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ADULT COELIAC DISEASE IN CLINICAL PRACTICE

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"Science moves, but slowly, slowly, creeping on from point to point"

Tennyson 1809-1892

To Bitte,
Karin Elisabeth
and Gunne, my dear uncle

CONTENTS

	Page
List of original papers	6
Abbreviations	7
Introduction	
Historical aspects	8
Diagnostic criteria	9
Histopathology	10
Serology	13
Pathogenesis	14
Epidemiology	15
Associated diseases	15
Management	16
Mortality and malignancy	17
Freedom from symptoms, and a perfect quality of life: the ultimate outcome	18
Aims of the study	19
Material and methods	
Patients and definition of coeliac disease	20
Serologic assays	22
Dietary compliance	24
Measuring GI symptoms	25
Results	
Paper I	
Epidemiology and associated diseases	26
Paper II	
Malignancies and mortality	27
Paper III	
Antibody titres decline quickly after start of a GFD	27
Paper IV	
Serological correlates to mucosal Remission	28
Paper V	
Gastrointestinal symptoms on a gluten free diet	28
Discussion	29
Conclusions	38
References	39

Acknowledgements	54
Comprehensive summary in Swedish	56
Abstract	58



This thesis is based on the following papers, which are referred to by their Roman numerals:

I Midhagen G, Järnerot G, Kraaz W. Adult coeliac disease within a defined area in Sweden. A study of prevalence and associated diseases. Scand J Gastroenterol 1988;23:1000-1004.

II Midhagen G, Järnerot G, Brandt L, Ekbom A, Ström M. Ischaemic heart disease, not malignancy, increases mortality in celiac disease. A population based study. Submitted.

III Midhagen G, Åberg A-K, Olcén P, Järnerot G, Valdimarsson T, Dahlbom I, Hansson T, Ström M. Antibody levels in adult patients with coeliac disease during gluten free diet a rapid initial decrease of clinical importance. J Int Med 2004;256: 519-24.

IV Midhagen G, Grodzinsky E, Grant C, Grännö C, Hallert C, Hultén S, Svensson H, Valdimarsson T, Ström M. Long-term follow up of patients with coeliac disease: Serological correlates of mucosal remission. In manuscript.

V Midhagen G, Hallert C. High rate of gastrointestinal symptoms in celiac patients living on a gluten free diet: controlled study. Am J Gastroenterol 2003;98:2023-2026.

ABBREVIATIONS

AGA	Anti-gliadin antibodies
CD	Coeliac disease
EmA	Endomysium antibodies
ELISA	Enzyme-linked immunosorbent assay
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition.
GFD	Gluten free diet
IEL	Intraepithelial lymphocytes
KVAST	KVAlitet STandardisering (Swedish Society of Pathology).
LP	Lamina propria
SMR	Standard Mortality Rate
SIR	Standard Incidence Rate
TTG	tissue transglutaminase
TTGgp	tTG guinea pig
TTGrh	tTG recombinant human

INTRODUCTION

Historical aspects

Coeliac disease (CD), also known as sprue or gluten-sensitive enteropathy, was first recognized as a clinical entity in the second century A.D. by a Greek physician named Aretaeus (Adams 1856). The name “sprue” was coined in the eighteenth century and is derived from the Dutch word spruw, meaning aphtous disease, so named because of the high prevalence of aphtous ulcers in these patients. Dr Samuel Gee later described the Coeliac Affection (Gee 1888), but his findings attracted little attention at that time. Bennet et al. studied 15 adult cases with idiopathic steatorrhoea and considered them to be examples of CD persisting into adulthood (Bennet 1930). In the Netherlands during World War II there had been a scarcity of cereals, bread in particular. Dicke, a Dutch paediatrician, observed that coeliac sprue diminished remarkably during this shortage. When, in “Operation Manna”, allied American and English aircraft dropped Swedish white bread over occupied Holland, coeliac children became ill again (Dicke 1950). Dicke and van der Kamer in the early 1950s elegantly identified gliadin residues in wheat, as well as related residues in barley, rye, and possibly oats. They considered these gliadin residues to be the damaging agents in CD (Dicke 1953).

In 1954 Paulley described the histological changes in the jejunum of four coeliac patients. The samples were collected by laparotomy (Paulley 1954). To be able to obtain biopsies from the jejunum without surgical intervention, the previously used gastric biopsy tube was extended (Shiner 1956). To further facilitate the procedure, Crosby invented the intestinal biopsy capsule (Crosby 1957), making small intestinal biopsies, necessary for accurate diagnosis, available.

Since the 1950s, it has generally been accepted that wheat, rye and barley or their prolamins gliadin, secalin, and hordein, are the major triggering factors in CD and in dermatitis herpetiformis (Reunala 1984). Rice and maize do not initiate the disease process and there is no scientific evidence that either oats or their prolamins avenin is harmful to patients with coeliac disease.

As early as in the 1970s, small studies about adding oats to a diet otherwise free from gluten, did not convincingly show that oats were harmful (Dissanayake 1974 A, Baker 1976). In the 1990s, a Finnish group was able to show that adults with CD tolerated 50g oats per day without clinical relapse or adverse effects on the small bowel mucosa (Janatuinen 1995).

Diagnostic criteria

Coeliac disease is characterised by malabsorption secondary to inflamed mucosa accompanied by a variable degree of small bowel villous atrophy.

The intake of gluten in gluten sensitive individuals causes inflammation of the mucosa of the small intestine and a characteristic, although not specific, lesion. The mucosal lesions vary considerably both in severity and extent. The upper part of the small bowel is most affected (Rubin 1960).

In the 1950s, the diagnosis of CD usually relied on clinical signs of malabsorption. When biopsies from the small intestine became available in the 1960s, the diagnosis of CD became based more on histopathology.

One definition that was widely accepted for many years uses a combination of histopathological and clinical signs (Cluysenaer 1977). According to these criteria the diagnosis of CD in adults requires that the specimens show mucosal lesions compatible with coeliac disease, plus at least two of the following three additional criteria: a) biochemical signs of malabsorption, b) a previous history suggestive of coeliac disease and c) morphological improvement of the small-intestinal mucosa on a GFD.

