et al. 2002).

2. DIAGNOSIS OF COELIAC DISEASE

2.1 Diagnostic criteria

According to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria for coeliac disease from the year 1990, the diagnosis is based on demonstration of small-bowel villous atrophy together with crypt hyperplasia during a gluten-containing diet. Additionally, clinical improvement or histological recovery on a gluten-free diet is requisite (Walker-Smith et al. 1990). The same criteria are applied in both adults and children (United European Gastroenterology 2001). For adults, a biopsy is still needed and also a second biopsy is generally recommended (United European Gastroenterology 2001). The presence of coeliac antibodies is not essential but supports the diagnosis. If necessary, genetic HLA typing can also be undertaken to obtain further evidence for the diagnosis of coeliac disease, as almost all sufferers carry either the HLA DQ2 or the DQ8 haplotype (Sollid et al. 1989, Mäki et al. 2003, Karell et al. 2003). The ESPGHAN criteria were recently revised and it was stated that if transglutaminase 2 (TG2) antibody titres are over ten times the cut-off limit for normal in a symptomatic child, further laboratory testing (antibody or genetic) could confirm the diagnosis even without a small-bowel biopsy (Husby et al. 2012). For the diagnosis of dermatitis herpetiformis, granular IgA deposits in the dermal papillae of healthy skin close to the active lesion have to be shown (van der Meer 1969).

2.2 Small-bowel mucosal biopsy

As discussed in the previous section, the diagnosis of coeliac disease is typically made from a small-bowel mucosal biopsy sample. Samples are taken by upper gastrointestinal endoscopy. It has been shown that the mucosal lesion typical for coeliac disease develops gradually from normal villous height with increased density of intraepithelial lymphocytes (IELs) (Marsh I) to crypt hyperplasia (Marsh II), finally followed by villous atrophy from patchy lesions to totally flat mucosa (Marsh III) (Marsh 1992). By reason of the possibly patchy nature of the mucosal lesion, multiple samples should be taken (Bonamico et al. 2004). Biopsy specimens should be well-oriented to allow proper interpretation (Granot et al. 1993) and interpretation of specimens is always somewhat interpretator-dependent. In addition, fully developed mucosal lesion is needed for the diagnosis of coeliac disease, which tenders the diagnosis of early-stage disease complicated (Walker-Smith et al. 1990). In borderline cases counting of IELs is recommended and an increase in the density of gammadelta positive T cells supports the diagnosis (Järvinen et al. 2003). Another problem is that villous atrophy with crypt hyperplasia is not pathognomic solely for coeliac disease but can be found, for example, in patients with giardiasis, food allergies, autoimmune-enteropathy and Crohn's disease (Green and Cellier 2007).

2.3 Coeliac antibodies

Antibodies against gluten peptides and autoantibodies against tissue structures can be detected in the sera of untreated coeliac disease patients. Serum antigliadin antibodies (AGA) analysed in IgA- and IgG-classes were previously widely used (Hill et al. 2005). However, the sensitivity and specificity vary between approximately 30% and 100% (Mäki et al. 1991, Sulkanen et al. 1998a, Mankaï et al. 2005, Kaukinen et al. 2007). Elevated AGA levels have also been found in non-coeliac subjects suffering, for example, from food allergy (Lindberg et al. 1985) or chronic inflammatory bowel disease (Kull et al. 1999), and even in healthy individuals without coeliac disease-associated genetics (Mäki et al. 1991, Ruuskanen et al. 2011). AGA is not recommended in clinical practice (Hill et al.

2005). Conversely, some studies have shown that antibodies against deamidated gliadin peptides have significantly higher diagnostic accuracy than those against whole gliadin (Schwertz et al. 2004, Kaukinen et al. 2007, Volta et al. 2008), offering thus a promisingtool for detecting coeliac disease and in follow-up.

The first autoantibodies against reticulin fibres (ARA) were detected in 1971 (Seah et al. 1971). These antibodies can be measured in IgA- and IgG-class by indirect immunofluorescence using rodent tissues, the IgA-class antibodies being more accurate in detecting coeliac disease (Mäki et al. 1984). Their specificity has also been shown to be higher than that of AGA (Seah et al. 1971, Mäki et al. 1984). In 1983, a new antibody reacting with endomysium from the smooth muscle of the monkey oesophagus was depicted (Chorzelski et al. 1983). These endomysial antibodies (EmA) were also measured by indirect immunofluorescence. It was subsequently found that human umbilical cord could be used as antigen instead of monkey oesophagus (Ladinser et al. 1994, Kolho and Savilahti 1997). The sensitivity of EmA ranges from 86% to 100% (Tensei et al. 2003, Ferreira et al. 1992, Biangi et al. 1999) and specificity from 90% to 100% (de Lecea et al. 1996, Biangi et al. 1999, Volta et al. 2008). However, the immunofluerescence method is laborious and test results are laboratory-dependent.

In 1997 Dieterich and associates (1997) identified transglutaminase 2 (TG2) as the autoantigen of coeliac disease. An enzyme-linked immunosorbent assay (ELISA) was established for the detection of both IgA and IgG TG2 antibodies, which made measurement of TG2 antibodies a useful tool in screening for latent or subclinical disease (Sulkanen et al. 1998b). Moreover, TG2 has also been shown to have an important role in the pathogenesis of coeliac disease (Molberg et al. 2002). Evidence shows that TG2 antibodies are synthesised at mucosal level and appear in the circulation due to a spillover effect (Marzari et al. 2001). The sensitivity and specificity of TG2 antibodies are high and comparable to those of EmA (Dieterich et al. 1998, Bonamico et al. 2001, Mankaï et al. 2005). However, the positive predictive value of TG2 antibodies is somewhat lower than that of EmA (Carroccio et al. 2002). Measurement of TG2 antibodies has also proved a viable method for developing accurate rapid tests to detect untreated coeliac disease. One promising tool is a whole-blood self-TG2-based point-of-care test (Korponay-Szabó et al. 2005, Raivio et al. 2006).

Even though EmA and TG2 have been considered highly specific and valuable predictors of forthcoming coeliac disease, these antibodies have been shown to fluctuate, and also negative seroconversion occurs without initiation of a gluten-free diet (Simell et al. 2005, Bister et al. 2005, Simell et al. 2007). However, it was recently reported that negative seroconversion can be temporary and does not exclude coeliac disease later in life (Kurppa et al. 2011). It should be noted that in patients with selective IgA deficiency the antibodies should be measured in IgG class (Korponay-Szabó et al. 2003).

The same IgA antibodies targeted against TG2 as those found in the sera of coeliac disease patients can be detected as extracellular depositions in patients' small-bowel mucosa (Korponay-Szabó et al. 2004). The IgA deposits appear early in disease development, even before EmA are present in the circulation (Korponay-Szabó et al. 2004, Salmi et al. 2006a). They can also be detected before the development of villous atrophy (Korponay-Szabó et al. 2004, Kaukinen et al. 2005, Salmi et al. 2006b). As the specificity of IgA deposits has been shown to be high, they could be used in the early detection of coeliac disease especially in uncertain cases (Kaukinen et al. 2005, Koskinen et al. 2008).

2.4 Diagnostic delay

Even though awareness of the wide variety of clinical presentations of coeliac disease has increased in recent decades, the delay from the onset of symptoms to the diagnosis in adults is still on average 4 to 13 years (Green et al. 2001, Lo et al. 2003, Häuser et al. 2007, Gray et al. 2010) (Table 5). During that period, patients may consult several gastroenterologists or other physicians about their symptoms. Some recent studies have found that the diagnosis of coeliac disease was made promptly or at first hospital referral in 54-64% of cases (Dickey et al. 1996, Green et al. 2001). However, it also emerged that prior to diagnosis, 14-27% of patients had consulted two or more gastroenterologists and 27% three or more physicians, and 21% had needed three or more hospital referrals to receive the correct diagnosis (Dickey et al. 1996, Green et al. 2001, Cranney et al. 2007). The delay in diagnosis and numerous consultations imply an incremental burden and time loss both to patients and to the health care system. Moreover, patients have indicated

Table 5. Delay from the onset of symptoms to the diagnosis of coeliac disease in different studies.

Study	Country	n	Study period	Delay in diagnosis, years	
				Mean	Median
Adults					
Gregory et al. 1983	UK	106	1976-1980	11	ND
Bodé and Gudmand-Høyer 1996	Denmark	50	1971-1992	ND	3
Corazza et al. 1996	Italy	419	1972-1995	10.3*	ND
Schramm and Lankisch 1997	Germany	15	Before 1975	16.1	8
		19	1975-1979	11	2.4
		40	1980-1984	11.2	9.5
		103	1993-1994	9.0	4.4
Green et al. 2001	USA	1611	1996-1997	11	ND
Lo et al. 2003	USA	57	1981-1993	9.0	ND
		170	Since 1993	4.4	ND
Rampetab et al. 2006	USA	14	1981-1985	10.6	ND
		33	1986-1990	6.4	ND

		60	1991-1995	4.6	ND
		172	Since 2001	4.0	ND
Cranney et al. 2007	Canada	369	2002	11.7	5
Häuser et al. 2007	Germany	446	2005	5.6	1
Ouaka-Kchaou et al. 2008	Tunisia	64	1991-2006	4.6	ND
Fernández et al. 2010	Spain	68	1985-2008	3	ND
Gray and Papanicolas 2010	UK	788	2007	13.2	ND
Rodrigo-Sáez et al. 2011	Spain	144	2000-2006	10	4
Norström et al. 2011	Sweden	1031	2009	9.7	4
Children					
Khuffash et al. 1987	Kuwait	20	1980-1985	3.2	ND
Rawashdeh et al. 1996	Jordan	34	1991-1994	ND	4
Poddar et al. 2006	India	300	1997-2003	3.5	ND
Roma et al. 2009	Greece	72	1978-1987	1.1	ND
		71	1988-1997	1.6	ND
		141	1997-2007	2.3	ND

ND not defined

*9.7 for those with extraintestinal symptoms and 14.0 for those with gastrointestinal symptom

earlier diagnosis as a factor which would improve their quality of life (Zarkadas et al. 2006, Cranney et al. 2007).

3. EPIDEMIOLOGY OF COELIAC DISEASE

With increased use of serological antibody tests and wider awareness of the variable presentation of coeliac disease, the rate of new diagnoses has risen. In recent screening studies, its prevalence has been reported to be around 1% (Mäki et al. 2003, Fasano et al. 2003, Mustalahti et al. 2010), and more recent studies have suggested that the prevalence is further increasing (Lohi et al. 2007, Rubio-Tapia et al. 2009). In addition, the prevalence has been reported to increase with age, reaching 2.7% seroprevalence among the elderly population (Vilppula et al 2009). This notwithstanding, the disease is still underdiagnosed and the clinical prevalence has been reported to be about 0.6% in Finland (Virta et al. 2009). In the 80s it was reported that the clinical picture had become milder and diagnosis had shifted towards older age groups (Logan et al. 1983, Mäki et al. 1988).

The prevalence of coeliac disease has been reported to be low among Afroamericans and in China and Japan. However, the highest seroprevalence of 5.6% has been reported in Saharawi children (Catassi et al. 1999). These differences around the world might be due to genetic variation. Coeliac disease-associated HLA risk alleles have been reported to be rare in for example the Japanese (Saito et al. 2000). In contrast, in northern the China, HLA distribution and consumption of wheat have been reported to resemble those in Caucasian populations (Yu et al. 2006, Wu et al. 2010) and differences in prevalence have been attributed to lack of awareness (Wu et al. 2010). Also environmental factors influence the prevalence of coeliac disease (see Section 4.) as seen in Sweden where a prevalence of up to 3% was noted among children born durig the epidemic of coeliac disease (Myléus et al. 2009).

4. PATHOGENESIS OF COELIAC DISEASE

According to current knowledge, the development of coeliac disease needs at least genetic predisposition in respect of the immune system and an environmental trigger, gluten peptides. In addition, viral infections (Kagnoff et al. 1984, Fine et al. 2001), age at gluten introduction, the amount of gluten consumed as well as breastfeeding (Ivarsson et al. 2002) have been held to have an impact on disease development. Further, economic environment, especially the standard of hygiene, has been presumed to affect the risk of coeliac disease (Kondrashova et al. 2008).

Coeliac disease has been strongly associated with the HLA-DQ region at 6p21.3 with alleles coding HLA DQ2 and DQ8 molecules (Solid et al. 1989). The HLA DQ2 molecule encoded by the alleles DQA1*0501 and DQB1*0201 is present in more than 90% of patients, while almost all the rest have DQ8 encoded by DQA1*0301 and DQB1*0302 (Sollid and Thornsby 1993, Karell et al. 2003). The gene dose effect of DQ2 has been suggested to be associated with more severe clinical presentation (Karinen et al. 2006), but results are somewhat contradictory (Greco et al. 1998, Thomas et al. 2009). The concordance rate reported among monozygotic twins is about 90% and among HLA-identical siblings about 30% (Greco et al. 2002). Coeliac disease-associated HLA class II genes are present in approximately 40% of the Caucasian population (Mäki et al. 2003). The HLA region has been thought to explain only 40% of the genetic background of the disease (Bevan et al. 1999). Several non-HLA regions have been shown to be associated with coeliac disease and some interesting genes have been found in these loci (Einarsdottir et al. 2009, Dubois et al. 2010). However, some of these associations have been found only in certain populations. Additionally, the roles of new candidate genes in the pathogenesis of coeliac disease remain mainly unsolved.

Triggers to the development of small-bowel villous atrophy are incompletely digested gluten peptides entering the lamina propria in the intestinal mucosa. The peptides are resistant to degradation by proteases in the gastrointestinal tract (Shan et al. 2002). It has been suggested that the increased permeability of the intestinal epithelium in coeliac disease patients might be caused by gliadin-induced

alterations in tight junctions, possibly due to zonulin protein, this allowing paracellular entrance (Fasano et al. 2000, Draco et al. 2006). Gluten peptides can also be imported via transcytosis (Zimmer et al. 1995, Heyman and Menard 2009, Rauhavirta et al. 2011). Once having entered the lamina propria, these peptides activate both the innate immune response and the adaptive immune response involving $CD4^+$ T cells. The non-immunogenic, so-called toxic gliadin (p31-43) induces rapidly increased production of interleukin 15 (IL-15), which has been thought to be a major contributor in the pathogenesis of coeliac disease (Maiuri et al. 2003, Hüe et al. 2004). Increased production of IL-15 activates IELs and leads to their overexpression (Mention et al. 2003) and exposes intestinal epithelial cells to the cytolytic effects of activated IELs (Hüe et al. 2004).

The adaptive immune response in genetically susceptible individuals is activated by the immunogenic parts of gliadin, especially p57-89, which is reported to have several epitopes for CD4+ T cell recognition (Shan et al. 2002). Overexpression of IL-15 has also been held to sustain a persistent activation of the adaptive immune system (Maiuri et al. 2003). Complete gliadin molecules have low affinity for HLA DQ binding (van de Wal et al. 1996). Deamidation of gliadin by TG2 increases the binding affinity to HLA DQ2 and DQ8 molecules and thus its capability to stimulate CD4+ T cells, this being an essential step in the pathogenesis of coeliac disease (Molberg et al. 1998). After deamidation and binding to DQ2 and DQ8 molecules of antigen presenting cells, gluten peptides are presented to CD4+ helper T lymphocytes (Th), which are then activated (Molberg et al. 1998). Proliferation of Th1 cells leads to production of proinflammatory cytokines such as TNF-α and interferon-γ (Nilsen et al. 1995). These cytokines activate fibroblasts and inflammatory cells to produce enzymes such as matrix metalloproteinases which can damage the mucosa, resulting in villous atrophy and crypt hyperplasia (Pender et al. 1997, Daum et al. 1999). The Th2 pathway leads to activation and proliferation of B cells, which then produce antibodies against, for example, transglutaminase 2 (Sollid et al. 1997).

TG2 antibodies have also been suggested to contribute to the pathogenesis of coeliac disease. Total IgA in untreated coeliac disease patients has been shown to inhibit the differentiation of epithelial cells *in vitro* (Halttunen and Mäki 1999). Coeliac autoantibodies have also been reported to increase the permeability of the intestinal epithelium (Zanoni et al. 2006), to contribute to epithelial cell

proliferation (Barone et al. 2007) and to disturb angiogenesis, thus possibly leading to disruption of the mucosal vasculature (Myrsky et al. 2008).

5. TREATMENT OF COELIAC DISEASE

5.1 Dietary treatment

The only currently known treatment for coeliac disease and dermatitis herpetiformis is a strict life-long gluten-free diet, meaning permanent avoidance of wheat, barley and rye in the diet. Previously, also oat was considered as harmful but in 1995 Janatuinen and associates (1995) showed that coeliac disease patients can tolerate oat, and histological remission is also possible on an oat-containing diet. Later, the same was shown in children (Högberg et al. 2004). Oat has also been proved to be safe for dermatitis herpetiformis patients (Reunala et al. 1998). In contrast, some patients have developed symptoms or mucosal lesion after ingestion of oat, indicating that not all coeliac disease patients tolerate oat similarly (Lundin et al. 2003, Peräaho et al. 2004). There has also been discussion as to whether the diet should be naturally gluten-free or are products containing trace amounts of gluten tolerated. Industrially purified wheat-starch-based gluten-free products have been shown to yield a dietary response similar to that to a naturally gluten-free diet (Kaukinen et al. 1999, Peräaho et al. 2003).

Clinical response to treatment is typically detectable soon after initiation of a gluten-free diet (Murray et al. 2004). Although mucosal improvement begins after removal of gluten from the diet, total histological remission may take several years (Yardelay et al. 1962, Wahab e al. 2002, Collin et al. 2004) and patients may have symptoms even after recovery of the small-bowel mucosa (Midhagen et al. 2003, Murray et al. 2004). In addition to alleviation of gastrointestinal symptoms, gluten-free diet has also been reported to resolve malabsorptive states such as iron deficiency anaemia (Annibale et al 2001). The diet also has a beneficial impact on

extraintestinal manifestations of the disease. An increase in bone mineral density has been reported in both symptom- and screen-detected patients (Mora et al. 1993, Mustalahti et al. 1999) and the risk of fractures has been shown to decrease on treatment (Olmos et al. 2008). A gluten-free diet may also have a beneficial impact on neurological symptoms such as ataxia, peripheral neuropathy and migraine (Kaplan et al. 1988, Pellechia et al. 1995, Gabrielli et al. 2003), arthritis (Bourne et al. 1985) and liver dysfunction (Hagander et al. 1977, Volta et al. 1998, Kaukinen et al. 2002). Further, dietary treatment has been reported to have positive effects in gynaecological and obstetric disorders (Sher et al. 1994, Smecuol et al. 1996, Collin et al. 1996b). Improvement on a gluten-free diet has also been noted in psychiatric complaints (Corvaglia et al. 1999, Addolorato et al. 2001, Pynnönen et al. 2005). The overall risk of malignancies does not differ between treated coeliac disease patients and the general population (Holmes et al. 1989, Collin et al. 1996). The diet has also been shown to reduce mortality (Corrao et al. 2001). Those suffering from dermatitis herpetiformis have been suggested to be more sensitive to ingested gluten than coeliac disease patients. In addition, skin symptoms respond slowly to a gluten-free diet and the anti-inflammatory drug dapsone is often required (Fry et al. 1973, Reunala et al. 1977, Reunala et al. 1984).

In a small percentage of adult-onset coeliac disease patients, treatment with a strict gluten-free diet does not result in clinical and histological recovery and patients develop primary or secondary resistance to the diet. If other causes of non-responsive coeliac disease and overt malignancy are absent, the condition is called refractory coeliac disease and is characterised by persistent villous atrophy and abnormal phenotype of IELs (Rubio-Tapia and Murray 2010). Such patients may benefit from treatment with immunosuppressive medication (Biagi and Corazza 2001). However, despite of a strict gluten-free diet some non-responsive patients carry an increased risk for severe complications such as enteropathy-associated T-cell lymphoma (Rubio-Tapia and Murray 2010).

Dietary treatment has been reported to result in improved quality of life (Hallert et al. 1998, Lohiniemi et al. 2000, Peräaho et al. 2003, Johnston et al. 2004, Nachman et al. 2009). However, a gluten-free diet is restrictive and difficult to maintain (Mäki et al. 2003, Sverker et al. 2005, Niewinski 2008). It may also have adverse affects on everyday life (see Section 1.5). Strict compliance with a gluten-free diet has varied in different studies between 17% and 96% (Troncone et

al. 1995, Dickey et al. 2000, Green et al. 2001, Norström et al. 2011). Dietary counselling by an experienced dietician has been considered important in enhancing compliance (Butterworth et al. 2004, Case 2005, Niewinski 2008). Especially challenging may be achieving compliance to a gluten-free diet in adolescents (Olsson et al. 2008) and ethnic minorities (Butterworth et al 2004). In addition, it has been suggested that dietary compliance is poorer among screen-detected patients than in symptom-detected patients (Fabiani et al. 2000, Shamir et al. 2007). In contrast, in some studies compliance in screen-detected patients has been reported to be comparable to that of symptom-detected patients (Mustalahti et al. 2002, Viljamaa et al. 2005a).