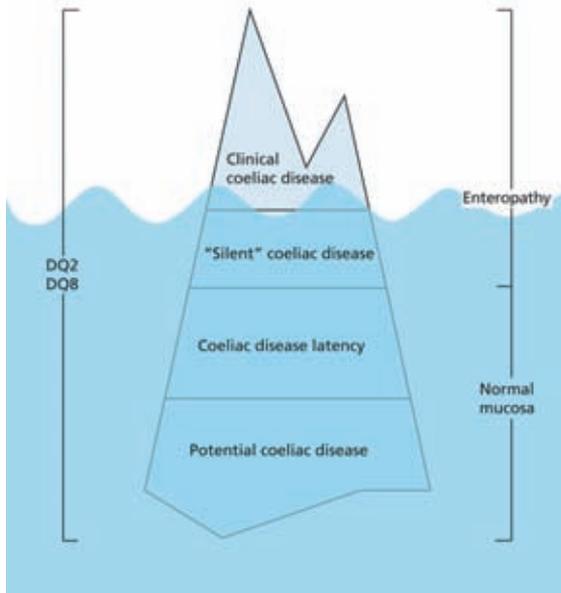
For children the first commonly accepted criteria for a diagnosis of CD were established in 1970 by the ESPGHAN group.

These criteria consisted of a) a structurally abnormal intestinal mucosa on a gluten containing diet b) clear improvement on a gluten free diet (GFD) c) deterioration during gluten challenge (Meuwisse 1970).

The ESPGHAN criteria were revised in 1990. The main criteria are now the finding of structurally abnormal intestinal mucosa on a gluten containing diet, followed by a clear clinical remission on a GFD (Walker-Smith 1990). An initial finding of circulating antibodies, e.g. antigliadin-, antireticulin-, antiendomysium- or tissue transglutaminase antibodies of IgA isotype and their disappearance on a GFD further supports the diagnosis. In patients without initial symptoms, histological recovery should be demonstrated by a second biopsy. Gluten challenge should be considered when the diagnosis is uncertain. This is recommended when assessment of the initial small intestinal biopsy is equivocal, and in children below two years of age at presentation, as the cause of the enteropathy might be a temporary sensitivity to cow's milk.

There are no clear-cut criteria for adult CD. In clinical practice modified ESPGHAN criteria are used. Logan coined the metaphor of the coeliac iceberg (Logan 1992). Patients with symptomatic CD represent the tip of the iceberg (see illustration), visible above the water line.

Silent CD patients are free from major symptoms but have typical damage to the mucosa. Latent coeliacs have no symptoms and only minor mucosal lesions. At the base of the iceberg are healthy people with intact mucosa, but with a genetic possibility of developing CD.



After Richard Logan 1992.

Histopathology

Diagnosis of CD based on histopathology became available as a routine method after a capsule for collecting biopsy specimens from the jejunum was constructed (Crosby 1957).

It was later shown that biopsies taken from the proximal duodenum during a gastroscopy had the same diagnostic value as biopsies taken from the jejunum with a capsule (Scott 1976, Gillberg 1977).

The Alexander classification

Alexander was the first to perform systematic validation of the histopathology in adults (Alexander 1975).

Table 1. Classification of small bowel biopsies according to Alexander.

Grade	Villi	Epithelium	Lamina propria
I	Tall, narrow	Columnar	Scanty cell content
II	Broad, fused	Columnar, brush border may be absent at times, round cell infiltration	Lymphocytes and plasma cells moderately increased
III	Broad, short, Partial atrophy	Degenerated on surface, trend towards cuboidal, elongated crypts	Lymphocytes and plasma cells considerably increased
IV	No villi, flat or mosaic surface	Degenerated on surface, elongated crypts	Dense infiltrate of lymphocytes, plasma cells, eosinophils

The Marsh classification

Marsh added the perspective of time in the gradual development of mucosal lesions (Marsh 1995). He proposed a four-grade scale (Table 2) with type III as the classic mucosal lesion, with varying degrees of mucosal atrophy. A division into subgroups depending on the degree of villous atrophy was later added (Oberhuber 1999).

Table 2. Classification of coeliac lesions according to Marsh and modified by Oberhuber.

Grade	Villi	Crypts	IEL
0	normal	normal	normal
I	normal	normal	increased
II	normal	increased in depth	increased
III	a)partial b)subtotal c)total atrophy	increased in depth	increased
IV	no villi	atrophy of the whole mucosa	increased

The Swedish Society of Pathology has adopted the Marsh-Oberhuber scheme. Their classification is roughly the same, but without type II which was only very rarely encountered and has mainly been observed under experimental conditions (Marsh 1992). Up to 20 lymphocytes per 100 epithelial cells

is accepted as normal. The KVASt-classification is now used in many Swedish pathology laboratories.

Table 3. The KVASt classification

	Normal mucosa	Borderline mucosa	Partial atrophy	Subtotal/total atrophy
Atrophy of villi	-	-	+	++
Hyperplasia of crypts	-	-	+	++
IEL	-	+	+	+
Lymphocytes and plasma cells in lamina propria	-	-(+)	+	+
Frequency of mitosis in the crypt epithelium	-	+	+	++

- = absent/lacking

+ = slight increase

++ = great increase

IEL= intraepithelial lymphocytes

Diagnostic difficulties occur, especially in borderline cases. The distinction between partial villous atrophy and normal mucosal structure is not always easy to determine. The diagnosis must be made on well-orientated samples. However, in clinical practice, oblique slicing of the specimens occurs.

Even at centres with a great deal of interest in CD, 12% of the biopsy specimens were not suitable for interpretation (Collin 2005A).

Intraepithelial lymphocytosis is a cardinal sign of CD (Kaukkinen 2001) but can also occur in other conditions (Table 4) (Ferguson 1971, Montgomery 1974, Kakar 2003).