5.2 New treatment options

As adherence to a gluten-free diet is often complicated, there is call for other treatment options. These several steps in the pathogenesis of coeliac disease could be targeted. It has been suggested that gluten could be detoxificated via targeted mutagenesis of cereals to modify the composition of T cell-stimulatory gluten peptides (Vader et a. 2003). Enzymatic degradation of gluten to nontoxic fragments would also prevent mucosal damage. Enzyme preparations could be used during baking, as food additives or as enzyme therapy (Gass et al. 2007, Stenman et al. 2009, Helmerhorst et al. 2010). Induction of antigen-specific tolerance to gluten by genetically modified Lactococcus lactis has also been suggested as a possible therapeutic approach (Huibregtse et al. 2009). However, these approaches are mainly in their preclinical stage. Paracellular permeability to gluten peptides in the intestine could be reduced by using zonulin antagonists, a strategy which has recently completed phase IIb in clinical trials (Paterson et al. 2007). The immune response to gluten might be reduced or prevented by IL-15 antagonists or IL-10, but these too are at the preclinical stage (Maiuri et al. 2003, Benahmed et al. 2007). In addition, TG2 inhibitors have been suggested as a possible means to reduce T cell activation (Molberg et al. 2001), and HLA-DQ-mediated T cell activation could also be blocked (Xia et al. 2007). Both modalities are at the preclinical stage. A peptide-based immunotherapy could be used as vaccination for gluten tolerisation and is now in phase I of clinical trials (Camarca et al. 2009). As the

development of these therapies is mainly preclinical or at an early phase of clinical trials, it will take years before they are available in the treatment of coeliac disease.

6. DISEASE-RELATED BURDEN

The burden of illness can be perceived in economic consequences for the affected individual and society, medical costs of care and disabilities, inconvenience and social impairment caused by the condition and its treatment and management. The economic impact of a disease can be divided into direct and indirect costs. The former are considered to consist of expenditures for prevention, detection and treatment, including medical facilities and professional services (Rice 1967). Indirect costs comprise economic losses due to morbidity and premature mortality, for example productivity losses at work, sickness absences, intangible costs such as pain and depressive mood, and lost leisure time (Rice 1967, Ruhl et al. 2008).

Coeliac disease is a significant burden to patients and their families, the health care system and society. There is abundant information on the impact of the disease on quality of life and emotional issues (See section 2.5). The economic aspects, however, are just emerging. Some studies have assessed the cost-effectiveness of diagnostic tools (Hopper et al. 2008) and screening for the disease (Hershcovici et al. 2010). Gluten-free products have been estimated to be over 200% more expensive than regular products (Stevens and Rashid 2008). A gluten-free diet usually results in alleviation of symptoms and thus diminished burden of illness. Otherwise, information as to how to reduce the burden related to coeliac disease is scant. Issues suggested to reduce the burden of illness comprise better availability and reduced cost of gluten-free products (Lee et al. 2007), intensified dietary counselling (Zarkadas et al. 2006, Cranney et al. 2007), better education of health care professionals (Lee and Newman 2003) and established doctor-patient communication (Ciacci et al. 2002).

THE PRESENT STUDY

1. AIMS

The aims of the present study were to assess the direct and indirect disease burden related to coeliac disease with different clinical presentations during the one-year periods prior to and after diagnosis, and to establish whether treatment with a gluten-free diet has any impact on this burden.

The specific aims were:

1. To assess the disease burden experienced by coeliac disease patients in terms of their perception of the disease and quality of life prior and after diagnosis, and to compare results to those of non-coeliac controls (**I-II**).

2. To establish whether dietary treatment would result in beneficial changes in BMI in coeliac disease patients, thus reducing the risk of co-morbidities related to under- and overweight, and to compare the BMI results to those of the general population (**III**).

3. To assess the direct and indirect burden to society and the health care system related to undetected coeliac disease measured as use of medical services, consumption of on-demand medication and sickness absence, and to establish whether dietary treatment would have any effect on these (**IV**).

2. PATIENTS

2.1 Coeliac disease patients (**I-IV**)

A large nationwide cohort of consecutive newly detected coeliac disease patients was evaluated prospectively. All 1864 individuals who joined the Finnish Coeliac Society between February 2007 and May 2008 were asked to participate in the study via a mailed study questionnaire. All adults (over 16 years of age) who were biopsy-proven coeliac disease patients diagnosed within one year were considered eligible. The accuracy of the diagnoses was based on the patients' own reports on whether their diagnosis was confirmed by small-bowel or skin biopsy. Altogether 1062 (57%) responded. Of the respondents, 364 were excluded: 157 were not diagnosed within a year, 132 were under 16 years of age and 73 had not received a biopsy-proven diagnosis of coeliac disease. In studies **I-III**, an additional two respondents were excluded because of inadequate data regarding clinical presentation. Thus, analyses were conducted in 698 (**I-III**) and 700 (**IV**) coeliac disease patients. Of the total respondents, 679 (97%) also participated in the follow-up conducted one year after the initial survey. A reminder was given by phone to non-responders. Of all patients, 76% were female and the median age was 49 years (range 16-84 years).

For studies **I-III**, the patients were categorised according to symptoms and signs leading to the diagnosis of coeliac disease into three study groups as follows: i) patients with classical intestinal symptoms or signs (e.g. abdominal pain, diarrhoea, flatulence, sideropenic anaemia, weight loss), ii) patients with extraintestinal symptoms or signs (such as dermatitis herpetiformis, neurological problems, infertility, arthralgia), and iii) patients detected by active screening in at-risk groups (such as first-degree relatives of coeliac disease patients, those having type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome or selective IgA deficiency). In addition, a sub-group analysis was carried out separately of screen-detected coeliac disease patients who considered themselves totally asymptomatic at diagnosis.

2.2 Coeliac disease controls for body mass index evaluations (**III**)

For comparison of BMI distributions among untreated and treated coeliac disease patients, data on 207 consecutive untreated coeliac disease patients (median age 49 years, range 18-79, 62% female) referred to Tampere University Hospital were collected. Follow-up data after one year on a strict serology-confirmed gluten-free diet were available for 141 patients. BMI values were calculated from weight and height measured by health care personnel at diagnosis and after a follow-up period of one year.

2.3 Controls for quality of life evaluations (**I**)

The control group for health-related quality of life analyses consisted of 110 non-coeliac adults (median age 48 years, range 23-87 years, 81% female) who were friends or neighbours of coeliac disease patients and had no first-degree relative with coeliac disease.

2.4 Population controls (**III-IV**)

Data on the general population for comparisons of BMI, reported consultations with a doctor and days of absence from work during the same period (2007-2008) were obtained from an annual nationwide postal survey conducted by the National Institute for Health and Welfare since 1978. The survey is entitled "Health Behaviour and Health among the Finnish Adult Population" and is mailed to a random sample of 5000 Finnish adults (15-64 years of age) each year (Helakorpi et al. 2008, Helakorpi et al. 2009).

2.5 Ethical considerations

Informed consent was obtained from all participants after a full written explanation of the objectives of the study, including considerations regarding ethics and data protection and the anonymous deposition of the questionnaires. Ethical approval for the coeliac disease control group for BMI evaluations was obtained from the Ethical Committee of Tampere University Hospital.

3. METHODS

3.1 Medical questionnaire (**I-IV**)

The baseline and follow-up questionnaires were self-developed in co-operation with coeliac disease patients, the Finnish Coeliac Society and Tampere Coeliac Disease Study group. The questionnaires included 31 questions and comprised items on sociodemographic conditions, clinical features and patients' perceptions of the impact of the diagnosis of coeliac disease and treatment with a gluten-free diet on their health and well-being, the latter two being evaluated on a three- to four-point Likert scale. Participants were also asked to report the number of all-cause visits to a health care professional, consumption of pharmaceutical agents and days of absence from work during the last year. The questionnaires also included open response questions on patients' wishes. The feasibility of the study questions was pre-tested by a group of coeliac disease patients. Also face and content validity of the tested items were reviewed by evaluation of the questionnaires by a coeliac disease focus group and gastroenterologists. To measure test-retest reliability, 11 coeliac members of the Finnish Coeliac Society recompleted the initial questionnaire a week after the initial appointment. Test-retest reliability was established using the intraclass correlation coefficient: for the

key items of the questionnaire, the kappa values ranged from 0.84 to 1.00 (values above 0.70 regarded as excellent).

3.2 Quality of life evaluation (**I**)

Health-related quality of life was evaluated using the structured Psychological General Well-Being (PGWB) questionnaire (Dupuy 1984; see Table 3) at diagnosis and after one year on dietary treatment. The questionnaire is validated and widely used in coeliac disease research (Hallert et al. 1998, Mustalahti et al. 2002, Usai et al. 2002, Hallert et al. 2002a). It measures self-perceived health-related well-being and distress and contains 22 items which can be divided into six sub-dimensions: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The scoring of each item is based on six-point Likert scale total scores ranging from 22 to 132, higher scores indicating better psychological well-being.

3.3 BMI and weight evaluations (**III**)

BMI was calculated from height and weight as reported by the participants. Favourable change in BMI was defined as changes towards normal weight: underweight patients gaining weight and overweight and obese patients losing weight. Unfavourable changes were the opposite, unfavourable gain comprising underweight and normal weight patients becoming overweight and overweight and obese patients gaining weight. BMI was categorised according to the WHO criteria. In comparisons to the general population different limits were used: BMI <20.0 kg/m^2 was regarded as underweight, 20.0-24.9 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight and ≥ 30 kg/m^2 as obese.

3.4 Statistical analyses (**I-IV**)

Statistical analysis was carried out using Statistical Package for Social Sciences for Windows software (SPSS version 17.0, SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as means and 95% confidence intervals (CI) or medians and ranges or lower and upper quartiles (**I, IV**). All testing was two-sided and p values <0.05 were considered statistically significant. When appropriate, chi-square test in cross tabulations (**I-IV**) and Student's t-test or Mann-Whitney U test were used to compare differences between groups, and paired t-test or Wilcoxon signed rank test to compare changes within groups (**I, IV**). The McNemar test was used to examine differences within groups (**II, III**). Binary logistic regression analyses were used in association analyses; results are shown as odds ratios and 95% CI (**II, III**).

4. RESULTS

4.1 Patients and clinical presentation (**I-IV**)

The sociodemographic data on the participants are shown in Table 5. The age and sex distribution of the responders did not differ from those of non-responders. Of the 698 coeliac disease patients (**I-III**), 490 (70%) suffered from intestinal symptoms or signs, and 62 (9%) from extraintestinal symptoms or signs and 146 (21%) were detected by screening. Among the screen-detected group, 23 individuals (3% of all) considered themselves totally asymptomatic at diagnosis. In the sub-group of screen-detected asymptomatic patients, there were more females and the subjects were slightly younger than in the other groups.

In Study **I**, the age and sex distribution of the controls was comparable to those of the study group. However, in the general population controls (**III, IV**) the proportion of men was higher than in the coeliac group (44% *vs*. 20%, respectively).

4.2 Quality of life (**I**) and patients' experiences and perceptions of coeliac disease (**II**)

Quality of life as measured in PGWB scores was significantly impaired in the coeliac disease group at diagnosis when compared to the non-coeliac controls (Table 6). The PGWB total score was similarly reduced in all study groups. In addition, in the intestinal symptoms group and in screen-detected patients all PGWB sub-scores were lower than those in the controls. Treatment with a gluten-free diet resulted in a significant improvement in quality of life in the coeliac group also when the different study groups were assessed separately, and in the follow-up, the total scores did not differ from those of the controls. Sub-analyses showed that, in the screen-detected asymptomatic group, PGWB total and sub-scores were

Table 6. Background data on the coeliac disease patients at diagnosis.

	All	Study groups			Sub-group
		Intestinal symptoms	Extraintestinal symptoms	Screen-detected, all	Screen-detected, asymptomatic
	n=700	n=490	n=62	n=146	n=23
Female, %	76	77	68	80	91
Median age (range), years	49 (16-84)	49 (16-84)	54 (20-75)	52 (18-82)	44 (19-82)
Social index, %					
Upper	26	26	31	24	13
Middle	55	54	61	56	52
Lower	13	13	7	12	13
Student	7	7	2	8	22
Duration of symptoms, years *					
Median (range)	3 (0-59)	3 (0-59)	1 (0-30)	2 (0-50)	0
25-75th percentile	1-7	1-7	0.2-3	0.5-5	0
Mean	5.6	6.1	4.1	4.7	0
Diagnosis given in, %					
Primary health care	40	41	27	45	44
Secondary health care	38	40	37	34	35

Tertiary health care	10	8	19	13	17
Private clinic	11	12	16	9	4
Referral to a dietician, %	76	76	79	73	77
Adherence to the diet, %[†]					
Strictly gluten-free	86	85	78	88	74
Occasional gluten	14	14	22	9	26
No diet	0.3	0.4	0	0	0

[*] Time interval between the onset of symptoms and the diagnosis of coeliac disease

[†] p=0.161 when compared between the three study groups and p=0.042 when compared between all four groups

Table 7. Mean Psychological General Well-Being (PGWB) total scores and sub-scores and 95% confidence intervals (CI) of total score in different study groups and controls at diagnosis and on a gluten-free diet.

	Study groups						Subgroup analysis		Controls
	Intestinal symptoms n=490		Extraintestinal symptoms n=62		Screen-detected, all n=146		Screen-detected, asymptomatic n=23		n=110
	At diagnosis	On a GFD	At diagnosis	On a GFD	At diagnosis	On a GFD	At diagnosis	On a GFD	
PGWB total score	88.8*	101.9‡	96.4†	104.8‡	92.7*	104.4‡	103.0	103.1	105.3
95% CI	86.9-90.6	100.3-103.5	91.2-101.5	100.3-109.3	89.5-96.0	101.6-107.3	95.9-110.1	94.0-112.2	103.0-107.6
Anxiety	20.1*	23.4‡	22.3†	24.8‡	21.2*	24.3‡	23.5	23.9	24.1
Depression	14.3*	16.1‡	15.2	16.2§	14.8*	16.2‡	16.1	16.1	16.2
Well-being	14.7*	16.7‡	15.8	17.4‡	15.3*	17.4‡	17.1	16.8	16.9
Self-control	13.4*	14.9‡	14.7	15.4§	13.9*	15.1‡	15.4	14.5	15.3
General health	11.1*	13.3*‡	12.2*	13.3‡	11.9*	13.5†‡	13.9	13.8	14.4
Vitality	15.2*	17.5†‡	16.2†	17.7§	15.7*	18.0‡	17.8	18.1	18.5

GFD gluten-free diet; CI confidence interval
*p<0.001 when compared to controls
†p<0.05 when compared to controls
‡p<0.001 when compared to self at diagnosis
§p< 0.05 when compared to self at diagnosis

comparable to those of the controls both at diagnosis and in the follow-up (Table 7).

At diagnosis, the majority of coeliac disease patients reported suffering from impaired health and were also concerned about their health status in general (Table 6). In the intestinal symptoms group, 94% reported having symptoms which disturbed their life at least to some degree. In the extraintestinal symptoms group the proportion was 79% and in the screen-detected group 82%. In the screen-detected asymptomatic group, the figure was 11%. Receiving the diagnosis of coeliac disease was a shock to 6% of patients, whereas 40% were relieved at having been diagnosed (see Figure 1 in Original publication **II**). Symptomatic patients reported a feeling of relief significantly more frequently than the screen-detected asymptomatic patients ($p<0.001$). Logistic regression analyses showed that a shock reaction was associated with considering the counselling by a physician insufficient (OR 3.4, 95% CI 1.7-6.6).

In the follow-up survey, 86% of all patients reported adherence to a strict gluten-free diet (Table 8). There were no differences between the different study groups. However, dietary lapses were more common in the screen-detected asymptomatic groups than in the other groups ($p=0.042$). After one year on a gluten-free diet, 81% of patients in the intestinal symptoms group, 66% in the extraintestinal symptoms group and 73% in the screen-detected group reported that their symptoms were totally abolished or had decreased markedly. In the screen-detected asymptomatic group, 22% reported such a change. Of the patients, 9% reported to have persistent symptoms. Those patients reported dietary lapses more frequently than those whose symptoms were totally abolished (OR 2.4, 95% CI 1.1-5.4). The patients were more satisfied with dietary counselling provided by dieticians than by physicians. The most common reasons for dissatisfaction were counsellor's lack of knowledge and scant information.

After one year on a gluten-free diet, 72% of the patients in the intestinal symptoms group, 70% in the extraintestinal symptoms group and 79% of the screen-detected patients had a positive attitude towards coeliac disease. In the screen-detected asymptomatic sub-group, the corresponding proportion was 65%. The differences were not statistically significant. Of all patients, 41% had experienced improvement in their self-perceived health status and in 53% concern

Table 8. Coeliac disease patients' experiences and perceptions of health and the disease at diagnosis and after one year on a gluten-free diet.

	Study groups			Sub-group
	Intestinal symptoms n=490	Extraintestinal symptoms n=62	Screen-detected, all n=146	Screen-detected, asymptomatic n=23
Self-perceived health at diagnosis, %				
Excellent	4	12	7	26
Good	34	44	41	57
Fair	47	33	42	17
Poor	16	12	10	0
Self-perceived health on treatment, %				
Excellent	14	15	15	22
Good	58	58	61	52
Fair	25	22	19	17
Poor	3	5	5	9
P value for change in self-perceived health	<0.001	0.106	<0.001	ND
Concern about health at diagnosis, %				
Not at all	8	21	14	61
Slightly	35	47	43	35
Moderately	37	21	27	4
Extremely	20	11	16	0
Concerned about health on treatment, %				
Not at all	28	32	34	39
Slightly	50	45	45	44
Moderately	19	17	14	4
Extremely	3	7	7	13
P value for change in concern about health	<0.001	0.523	<0.001	<0.001

ND not definable because some cells have value <1 in comparison

over their health status was reduced (Table 8). Sub-analyses among screen-detected asymptomatic patients revealed that in this group, patients had a more negative overall attitude towards coeliac disease and experienced the impact of the diagnosis and a gluten-free diet more negatively than the other groups. In this group, perception of health was reduced and concern for personal health status increased on dietary treatment (Table 8). However, none regretted being diagnosed with coeliac disease. Experiencing the impact of a gluten-free diet as negative was associated with having received no information from the physician concerned (OR 1.7, 95% CI 1.02-2.9) or considering it insufficient (OR 2.1, 95% CI 1.3-3.5) and with age under 29 years at diagnosis (OR 2.1, 95% CI 1.2-3.7). A negative attitude towards the disease was associated with being dissatisfied with counselling provided by a physician (OR 1.9, 95% CI 1.03-3.6), young age at diagnosis (OR 2.1, 95% CI 1.04-4.3), having difficulties in following a gluten-free diet (OR 9.7, 95% CI 3.1-30.3) and rating one's own level of knowledge of coeliac disease as poor (OR 3.0, 95% CI 1.3-6.9).

The most common wish for future research on coeliac disease indicated by the patients was the development of a pill which would allow them to eat gluten-containing food or a vaccine which would cure the disease. In addition, patients called for an improvement in the level of knowledge of coeliac disease among physicians (See Figure 2 in Original publication **II**).