Table 4

Conditions other than coeliac disease, where an increased density of small intestinal intraepithelial lymphocytes is possible
Tropical sprue Non-steroidal anti-inflammatory drugs Autoimmune diseases Crohn's disease Lymphocytic gastroenteritis Bacterial overgrowth

In patients with one such discrete sign of possible CD, the markers HLA DQ2 or DQ8 compatible with CD, or the demonstration of gluten dependence (Collin 2005A). Villous tip intraepithelial lymphocytes might be a more reliable way of distinguishing early CD from non-specific changes (Järvinen 2004).

Serology

The gold standard for diagnosis of CD remains the small bowel biopsy (Murray 1999, Dewar 2005). During the last 30 years, however, many clinicians have sought a less invasive test for screening, diagnosis and follow up. Tests of circulating antibodies to gluten or gliadin using immunofluorescence or the enzyme linked immuno-sorbent assay (ELISA) techniques have been considered potential screening tests for CD (Ferreira 1993).

The first antibody method for diagnosis was reticulin, discovered in 1971 (Seah 1971). For diagnostic purposes specificity is high, up to 100% in many reports. However, sensitivity in most studies is only about 50% (Aurichio 1988) and reticulin antibodies are rarely used in clinical practice today.

Ten years later IgA anti-gliadin antibodies were first described (Unsworth 1981). Gliadin antibodies are easily determined using the quick, inexpensive ELISA method, but only with a suboptimal degree of sensitivity (80%) and specificity of about 20% (Lerner 1991, Valdimarsson 1996). A micro-ELISA is most frequently used, although some authors prefer a method with diffusion in gel (DIG-ELISA) (Kilander 1983, Friis 1986). At least in children the methods seem comparable (Fälth-Magnusson 1994).

In 1983 Chorzelski et al. described an antibody directed against the membrane of the smooth muscle bundles of primates. This endomysial antibody was present in patients with dermatitis herpetiformis and CD. It was found to be a very specific marker of CD (Ferreira 1992, Valdimarsson 1996). However, this is an indirect immunofluorescence method and requires access to monkey oesophagus or human umbilical cord tissue, as a substrate. The analyses are also time-consuming. They are therefore not easily used in a large-scale screening situation.

In the 1990s tissue transglutaminase (tTG) was identified as an auto-antigen in CD (Dietrich 1997). TTG is also the main antigen of endomysium antibodies. Tissue transglutaminase antibodies can be read with an ELISA method, which is less work-intensive than the EmA method. The clinical value of antibodies against tissue transglutaminase with the ELISA technique was initially studied by Sulkanen et al. (Sulkanen 1998). After comparing 13 different methods for commercially available guinea pig and recombinant human tTG, it was concluded that the recombinant human methods were

superior to the guinea pig ones, especially concerning sensitivity (Wong 2002). The recombinant human tTG-antibody test was found to be as good as EmA (Burgin-Wolf 2002). Ninety-nine per cent of the patients had concordant positive and negative results.

A pitfall in the diagnostic procedure is that 2.6-7% of patients with CD have selective IgA deficiency, a 10-16-fold higher rate than in the general population (Cataldo 1998). This affects sensitivity, since most of the antibody tests use IgA-antibodies.

Pathogenesis

Coeliac disease is a complex inflammatory disorder. The disease is dependent on the presence of gluten. Gluten is a storage protein in wheat, important to the growing seed (Shewry 1992).

It has long been clear that genetic factors are crucial to the pathogenesis. In monozygotic twins, the concordance rate is estimated to be 70% (Polanco 1981). Prevalence among first-degree family members is about 10% (Rabassa 1981).

HLA is the single most important genetic factor. The disease is associated with HLA-DQ2 in most patients and HLA-DQ8 in some (Sollid 2002).

About 25% of the Norwegian population has HLA-DQ2 but only a few of them are diagnosed with CD (Sollid 2002). This highlights the importance of other factors than HLA-genes in the aetiology of the disease.

In recent years we have learned more about what happens at cellular level. A T-cell response to gluten in the intestine is specific to individuals with CD. Gluten-specific CD4⁺ T-cells can be isolated from the small intestinal mucosa of CD patients but not of controls without CD (Sollid 2002). The reason for this is unknown, but changes in the intestinal permeability secondary to alterations in the intercellular tight junctions or in the processing of gluten are possible mechanisms (Sollid 2002, Fasano 2000).

Gliadin is an excellent substrate for tTG (Dietrich 1997), a calcium dependent enzyme that transforms positively charged glutamin to negatively charged glutamic acid residues by deamidation (Dietrich 1997). This finding led to the recognition that anti-gluten CD4 T-cells in adults were mainly directed against deamidated peptides (van de Wahl 1998, Molberg 1998). Intestinal CD4 T-cells that recognise deamidated peptides presented by DQ2 and DQ8 produce interferon gamma, which provokes inflammation and leads to villous atrophy and crypt hyperplasia.

Epidemiology prior to 1986.

Thirty to forty years ago, coeliac disease was thought to be a rare condition. One of the earliest epidemiological studies reported the prevalence in England and Wales to be 1/8000 and in Scotland 1/4000 (Davidson 1950). An early study of CD among Swedish adults found a prevalence of 1:3700 (Ek 1970).

A paediatric study from southern Sweden later showed an incidence of 1:982, indicating that CD was much more common than previously thought (Berg 1979)

The higher prevalence in paediatric populations implied that there might be a considerable number of unrecognized coeliacs in the adult population, provided it is a lifelong condition. A major problem in diagnosing adult CD is the very variable clinical presentation of the disorder, making the patients apt to present at almost any hospital department (Barry 1974).

Early epidemiologic studies of CD showed considerable regional differences in prevalence. In Western Ireland a childhood ratio of 1/597 was observed (Mylotte 1973) and prevalence in the adult population of 1/300 was proposed. In Sweden prevalence figures around 1/1000 was found (Berg 1979, Hallert 1981). It was suggested that CD was under-diagnosed (Swinson 1980).

Even at that time the symptoms at diagnosis of the disease had begun to change. An increasing number of patients were diagnosed but fewer had classical malabsorption signs (Logan 1983).

Associated diseases

The most common associated disease to CD is dermatitis herpetiformis. A small bowel biopsy in patients with dermatitis herpetiformis often demonstrates only mild and patchy gluten-sensitive enteropathy. The skin lesions respond to the withdrawal of gluten from the diet or to treatment with avlosulfon.