4.3 Body mass index (**III**)

At baseline, 4% of all coeliac disease patients were underweight, 57% normal weight, 28% overweight and 11% obese. After one year on a gluten-free diet, the percentages were 2%, 54%, 34% and 11%, respectively. The proportions of patients in different BMI categories were similar in screen- and symptom-detected patients both at baseline and after one year (see Table 3 in Original publication **III**; Table 9). In analyses, weight changes of at least three kilos were considered clinically significant. Of those underweight at diagnosis none lost and 69% gained weight. Among the other initial BMI category groups, 10% lost and 38% gained weight among those with normal BMI, 18% and 22% among overweight patients and 42% and 16% among obese patients, respectively. Favourable changes (that is

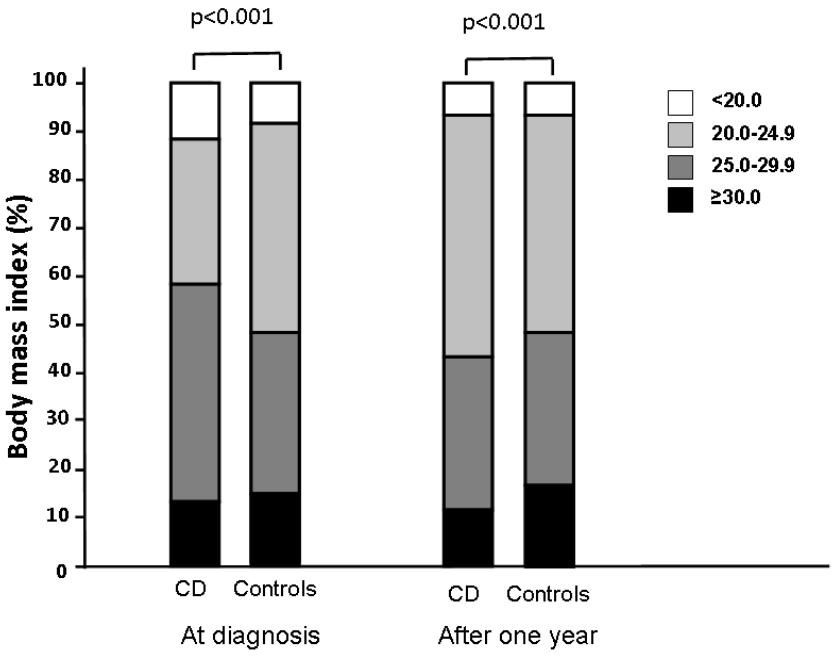
Table 9. Weight and body mass index (BMI) changes in different study groups after one year on a gluten-free diet according to WHO criteria for BMI

Clinical presentation	Patients, %	Weight change*, %			BMI on a gluten-free diet, %				
		Weight gain	Stable	Weight loss	Underweight	Normal	Overweight	Obese	P value†
All	100	33	52	16	2	54	34	11	<0.001
Study groups									
Intestinal symptoms	70	34	51	15	2	55	31	11	<0.001
Extraintestinal symptoms	9	18	64	18	2	43	45	10	0.107
Screen-detected, all	21	34	47	19	3	51	36	10	0.321
Sub-group analysis									
Screen-detected, asymptomatic	3	13	61	26	9	61	22	9	0.644

* changes of at least three kilos were recorded
† for change when compared to oneself at diagnosis

underweight patients gaining and overweight and obese patients losing weight) or BMI remaining in the normal category were observed in 62% of coeliac disease patients: in 64% of the intestinal symptoms group, 57% in the extraintestinal symptoms group, 58% in the screen-detected group and 65% in the screen-detected asymptomatic sub-group. Changes in BMI were similar in the coeliac disease control group from a local referral center: at diagnosis, 2% were underweight, 48% normal weight, 36% overweight and 13% obese and favourable changes in BMI after one year on a gluten-free diet were observed in 57%.

Figure 1. Body mass index among coeliac disease patients (CD) at diagnosis and after one year on a gluten-free diet compared to the general population in the same period. Analyses limited to subjects 16-64 years of age (patients n_1=587, n_2=571; controls n_1=3186 and n_2=3139).



When compared to the general population, the coeliac disease study group appeared to have significantly lower BMI both at diagnosis and on treatment (Figure 1). In addition, those with intestinal symptoms and the screen-detected asymptomatic group had significantly lower BMI than the general population at diagnosis and after one year on a gluten-free diet. Those with extraintestinal symptoms and the screen-detected group differed from the controls neither at

diagnosis nor after follow-up. Favourable changes in BMI were associated with self-assessed expertise on a gluten-free diet (OR 2.0, 95% CI 1.05-3.7) and young age at diagnosis (OR 2.1, 95% CI 1.2-3.6). No issue associated with unfavourable outcome could be identified.

4.4 Disease burden to the health care system and society (**IV**)

Before coeliac disease was diagnosed, 66% of the patients had consulted a physician about the symptoms which eventually led to diagnosis on average twice (mean 4.8, range 0-100). The use of health care services reported as all-cause consultations prior to and after the diagnosis of coeliac disease is shown in Table 10. During the year prior to diagnosis, the mean number of all consultations with a physician was 4.4. During the year following the diagnosis, the number of consultations was reduced to 3.1. The reduction in the number of consultations was mainly due to decrease in consultations in primary health care. There were no changes in outpatient consultations in secondary or tertiary health care or in the number of admissions to hospital between the years prior to and following the diagnosis. The changes were similar in both genders. Compared to the general population, the number of consultations with a physician together with the number of hospital admissions among coeliac disease patients was significantly increased at diagnosis ($p<0.001$) (Figure 2A). After initiation of a gluten-free diet, the total number of consultations had decreased and did not differ from that among the general population (Figure 2B).

During the year before diagnosis, the number of days of sickness absence from work among coeliac disease patients (a mean 8.4 days) was significantly lower than that of the general population ($p<0.001$) (Figure 3). The difference remained constant on a gluten-free diet and coeliac disease patients took fewer sick leaves (a mean 8.8 days) than the general population.

The consumption of pharmaceutical agents also showed a decreasing trend (Table 11). The consumption of on-demand painkillers and medicines for dyspepsia and heartburn diminished on a gluten-free diet, whereas the figures for vitamins, micronutrients and herbal products taken per month increased

Table 10. Changes in the mean number of all-cause medical consultations among coeliac disease patients between the year prior to and after the diagnosis of the disease.

	All n=700	Female n=534	Male n=166
Outpatient visits in primary health care			
Year prior to diagnosis	3.6	3.7	3.1
Year after diagnosis*	2.3	2.5	1.9
Mean change (95% CI) P value†	-1.2 (-1.5 to -0.9) <0.001	-1.3 (-1.6 to -0.9) <0.001	-1.2 (-1.7 to -0.7) <0.001
Outpatient visits in secondary and tertiary health care			
Year prior to diagnosis	0.8	0.8	0.8
Year after diagnosis*	0.8	0.8	0.8
Mean change (95% CI) P value†	0.0 (-0.2 to 0.1) 0.664	0.0 (-0.2 to 0.2) 0.630	0.0 (-0.3 to 0.4) 0.906
Admissions to hospital			
Year prior to diagnosis	0.2	0.2	0.2
Year after diagnosis*	0.2	0.2	0.2
Mean change (95% CI) P value†	0.0 (-0.0 to 0.1) 0.708	0.0 (-0.1 to 0.1) 0.521	0.0 (-0.1 to 0.1) 0.724
Other medical consultations‡			
Year prior to diagnosis	4.1	4.5	2.7
Year after diagnosis*	3.6	4.0	2.4
Mean change (95% CI) P value†	-0.5 (-1.0 to 0.1) 0.340	-0.5 (-1.2 to 0.2) 0.245	-0.3 (-1.2 to 0.7) 0.797

CI confidence interval

*On a gluten-free diet

†For change between the year prior to and after the diagnosis

‡Consultations with a nurse, a psychologist or a dietician, home nursing care, physiotherapy, laboratory and imaging services

Figure 2A. The number of all-cause outpatient and inpatient consultations with a physician among coeliac disease patients (CD) during the year prior to diagnosis (A) and after one year on a gluten-free diet (B) compared to that in the general population over the same period. Analyses limited to subjects 16-64 years of age (patients n_A=576, n_B=567; controls n_A=3201, n_B=3190).

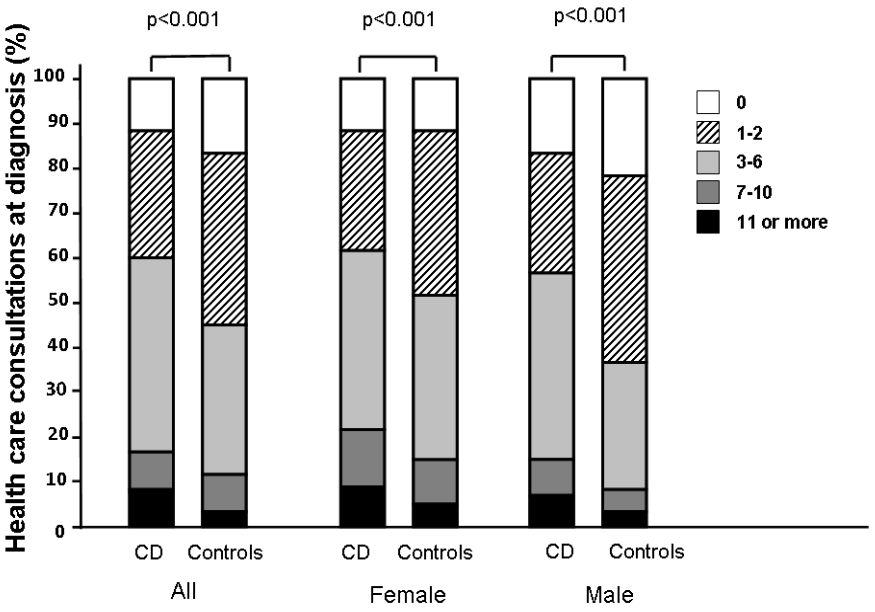


Figure 2B.

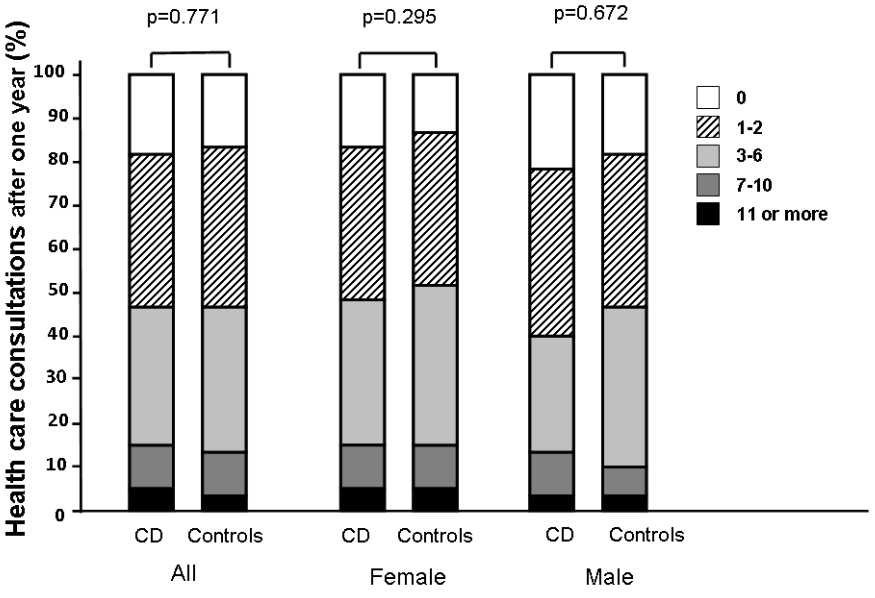
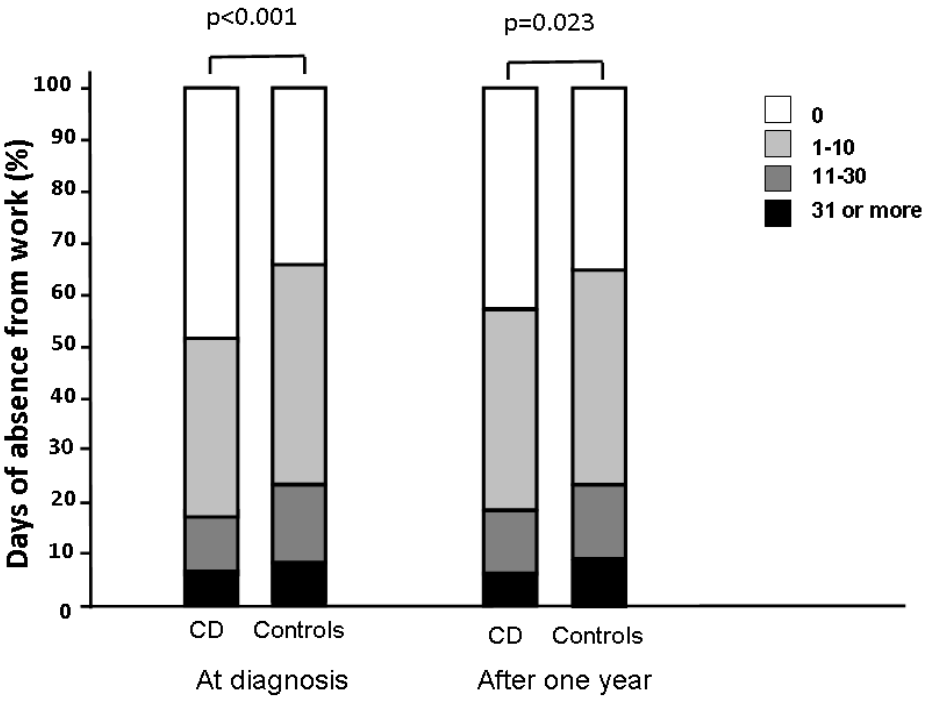


Figure 3. The number of days of sickness absence from work among coeliac disease patients (CD) at diagnosis and after one year on a gluten-free diet compared to the general population in the same period. Analyses limited to subjects 16-64 years of age (patients n_1=480, n_2=477; controls n_1=2949, n_2=2976).



significantly. Additionally, the number of antibiotic prescriptions per year was significantly reduced on dietary treatment. In sub-analyses according to gender, the consumption of painkillers decreased among females but did not change among males.

Table 11. Changes in reported consumption of pharmaceutical agents among coeliac disease patients (pills per month on average) between the year prior to and following the diagnosis of coeliac disease.

	All n=700	Female n=534	Male n=166
All on-demand medicines[*]			
Year prior to diagnosis	12.0	12.2	11.4
Year after diagnosis[†]	9.3	9.1	10.0
Mean change	-2.7	-3.1	-1.4
(95% CI)	(-4.3 to -1.2)	(-4.9 to -1.4)	(-4.8 to 2.0)
P value[‡]	<0.001	<0.001	0.011
Painkillers			
Year prior to diagnosis	6.8	7.2	5.6
Year after diagnosis[†]	5.5	5.2	6.4
Mean change	-1.3	-2.0	0.8
(95% CI)	(-2.6 to -0.1)	(-3.4 to -0.5)	(-2.1 to 3.7)
P value[‡]	<0.001	<0.001	0.432
Medicines for dyspepsia			
Year prior to diagnosis	3.7	3.5	4.4
Year after diagnosis[†]	2.5	2.4	2.6
Mean change	-1.27	-1.1	-1.8
(95% CI)	(-2.10 to -0.44)	(-2.0 to -1.2)	(-3.7 to 0.1)
P value[‡]	<0.001	<0.001	0.015
Antibiotic treatment[§]			
Year prior to diagnosis	0.6	0.7	0.4
Year after diagnosis[†]	0.5	0.5	0.3
Mean change	-0.1	-0.2	-0.1
(95% CI)	(-0.2 to -0.1)	(-0.3 to -0.1)	(-0.3 to 0.1)
P value[‡]	0.001	0.001	0.302
Vitamins, micronutrients, herbal products			
Year prior to diagnosis	18.4	20.7	10.8
Year after diagnosis[†]	22.6	24.6	16.2
Mean change	4.2	3.9	5.5
(95% CI)	(1.8 to 6.7)	(0.9 to 6.8)	(1.8 to 9.1)
P value[‡]	<0.001	0.003	0.002

CI confidence interval
[*]Painkillers, medicines for dyspepsia, sleeping pills
[†]On a gluten-free diet
[‡]For change between the year prior to and after the diagnosis
[§]Not reported as pills per month but as number of courses per year

5. DISCUSSION

5.1 Disease-related burden

5.1.1 Quality of life

In the present series, quality of life in coeliac disease patients was assessed in a large, nationwide cohort comprising a substantial number of both symptom- and screen-detected patients. Previous studies of quality of life in screen-detected patients have mainly involved only a small number of patients (see Table 4 in section 2.5). In this study, the quality of life of coeliac disease patients was poorer at diagnosis when compared to that of non-coeliac or healthy controls and improved significantly on a gluten-free diet, which is in accord with previous findings (Peräaho et al. 2003, Mustalahti et al. 2002, Johnston et al. 2004). The trend was similar in symptom- and screen-detected patients.

Previously, impaired quality of life has been associated with the presence of symptoms (Johnston et al. 2004, Casellas et al. 2008). In the present study, 93% of symptom-detected and 82% of screen-detected patients experienced symptoms which had disturbed their lives prior to diagnosis. Even if 85% reported that their symptoms had diminished on dietary treatment, only 68% of all patients experienced the impact of the diet as positive. In addition to physical symptoms, especially anxiety and depression were increased among untreated patients and alleviated on treatment, findings similar to those reported elsewhere (Ciacci et al. 1998, Addolorato et al. 2001).

After one year on a gluten-free diet, a majority of both symptom- and screen-detected patients experienced improved health status and were pleased that they had been diagnosed with coeliac disease. However, treatment with a gluten-free diet failed to induce improvement in quality of life in the screen-detected asymptomatic patients. Even though their states as measured by PGWB remained unchanged, the perception of poor health increased, patients became more concerned over their health status and had more perceptions of the impact of treatment frequently negative than the other groups. This discrepancy in the impact

of a gluten-free diet on the quality of life between screen-detected symptomatic and asymptomatic patients may be explained by the influence of symptoms existing at diagnosis. Nevertheless, screen-detected asymptomatic patients were similarly pleased at being diagnosed as the other patients, this possibly due to that their awareness of complications associated with untreated coeliac disease.

The delay between the onset of symptoms and the diagnosis of coeliac disease also has a negative impact on the quality of life (Norström et al. 2011). In addition to longer duration of symptoms, patients reported several medical consultations due to the same symptoms finally leading to diagnosis, and increased consumption of on-demand medication. As here, coeliac disease patients have also previously indicated earlier diagnosis as an issue which would enchance their quality of life (Zarkadas et al. 2006).

A gluten-free diet is restrictive, expensive and often hard to follow, having a major impact on the everyday lives of affected individuals (Mäki et al. 2003, Sverker et al. 2005, Lee et al. 2007, Niewinski 2008), all of which may cause deterioration in quality of life. A call for alternative treatment options was noted here as elsewhere, as patients desired the development of a medicine or a vaccine enabling them to tolerate gluten. Placing the burden caused by a gluten-free diet especially on screen-detected patients who may have no complaints at diagnosis should be considered carefully. It has been suggested that the advantages of treatment in screen-detected patients are reversed by poor dietary compliance (Fabiani et al. 2000, Shamir et al. 2007). In a recent systematic review, no difference was noted in adherence between screen- and symptom-detected patients (Hall et al. 2009). In the present study, a good dietary compliance was achieved among screen-detected patients, but the screen-detected asymptomatic sub-group had dietary transgressions more frequently than the others. The present findings of good dietary compliance are in line with previous Finnish studies (Kemppainen et al. 1999, Mustalahti et al. 2002, Viljamaa et al. 2005).

Special attention should be paid to the treatment of adolescents and young adults to reduce the disease burden they experienced. Young adults here reported negative perceptions of coeliac disease more frequently than those diagnosed at older age. Previously, adolescents have been shown to be more prone to experience negative effects of treatment (Sverker et al. 2005, Olsson et al. 2009). The health care system should thus be more sensitive to the needs of those diagnosed at young

age. A team approach in addition to individualised patient education has been suggested to be important in the successful management of coeliac disease (Case 2005). In addition, a high level of confidence in treatment information has been reported to enhance dietary compliance (Lamontagne et al. 2001). It has previously been reported that the physician's attitude when presenting the diagnosis of coeliac disease is an important contributor to the patient's ability to adapt to the disease (Ciacci et al. 2002). In the present study, poor counselling by a physician was associated with a shock reaction at diagnosis, emphasising the role of the physician in supporting patients in major changes in life-style.

5.1.2 Body mass index and co-morbidities

At diagnosis, only 4% of coeliac disease patients in the study cohort were underweight, with 39% overweight or obese. Similar findings have been reported in the UK (Dickey et al. 2006), indicating a change in the clinical presentation of the disease towards milder symptoms, as previously reported (Mäki et al. 1988, Green and Cellier 2007). These findings also reflect the current trend towards increasing BMI in the general population, with reports of about half being overweight or obese (Ogden et al. 2010, Fryar et al. 2010, Sundquist et al. 2010, Helakorpi et al. 2010). In contrast, some recent studies have reported that 16-33% of coeliac disease patients are underweight at diagnosis (Murray et al. 2004, Olén et al. 2009, Cheng et al. 2010). Interestingly, while treated coeliac disease patients gained weight in a study conducted by Dickey and associates (2006), the impact of treatment with a gluten-free diet on BMI among both screen- and symptom-detected coeliac disease patients was beneficial in the present series. Additionally, Cheng and associates (2010) had previously reported similar results. Moreover, the BMI of the coeliac disease patients was lower than that in the general population both at diagnosis and on treatment. Another recent study found ongoing weight gain among coeliac disease patients (Kabbani et al. 2012). In that study, overweight at diagnosis was associated with poor dietary adherence. In contrast, it has been reported that adolescents having dietary transgressions had lower BMI than those on a strict gluten-free diet, which would imply weight gain on dietary treatment (Mariani et al. 1998). In the present study, overweight and obese patients

had dietary lapses more frequently than those underweight or normal weight at diagnosis, though the difference was not statistically significant.

As has been shown elsewhere, elevated BMI is associated with increased morbidity and mortality (Adams et al 2006, Guh et al. 2009, Berrington de Gonzalez et al. 2010), making overweight a major health burden affecting both individuals and also society. Increased morbidity may burden the health care system and cause incremental costs in addition to reduced well-being experienced by affected individuals. Thus, current findings of favourable BMI outcome on a gluten-free diet make the diet a valuable tool in the effort to reduce the overall burden of illness related to coeliac disease. However, there have been alarming results indicating the inadequate nutritional value of gluten-free products and diet (Mariani et al. 1998, Hallert et al. 2002b, Hopman et al. 2006, Wild et al. 2010). Patients on a gluten-free diet have been reported to consume increased amounts of lipids and to have reduced fibre, vitamin and iron intake. A nutritionally unbalanced diet may lead to long-term complications and counter the beneficial effects on BMI. Regular follow-up consultations with a dietician feel to be necessary to ensure nutritional adequacy and to prevent malnutrition while adhering to a gluten-free diet for life (Niewinski 2008). However, specific dietary supplements after the diagnosis is not routinely recommended in current clinical guidelines in Finland (Current Care Guideline working group 2010).

Contrary to earlier suggestions (Butterworth et al. 2004, Cheng et al. 2010), dedicated and careful dietary counselling and follow-up were not associated with favourable changes in BMI. Possibly the management of coeliac disease differs between the countries. In addition, patients in Finland may obtain dietary advice from other sources such as the Coeliac Society. The present findings imply that the current clinical practice in Finland is sufficient to induce beneficial changes in BMI at least during the first year on dietary treatment. However, to achieve such changes, patients should attain to a sufficient level of knowledge of the diet.

5.1.3 The use of health care resources

According to the present findings, untreated coeliac disease was associated with increased consumption of health care services with a significant reduction after initiation of a gluten-free diet. Similar findings have also been reported in earlier studies (Cannings-John et al. 2007, Green et al. 2008, Long et al.2010). However, there are differences in study design between those and the present study. The earlier studies were conducted in special centres and were retrospective, which might limit their applicability in other populations, whereas the present study was prospective and nation wide.

In the present study, the excess in consumption of health care services was due mainly to an increased number of office visits in primary health care. A similar trend was observed when the coeliac cohort was analysed according to the initial clinical presentation. Dietary treatment had no effect on consultations with a physician in secondary or tertiary health care or on hospitalisations. This implies that the increased morbidity related to untreated coeliac disease is not typically manifested in grave symptoms; existing complaints can be treated in primary health care. In contrast to previous reports (Green et al. 2008, Long et al.2010), no increase in the number of health care visits due to medical investigations compared between one-year periods prior to and post diagnosis was noted. Compared to the general population, coeliac disease patients had significantly more consultations with a physician in the year prior to diagnosis. It is of note that after placement on a gluten-free diet, the consumption decreased and did not differ from that in the general population, even though follow-up visits and medical investigations related to coeliac disease were not excluded. In comparison, Green and associates (2008) reported increased costs due to coeliac disease-related visits during the 12-month period post-diagnosis, after which use of health care services decreased. Interestingly, in contrast to increased numbers of medical consultations when untreated, coeliac disease patients had less sickness absence days from work than the general population both prior to and after the diagnosis.

Coeliac disease patients significantly reduced the consumption of painkillers and medication for dyspepsia after placement on a gluten-free diet. As these were on-demand and possibly symptom-targeted drugs, it suggests that untreated coeliac disease can also cause affected individuals additional out-of-pocket costs. In

addition, the number of antibiotic prescriptions was significantly reduced on a gluten-free diet, suggesting an achieved health gain. Two recent studies (Shaw et al. 2011, Virta et al. 2012) assessing the use of antibiotics and the risk of developing Crohn's disease found that affected individuals were more likely to have been prescribed several antibiotic courses before the diagnosis. Shaw and associates (2011) speculated that the use of antibiotics could be a predisposing factor and Virta and associates (2012) thought that frequent use of antibiotics may trigger the development of Crohn's disease or be a sign of proneness to infections before the intestinal disease is diagnosed. The finding in the present study that fewer patients had been prescribed antibiotics post than pre-diagnosis supports the latter explanation in the context of coeliac disease.

Considering that the delay in the diagnosis of coeliac disease can be several years (Green et al. 2001, Lo et al. 2003, Häuser et al. 2007, Gray et al. 2010), undetected patients may burden the health care system and cause increased costs over a long period, as reported by Long and associates (2010). In the present study, patients had coeliac disease-related consultations a mean 4.8 times before the disease was detected. As treatment with a gluten-free diet resulted in normalisation of the use of health care services and reduced consumption of on-demand medication, resource and cost-savings could be attained by early detection and treatment of the disease. However, studies with longer follow-up periods are lacking. A recent study reported that coeliac disease females use significantly more health care services than non-coeliac controls despite having followed a gluten-free diet for a median of four years (Roos et al. 2011). Health care consultations were mostly related to gastrointestinal symptoms, mental and behavioural disorders and diseases of the musculoskeletal system. The results imply that despite dietary treatment, coeliac disease patients may suffer from impaired health and well-being and experience a significant disease burden. Such findings suggest that the positive results observed in the present series might not be permanent. In addition, it is possible that cost-savings in the health care system shift to out-of-pocket costs to patients caused by high costs of gluten-free products.

5.2 Screening for coeliac disease

According to the principles of screening, that is early disease detection, a disease must be common, an important health problem, detectable and treatable (Wilson and Jungner 1968). At present, screening for coeliac disease is recommended among at-risk groups and those betraying any symptoms associated with the disease (Hill et al. 2005). In the present study, 21% of the patients were detected by screening. Most of the screen-detected patients were symptomatic which is in line with previous observations (Johnston et al. 1998, Hoffenberg et al. 2004), and possibly had accepted their impaired health status as normal and thus considered themselves healthy. Only 16% of the screen-detected patients, (3% of all patients) were totally asymptomatic at diagnosis. As discussed in previous sections, in the present series, the screen-detected group resembled those with gastrointestinal symptoms. However, when the asymptomatic patients were analysed separately, the outcome on treatment was not as good as among symptomatic patients.

If coeliac disease is to be screened for, the advantages of detection of the disease should be balanced against the burden of illness and its treatment from the standpoint of both the coeliac disease patients and the health care system. A recent study investigating experiences of screen-detected adolescents found that from the patient's point of view health benefits are not always balanced against social sacrifices regardless of initial symptoms (Rosén et al. 2011). Thus, the screening issue is complex and warrants further evaluation. Until these unsolved issues are elucidated, active or augmented case finding seems to be an optional diagnostic approach, as previously recommended (Fasano et al. 2003, Mearin et al. 2005, Evans et al. 2011).

5.3 Limitations of the study and future objectives

Among the assets of the present study in the fact that it comprises a large, nationwide cohort of newly-detected coeliac disease patients. In addition to readily measurable parameters, it assesses patients' own perceptions of the disease, how the diagnosis was made, dietary treatment and the management of the disease. Moreover, it was thus possible to evaluate the consumption of on-demand medication, which is not otherwise registered. One special gain is that the participants were used as their own controls, thus allowing better assessment of changes within the study population.

In addition to these advantages, some limitations of the study should be discussed. First, all patients involved were members of the Finnish Coeliac Society, which may have affected their answers and made the results too positive. Further, the results might not be applicable to coeliac disease patients in general. The age and gender distributions of the non-respondents and those who responded were similar but respondents may have been the better motivated, which may have influenced the results obtained. It has been reported that membership in an advocacy group is associated with better dietary compliance (Hall et al. 2008). However, the compliance percentage was similar to those previously reported in Finland (Kemppainen et al. 1999, Mustalahti et al. 2002, Viljamaa et al. 2005), and the participation rate was good and comparable to those in previous cross-sectional health surveys in coeliac disease (Cranney et al. 2007, Häuser et al. 2007).

As the study was conducted by a self-help organisation, it was impossible to verify medical data on the diagnosis and co-morbidities from clinical records. Co-morbidities have been shown to impact on quality of life (Häuser et al. 2007). Nevertheless, the large size of the study cohort may suffice to minimise the confounding effect of a single patient. Without adjustment, the study cohort could have represented the coeliac population better. Also BMI was calculated from self-reported weight and height. However, BMI based on self-reported values has proved reliable and valid in epidemiological studies (Willet 1998, Burton et al. 2010). In addition, parallel results were obtained in a coeliac disease control group from a local referral centre. Reference values for the general population were similarly based on self-reported weight and height. The evaluation of the impact of a gluten-free diet on BMI was also limited by the lack of a dietary questionnaire,

which made it impossible to confirm whether changes were caused by alteration in caloric intake or healing of the intestinal mucosa. Even if caloric intake was different this might be assumed to be induced by starting dietary treatment.

Self-reported data were also applied when assessing the use of health care services and pharmaceutical agents, which may have lad to inexact values. There could also have been a recall bias. However, a recall period of the previous one year has been shown to be reliable and appropriate in evaluating consumption of health care services and medication (Longobardi et al. 2011). Consumption was also asked similarly at baseline and in the follow-up survey and the reference values for the general population were correspondingly self-reported.

One major limitation of the study is that the follow-up period was only one year. Even though a clinical response to a gluten-free diet is usually observed within a few weeks (Murray et al. 2004), total histological recovery may take over two years (Wahab et al. 2002, Lee et al. 2003, Collin et al. 2004). Thus, a longer follow-up time might be needed to establish the long-term impact of dietary treatment.

The present study identified a number of issues which impact on the burden of coeliac disease. Treatment with a gluten-free diet typically results in improved health and well-being, but does not always seem to be solely beneficial. Especially certain special patient groups might need detailed dietary counselling and patient education and skilled doctor-patient communication to increase dietary compliance and to reduce disease-related distress. One important issue relevant to the burden related to coeliac disease is the long delay in time between the onset of symptoms and diagnosis. Advanced diagnostic procedures should be established to allow earlier diagnosis. However, before, for example, extended screening programmes are established, there should be a consensus as to who should be screened and subsequently treated. In addition, further studies are needed to establish the long-term impact of the diet on patients' BMI and how to better promote normalisation of weight after prescription of a gluten-free diet. Additionally, thus far, studies considering thoroughly health-economic aspects are lacking. The data obtained in the present study could be used as a basis for health-economic evaluations, but a longer follow-up time is needed.

6. SUMMARY

This study demonstrated that coeliac disease puts a significant disease burden on patients and the health care system having, a major medical and economic impact in addition to effects on life-style and quality of life. Untreated coeliac disease was seen to be associated with impoverished quality of life and self-perceived health and well-being in both symptom- and screen-detected patients. After initiation of a gluten-free diet, quality of life and self-perceived health improved and concern over health decreased similarly in both groups. Screen- and symptom-detected patients also equally reported a positive effect of the diet on their lives and symptoms, an optimistic attitude towards the disease and satisfaction at being diagnosed with coeliac disease. Dietary treatment induced similar beneficial changes in BMI in both symptom- and screen-detected patients as underweight patients gained and overweight and obese patients lost weight. Only a sub-group of totally asymptomatic screen-detected patients failed to improve on treatment. Their quality of life was not poor at diagnosis and remained unchanged on treatment, but they became more concerned about their health status and their perception of health deteriorated. Of note, even if quality of life as assessed by PGWB scores did not improve on dietary treatment in screen-detected asymptomatic patients, no deterioration was noted and the quality of life was similar to that of non-coeliac controls both at diagnosis and after follow-up. However, the asymptomatic patients were pleased at having been diagnosed and had a positive attitude towards coeliac disease similarly to the other patients, which is important when assessing the disease burden among these patients. In addition, treatment with a gluten-free diet resulted in analogous favourable changes in BMI also in the asymptomatic patients.

The study also showed that consumption of health care services and on-demand pharmaceutical agents was increased prior to the diagnosis of coeliac disease. After initiation of a gluten-free diet, the use of health care services and symptom-targeted medication decreased, indicating health gain on dietary treatment and thus a reduction in the burden caused by the disease to the health care system. When compared to the general population, patients used health care services excessively

prior to the diagnosis. After one year on dietary treatment, no such difference was noted. The number of days of absence from work was lower among coeliac disease patients than among the general population both at diagnosis and after follow-up.

Screening for coeliac disease would result in earlier detection of affected individuals. According to the present findings, both symptom- and screen-detected patients would benefit from earlier treatment. In addition, earlier diagnosis would save health care resources. However, totally asymptomatic patients do not appear to profit from treatment to the same extent as symptomatic patients, which should be taken into account in the management of this patient group and when considering screening policies for the disease. Similarly, those diagnosed at young age may need additional support and special education.

In conclusion, the burden of coeliac disease can be reduced by treatment with a gluten-free diet, this emphasising the benefits of early diagnosis and treatment. However, further studies are needed on the long-term health-economic impact of coeliac disease. Further, more knowledge should be obtained to establish optimal screening strategies and practices in the management of coeliac disease to make the diagnosis and treatment acceptable to all patients. At present, active case-finding is preferred.

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ORIGINAL PUBLICATIONS

Diet Improves Perception of Health and Well-being in Symptomatic, but Not Asymptomatic, Patients With Celiac Disease

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BACKGROUND & AIMS: The benefits of serologic screening and early diagnosis of celiac disease in asymptomatic patients are not known. We investigated the impact of a gluten-free diet on self-perceived health and well-being in symptomatic and asymptomatic patients with celiac disease. **METHODS:** We performed a prospective study of 698 consecutive adults newly diagnosed with celiac disease because of classic (n = 490) or extraintestinal (n = 62) symptoms or through screening of at-risk groups (n = 146; 23 were asymptomatic and analyzed separately). The survey included questions on health and well-being; quality of life was evaluated by the psychological general well-being (PGWB) questionnaire. Patients were followed for 1 year of treatment; 110 healthy subjects served as controls. **RESULTS:** On a gluten-free diet, self-perceived health improved significantly among patients with classic symptoms and those detected by screening. Patients in all groups were equally concerned about their health before the diagnosis, but anxiety was alleviated by the gluten-free diet. At diagnosis, the quality of life reduced among all 3 groups but improved significantly among patients on the diet. Among the 23 asymptomatic patients, perception of health worsened and concern about health increased while they were on the diet. **CONCLUSIONS: Self-perceived health and well-being were low among patients at the time they were diagnosed with celiac disease. Most patients benefited from a gluten-free diet, so it is important to identify patients with celiac disease. Perception of health decreased among asymptomatic cases, which discourages population-based screening.**

Keywords: Burden; Diagnostic Delay; Prospective; Unrecognized.

Celiac disease is an autoimmune-mediated enteropathy triggered by the ingestion of a dietary gluten. Recent screening studies have revealed that the prevalence is as high as 1%–2%; celiac disease is thus the most common food-related lifelong disorder in Western countries.[1–3] The clinical features of celiac disease are often subtle and variable, for which reason up to 75%–90% of affected individuals remain undiagnosed.[1,3,4] This raises the question whether population-based screening should be considered to identify this gluten-intolerant subpopulation. In symptomatic celiac disease, a gluten-free diet results in clinical improvement and recovery from small-bowel mucosal damage and reduces the risk of complications such as malignancies and osteoporotic fractures.[5–7] However, it has not been proved whether screening and lifelong dietary treatment in apparently asymptomatic celiac disease cases results in a similar health gain.[8–13] Individuals who were found through screening programs to have celiac disease might have considered themselves healthy, and the stigma of a chronic disease and the requirement to adhere to a restrictive treatment might even increase burden of illness and impair quality of life.[14,15] Altogether, patients' own perceptions of the benefits and disadvantages of the diagnosis and treatment of celiac disease, particularly in cases with atypical or no symptoms, have remained obscure, and these issues need to be resolved before implementation of screening in the general population. The aim of this prospective study was to evaluate self-perceived health and well-being by structured questionnaires in a large nationwide cohort of symptom-detected and screen-detected celiac disease adult patients, both at diagnosis and after 1 year on a gluten-free diet.

Patients and Methods

Patients, Controls, and Study Design

The study was conducted in collaboration with the Finnish Celiac Society. Approximately 70% of patients with celiac disease soon after diagnosis join the society, which today embraces 20,205 members. Between February 2007 and May 2008, a questionnaire on self-perceived health and well-being was mailed to all new members of the society. Newly diagnosed (within 1 year) biopsy-proven celiac disease patients who were older than 16 years of age were eligible for the study. A follow-up questionnaire was sent to the participants after 1 year; a reminder was given by phone to nonresponders. Data were blindly coded before analysis. One hundred ten non–celiac disease subjects (median age, 48 years; range, 23–87 years; 81% female) who had no first-degree relative with celiac disease served as controls.

Informed consent was obtained from all study subjects after a full written explanation of the aims of the study, including considerations regarding ethics and data protection and the anonymous deposition of the questionnaires.

The Questionnaires

The baseline and follow-up questionnaires were designed by celiac disease patients together with the Finnish Celiac Society and clinical researchers with expertise in celiac

Abbreviation used in this paper: PGWB, psychological general well-being.

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disease. The survey consisted of questions about sociodemographic conditions, clinical features at diagnosis, and the impact of the diagnosis of celiac disease and the dietary treatment on self-perceived health and well-being. Self-estimated health status was assessed by asking the patients to rate their health on a 4-point Likert scale as follows: excellent, good, fair, poor. Such self-rated health has been found to be predictive of survival, which supports the validity of this measure.[16] Concern of personal health status in general was measured similarly by a question in which responses ranged from "not at all" to "extremely" on a 4-point Likert scale, disturbance of symptoms ranging from "not at all" to "very much" on 3-point Likert scale, and the change in symptoms on a gluten-free diet from "complete alleviation" to "worsened" on a 4-point Likert scale. The feasibility of the questions was pretested by a group of members of the Finnish Celiac Society. A subset of 11 participants also completed the initial questionnaire 1 week after the initial appointment, and test-retest reliability was established by using intraclass correlation coefficient. For the key items of the questionnaire, the kappa values for test-retest reliability ranged from 0.84–1.00 (values above 0.70 regarded as excellent). Because the inquired items were separated, a Cronbach α was not calculated. Face and content validity of the initial items was ensured through the evaluation of the survey content by both gastroenterologists and celiac disease focus group.

Causes leading to the diagnosis of celiac disease were categorized as follows: (1) classic symptoms comprising any type of gastrointestinal symptoms (eg, indigestion, flatulence, abdominal pain, constipation, in addition to diarrhea) or symptoms or signs of malabsorption (eg, sideropenic anemia or weight loss); (2) extraintestinal symptoms such as dermatitis herpetiformis, arthralgia, or arthritis, neurologic problems, or infertility; and (3) cases detected by screening of at-risk groups (first-degree relatives of celiac disease patients, patients with autoimmune disorders such as type 1 diabetes mellitus or autoimmune thyroid disease). Furthermore, a subgroup analysis of screen-detected celiac disease patients who considered themselves totally asymptomatic at diagnosis was performed separately.

Quality of life was evaluated by the structured psychological general well-being (PGWB) questionnaire at the diagnosis of celiac disease and after 1 year on a gluten-free diet. The questionnaire measures self-perceived health-related well-being and distress and has been previously validated[17] and widely applied in celiac disease research.[7,9,18–20] The questionnaire contains 22 items, which can be divided into 6 subdimensions: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. Total scores might range from 22–132; higher scores indicate better psychological well-being.

Statistical Analysis

Quantitative data were expressed as medians, lower and upper quartiles, and range, or means and 95% confidence intervals. When appropriate, χ^2 in cross tabulations and Student t test or Mann–Whitney U test were used to compare differences between groups, and paired t test or Wilcoxon signed rank test was used to compare changes within groups. All testing was two-sided, and P values $<.05$ were considered statically significant. The statistical testing was performed by using Statistical Package for Social Sciences for Windows software (SPSS 17.0; SPSS Inc, Chicago, IL).