The link between dermatitis herpetiformis and CD is so close that many researchers consider dermatitis herpetiformis as a manifestation of coeliac disease (Mäki 1997). For some reason, however, 10% of the dermatitis herpetiformis patients do not respond to a gluten free diet (Reunala 1984).

Many conditions occur in association with CD. In the 1960s, several case reports on the association between CD and autoimmune diseases were published. The first report on a group of CD patients was published in 1974. Nineteen percent of the patients had an autoimmune disease of some kind (Lancaster-Smith 1974).

Since then the enhanced risk of developing an autoimmune disease in CD patients is well established

(Collin rev 2002). Thyroid disorders and type 1 diabetes are particularly common in patients with CD. The prevalence of CD in patients with type 1 diabetes is 3-8% (Counsell 1994, Cronin 1997, Sjöberg 1998).

Several studies have reported an association between CD and chronic liver disease. The association between PBC and CD has been studied (Olsson 1982, Löfgren 1985, Kingham 1998), and between CD and autoimmune hepatitis (Lindberg 1979).

Several other diseases have also been reported to be associated with CD. Connective tissue disorders such as Sjögren's syndrome, rheumatoid arthritis, vasculitis, sarcoidosis and neurological disorders such as epilepsy and dementia may be mentioned (Lancaster-Smith 1974, Cooper 1978, Biemond 1987, Collin 1994A).

Insulin dependent diabetes mellitus, Sjögren's syndrome, Addison's disease and Grave's disease share the HLA haplotype, HLA D3, with CD patients (Collin 1994A).

A great number of studies in possible relations between *Helicobacter pylori* and several diseases in man have been reported in recent years. An American group reported an increased prevalence of *Helicobacter pylori* infection in CD patients (Konturek 2000). However, this relationship between *Helicobacter* and CD could not be verified (Borch 2001).

Management

Patients with CD must adhere to a gluten free diet permanently. Follow-up studies showed that 50-70% of patients with CD maintain a strict GFD later in life and that poor compliance is the main reason for poor response to treatment (Mäki 1997).

Wheat-starch based gluten free flours may contain up to 40-60mg gluten per 100g (200-300 ppm (mg/kg) gliadin). Patients from many European countries have followed GFD, yet wheat-starch containing, diet and their small bowel mucosa has been restored. The safe threshold for gluten contamination in gluten free products can be set at 100 ppm (Collin 2004). On an otherwise strict gluten free diet neither excess mortality (Collin 1994B) nor over-representation of malignancies (Holmes 1989) has been noticed. The new recommendation of pure oats diversifies the GFD (Peräaho 2004) and could possibly increase compliance with the diet.

There is little data to help determine the most effective monitoring of adult CD patients. Serological follow up with EmA or tTG has been found to be insufficient (Dickey 2000, Tursi 2003). The UEWG Working Group on CD in adults advised in Amsterdam in 2001 that the biopsy should be repeated after one year (UEGW 2001). In a recent overview Mulder suggested that mucosal recovery is the

only protection against complications (Mulder 2005).

Mortality and malignancy

Before the introduction of the gluten free diet the outlook for individuals with coeliac sprue was poor, with increased mortality rates varying between 10% and 30%, owing to malabsorption and its complications (Ciclitira 2001).

After the introduction of the gluten free diet, mortality rates fell markedly (Sheldon 1969).

Historically, CD is associated with an increased risk of malignancy.

The first association of malignant lymphoma with idiopathic steatorrea indicating CD was reported in the late 1930s (Fairley 1937). Several studies have reported that patients with CD or dermatitis herpetiformis have notably increased risks of developing non-Hodgkin's lymphoma and certain carcinomas of the gastrointestinal tract (Gough 1962, Harris 1967, Brandt 1978, Selby 1979, Cooper 1982, Holmes 1989, Logan 1989, Collin 1994B).

Coeliac disease has been linked to a characteristic lymphoma of the small intestine, now referred to as enteropathy-type T-cell lymphoma (ETTL) according to the most recent lymphoma classification (Jaffe 2001).

Harris was early to express the impression, although he could not prove it statistically, that a gluten free diet could protect the patient against malignancy (Harris 1967). More than 20 years later Holmes was able to show the protective role of a strict GFD against malignancy in CD patients (Holmes 1989).

Previous evidence suggested that the mortality rate was twice that in a matched control population (Holmes 1976, Cooper 1980, Corrao 1995, Cottone 1999). These studies were mostly small or not population based and the findings probably do not reflect the risks today (West 2004). Data from Sweden's hospital inpatient register showed a more modest increase of the risks in people with CD, but still found an increased risk of certain malignancies and of death (Askling 2002, Peters 2003). In contrast, two studies showed a decreased risk of breast cancer in people with CD. The reason is not clear (Logan 1989, Askling 2002).

To provide estimates for the absolute and relative risks of malignancy and mortality in CD, a population based cohort study in CD patients was carried out in Great Britain (West 2004). The UK general practice research database was the tool. They concluded that patients with CD have a modest increase in overall risks of malignancy and mortality. The increased risk of non-Hodgkin's lymphoma, cancer of the mouth, pharynx and oesophagus was confirmed and overall there was a

two-fold increased relative risk of cancer. Most of this excessive risk occurs in the year after the diagnosis. Only the risk of lymphoproliferative disease persists longer. The risk for coeliac patients in general, however, may well be lower as patients without symptoms or only mild ill health may never be diagnosed and will therefore be excluded from calculations of prevalence. On the other hand, there are patients with lymphoma who also have coeliac disease that may never have been diagnosed (Freeman 1977).

Freedom from symptoms, and perfect quality of life: the ultimate outcome.

Physicians often focus on treating the biological aspects of the disease, believing this will be sufficient to alleviate any psychological distress (Tatal 1995).

Unfortunately biological and physiological measures generally correlate poorly with functional capacity and well-being (Guyatt 1993) and have little relevance to patients' perception of disease impact (Garett 1990).

Until recent years, the main outcome of clinical trials has been mortality, morbidity, and disease activity measured by objective outcomes such as laboratory tests and histology.

However, to obtain the full perspective of health one has to integrate traditional criteria with measures of symptoms and health-related quality of life (HRQOL), i.e. disease impact on daily activities and well-being.

Treatment of coeliac disease, a gluten free diet, restores the function and structure of the intestinal mucosa and gives a clinical response characterized by a quick return to more normal health and new found vitality described already in the 1980's (Swinsson 1980, Cooke 1984). Whereas it is generally believed that patients with CD must withdraw gluten from their diet for the rest of their lives to prevent ill health (Mäki 1997), there is remarkably little data on the full range of health status of coeliacs who have spent years on a GFD. One year after diagnosis CD patients who follow a GFD have improved in terms of both symptoms and quality of life (Mustalahti 2002). However, not much is known about what happens to the CD patients in the long run in respect of freedom from symptoms and health related quality of life.

AIMS OF THE STUDY

The aims of the investigations were:

Paper I

To perform an epidemiologic survey of coeliac disease in a geographically defined area of Sweden.

Paper II

To quantify the risks of mortality and malignancy in patients with CD living in two geographically defined areas compared with the general population.

Paper III

To determine the time for which the serologic tests remain predictive of the disease after the introduction of a gluten free diet.

Paper IV

To evaluate the usefulness of serological and biochemical markers in predicting the appearance of the small bowel mucosa in the long term follow up of patients with coeliac disease.

Paper V

To determine the occurrence of GI symptoms in adults with coeliac disease treated with a gluten free diet for ten years.



MATERIAL AND METHODS

Patients and definition of coeliac disease

These five papers are based on three different patient materials over an inclusion period of thirty years during which the diagnostic criteria have changed.

Paper I

The first study concerns adult patients with diagnosed coeliac disease (CD) living in Örebro County who had been diagnosed before Dec 31 1986. To identify the patients we used our registers of coeliac disease patients at the Departments of Medicine and Pediatrics, the register kept by the dieticians, and the register concerning dermatitis herpetiformis at the Department of Dermatology. Furthermore, the reports of all small bowel biopsy specimens were scrutinized. All specimens that indicated changes possibly compatible with coeliac disease were re-evaluated by one pathologist. The specimens were classified in accordance with Alexanders' classification and had to show mucosal lesions compatible with coeliac disease. Three additional criteria were also used: biochemical signs of malabsorption, a medical history suggestive of CD, and a morphological improvement of the small bowel mucosa on a gluten free diet. For a diagnosis of CD, mucosal lesions in combination with at least two of the three criteria were required (Cluyesenaer 1977). The medical histories of all patients fulfilling these criteria were carefully scrutinized.

Paper II

The same patients as in paper (I) were included. In addition the same patient cohort from Linköping County was identified and included in the study. The Linköping patient biopsy specimens were re-evaluated at clinical conferences before a definite histopathological diagnosis.

At diagnosis all but two patients had mucosal lesions of Alexander grade III-IV, in combination with at least two of three additional criteria (Cluysenaer 1977). The medical histories of all patients fulfilling these criteria were carefully scrutinized.

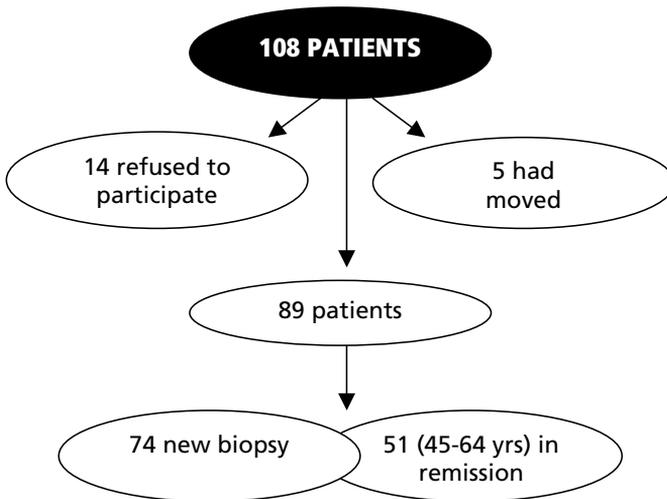
Control population

Statistics Sweden (SCB) identified 4-5 controls for each of the 258 patients (n=1257), matched for age and sex, and living in the same geographical area as the patient on Dec 31 1986.

Paper III

Twenty-two adult CD patients consecutively diagnosed: 12 female, median age 62 years, range (29-86), histologically at least grade III according to the Marsh classification, diagnosed 1998-99 at Linköping University Hospital.

Papers IV-V



Patients with CD diagnosed at six hospitals in Southeast Sweden in 1984-88, were reinvestigated 8-12 years after the initial diagnosis. The small intestinal biopsy at diagnosis showed mucosal lesions diagnostic for gluten sensitivity according to a modification of the Marsh-classification (KVAŠT). Patients with concomitant dermatitis herpetiformis were not enrolled. Fourteen out of 108 identified patients refused to participate. Five patients had moved out of the area. Eighty-nine patients remained.

Paper IV

A repeat intestinal biopsy was obtained in 74 patients (77%). Mean age was 56 years (range 32-75), and 58% were women.

Paper V

In the symptomatic evaluation we studied the 51 patients who were middle aged (45-64 years), 59% were women and all patients proved to be in serological remission, and 42 of them also in histological remission.

A general population sample consisting of 182 adults (57% women) aged 45-64 years served as controls.

Serologic assays

Anti-gliadin antibodies

Paper III

AGA was tested using a commercially available test, Unicap Gliadin IgA (Pharmacia Diagnostics, Uppsala Sweden) and was defined as positive with a result $> 3\text{mg/AL}^{-1}$.