Results

The questionnaires were mailed to 1864 new members of the Finnish Celiac Society, of whom 1062 (57%) responded (Supplementary Figure 1). The sex and age of the nonresponders did not differ from those of the responders. In subsequent analysis, 364 respondents proved not eligible for the study; 157 had been diagnosed before the enrollment period, 132 were <16 years of age, 73 did not fulfill the diagnostic criteria for biopsy-proven celiac disease, and 2 had inadequate data. Thus, 698 newly detected celiac disease patients were enrolled. A follow-up survey was conducted after 1 year, and the response rate was then 97% (n = 677).

Of the 698 newly detected celiac disease patients, 490 (70%) had classic and 62 (9%) had extraintestinal symptoms; 146

Table 1. Sociodemographic Characteristics of the Celiac Disease Patients in Different Study Groups

	Study groups			Subgroup analysis
	Classic symptoms (n = 490)	Extraintestinal symptoms (n = 62)	Screen-detected, all (n = 146)	Screen-detected, asymptomatic[a] (n = 23)
Female, %	77	68	80	91
Median age, range (*y*)	49 (16–84)	54 (20–75)	52 (18–82)	44 (19–82)
Marital status, %				
Single	24	20	28	44
Married/with partner	76	80	72	56
Occupational status (%)				
Employed	65	69	60	52
Training	7	2	8	22
Homemaker	2	2	3	0
Unemployed	2	0	3	0
Retired	24	27	27	26
Employment status (%)				
Full-time	63	68	60	65
Part-time	7	5	8	4
Not working	30	32	32	30

[a]Patients did not report any symptoms at the time of diagnosis of celiac disease.

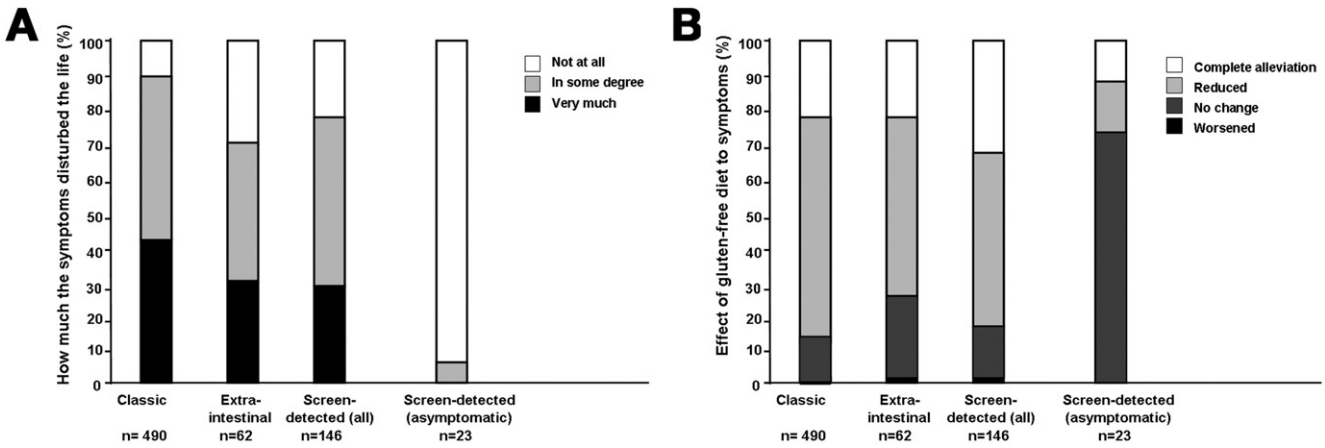

Figure 1. The self-perceived symptoms in different study groups at the time of diagnosis of celiac disease (*A*) and the effect of a gluten-free diet (*B*). A subgroup analysis of initially asymptomatic screen-detected celiac disease patients is shown separately.

(21%) were detected by active screening in risk groups. Baseline characteristics were well-balanced between these 3 study groups (Table 1). A subgroup analysis was carried out in 23 screen-detected individuals, who reported themselves to be asymptomatic at diagnosis. In this subgroup with more women, the subjects appeared to be slightly younger and more rarely with partner than individuals in other study groups (Table 1).

The median delay in the diagnosis of celiac disease after onset of symptoms was 3 years in the study group with classic symptoms and 1 year in that with extraintestinal symptoms (range, 0–59 years and 0–30 years, respectively). The majority (84%) of screen-detected celiac disease patients had experienced symptoms before the diagnosis, and the median interval between the onset of symptoms and diagnosis was 2 years (range, 0–50 years). At diagnosis, 90% of the patients in the classic symptom group and approximately 70% in other study groups reported that their symptoms disturbed everyday life at least to some degree (Figure 1*A*). Self-rated adherence to a gluten-free diet was similar in the 3 study groups (85% in the classic, 78% in the extraintestinal symptoms, and 91% in the screen-detected group). Nevertheless, when the initially asymptomatic screen-detected group was assessed separately, it was noted that they reported more dietary lapses than those in the other groups (26%, $P = .042$). Only 2 (0.4%) patients in the classic symptom group and none in the other groups consumed normal gluten-containing diet. A notable relief of symptoms was perceived in all 3 study groups on a gluten-free diet, but despite good self-reported adherence to a strict diet, the symptoms were totally abolished in only 22%–28% of the patients after 1 year (Figure 1*B*). However, the severity of symptoms reduced in 73%–86% of the patients. In subgroup analysis an alleviation of symptoms was experienced in 30% of the asymptomatic, screen-detected patients on the treatment, although they reported no symptoms at the diagnosis (Figure 1).

Self-perceived health before the diagnosis of celiac disease was poor in 16% in the classic symptom group, in 12% in the extraintestinal symptom group, and in 10% in the screen-detected group and good or excellent in 37%, 55%, and 48%, respectively (Figure 2*A*). In the classic symptom and screen-detected groups a significant improvement of health was evident after 1 year on a diet ($P < .001$). However, in the subgroup analysis of asymptomatic screen-detected cases the trend was different, and the perception of poor health even became more common (Figure 2*A*). All study groups were

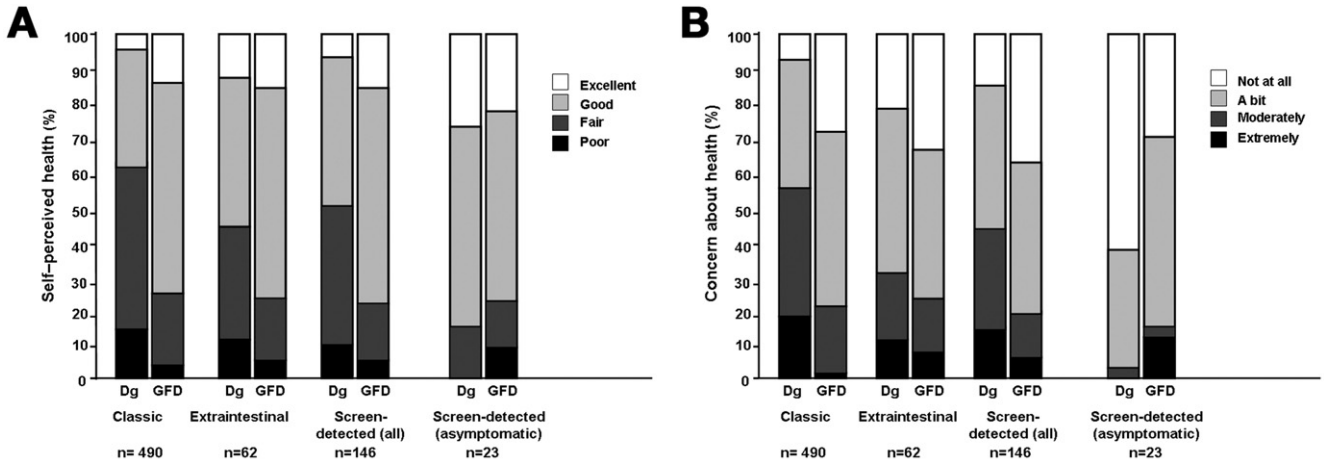

Figure 2. Self-perceived health (*A*) and concern about health (*B*) in celiac disease patents in different study groups at the time of diagnosis (*Dg*) and after 1 year on a gluten-free diet (*GFD*). A subgroup analysis of asymptomatic screen-detected celiac disease patients is shown separately.

Table 2. Mean PGWB Total and Subscores and 95% Confidence Intervals of Total Score in Different Study Groups and Controls

	PGWB total scores (95% confidence interval)	PGWB subscores					
		Anxiety	Depression	Well-being	Self-control	General health	Vitality
Study groups							
Classic symptoms							
At diagnosis	88.8 (86.9–90.6)[a]	20.1[a]	14.3[a]	14.7[a]	13.4[a]	11.1[a]	15.2[a]
On gluten-free diet	101.9 (100.3–103.5)[b]	23.4[b]	16.1[b]	16.7[b]	14.9[b]	13.3[a,b]	17.5[b,c]
Extraintestinal symptoms							
At diagnosis	96.4 (91.2–101.5)[c]	22.3[c]	15.2	15.8	14.7	12.2[a]	16.2[c]
On gluten-free diet	104.8 (100.3–109.3)[b]	24.8[b]	16.2[d]	17.4[b]	15.4[d]	13.3[b]	17.7[d]
Screen-detected, all							
At diagnosis	92.7 (89.5–96.0)[a]	21.2[a]	14.8[a]	15.3[a]	13.9[a]	11.9[a]	15.7[a]
On gluten-free diet	104.4 (101.6–107.3)[b]	24.3[b]	16.2[b]	17.4[b]	15.1[b]	13.5[b,c]	18.0[b]
Non–celiac disease controls	105.3 (103.0–107.6)	24.1	16.2	16.9	15.3	14.4	18.5
Subgroup analysis							
Screen-detected, asymptomatic							
At diagnosis	103.0 (95.9–110.1)	23.5	16.1	17.1	15.4	13.9	17.8
On gluten-free diet	103.1 (94.0–112.2)	23.9	16.1	16.8	14.5	13.8	18.1

[a]$P < .001$ when compared with controls.
[b]$P < .001$ when compared with oneself at diagnosis.
[c]$P < .05$ when compared with controls.
[d]$P < .05$ when compared with oneself at diagnosis.

equally concerned about their health status before the diagnosis, and the concern had been reduced after 1 year on a gluten-free diet (Figure 2*B*). Again, in the asymptomatic screen-detected subgroup, the follow-up findings were the opposite, because more subjects experienced concern of their health status ($P < .0001$; change in a subgroup vs changes in 3 other groups) (Figure 2*B*).

At the diagnosis of celiac disease, quality of life measured by PGWB total score was significantly reduced in all 3 study groups when compared with that in the non–celiac disease control group (Table 2). A substantial improvement on a gluten-free diet was observed in all 3 study groups, and after 1 year the PGWB total scores were not different from those among controls. A similar trend was seen in all PGWB subdimensions. As to the asymptomatic screen-detected subgroup, neither the PGWB total score nor the subscores differed from those in the non–celiac disease control group at diagnosis and after treatment. Furthermore, in that subgroup the PGWB scores did not change on dietary treatment (Table 2).

Discussion

The relevance of the diagnostics and treatment of celiac disease has traditionally been measured in terms of the prevalence of the disease and its complications and mortality rates.[5,10,11] However, the impact of celiac disease extends beyond these outcomes, and effects also include self-rated perceived health and well-being.[14,21,22] In this prospective survey we showed that both symptom-detected and screen-detected adult patients with celiac disease aspire to an improved health status and quality of life when they are diagnosed and treated by a gluten-free diet. Similar findings on quality of life have been reported in smaller prospective series consisting mainly of celiac disease patients with abdominal symptoms or those with malabsorption or anemia.[7,9,23] In the present study we were able to enroll a substantial number of celiac disease patients presenting with extraintestinal manifestations including skin and neurologic symptoms and reproductive problems, as well as apparently asymptomatic patients detected by screening in at-risk groups. It is important to note that also these patients experienced impaired self-rated well-being while undiagnosed, and treatment with a gluten-free diet yielded favorable results (Table 2).

In this study a majority of the screen-detected celiac disease patients were not asymptomatic but afterward recognized that they had experienced celiac disease–related symptoms before the diagnosis. The benefits of serologic screening for celiac disease in asymptomatic individuals have remained obscure. Earlier we investigated quality of life in 19 screen-detected celiac disease patients and found the quality of life to be similar at the time of diagnosis in them and in the non–celiac disease controls, but dietary treatment yielded a significant improvement in the celiac disease patients.[9] We believe that many undiagnosed celiac disease patients accept a state of chronic vague ill health as normal and recognize the presence of symptoms only after they have been placed on a gluten-free diet. By contrast, in 2 small studies no beneficial effect was found with a gluten-free diet in 8–14 subjects with asymptomatic celiac disease.[23,24] A similar lack of effect could also be seen in a subanalysis of 23 asymptomatic, screen-detected celiac disease patients in our current study. In this subgroup, some individuals became even more anxious and experienced deterioration in self-perceived health on a gluten-free diet (Figure 2). Although these cases represent only a minority of the screen-detected celiac disease group, the findings suggest that early detection of celiac disease by mass screening in a healthy adult population would not unequivocally result in self-perceived health gain. Thus, our findings suggest that unselected mass screening of celiac disease is not justified. Instead, we recommend active case-finding in individuals with even mild gastrointestinal or extraintestinal symptoms compatible to celiac disease.

In a recent cross-sectional survey among treated celiac disease patients, 50% with initially classic symptoms and 34% with minor or no symptoms subsequently reported poor health before the diagnosis.[15] The respective percentages in our prospective study were lower, 16% and 10%. It is notable that the diagnostic delay in our series was shorter (median, 1–3 years) than reported elsewhere.[25–29] A high, up to 0.7% clinical prevalence of the disease in our country[30] supports the conclusion that our patients will be diagnosed early enough. Nevertheless, some subjects had experienced symptoms as long as 50 years, which warrants continuous awareness of celiac disease among health care professionals in primary care.

One argument against screening of celiac disease is that compliance with a gluten-free diet would be worse in screen-detected than in symptom-detected patients.[31,32] Here a good dietary compliance was achieved also in screen-detected celiac disease patients, but dietary lapses were more common in the initially asymptomatic screen-detected patients than in the symptomatic patients. It is of note that in celiac disease the full histologic recovery might take more than 1 year,[33,34] and in some patients the symptoms might persist even when the small-bowel mucosal morphology has normalized.[35,36] In fact, complete alleviation of symptoms on treatment was noted in only a minority, and a fourth of our patients still considered their health fair or poor (Figures 1*B* and 2*A*). However, the quality of life as measured by PGWB total scores was similar to that in the controls after 1 year on diet (Table 2).

Some limitations of the study must be discussed. All patients were members of the Celiac Society, and the results might not be applicable to celiac disease patients in general, because those who responded might have been the most symptomatic and motivated ones. Because the inquiries were carried out by a self-help organization, it was impossible to verify medical data on the diagnosis and comorbidities from clinical records. On the other hand, the participation rate was good and comparable to that found in earlier cross-sectional health surveys in celiac disease,[27,37] and there were no major differences in the sex and age distribution between participants and nonrespondents in the study. In our previous studies the distributions of different presentations of the disease have also been comparable,[38,39] and we believe that the patient series of the current study represents well the diagnosed adult celiac disease population in our country. Furthermore, the consistency of the results across a broad range of outcome measurements supports the conclusions of the study. Even though negative impact on self-perceived health and increased concern of health were reported by some asymptomatic screen-detected patients, these findings did not reflect as impaired quality of life. It is possible that PGWB is not a disease-specific instrument and thus might not assess all issues having impact on life in celiac disease patients.

Celiac disease—even apparently asymptomatic—is an important contributor to the burden of ill health and impaired quality of life. Celiac screening and early detection and treatment with a gluten-free diet were beneficial in the majority of celiac disease patients. Because no such positive effect could be seen in a subgroup of patients who were completely asymptomatic at diagnosis, it seems more justified to recommend case-finding in preference to mass screening. Further studies should evaluate other outcome variables such as fractures and nutritional deficiencies in undetected celiac disease to determine the optimum screening strategies for celiac disease.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.10.011.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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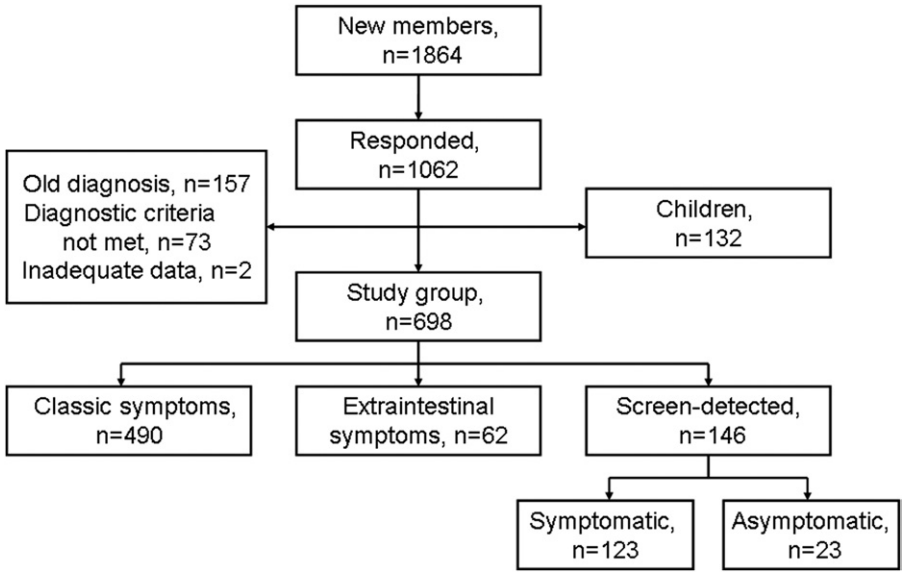

Supplementary Figure 1. Flow chart of the study.

Patients' Experiences and Perceptions of Living with Coeliac Disease - Implications for Optimizing Care

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Abstract

Background & Aims: Little is known regarding the impact of coeliac disease on daily living from patients' own viewpoints. The aim of the study was to investigate patients' perceptions of their disease, dietary treatment and self-rated healthcare needs. **Methods**: This prospective study involved 698 newly detected adult coeliac disease patients diagnosed due to classical abdominal symptoms, extraintestinal symptoms or active screening in at-risk groups. Participants were asked about their experiences of living with coeliac disease and of adopting a gluten-free diet, as well as their disease-related needs at diagnosis and after one year on treatment. **Results**: All patients were equally satisfied that they had been diagnosed with coeliac disease irrespective of initial clinical presentation. However, young patients and those with extraintestinal symptoms or asymptomatic and detected by screening in at-risk groups rated the impact on daily living of the disease and adherence to a gluten-free diet with significantly more disapproval than those with classical symptoms. The former groups clarify also reported dietary lapses and a negative attitude to the disease more frequently. Negative perceptions were associated with dissatisfaction with the quality of doctor-patient communication and younger age at diagnosis. **Conclusions**: Established doctor-patient communication is essential in minimizing the disease burden. Particularly young and screen-detected asymptomatic patients and those with extraintestinal manifestations require extensive support.

Key words

Coeliac disease – gluten-free diet – screen-detected – prospective study.

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Introduction

From the medical perspective, the benefits of treatment in symptomatic coeliac disease are obvious. A strict gluten-free diet results in the disappearance of clinical symptoms and malabsorption as well as the prevention of long-term complications such as malignancies and osteoporosis [1-3]. In addition to the classical gastrointestinal symptoms, the disease may express itself with extraintestinal manifestations or even be clinically silent. Recent population-based serological screening studies have revealed that, at present, coeliac disease affects about 1-2% of the general population in Western countries [4-6]. Since up to 90% of the coeliac population remain unrecognized due to atypical or absent symptoms, even population screening has been suggested [1, 3, 7]. Nevertheless, the advantages of dietary treatment in such individuals remain doubtful [8-13]. A life-long gluten-free diet is restrictive, costly and often difficult to maintain and may also adversely affect lifestyle and upset normal everyday life [4, 15, 16]. Furthermore, the diagnosis of coeliac disease may carry the stigma of a chronic disorder, making some patients even ashamed and resulting in possibly trying to hide their condition [17].

Traditionally, decision-making in medical care has been based more on healthcare providers' than patients´ assumptions as to what is in the patient's best interest. Only recently has increasing attention been devoted to the patient's perspective in clinical practice and medical research. It is obvious that the patient's view in the care process must be also taken into consideration when new strategies for screening are being established.

This prospective study was conducted in a large nationwide cohort to evaluate the impact of the diagnosis and treatment of coeliac disease. Particularly patients' own perceptions of their disease and treatment with a gluten-free diet and their self-reported needs were assessed. Further, we investigated whether these issues were associated with the clinical presentation of the disease or education provided by healthcare staff.