Papers IV-V

An ELISA, developed in Linköping was used for detection of IgA-AGA (Grodzinsky 1990). Microtitre plates were coated with 50 $\mu\text{g/ml}$ gliadin dissolved in ethanol (Sigma, St.Louis, MO, USA). The plates were incubated for 60 minutes with negative and low/high positive control, titrated reference serum and patient sera diluted in 10 phosphate-buffered saline (PBS) containing 0.5% human serum albumin and then washed. Peroxidase-conjugated anti-human IgA-antibodies (Dakopatts, Glostrup, Denmark), were used to detect the IgA-AGA. The absorbance was read spectrophotometrically in a Dynatech minireader II (Dynatech, Alexandria, VA, USA) and set against the titrated positive serum. The optical density (OD) of the reference was converted to units using a program (Dynatech) for semi-log fit. The cut off for a positive outcome (42.5 units) was defined as approximately the 97.5th percentile for a blood donor population ($n=1866$).

Anti-endomysium antibodies

Paper III

Detection of IgA-EmA was performed with indirect immunofluorescence using monkey oesophageal tissue as antigen (in house assay). Tissue sections of Marmoset monkey oesophagus were mounted on microscopic slides. Undiluted sera and sera diluted 1:25 with phosphate-buffered saline (PBS) were applied to slides, which were then incubated for 30 minutes at room temperature. After washing

with PBS the sections were covered with fluoresce conjugated rabbit-antihuman IgA (Dao, Copenhagen, Denmark) for 30 minutes, washed with PBS and examined using fluorescence microscopy. Positive sera were further diluted (1:5, 1:10, 1:25, 1:100, 1:400, and 1:1600). Sera positive in dilution at 1:10 or more were defined as positive.

Papers IV-V

We used indirect immunofluorescence microscopy (Grodzinsky 1995) with fixed cryostat sections of monkey oesophagus (Scimedx, Denville, NJ, USA) as an antigen substrate. The patient sera were screened at a dilution of 1:10 in PBS pH 7.4 together with a positive and a negative control. Polyclonal fluorescence in isothiocyanate (FITC)-labelled rabbit anti-human IgA (Dakopatts) was used as the secondary antibody. The antibody titre was defined as the highest serum dilution yielding positive fluorescence.

Anti-tissue transglutaminase antibodies

Paper III

Two commercial ELISA-tests were used. One was with tissue transglutaminase (tTG) derived from guinea-pig (Immuno-Lisa) which was compared to recombinant human tTG(tTGrh).

The human recombinant method Celikey, tTGrh, IgA antibody assay (Pharmacia Diagnostics, Freiburg, Germany) was defined by the producer as positive when $>8\text{U ml}^{-1}$, negative when $<5\text{U ml}^{-1}$, borderline between 5 and 8 U ml^{-1} . All sera were analysed using the same batch of tTGrh test. The upper borderline levels was used as a cut-off point, as recommended by the producer. The intra-assay variation was reassured as CV% (CV=coefficient of variation) and was 6.0, 9.3 and 9.4 for low medium and high values respectively.

The result of the method with guinea pig derived tTG, ImmuLisa,(IMMCO, Buffalo, NY, USA), was defined as positive by the producer when $>25\text{U}$, negative when $<20\text{U}$ and borderline when 20-25U.

The CV values were 3.9, 2.6, and 3.4 for low, medium and high values.

The inter-assay variation measured as CV percentage was 13.3 for Celikey and 6.8 for ImmuLisa measured with a medium-high in-house control.

Papers IV-V

At the time for registering patients for papers IV-V, recombinant human tTG was not yet available. For that reason, a guinea pig antigen method was used.

IgA-tTG was analysed with a commercially available ELISA QUANTA Lite TM tTG (INOVA diagnostics, Inc., San Diego, CA) using tTG from guinea pig liver as antigen. Negative, low/ high positive and patient sera diluted 1:101 in sample diluents were added to the micro-plates and incubated for 30 minutes at room temperature. The plates were then washed three times with a washing buffer. Peroxidase-conjugated anti-human IgA-antibodies were used as a secondary antibody. The plates were incubated and washed as above. TMB Chromogen was used as a substrate, and after 30 minutes of incubation, the reaction was stopped with stop

solution. The optical density was read spectrophotometrically (Dynatech). As recommended by the manufacturer we classed the results as positive using ≥ 30 units as cut-off level.

All sera were analysed for total serum-IgA with a routine nephelometric assay to diagnose IgA deficiency.

Dietary compliance

Papers I-II

No follow up of the GFD was performed.

Paper III

All patients were asked about compliance with the GFD at 1, 3, 6 and 12 months after start of a strict GFD.

Papers IV-V

All patients reported their dietary compliance in a questionnaire and the answers were analysed by the physician at the medical examination. The self-reported dietary compliance was graded into strict gluten free diet (practically no deviations) or not (reduced gluten intake or normal diet).

Measuring GI symptoms

Paper V

To assess GI symptoms we used the GI Symptom Rating Scale (GSRS) a validated disease specific questionnaire designed to evaluate common GI symptoms (Svedlund 1988). The GSRS includes 15 symptoms and uses a 7-point Likert scale in which one represents the most positive option and seven the most negative. The items are combined into five clinical syndromes: Indigestion, Diarrhoea, Constipation, Abdominal pain, and Reflux. Using a scoring algorithm, a GSRS total score is calculated.



RESULTS

Paper I

Prevalence

Through December 31 1986, 136 patients in the catchment area of Örebro County Hospital aged 15 or older had been diagnosed with CD. The female: male proportion was 1.7:1.

Three of these 136 patients had left the area before Dec 31 1986 and seven had died.

Three patients with a previous diagnosis of CD had moved into the area and thus, 129 coeliac patients were residing there. The prevalence in adults was 95.5/100,000 inhabitants (1:1047). The peak prevalence (1/562) was reached in the group of patients aged 65-74 years. The prevalence for women was 117/100,000 and for men 72/100,000 inhabitants.

Symptoms at diagnosis

About half the patients were investigated because of gastrointestinal symptoms only or in combination with signs of malabsorption. However, 46.8% of the patients had no gastrointestinal complaints at all. The reasons for investigating these patients were dermatitis herpetiformis in 13.7% and anaemia in 20.9%. The other 12.2% were investigated for various reasons such as poor increase of height or weight, tetany, osteomalacia, muscle symptoms, allergic complaints, or the existence of other coeliacs in the family.

Laboratory test results at diagnosis

A haemoglobin level <115g/l was found in 48.2% before diagnosis. Subnormal values of vitamin B12 were found in 26.8%, of serum folate in 70.4%, of serum zinc in 46.9% and of serum calcium in 27.5% of the patients tested.

Associated diseases

The most remarkable finding was that 10.8% of the patients had either hyper- or hypothyroidism. All cases with hypothyroidism were spontaneous, so no case was the result of surgery or treatment with radioiodine. In four patients malignant disease were found: colonic adenocarcinoma (n=1), reticulosarcoma of the stomach (n=1), breast cancer (n=1) and Hodgkins' disease (n=1).

Deaths

Seven patients had died. Two of them died from a disease that could be related to coeliac disease, chronic active autoimmune liver disease.

Paper II

Malignancies and mortality

There was a 47% lower risk of all malignancies in our total coeliac population (SIR= 0.53, C.I. 0.31-0.83) in spite of a tendency to increased occurrence of lymphoma (SIR = 1.71, 95% C.I.0.21-6.17). The total mortality was increased by 38% (SMR =1.38, 95% C.I. 1.08 – 1.75), most pronounced in patients over 65 (SMR= 1.46, 95% C.I. 1.00-2.06). This was mainly explained by a 48% increased death rate in ischaemic heart disease, significant in patients over 65 (SMR=1.58, 95% C.I.1.00-2.06).

Paper III

Antibody titres decline quickly after the start of a GFD

In 21 patients with normal IgA, 76% were AGA-positive, 86% EmA-positive, 71% tTG_rh positive and 95% tTG_gp positive, with antibody levels above the cut-off point for each test.

After introduction of a GFD the antibody levels fell successively. One month after start of a GFD, 58, 84, 74 and 53 percent of all patients had positive antibody levels of tTG_rh, tTG_gp, EmA and AGA, respectively.

Of the patients with positive tTG_rh at the start 85, 43 and 29% were still positive after 1, 3 and 6 months. After 12 months, none of the patients was tTG_rh or AGA-positive while 13% were positive to EmA. In contrast, 35% of the patients had tTG_gp-positive titres after 12 months of a GFD.

In one patient who stopped the GFD after three months, the initial decrease in antibody levels was followed by a gradual increase up to pre-diet levels.

Of the patients who underwent a second biopsy after 1 year on a GFD, 16 of 18 were in remission. The two patients who were not in remission after one year were both in remission at further follow-up biopsies.

Paper IV

Clinical correlates of mucosal remission

Out of 74 CD patients who underwent a repeat biopsy after 8-12 years on the diet, the duodenal mucosa of 82% of the patients was in remission. Five of seven patients admitting non-compliance to a strict GFD had mucosal changes corresponding to Marsh III.

Sixty-seven asserted that they followed a strict GFD. Of them, 12% had mucosal lesions consistent with CD. One patient had IgA-deficiency. IgA- AGA, EmA and tTG were measured in the other 66 patients and titres below cut-off were associated with mucosal remission in 93%.

Folate and zinc were measured in those 44 and 52 respectively who did not take supplements. Eighty-six percent and 94% with normal levels had mucosal remission.

Paper V

Gastrointestinal symptoms on a GFD compared with controls

Adult patients with CD and normal mucosa after a strict GFD for 8-12 years reported significantly more GI symptoms (2.0, C.I. = 1.79-2.27) than controls (1.7, C.I.= 1.57-1.81) as assessed by the GSRS total score. This was particularly true for women, who scored generally worse on the GSRS scales than their female controls, notably for indigestion ($p<0.006$), diarrhoea ($p<0.04$), constipation ($p<0.001$), and abdominal pain ($p<0.002$). In contrast, men with CD did not have more GI symptoms than their male controls.



DISCUSSION

CD was long considered more or less a disease of childhood, extremely rare in adults. Nowadays we know that CD is one of the most common food intolerance disorders, with widely varying symptoms.

Epidemiology

Developments after 1986 can be described in terms of the growing importance of serology in diagnostic work and the increased awareness of the various clinical expressions of CD.

We studied prevalence in a geographically defined area, the catchment area of Örebro County Hospital, and found it to be 1/1047. Five years earlier the prevalence of CD in the adjacent county of Linköping, was reported to be 1/1700 inhabitants (Hallert 1981). In contrast to Hallert we found the peak prevalence not in the middle-aged population but in the group 65-74 years old, 1/562. No antibody tests were used regularly in either of the studies. The nearly doubled prevalence in 5 years is probably an effect of increased awareness of the disease among GPs as well as the increasing number of gastroenterologists at that time in Sweden.

Since the 1980's serologic diagnostic methods have been developed. Screening of blood donors using antibodies against gliadin was performed in Linköping, Sweden. A prevalence of 1/266 was found (Hed 1986). This study was biopsy proven. In 2003 Mäki et al. found a higher prevalence of 1/67 in a cohort of 3,654 Finnish schoolchildren. They had positive antibodies in combination with the DQ2 or the DQ8 haplotype. The estimated biopsy-proved prevalence was 1/99 (Mäki 2003). The prevalence of CD in different populations, scrutinized in an epidemiologic way without a screening procedure, was found to be about 1/300 (Collin 1997, Catassi 1994).

Based on the occurrence of EmA rather than biopsy-proven cases,

McMillan suggested that the prevalence might be as high as 1/100 (McMillan 1996). In a study of a population sample Borch found a prevalence of 1.9% (Borch 2001). In Sweden there was an epidemic

of CD among children, mostly under two years of age, which has no equivalent anywhere in the world. This was partly an effect of changes in national dietary recommendations and the food content of industrially produced infant foods (Ivarsson rev.2005). The epidemic lasted from the mid-1980s to the mid-1990s. In the early 1980s the parents were recommended to introduce gluten into their children's diets abruptly and in large amounts at the age of six months, often simultaneously with weaning from breastfeeding. The continuation of breastfeeding at the time the antigen is introduced seems to be of crucial importance (Hanson 1998, Ivarsson 2002). On the basis of epidemiological

studies (Ascher 1991), the national recommendation was altered in the mid-1990s with the introduction of small amounts of gluten while breastfeeding was continued. The incidence of CD in small children then fell to levels comparable to prior to the epidemic (Ivarsson 2000).