Materials and methods

Patients and study design

The study was conducted in collaboration with the Finnish Coeliac Society. About 70% of coeliac disease patients join the society soon after diagnosis, and it currently embraces more than 20,000 members. A study questionnaire was mailed to all new members joining between February 2007 and May 2008. Subjects who were at least 16 years old and had biopsy-proven celiac disease diagnosed within one year were considered eligible. A further follow-up questionnaire was sent to all suitable respondents after one year on a gluten-free diet. Participants under 29 years old at diagnosis were classified as young [18]. All data were blindly coded before the final analysis. The study was carried out according to national ethical standards and informed consent was obtained from all study subjects after a full written explanation of the aims of the study.

The questionnaires

The baseline and follow-up questionnaires were developed and designed in co-operation with coeliac disease patients, the Finnish Coeliac Society and researchers with high expertise on coeliac disease. The survey comprised questions on sociodemographic characteristics and self-assessed well-being and symptoms. In addition, patients were asked to report on how the diagnosis of coeliac disease and dietary treatment affected their lives, also on possible unmet care requirements. The questionnaires included both free text questions and questions with multiple options measured by the Likert scale [19]. Respondents' reactions to receiving the diagnosis were recorded at baseline and assessed on a four-point scale with alternatives "it was a shock", "no effect", "confused but confident" and "it was a relief". In the follow-up study, the self-assessed easiness of adhering to the diet was evaluated on a three-point scale from "easy" to "hard" and the impact of the diet and the personal attitude to coeliac disease were assessed similarly on a three-point scale, options ranging from "positive" to "negative". The respondents were also given the possibility to state their special needs or wishes in the context of the coeliac disease. The feasibility of the questionnaires was pre-tested by a group of coeliac disease members of the Finnish Coeliac Society. For test-retest reliability, 11 treated patients completed the same questionnaire again 1 week after the initial contact and the intraclass correlation coefficient was measured. The kappa values ranged from 0.84 to 1.00 (values above 0.70 are regarded as excellent). Crohnbach's α was not calculated as the test items were separated. Both gastroenterologists and coeliac disease patients reviewed the tested items to ensure content validity.

Three groups were created according to self-reported clinical presentation: 1) classical symptoms (any kind of abdominal symptoms or symptoms or signs of malabsorption: dyspepsia, flatulence, abdominal pain, diarrhea, iron deficiency anemia, weight loss); 2) extraintestinal symptoms (for example dermatitis herpetiformis, neurological complaints, arthralgia or infertility) and 3) those who were identified by screening in known at-risk groups (first-degree relatives of coeliac disease patients, patients having another autoimmune disorder: type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome, rheumatoid arthritis, IgA deficiency). A separate subgroup analysis was carried out in those screen-detected coeliac disease patients who considered themselves totally asymptomatic at diagnosis.

Statistical analysis

Data were analysed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Chi-square tests were used to examine differences between groups and McNemar tests for differences within groups when appropriate. Binary logistic regression was used in estimating issues associated with either positive or negative reaction to receiving the diagnosis, attitude towards the disease and impact of the diet on one's life. These results were shown as odds ratios (OR) and 95% confidence intervals (CI). P values <0.05 were considered statistically significant.

Results

Study cohort

Of the 1,864 new members of the Finnish Coeliac Society contacted, 1,062 (57%) responded. The age and sex distributions of non-responders did not differ from those of the responders. Of these, 362 were excluded as they had been diagnosed more than one year previously (n=157), were less than 16 years old (n=132), did not have biopsy-proven coeliac disease (n=73), or because the data were inadequate (n=2). Thus, 698 individuals were enrolled in the study; median age at diagnosis was 50 years (range 16-84) and 76% were female. Of the total, 490 suffered from classical and 62 from extraintestinal symptoms and 146 had been detected by screening in at-risk groups. The subgroup of screen-detected, asymptomatic patients comprised 23 individuals. The response rate to the follow-up questionnaire sent after one year was 97% (n=677).

Receiving the diagnosis of coeliac disease

Patients' self assessed reactions to the diagnosis of coeliac disease are shown in Fig. 1. Screen-detected asymptomatic patients and those with extraintestinal symptoms experienced the diagnosis more negatively than those having classical symptoms prior to the diagnosis ($p<0.001$). Logistic regression analysis showed that a shock reaction was significantly associated with insufficient baseline counseling provided by a physician at the time of the diagnosis of coeliac disease (OR 3.4, 95% CI 1.7-6.6), and with being a student as compared to those with the highest socioeconomic index (OR 4.7, 95% CI 1.5-14.1). Otherwise, the socioeconomic index did not affect the results (data not shown). Significant relief was associated with having symptoms for at least two years prior to the correct diagnosis (OR 2.2, 95% CI 1.6-3.2). None of the items assessed depended on the gender or age of the patients.

Experiences and satisfaction regarding dietary counseling

Of the total respondents, 85% had received dietary counseling from their physician and 76% from their dietician. In general, the patients were more satisfied with the counseling provided by dietitians than that provided by physicians. The information offered was considered insufficient in 28% of cases for physicians and 12% of cases for dietitians. The most common reasons for patients´ dissatisfaction were scant information (59% for physicians and 20% for dieticians) and lack of knowledge in the counselor (7% and 18%, respectively). Ten per cent felt that the physician was too busy and 49% complained of the long time lag between the diagnosis and an appointment with a dietician. Four per cent reported that their physician only told them the diagnosis and suggested seeking information from the Internet or a dietitian.

The follow-up survey

In the follow-up survey, 86% of participants reported strict adherence to a gluten-free diet. Occasional lapses were more common in those with extraintestinal symptoms and in the subgroup of initially asymptomatic screen-detected patients (Table I). Of all patients, 12% reported having problems with adherence to a gluten-free diet. Reasons comprised lack of knowledge (82%), poor labeling of gluten-free products (15%) and difficulties in identifying gluten-free food when dining out (3%). There was no association between self-assessed level of knowledge of the diet and dietary counseling received. Of the patients, 9% reported to have persistent symptoms whereas total or significant alleviation was reported by 78%. Those with persistent symptoms reported dietary lapses more frequently than those whose symptoms were totally abolished (OR 2.4, 95% CI 1.04-5.4). Additionally, they experienced adhering to the diet more often difficult than those whose symptoms were alleviated (24% vs. 5%, respectively, p<0.001).

After one year on a gluten-free diet, the self-perceived impact of the diet on life was reported as negative more often by patients with extraintestinal symptoms (OR 2.9, 95% CI 1.6-5.5) or those who belonged to the screen-detected asymptomatic subgroup (OR 2.5, 95% CI 1.0-6.8) than by those with classical symptoms (Table I). Those who had received no information from their physician (OR 1.7, 95% CI 1.02-2.9) or considered it insufficient (OR 2.1, 95% CI 1.3-3.5) more frequently reported a negative impact than others. A negative impact was also related to being less than 29 years old at diagnosis (OR 2.1, 95% CI 1.2-3.7) and having persistent symptoms compared to total alleviation (OR 4.8, 95% CI 2.1-10.9) but not to gender.

Despite all the disadvantages attending a gluten-free diet, the great majority of patients in all study groups had a positive general attitude towards their disease and expressed contentment at being diagnosed as a coeliac disease patient (Table II). Reported negative attitudes were associated with having received unsatisfactory counseling from a physician (OR 1.9, 95% CI 1.03-3.6), young age (OR 2.1, 95% CI 1.04-4.3), having difficulties in following a gluten-free diet (OR 9.7, 95% CI 3.1-30.3) and rating one's own level of knowledge of coeliac disease as poor (OR 3.0, 95% CI 1.3-6.9). In addition, those having persistent symptoms or who stated having been asymptomatic reported a negative

Table I. Coeliac disease patients' self-reported perceptions of a gluten-free diet (GFD) after one year on dietary treatment

	Study groups			Subgroups analysis
	Classical symptoms n=490	Extraintestinal symptoms n=62	Screen-detected, all n=146	Screen-detected, asymptomatic n=23
Self-rated adherence to a GFD, %[a]				
Strict	85	78	91	74
Occasional gluten	14	22	9	26
No diet	0.4	0	0	0
Following a GFD is, %[a,b]				
Easy	22	24	26	17
Of its own	66	61	64	74
Hard	11	15	11	9
Manages a GFD, %[a,b]				
Yes	94	90	96	87
No	6	10	4	13
Impact of GFD on one's life[a,c]				
Positive	72	46	64	33
No effect	14	23	19	38
Negative	14	32	17	29

[a] p=non-significant when compared between the three study groups; [b] p=non-significant when compared between all four groups; [c] p<0.001 when compared between all four groups

Table II. Patients' perception of coeliac disease after one year on a gluten-free diet

	Study groups			Subgroups analysis
	Classical symptoms n=490	Extraintestinal symptoms n=62	Screen-detected, all n=146	Screen-detected, asymptomatic n=23
Attitude to coeliac disease, %[a]				
Positive	72	70	79	65
Indifferent	19	12	16	17
Negative	9	18	5	17
Pleased at being diagnosed, %[a]				
Yes	93	95	92	83
Does not know	6	3	7	17
No	1	2	1	0

[a] p=non-significant when compared between all four groups

attitude more frequently than those whose symptoms had been eradicated or decreased significantly (OR 4.5, 95% CI 1.8-11.6 and OR 3.3, 95% CI 1.1-9.6, respectively). Only 2% of all patients regretted being diagnosed with coeliac disease and, of note, none of those belonged to the asymptomatic, screen-detected group.

Needs and requests for researchers

In the open questionnaire the patients were asked to indicate in their own words what requests they had for future research on coeliac disease (Fig. 2). The most common desire was the development of a pill or an injection allowing the patients to eat gluten-containing food or alternatively a vaccine which would cure the disease; these issues became more evident after a year on a gluten-free diet. Also earlier diagnosis and intensified or even population screening were frequently requested. In addition, patients called for an increase in the level of physicians´ knowledge of the disease.

Discussion

This study focused on patient-centered outcomes concerning the subjective burden of coeliac disease. For this reason we did not use traditional quality-of-life parameters but instead sought the hidden issues which patients find relevant when considering the burden of coeliac disease. Regardless of the initial clinical presentation the majority of patients were satisfied at being diagnosed with coeliac disease and adapted to living with their condition. However, those presenting with extraintestinal symptoms at diagnosis more often experienced negative feelings than the others while on a gluten-free diet. Similarly, dietary lapses and pessimistic attitudes towards the disease were more common in the extraintestinal symptoms group.

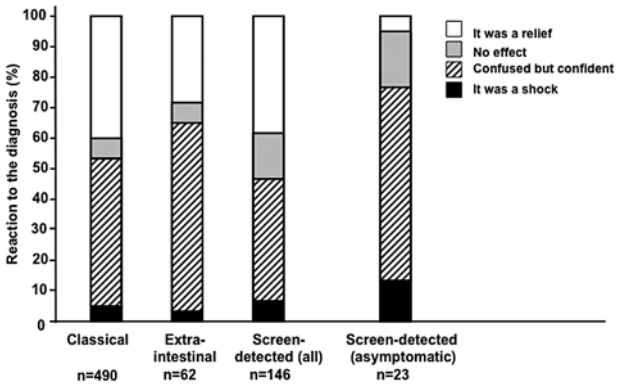

Fig 1. Reaction to the diagnosis of coeliac disease in different study groups. A subgroup analysis of initially totally asymptomatic screen-detected coeliac patients is shown separately. Difference between the groups significant ($p<0.001$).

In accord with previous results [20], a substantial proportion of all patients reported being relieved that coeliac disease was diagnosed. The relief experienced showed a positive correlation with the reported severity and duration of the initial symptoms but not with the counseling provided by a physician. In contrast, a shock reaction was associated with the way physicians presented the diagnosis. Relief was also experienced more frequently in the classical symptom group than the other groups, a reaction which might be explained by the identification of disruptive and hitherto unexplained symptoms. For screen-detected patients, in turn, the diagnosis was unexpected. Unfavorable emotions and distress have been a common initial reaction when receiving a positive result in a screening test in general, but no differences between those tested positive and negative were observed in the long term [21].

In this survey, the subgroup of screen-detected asymptomatic patients had the most negative perceptions of coeliac disease and a gluten-free diet. They reported most dietary lapses and least beneficial impact of the diet on their lives. This group most frequently evidenced a negative attitude towards coeliac disease. Nevertheless, the initially asymptomatic patients were as satisfied as other patients with the fact that the disease had been detected. It has been suggested that coeliac disease patients with initially mild symptoms are more dissatisfied at being diagnosed and prescribed life-long dietary treatment than those with more severe symptoms [22]. On the other hand, experienced diet-related restrictions on daily living are reported similarly regardless of clinical presentation [23]. One explanation

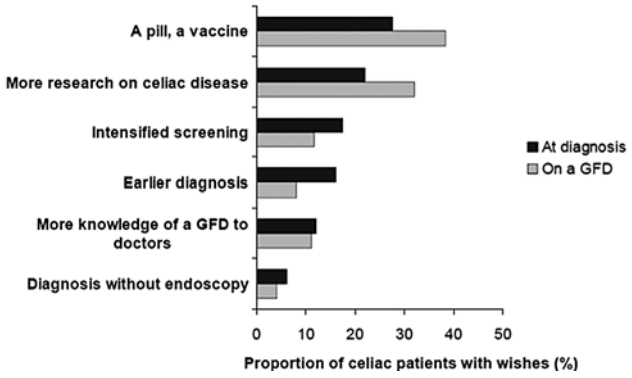

Fig 2. Coeliac patients' unprompted wishes for research at diagnosis and after one year on a gluten-free diet (GFD).

for the finding that our patients were equally satisfied at being diagnosed might be that in a country of high clinical prevalence, patients are in general detected when their symptoms are still mild [24], and we may thus lack the "severe symptoms" group. Admittedly, the responders may have been such who had the most positive attitude towards the disease at the outset. This notwithstanding, the participants also reported a substantial negative and disruptive effect of coeliac disease on their lives.

In the present study, physicians' attitudes and counseling provided at the time of the diagnosis had a major impact on the patients' lives and experiences of coeliac disease after one year under treatment. Unsatisfactory doctor-patient communication and scant information were associated with a shock reaction, disapproval and negative attitude towards coeliac disease and the diet. Also in the free text section of our questionnaire physicians were accused of lack of knowledge, inappropriate attitudes towards the patient and underestimation of the disease. However, no such correlation between counseling or follow-up by a dietician and patients' perceptions of coeliac disease were noted in the structured questions. Previous studies have shown that one important contributor to the optimal management of coeliac disease is a good doctor-patient relationship, which enhances dietary compliance and patients' ability to adapt [20, 25-27]. Improper communication has been associated with a decreased quality of life [28]. Our findings indicate that doctor-patient communication has extensive long-term effects on the disease burden. However, those with persistent symptoms experienced a gluten-free diet with more difficulty and reported more frequently a negative impact of the diet on life than those whose symptoms were eradicated or reduced significantly, which implies that those patients would benefit from more detailed dietary counseling. In addition, in a recent study perceived degree of difficulty adhering to a gluten-free diet was associated with reduced well-being [29]. Of note, in that study 80% reported difficulty adhering to the diet compared to 12% in the present study. This discrepancy might be explained by differences in perceptions in different cultures, however, further research in this field is clearly needed.

One interesting aspect was that a shock reaction was more common in coeliac disease patients diagnosed at a young age. This group also reported more negative impact and resigned attitude towards the condition than those diagnosed later in adulthood. Previously coeliac disease patients diagnosed at a younger age have also been reported to have poor dietary compliance [20, 30], possibly due to deficient adaptation to the disease. In addition, young adults have been more vulnerable to stigmatization and have felt different because of their condition [16, 17]. It is possible that our healthcare system is not sensitive enough to the special needs of adolescent coeliac disease patients and thus not able to offer all the social support they require [31].

In this study the patients were asked to indicate in their own words their special wishes and needs vis-à-vis future coeliac disease research. Frequently mentioned issues included better labeling and availability of gluten-free products, early diagnosis and more detailed dietary counseling. Similar findings have previously been reported when participants were asked to indicate what issues would enhance their quality of life most [32, 33]. A novel finding, however, was the spontaneously reported desire for a medicine for coeliac disease, which was in fact the commonest desideration. In a recent study, 42% of coeliac disease patients were dissatisfied with a gluten-free diet and all reported to be interested in alternative therapies [34]. Even though the range of gluten-free products is expanding, a need to make the management of coeliac disease simpler and more patient-centered was obvious.

Even though a vast majority of Finnish coeliac disease patients belong to the national Coeliac Society, membership might have affected the results obtained and limited their applicability in general. Another limitation is that those who responded might have been the best motivated, this making our findings too positive. On the other hand, the participation rate was relatively good and comparable to those in previous studies assessing quality of life with a postal or a mail-out survey [31, 35].

Conclusion

Despite the indisputable burden of a gluten-free diet in general, coeliac disease patients are satisfied with the diagnosis and willing to adhere to the diet. Nevertheless, particularly those who are diagnosed young, who suffer from extraintestinal symptoms or who are totally asymptomatic require additional reinforcement. This should be taken into consideration when an increasing proportion of patients may be diagnosed by active screening. A comprehensive approach in patient education at diagnosis is an important factor in reducing disease-related distress and in improving the management of coeliac disease.

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Conflicts of interest

None to declare.

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Original article

Changes in body mass index on a gluten-free diet in coeliac disease: A nationwide study ☆

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ABSTRACT

Objective: The clinical presentation of coeliac disease has changed and patients are often overweight at diagnosis. There is concern that patients might gain further weight while on a gluten-free diet (GFD). The aim of the study was to evaluate the impact of a GFD on the body mass index (BMI) in a nationwide cohort of coeliac patients and to determine variables predictive of favourable or unfavourable BMI changes.
Methods: We prospectively investigated weight and disease-related issues in 698 newly detected adults diagnosed due to classical or extraintestinal symptoms or by screening. BMI at diagnosis and after one year on a GFD were assessed and compared with that in the general population.
Results: At diagnosis, 4% of subjects were underweight, 57% normal, 28% overweight and 11% obese. On a GFD, 69% of underweight patients gained and 18% of overweight and 42% of obese lost weight; in the rest BMI remained stable. Changes were similar in both symptom- and screen-detected patients. The coeliac group had a more favourable BMI pattern than the general population. Favourable BMI changes were associated with subjects' self-rated expertise on GFD and young age at diagnosis, but not dietary counselling received.
Conclusions: BMI improved similarly in screen- and symptom-detected coeliac disease patients on a GFD.

1. Introduction

Coeliac disease is one of the most common autoimmune-based disorders affecting about 1–2% of the population in the Western countries [1–3]. In the recent decades there have been several reports of a changing clinical picture of the disease. In particular, the proportion of patients suffering from classical gastrointestinal symptoms seems to be decreasing and an increasing number are diagnosed because of extraintestinal symptoms or screening in at-risk groups [4,5]. At the same time, the proportion of patients who are rather over- than underweight at diagnosis is increasing [6–10]. More recently concern has increased for treated coeliac disease patients gaining weight on a gluten-free diet (GFD) concomitant with improved absorption of nutrients [8], as excessive weight gain may increase the risk of morbidity i.e., metabolic syndrome, type II diabetes mellitus and a higher risk of vascular diseases [11,12]. This fear is supported by a recent study showing that an elevated body mass index (BMI) is associated with increased all-cause mortality [13]. This concern over weight gain applies especially to screen-detected coeliac disease patients, and it would thus be essential to evaluate the consequences of gluten-free dietary treatment on the BMI of coeliac patients today before any screening programs for the disease are instituted.

In Finland, a substantial proportion of coeliac disease diagnoses are made in primary healthcare and relatively mild and atypical symptoms dominate the clinical picture [14]. This augmented diagnostic approach has increased adult coeliac disease diagnoses twenty times during the past 30 years, and the current clinical prevalence of 0.5% equals the figures found in many population screening studies [3,14]. The aim of this nationwide prospective study was to assess the distribution of BMI at diagnosis in a large adult coeliac disease population containing both symptom- and screen-detected patients and to evaluate the impact of one year on a GFD on the BMI of the patients. In addition, variables predicting either favourable BMI changes or unfavourable weight gain were evaluated.

2. Materials and methods

Data for the study were obtained in a nationwide survey conducted in collaboration with the Finnish Coeliac Society. About 70% of newly diagnosed coeliac disease patients join the Society shortly

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after diagnosis. A validated questionnaire was mailed to all new members who joined the Society between February 2007 and May 2008. Those with biopsy-proven coeliac disease diagnosed within one year were considered eligible to the study. A follow-up questionnaire was sent to the respondents after one year. The questionnaires were developed in co-operation with the Coeliac Society, coeliac disease patients and clinical researchers [15]. They comprised questions on personal health status, including current height and weight, and symptoms and signs prior to the diagnosis of coeliac disease and after initiation of a gluten-free diet. Patients were also asked about their self-rated adherence to the diet, dietary counselling they received and follow-up visits. BMI was calculated as body weight/height^2 (kg/m^2). The BMI values were categorized according to the World Health Organization (WHO) criteria as follows: <18.5 kg/m^2 as underweight, 18.5–24.9 kg/m^2 as normal weight, 25–29.9 kg/m^2 as overweight and ≥30 kg/m^2 as obese. Changes in BMI were classified as favourable if underweight patients gained weight, those with normal weight remained normal and overweight and obese patients lost weight. Weight gain was rated unfavourable if overweight or obese patients gained weight and those with normal weight became overweight or obese. Weight changes of at least three kilos were regarded as clinically relevant.

The feasibility and test-retest reliability of the questionnaires as well as face and content validity of the tested items were pre-tested by a group of coeliac disease members of the Finnish Coeliac Society, as previously described [15]. The repeatability of reported height was also measured and in 95% of cases the difference between reported height at baseline and at follow-up was less than two standard deviations. All clinical data were blindly coded before the analysis. Informed consent was obtained from all study subjects after a full written explanation of the aims of the study.

All subjects who were at least 16 years old and had a biopsy-proven coeliac disease diagnosis were enrolled in the study. Patients were classified into three study groups as follows: I, patients with classical symptoms (dyspepsia, flatulence, abdominal pain, diarrhoea, iron deficiency anaemia, weight loss etc.); II, patients with extraintestinal symptoms (for example dermatitis herpetiformis, neurological complaints, arthralgia or infertility); and III, those who were identified by screening in at-risk groups such as first-degree relatives of coeliac disease patients and those with type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome or selective IgA deficiency. A subgroup of screen-detected initially asymptomatic patients was also analyzed separately. Patients who were less than 29 years of age at diagnosis were considered young [16].

For comparison, data from 207 consecutive untreated biopsy-proven coeliac disease patients (median age 49 years, range 18–79, 62% female) were collected from a local referral centre. Of them, follow-up data after one year on a strict serology-confirmed GFD were available of 141 patients. Weight and height of these patients were measured by healthcare personnel. Ethical approval was obtained from the Ethical Committee of Tampere University Hospital. All participants gave written informed consent.

Data for comparison to the Finnish general population during the same period (2007–2008) were attained from an annual postal survey conducted by the National Institute for Health and Welfare since 1978. The survey is entitled "Health Behaviour and Health among the Finnish Adult Population" and is mailed to a random sample of 5000 Finnish adults (15–64 years old) each year [17,18]. In this survey, differing from the WHO definition, underweight is categorized as BMI less than 20 kg/m^2. This was thus the limit used in comparisons to the general population. We also limited comparison to responders of the same age (16–64 years old).

Statistical analysis was carried out using Statistical Package for Social Sciences for Windows software (SPSS version 17.0, SPSS Inc., Chicago, IL, USA). All testing was two-sided and $p<0.05$ was considered statistically significant. Chi square test was used in cross tabulations and McNemar test for evaluating change within the groups. Binary logistic regression analyses were used to estimate associations between BMI and demographics, dietary counselling or follow-up. These results are shown as odds ratios (OR) and 95% confidence intervals (CI).

3. Results

The study questionnaires were mailed to 1864 individuals joining the Finnish Coeliac Society and 1062 (57%) responded. The age and sex distributions did not differ from those of non-responders. A total of 364 individuals were excluded: 157 had not been diagnosed within a year, 132 were under 16 years old, 73 did not have biopsy-proven coeliac disease and 2 yielded insufficient data. The final analyses were thus conducted on 698 adults, of whom 677 (97%) also responded in the follow-up survey. Altogether 490 (70%) of the respondents suffered from classical and 62 (9%) from extraintestinal symptoms, and the remaining 146 (21%) subjects were detected by screening. Of the screen-detected group, 23 reported having been totally asymptomatic prior to the diagnosis. Characteristics of the patients in the different study groups are shown in Table 1. Age and sex distributions and socio-economic index did not differ between the groups (Table 1). At diagnosis, 4% of all patients were underweight, 57% normal weight, 28% overweight and 11% obese. The percentages were similar in both screen- and symptom-detected patients (Table 1). Of the referral centre coeliac disease controls, 2% were underweight, 48% normal weight, 36% overweight and 13% obese at diagnosis.

After one year on dietary treatment, 33% of all coeliac disease patients had gained and 16% lost at least 3 kg. There were no differences between subjects with classical or extraintestinal symptoms and the screen-detected group. However, in the screen-detected asymptomatic group the percentages were 13% and 26%, respectively, which differed significantly from the other groups ($p=0.046$). Favourable changes or BMI remaining normal were noted in 62% of the study subjects, the percentages being similar in both screen- and symptom-detected patients. Equal favourable changes in BMI were evident also in referral centre controls, among whom the percentage was 57%. After a GFD, 2% of all patients were underweight, 54% normal weight, 34% overweight and 11% obese. The percentages were analogous in all study groups. BMI and weight changes categorized according to the initial BMI are shown in Table 2. A GFD resulted in 69% of initially underweight patients achieving normal weight. Of those of normal weight, 87% remained in the same BMI category. Weight loss was observed in 18% of overweight and 42% of obese patients, respectively. Dietary compliance was similar in all groups and 89% reported being on a strict GFD.

The coeliac group as a whole had BMI significantly lower than that in the general population both at diagnosis and after one year on a GFD (Table 3). Interestingly, in a gender sub-analysis the male patients had significantly lower BMI than the controls at diagnosis (11% underweight, 49% normal weight, 28% overweight and 12% obese, *versus* 4%, 39%, 41% and 16% respectively, $p<0.001$) but not in the follow-up (3%, 49%, 35% and 13% *versus* 4%, 40%, 40% and 15% respectively, $p=0.323$), whereas in female patients the BMI did not differ from that of the controls at diagnosis (11% underweight, 51% normal weight, 26% overweight and 12% obese, *versus* 11%, 46%, 29% and 14% respectively, $p=0.258$), but was notably lower on dietary treatment (8%, 51%, 32% and 10%, *versus* 10%, 46%, 28% and 16% respectively, $p=0.002$).

Analyses of variables predicting favourable changes in BMI revealed that only self-assessed expertise on GFD (OR 2.0, 95% CI 1.05–3.7) and young age at diagnosis (OR 2.1, 95% CI 1.2–3.6) were associated with improved BMI. Gender, clinical presentation, dietary counselling and whether the disease was diagnosed in primary, secondary or tertiary healthcare had no impact on BMI. None of the parameters assessed was associated with unfavourable weight gain. Adherence to a GFD was not associated with either favourable or unfavourable changes in BMI.

Table 1
Characteristics of coeliac disease patients in different study groups at diagnosis, body mass index (BMI) according to WHO criteria.

	Study groups			Subgroup analysis
	Classical symptoms n = 490	Extraintestinal symptoms n = 62	Screen-detected, all n = 146	Screen-detected, asymptomatic n = 23
Female, %[a,b]	77	68	80	91
Median age (range/years)[a,b]	49 (16–84)	54 (20–75)	52 (18–82)	44 (19–82)
BMI at diagnosis, %[a,b]				
Underweight	4	2	3	4
Normal weight	58	48	56	61
Overweight	27	34	29	22
Obese	11	16	12	13
Socio-economic index, %[a,b]				
I	26	31	24	13
II	54	61	56	52
III	13	7	12	13
Student	7	2	8	22
The place of diagnosis, %[b]				
Primary healthcare	41	27	45	44
Secondary healthcare	40	37	34	35
Tertiary healthcare	8	19	13	17
Private clinic	12	16	9	4
Referral to a dietician, %[a,b]	76	79	73	77

[a] p = non-significant when compared between the three study groups.
[b] p = non-significant when compared between all four groups.

4. Discussion

Recent population-based studies have shown that the mean BMI is increasing in the Western countries, and currently approximately half of the adult population are overweight or obese (Table 4). Significantly, a similar trend was seen in coeliac disease patients in the present study as only a few per cent were underweight at diagnosis, whereas almost 40% were overweight or obese. Here, however, it must be noted that our study population consisted mainly of patients with mild if any symptoms and only few suffered from a severe disease. Interestingly, analogous results were obtained in a recent study from the UK in which 5% of the patients were underweight and 39% overweight or obese [8]. In the study in question, 81% of the patients gained weight on a GFD and, after two years on dietary treatment, 51% were overweight or obese. Nevertheless, when compared to the UK findings, the dietary response in our coeliac group was the opposite, as while on a GFD the overweight and obese patients lost and underweight patients gained weight. When compared to the general population, there were more patients of normal BMI in the coeliac disease group than in the population controls both at diagnosis and in the follow-up. There were some design differences between the UK and the present study that may have impacted the results. The UK study was retrospective and the study period was two years. In addition, the study population was smaller and comprised antibody positive patients that had converted negative after one year on a GFD and were seen by a single gastroenterologist. Moreover, in the present study only weight changes of at least three kilos were considered which might explain the different percentages of those who gained weight on a GFD. However, a parallel trend to our results was demonstrated in a recent American study in which the majority of treated coeliac disease patients either attained or remained normal weight and showed a more favourable BMI pattern both at diagnosis and on treatment than the general population [9].

One interesting aspect in the present study is that we were able to assess the impact of a GFD on BMI in a substantial number of both symptom- and screen-detected coeliac disease patients. At diagnosis, the BMI profile was parallel in all study groups. In addition, the positive effects of the diet on BMI were similar regardless of whether the disease was detected due to classical or extraintestinal symptoms or by active screening. Similarly, in a population-based cohort of screen-detected children with initially low BMI, a significant increase in BMI was noted on a GFD [19]. The finding that male coeliac disease patients had a lower BMI than the general population at diagnosis but not after dietary treatment whereas the results among female patients were the opposite is a subject for further studies. The difference might be explained by different dietary habits between male and female patients. Female patients might have adopted a healthier life-style after being placed on dietary treatment which had resulted in improved BMI. In addition, male could have suffered from more severe symptoms than female.

It has been suggested by some authors that specialized follow-up and dietary counselling are essential for the appropriate management of coeliac disease [9,20]. In Finland an increasing number of coeliac patients are diagnosed in primary healthcare by internalists or general physicians (Table 1). Subsequently, only a minority of patients are seen by gastroenterologists or investigated in special clinics with expertise in coeliac disease. However, there were no differences in the management of the disease and the results achieved between the different healthcare

Table 2
Weight and body mass index (BMI) changes in different BMI categories after one year on a gluten-free diet according to WHO criteria for BMI.

Initial BMI	Patients, %	Weight change[a], %[b]			BMI on a gluten-free diet, %[b]			
		Weight loss	Stable	Weight gain	Underweight	Normal	Overweight	Obese
Underweight	4	0	31	69	40	60	0	0
Normal	57	10	51	38	1	87	11	1
Overweight	28	18	60	22	0	8	84	8
Obese	11	42	43	16	0	0	29	71
All	100	16	52	33	2	54	34	11

[a] Changes of at least three kilos were recorded.
[b] <0.001 when compared between the initial BMI category groups.

Table 3
Body mass index (BMI) of coeliac disease patients in different study groups at diagnosis and after one year on a gluten-free diet compared to a sample of the general population in 2007 and 2008 (limited to 16–64 years old, see Materials and methods).

	BMI (kg/m^2)				P value (compared to controls)
	Underweight <20	Normal weight 20–24.9	Overweight 25–29.9	Obese ≥30	
All coeliac disease patients, n = 589 (%)					
At diagnosis	11	51	27	12	<0.001
On a gluten-free diet	7	50	32	11	0.004
Classical symptoms, n = 416 (%)[a]					
At diagnosis	11	53	25	11	<0.001
On a gluten-free diet	6	53	29	11	0.004
Extraintestinal symptoms, n = 51 (%)[b]					
At diagnosis	8	43	31	18	0.950
On a gluten-free diet	4	44	44	8	0.220
Screen-detected, all, n = 122 (%)[b]					
At diagnosis	12	47	30	12	0.310
On a gluten-free diet	9	44	38	9	0.280
Screen-detected, asymptomatic, n = 18 (%)[b]					
At diagnosis	28	39	22	11	0.020
On a gluten-free diet	28	39	28	6	0.010
Population controls (%)					
2007, n = 3186	8	43	34	15	
2008, n = 3139	7	44	33	16	

[a] p<0.001 for change within the group.
[b] p = non-significant for change within the group.

levels. In addition, the dietary counselling offered and reported compliance in the present cohort were comparable to those in previous studies [7,21,22].

In the present study, we could not find any association between dietary counselling received and changes in BMI. In Finland, patients are offered dietary advice from the healthcare system and patient organisations. In contrast, in the USA study dietary counselling was an important factor in obtaining beneficial changes in BMI [9]. Additionally, in the UK study the authors suggested that dieticians should modify advice depending on BMI [8]. Opposite results obtained in the present study might be due to differences in the management of coeliac disease and dietary counselling offered between the countries. In the UK study, overweight and obese patients suffered from milder symptoms than their counterparts [8]. However, in the present study clinical presentation had no significant impact on BMI outcome. Nevertheless, a self-rated good level of knowledge of the diet was associated with a beneficial BMI outcome. However, the self-rated level of knowledge of a gluten-free diet as predictor of improved BMI outcome in coeliac disease patients can be biased as the participants of the current study may have been the most highly motivated to adopt a healthier diet in general. In addition, diagnosis at younger age was associated with improved BMI. Changing one's dietary habits might be easier to those diagnosed at young age. In contrast, we could not determine any variables predicting unfavourable weight gain. This may be due to the fact that multiple factors have an impact on BMI and changes in weight, as is also seen at the population level.

Weight and height in the present study were self-reported, which might in theory have led to underestimation of the actual BMI. Nevertheless, BMI measured by self-reported height and weight has been shown to be reliable and valid in epidemiological studies [23,24]. In addition, the control data from a sample of the general population was similarly based on self-reported values. Our results are also supported by parallel BMI results observed in coeliac disease controls obtained from the referral centre. One benefit of this study setting was that we were thus able to collect nation-representative data. However, our results might be applicable only to members of coeliac disease community. Other limitation to the present study was that the follow-up time was rather short. Typically, the most significant

Table 4
Body mass index in untreated coeliac disease patients and control subjects in different studies according to WHO criteria for body mass index.

Country	n	Study period	Body mass index, (%)			
			Underweight	Normal	Overweight	Obese
Untreated coeliac disease						
USA [6]	215	1984-1998[a]	33	32	14	12
USA [9]	369	1981-2007	17	61	15	7
Sweden [10]	244	1983-2000	16	73	11	ND
UK [8]	371	1995-2005	5	57	26	13
Finland, current study	698	2007-2008	4	57	28	11
Control population						
USA [27,28]	4881	2007-2008	2	30	34	34
Sweden [29]	10,000	2004-2005	ND	ND	40	11
UK [30]	17,925	1987-2002	2	49	34	15
Finland [17]	3186	2007	8	43	34	15

ND not defined.
[a] Retrospective study, data missing in 9%; different from the WHO definition, underweight is categorized as body mass index less than 20 kg/m^2.

clinical and histological changes in the intestines occur within the first year on a GFD. However, it has been shown that full histological recovery in coeliac disease may sometimes take longer than 12 months [25,26] which might have an additional impact on BMI. The study also lacked a dietary questionnaire and thus it was impossible to verify if changes is BMI were linked to the normalization of intestinal absorptive function or to a different caloric intake.

In conclusion, the BMI profile of the coeliac disease group resembled that of the general population, being still significantly more favourable. Treatment with a gluten-free diet induced similarly beneficial changes in BMI in both symptom- and screen-detected coeliac disease patients, this improvement being slightly associated with young age at diagnosis and self-rated expertise on the diet.

5. Learning points

- At diagnosis, only a few percents of coeliac disease patients are underweight whereas up to 39% are overweight or obese.
- Treatment with a gluten-free diet is effective in achieving beneficial changes in coeliac disease patients, both underweight and overweight at diagnosis.
- Attaining a good self-rated level of knowledge of a gluten-free diet predicts improved BMI outcome in coeliac disease patients.

Conflict of interest statement

None to declare.

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Use of health care services and pharmaceutical agents in coeliac disease: a prospective nationwide study

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Abstract

Background: Approximately 1% of the population suffer from coeliac disease. Due to a wide clinical spectrum and mild symptoms, the disease is heavily underdiagnosed. Unexplained symptoms may lead to incremented medical consultations and productivity losses. The aim here was to estimate the possible concealed burden of untreated coeliac disease and the effects of a gluten-free diet.

Methods: A nationwide cohort of 700 newly detected adult coeliac patients were prospectively evaluated. Health care service use and sickness absence from work during the year before diagnosis were compared with those in the general population. Additionally, the effect of one year on dietary treatment on the aforementioned parameters and on consumption of pharmaceutical agents was assessed.

Results: Untreated coeliac patients used primary health care services more frequently than the general population. On a gluten-free diet, visits to primary care decreased significantly from a mean 3.6 to 2.3. The consumption of medicines for dyspepsia (from 3.7 to 2.4 pills/month) and painkillers (6.8-5.5 pills/month) and the number of antibiotic courses (0.6-0.5 prescriptions/year) was reduced. There were no changes in hospitalizations, outpatient visits to secondary and tertiary care, use of other medical services, or sickness absence, but the consumption of nutritional supplements increased on treatment.

Conclusions: Coeliac disease was associated with excessive health care service use and consumption of drugs before diagnosis. Dietary treatment resulted in a diminished burden to the health care system and lower use of on-demand medicines and antibiotic treatment. The results support an augmented diagnostic approach to reduce underdiagnosis of coeliac disease.

Trial registration: ClinicalTrials.gov NCT01145287

Keywords: Coeliac disease; gluten-free diet; burden of illness; health care service use; sickness absence

Background

Untreated coeliac disease may cause a significant burden to the health care system. The disease is one of the commonest chronic gastrointestinal disorders, with a prevalence of up to 2% in the adult population [1], the figure in fact even increasing [2]. The clinical picture is heterogeneous and comprises mild or extraintestinal symptoms such as osteoporosis and neurological complaints [3,4]. Up to 90 per cent of coeliac disease patients remain undiagnosed [1,5,6] and may suffer from impaired health and repeatedly seek help for non-specific complaints [7-9]. This may lead to excessive use of health services, for example frequent outpatient visits and expensive medical investigations. Furthermore, physicians or patients themselves may try to treat the unexplained symptoms and poor well-being with a variety of pharmaceutical agents or micronutrients in addition to non-medical treatments. Possible false diagnoses and futile measures might cause a further burden to the health care system. It could also be hypothesized that undetected coeliac disease leads to an increased number of days of absence from work. As treatment with a gluten-free diet usually results in alleviation of symptoms it could thus also diminish the burden related to the disease. Remarkably, the mean diagnostic delay in coeliac disease is between 4 and 13 years [8-12], indicating that the burden caused by undiagnosed disease might be long-standing. Now that accurate serological screening tests are available for screening for coeliac disease, an active screening policy would shorten this period of latency and reduce the burden related to undetected disease. The data thus far available on the use of health care services, consumption of symptom-targeted medication and sickness absence among undiagnosed and treated coeliac disease patients are limited.

In this country, an increasing number of coeliac disease patients are diagnosed in primary health care [13]. Due to intensified case finding and screening, mild or atypical symptoms dominate the clinical picture and the detection rate is up to 0.7%. We aimed here to estimate prospectively the possible concealed burden of untreated coeliac disease and the effects of a gluten-free diet in a large nationwide cohort of newly detected coeliac disease patients. We also compared the results of health care service use and reported days of absence from work with national data from the general Finnish population during the same period.

Methods

A nationwide cohort of consecutive newly detected coeliac disease patients were prospectively evaluated. A structured and validated study questionnaire was mailed to all new members joining the Finnish Coeliac Society between February 2007 and May 2008. In Finland, approximately 70% of coeliac disease patients join the Society shortly after being diagnosed. Respondents over 16 years of age with biopsy-proven coeliac disease diagnosed within one year were eligible. A follow-up questionnaire was sent to all respondents after one year. The questionnaires were designed in co-operation with the Finnish Coeliac Society, coeliac disease patients and clinical researchers with expertise in the disease [14], and comprised questions on personal health and issues related to the diagnosis. Self-reported consumption of on-demand pharmaceutical agents and supplements, both prescribed and over-the-counter agents, was inquired. The use of health care services, including all-cause visits (inpatient, outpatient, other medical services; the causes of visits were not asked) and also visits related to the diagnosis and follow-up were recorded during one year prior to the diagnosis of coeliac disease and after initiation of a gluten-free diet. Patients were also asked to report the number of days of sickness absence from work during the same periods. The appropriateness of the questions together with the face and content validity of the tested items were pre-tested by a group of coeliac disease members of the Society as previously described [14]. Test-retest reliability was established using an intraclass correlation coefficient. For the key items measured, the kappa values for test-retest reliability ranged from 0.84 to 1.00 (values above 0.70 being regarded as excellent). All data were blindly coded before analyses. Informed consent was obtained from all study subjects after a full written explanation of the aims of the study, including considerations regarding ethics and data protection and the anonymous deposition of the questionnaires.

Data on self-reported visits to a physician and days of absence from work among the general Finnish population during the same period (2007-2008) were obtained from an annual nationwide postal survey conducted by the National Institute for Health and Welfare since 1978. The surveys are mailed to a random sample of 5000 Finnish adults (15-64 years of age) each year [15,16]. In the present study, comparisons on the aforementioned issues between the coeliac group and the general population were limited to study subjects of the same age. The groups were not adjusted for gender.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). All testing was two-sided and $p<0.05$ was considered statistically significant. Chi square test was used in cross tabulations, Wilcoxon signed rank test for evaluating changes within groups and Mann-Whitney U test for assessing changes between groups. Results are given as means and 95% confidence intervals (CI).

Results

The study questionnaires were mailed to 1864 coeliac disease patients, of whom 1062 (57%) responded. There were no differences in age or gender distribution between respondents and non-responders. Altogether 362 individuals were excluded: in 157 cases the diagnosis had been made more than one year previously, 132 were under 16 years of age and 73 did not have a biopsy-proven diagnosis. Thus, 700 adult patients were enrolled (Table 1). Of these, 679 (97%) also completed the follow-up survey. After one year, 86% of the patients reported adherence to a strict gluten-free diet, only two having continued on a gluten-containing diet.

In the year prior to the diagnosis of coeliac disease, the patients had consulted either a primary care or a hospital physician a mean 4.4 times. In the year following the diagnosis while on a gluten-free diet, the corresponding figure was 3.1. A significant reduction was observed in use of primary health care services. There were no changes in the number of consultations in secondary or tertiary health care or in admissions to or consumption of other medical services (Table 2). The use of health care services assessed as all-cause consultations with a physician and admissions to a hospital was significantly higher in both genders in the coeliac disease group than in the general population ($p<0.001$) (Figure 1). After one year on a gluten-free diet, no such difference was observed.

The reported number of days of sickness absence from work was significantly lower in the coeliac group than in the general population in the year prior to the diagnosis (Figure 2A). In the year following the diagnosis, sickness absences had increased to population level among males but not among females (Figure 2B). When the male group was analysed by age, only the youngest (16 to 24 years old) and the oldest (55 to 64 years old) age groups differed significantly from the controls, $p=0.018$ and $p=0.005$, respectively. Those 55 to 64 years old had the biggest increase in the number of days of absence, a mean of 5.6 days. Among the youngest age group the mean increase was 1.8 days.

The coeliac disease patients' consumption of pharmaceutical agents in the year prior to and following the diagnosis is shown in Table 3. There was a significant reduction in all on-demand medicines on treatment. In particular, the use of drugs for dyspepsia decreased significantly in both genders, and that of painkillers and the number of antibiotic prescriptions in females (Table 3).

In contrast to other pharmaceutical agents, the consumption of vitamins, micronutrients and herbal products increased significantly in both genders on a gluten-free diet (Table 3). Males increased their consumption even more than female. While at diagnosis 49% of the patients reported at least occasional use of vitamins, micronutrients or herbal products, the corresponding figure after one year on treatment was 55%.

Discussion

In this prospective, nationally representative study we found that untreated adults with coeliac disease made more outpatient health care visits than the general population. In addition, implementation of a gluten-free diet resulted in the disappearance of this increased consumption of medical services. The burden of unrecognized coeliac disease was concentrated particularly in primary health care. In parallel to these findings, a significant reduction in the use of on-demand drugs and the number of antibiotic prescriptions was observed while on dietary treatment. To our knowledge, this was the first study to investigate sickness absence and consumption of on-demand medication among coeliac disease patients.

A possible explanation for the increased use of health care services and symptom-targeted medication prior to diagnosis might be related to the presence of diverse symptoms: untreated coeliac disease is known to be associated with various unspecific complaints – e.g. indigestion and heart burn [17], regurgitation [18], migraine [19] and joint pain [20], which may resolve on a gluten-free diet. It has also been suggested that active coeliac disease may be associated with an increased susceptibility to infections [21,22]. Our findings suggest that the diagnosis and subsequent treatment of coeliac disease are able to reduce the burden of disease in the health care system in addition to the alleviated burden experienced by patients [14].

Earlier data on the use of health care services in coeliac disease are limited. Two recent retrospective studies from the USA found that treatment with a gluten-free diet resulted in decreased medical costs due to reduced use of health care services among coeliac disease patients. However, these studies concentrated on direct costs and obtained study participants in high-volume referral centres or administrative claim registers [23,24], which may limit extrapolation of the data to the whole coeliac disease population. It is of note that the main findings - excessive health care service use before the diagnosis of coeliac disease and reduction in the consumption of these services during a gluten-free diet - were in line, despite the difference in settings between these earlier trials and our current prospective nation-wide study. However, in contrast to the results reported by Long and associates [24] we found no difference in the number of hospitalizations between the years prior to and following the diagnosis of coeliac disease. In addition, in the present study expenditure on laboratory services and imaging were not increased prior to diagnosis.

Nowadays the proportion of coeliac disease patients suffering from severe gastrointestinal symptoms and malabsorption is decreasing and milder symptoms predominate. Consultations on these possibly vague and unspecific symptoms might add to the burden in primary health care, which patients first contact upon any complaints. Additionally, the diagnostics and follow-up of coeliac disease among adults are focused in primary health care in Finland [13], all these aspects possibly explaining the increased use of primary health care services observed in the present study.

Even though the consumption of health care services among coeliac disease patients was reduced to the population level during one year on a gluten-free diet, further studies are needed to establish the long-term impact of dietary treatment. A recent study from Sweden reported that, in spite of a median of 4 years on a gluten-free diet, female coeliac disease patients used more health care services than non-coeliac controls [25]. It was also shown that the majority of complaints were related to gastrointestinal symptoms, mental and behavioural disorders and diseases of the musculoskeletal system. There is further evidence that regardless of a long-term gluten-free diet and histological remission, coeliac disease patients may evince significant symptoms and impaired health-related quality of life [26,27].

It was somewhat surprising that the patients in our study reported no increased sickness absence from work prior to diagnosis. Actually, the number of days of absence was even

lower than that among the general population. This would imply that currently the majority of coeliac disease patients present with relatively mild clinical symptoms. However, although untreated coeliac disease is known to be associated with increased anxiety and depression [28], reduced vitality [29] and sleeping disorders [30], we did not here inquire in to the possible decrease in productivity among undetected coeliac disease patients. The reason why male but not female coeliac disease patients increased their number of days of absence from work in the follow-up remains unsolved. Possibly, once given a diagnosis of a chronic disease the patients may have thought to be "validated" or "vindicated" in being off work. Unfortunately, we could not ascertain whether sick leaves were concentrated during the period short after diagnosis or were evenly distributed along the follow-up period.

Even though decrease in the number of antibiotic prescriptions was not big it can be regarded as clinically significant. Two recent studies [31,32] have investigated use of antibiotics and risk of developing Crohn's disease or ulcerative colitis. They found that subjects with those diseases were more likely to have been prescribed antibiotics before the diagnosis. Shaw and associates [31] speculated that the use of antibiotics could be a predisposing factor, whereas Virta and associates [32] considered that frequent use of antibiotics may trigger the development of Crohn's disease or be a sign of being prone to infections before the intestinal disease is diagnosed. Our hypothesis about coeliac disease patients is similar to the latter consideration and is supported by the fact that fewer patients had been prescribed antibiotics post than pre-diagnosis.

Interestingly, the use of vitamins, micronutrients and herbal products increased significantly after the diagnosis of coeliac disease. It has been reported that about 15-38% of untreated coeliac disease patients suffer from anaemia or nutritional deficiencies [33-35]. Nevertheless, these are usually abolished on a gluten-free diet [33,36], and implementation of specific dietary supplements after the diagnosis is not routinely recommended in current clinical guidelines [37]. Consequently, we believe that in most cases the supplements were not prescribed by a physician but started voluntarily by the patients.

The fact that we used self-reported data might be considered a limitation to the study in that it may involve inaccuracies. However, a unique strength of such a setting in a nation-wide study was that by using self-reported data it was possible to explore all aspects of health care use instead of data captured in a single database. Subsequently, we were able to assess not

only issues related to direct costs of care but also the indirect burden falling on coeliac disease patients themselves. However, similar methods have previously been used in studies concerning gastrointestinal disorders and a recall period covering the preceding twelve months in self-reported use of health care services and pharmaceutical agents has been shown to be feasible and reliable [38]. Moreover, patients were asked to report issues similarly at baseline and in the follow-up, which makes the changes observed more reliable. Likewise, the data on the general population were based on self-reported values.

Conclusions

Excessive use of primary health care services and pharmaceutical agents was observed among untreated coeliac disease patients. Treatment with a gluten-free diet resulted in decreased consumption of health care services, on-demand medicines and antibiotic prescriptions. The results imply that unrecognized coeliac disease contributes markedly to the burden on affected individuals and the health care system.

Abbreviations

OEGD	oesphago-gastroduodenoscopy
CD	coeliac disease
GFD	gluten-free diet
CI	confidence interval

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Authors' contributions

AU participated in the study design, performed part of the statistical analysis and drafted the manuscript. KKu was involved in the study design and preparing the manuscript. PC participated in the study design and preparing the manuscript. HH performed part of the statistical analysis and critically reviewed the manuscript. LF participated in the interpretation of the data and critically reviewed the manuscript. LK participated in the study design and critically reviewed the manuscript. MM was involved in the study design and critically reviewed the manuscript. KKa participated in the study design and drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. All-cause outpatient and inpatient consultations with a physician in the year prior to and following the diagnosis of coeliac disease. The number of consultations is compared with that in the general adult population during the same period and limited to subjects 16-64 years of age.

Figure 2. Days of sickness absence from work in the year prior to (A) and following (B) the diagnosis of coeliac disease. The number of days of absence is compared with that in the general adult population during the same period and limited to subjects 16-64 years of age.

Table 1. Baseline characteristics of the coeliac disease study group

	All n=700	Female n=534 (76%)	Male n=166 (24%)
Median age (range), years	49 (16-84)	48 (16-84)	53 (16-83)
Clinical presentation, %			
Gastrointestinal symptoms and signs	70	70	70
Extraintestinal symptoms	9	8	12
Detected by screening	21	22	18
Duration of symptoms			
Median (range), years	3 (0-59)	3 (0-51)	2 (0-59)
25-75th percentile	1-7	1-7	1-5
OEGD at diagnosis, %	100	100	100
OEGD prior to diagnosis of CD, %*	21	19	27
Diagnosis was established in, %			
Primary health care	52	55	42
Secondary health care	38	36	44
Tertiary health care	10	9	14

OEGD oesphago-gastroduodenoscopy
CD coeliac disease
* Other than the oesphago-gastroduodenoscopy by which the diagnosis of coeliac disease was confirmed

Table 2. Changes in the mean number of all-cause medical consultations among coeliac disease patients between the year prior to and after the diagnosis of the disease.

	All n=700	Female n=534	Male n=166
Outpatient visits in primary health care			
Year prior to diagnosis	3.6	3.7	3.1
Year after diagnosis on a GFD	2.3	2.5	1.9
Mean change (95% CI)	-1.2 (-1.5 to -0.9)	-1.3 (-1.6 to -0.9)	-1.2 (-1.7 to -0.7)
P value	<0.001	<0.001	<0.001
Outpatient visits in secondary and tertiary health care			
Year prior to diagnosis	0.8	0.8	0.8
Year after diagnosis on a GFD	0.8	0.8	0.9
Mean change (95% CI)	0.0 (-0.2 to 0.1)	0.0 (-0.2 to 0.2)	0.0 (-0.3 to 0.4)
P value	0.664	0.630	0.906
Admissions to hospital			
Year prior to diagnosis	0.2	0.2	0.2
Year after diagnosis on a GFD	0.2	0.2	0.2
Mean change (95% CI)	0.0 (-0.03 to 0.1)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)
P value	0.708	0.521	0.724
Other medical services*			
Year prior to diagnosis	4.1	4.5	2.7
Year after diagnosis on a GFD	3.6	4.0	2.4
Mean change (95% CI)	-0.5 (-1.0 to 0.1)	-0.5 (-1.2 to 0.2)	-0.3 (-1.2 to 0.7)
P value	0.340	0.245	0.797

GFD gluten-free diet
CI confidence interval
* Consultations with a nurse, a psychologist or a dietician, home nursing care, physiotherapy, laboratory and imaging services

Table 3. Changes in reported consumption of pharmaceutical agents among coeliac disease patients (pills per month on average) between the year prior to and following the diagnosis of coeliac disease.

	All n=700	Female n=534	Male n=166
All on-demand medicines*			
Year prior to diagnosis	12.0	12.2	11.4
Year after diagnosis on a GFD	9.3	9.1	10.0
Mean change (95% CI)	-2.7 (-4.3 to -1.2)	-3.1 (-4.9 to -1.4)	-1.4 (-4.8 to 2.0)
P value	<0.001	<0.001	0.011
Painkillers			
Year prior to diagnosis	6.8	7.2	5.6
Year after diagnosis on a GFD	5.5	5.2	6.4
Mean change (95% CI)	-1.3 (-2.6 to -0.1)	-2.0 (-3.4 to -0.5)	0.8 (-2.1 to 3.7)
P value	<0.001	<0.001	0.432
Medicines for dyspepsia			
Year prior to diagnosis	3.7	3.5	4.4
Year after diagnosis on a GFD	2.5	2.4	2.6
Mean change (95% CI)	-1.27 (-2.10 to -0.44)	-1.1 (-2.0 to -1.2)	-1.8 (-3.7 to 0.1)
P value	<0.001	<0.001	0.015
Antibiotic treatment†			
Year prior to diagnosis	0.6	0.7	0.4
Year after diagnosis on a GFD	0.5	0.5	0.3
Mean change (95% CI)	-0.1 (-0.2 to -0.1)	-0.2 (-0.3 to -0.1)	-0.1 (-0.3 to 0.1)
P value	0.001	0.001	0.302
Vitamins, micronutrients, herbal products			
Year prior to diagnosis	18.4	20.7	10.8
Year after diagnosis on a GFD	22.6	24.6	16.2
Mean change (95% CI)	4.2 (1.8 to 6.7)	3.9 (0.9 to 6.8)	5.5 (1.8 to 9.1)
P value	<0.001	0.003	0.002

CI confidence interval
GFD gluten-free diet
* Painkillers, medicines for dyspepsia, sleeping pills
† Not reported as pills per month but as number of courses per year

Figure 1.

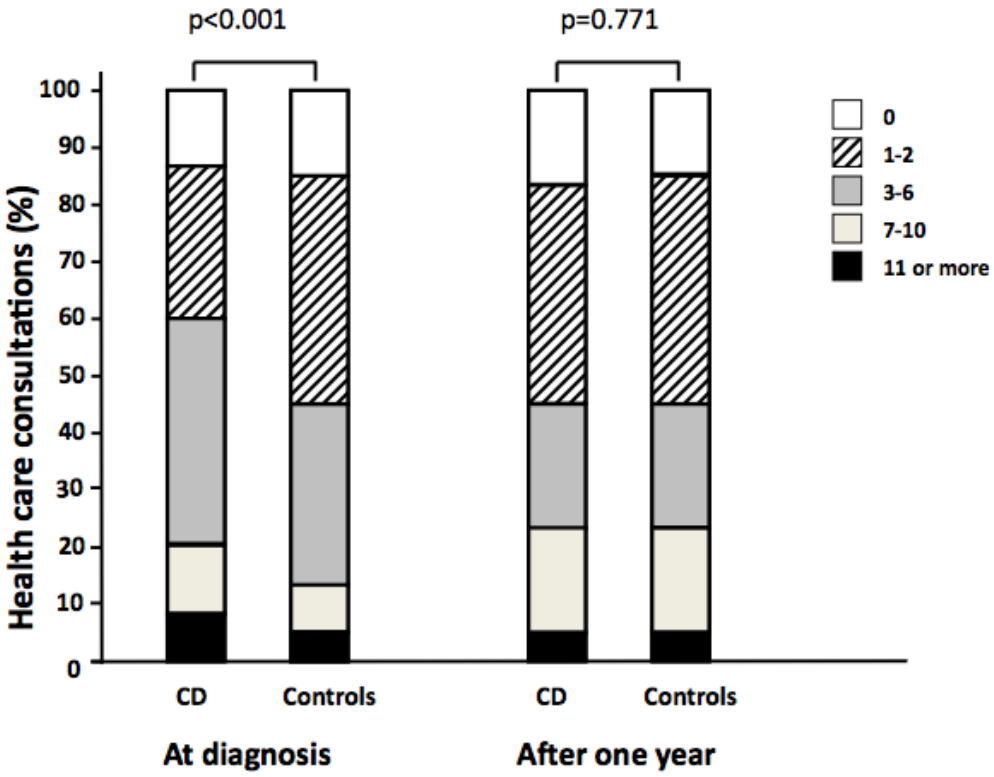
p<0.001
p=0.771
Health care consultations (%)
100
90
80
70
60
50
40
30
20
10
0
CD
Controls
CD
Controls
At diagnosis
After one year
0
1-2
3-6
7-10
11 or more

Figure 2A.

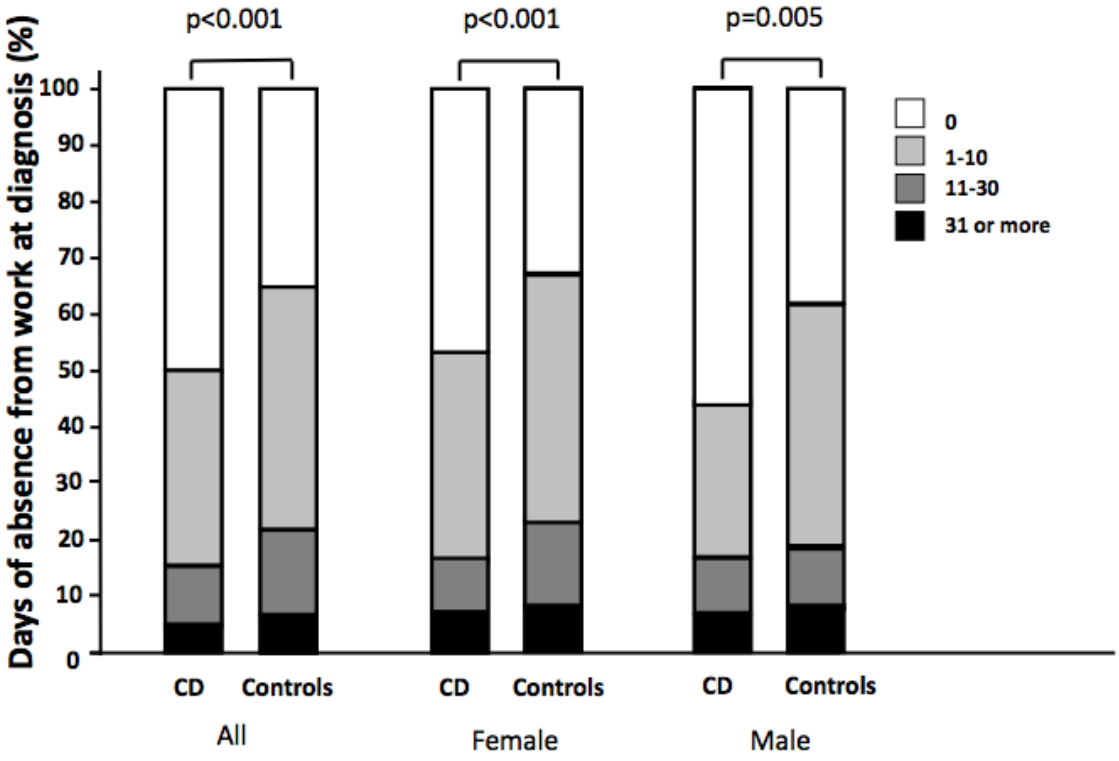

Figure 2B.