Associated diseases

Associated diseases are frequent in patients with CD. Dermatitis herpetiformis (DH) was the most common finding in our series (19%). Some authors consider DH and CD as two manifestations of the same disease (Mäki 1997).

It is of interest that 6.5% of the patients in Paper 1 had had psychiatric problems to an extent that they had sought medical advice. Hallert reported, when looking at psychiatric illness among CD patients, a figure more than 3 times higher than the 5% among his control population (Hallert 1981).

For thyroid disease we had the highest figures published at the time, 10.8%. More recently even higher prevalence figures for hypothyroidism, approaching 20%, have been reported (da Silva Kotze 2006). In another study of patients with thyroid disease it was found that 4.8% had CD (Collin 1994C).

We also found diabetes mellitus in 5% of our patients. Two years later the Finnish group found a high frequency of CD, 4.1%, in adult patients with type I diabetes (Collin 1989). In a review, Green approximated the prevalence of other autoimmune diseases among CD patients as 10 times higher than among controls (Green 2003).

Two patients in Paper I who had died at the follow up had had autoimmune hepatitis. A CD prevalence of 19% has been found in patients with autoimmune hepatitis (Lindberg 1979). Cases of severe autoimmune liver disease have been reported, in which a GFD has prevented progression to hepatic failure, even in cases where liver transplantation had been considered (Kaukkinen 2002).

The duration of gluten exposure has been proposed to be associated with the prevalence of associated autoimmune diseases, which is an additional rationale for early diagnosis and treatment of CD. When adolescents with CD in Italy were screened, it was found that 35% had a coexisting autoimmune disease, when diagnosed at the age of 20 years or older. In patients diagnosed and treated with a strict GFD since 2 years of age or younger, coexisting autoimmune disorders were only 5% (Ventura 1999). However, others have been unable to verify the proposed connection between early CD diagnosis and onset of autoimmune diseases (Sategna 2001, Viljamaa 2005A).

Declining antibody titres after start of a gluten free diet

Nowadays, when people often seek information from the Internet, it is common that the patients have omitted gluten-containing foods before consulting a clinician. It is essential to know if the serological tests are useful in these subjects. This was the starting point for paper III.

As early as after one month on a GFD, 15-30% of the patients with initially high antibody titres had no antibody titres above the cut-off levels. After three months on a GFD the corresponding figure was more than 50%. Our findings are in line with findings from treated children (Bürgin-Wolff 1989, Hansson 2002).

It seems to be of utmost importance to determine whether or not the patient has self-initiated a GFD prior to analysis of antibodies. Antibodies against tTG derived from guinea pig fall more slowly than the others we tested. This may be related to the fact that tTGgp is less pure than the recombinant human antigen (Fabiani 2001).

Adequate treatment is perfect compliance with a gluten free diet.

The treatment of CD consists of a gluten free diet. In the past, this was assumed to mean abstinence from products containing wheat, rye, barley and oats, but the toxicity of oats has long been questioned (Dissanayake 1974A). In recent years Finnish investigators have convincingly shown that intake of oats up to 50g daily is harmless (Janatuinen 1995), although occasional reports on oat toxicity have been published (Lundin 2003).

The possibility of including oats has diversified the diet (Peräaho 2004). This might positively influence compliance, which has always been the main obstacle to successful treatment. When analysing compliance in our 10-year follow-up study we relied on a simple questionnaire with four questions. We know that the physicians' evaluations are not as good as dieticians' (Moi 1987). In our material we had a compliance rate of 78%, which is fairly high in comparison with other follow-up studies. They report that 50-70% of the patients stick to a strict GFD (Mäki 1997). In the serological follow-up study (Paper III) we had more than 90% compliance. These 22 patients were followed extensively with blood samples for serology at 0, 1, 3, 6 and 12 months after diagnosis. To my knowledge there are no studies of whether intensive follow up directly after diagnosis results in better compliance in the long run than traditional follow up.

However, our figures also show that after 10 years 22% of the patients were not in compliance with the diet, which would influence the outcome. In addition, some patients regarded as being in

compliance with the diet may have a non-compliant diet involuntarily caused by eating gluten containing food of which the patients are unaware (Baker 1975).

Mucosal remission and serology

It is a clinical challenge to estimate the effects of the GFD on mucosal restoration. This can be done by biopsy which, however, is an invasive procedure. In spite of the fact that CD in adults has been diagnosed for 3 decades, there is no consensus how to follow them up. This was the incentive for us in Paper IV. We know there is a good correlation between the amount of ingested gluten and the condition of the patient's intestinal mucosa (Dissanayake 1974B, Baker 1975, Catassi 1993). Biopsy control has been proposed to be the best choice in the follow up of patients (Murray 1999, Dewar 2005). Recent authors have classified a mucosa improved to at least Marsh grade II (Oberhuber 1999) as being in remission (Vahab 2002, Kaukinen 2002B). We used the same definition of remission in our study but there is no consensus as to define mucosa in remission. We compared diet history, antibody tests, and nutritional markers with the histological findings.

The results showed a very high predictive value (93-98%) of mucosal remission using IgA-AGA, EmA or tTG. However, these tests are less efficient in predicting un-recovered mucosa; 35-55%. Other investigators have found a lack of correlation between antibody titres and mucosal appearance. The correlation between negative tests and recovered mucosa has turned out to be particularly insufficient (Dickey 2000, Vahedi 2003, Tursi 2003A). How good is diet history as a predictive tool? In our hands it was a fairly good indicator of mucosal remission, with a predictive value of 88%. In patients assuming they kept to a strict GFD there were more men than women who had a mucosa in remission. We have not been able to explain the difference between women and men. In the hands of others, diet history has turned out to be less reliable. A physician or non-specialist dietician will miss about 30% of gluten transgressions when taking a diet history from CD patients, as compared with specialized dieticians (Vahedi 2003). The interest in nutritional markers was greater before the era of antibodies (Weir 1974, Jameson 1981). In our series, several patients were on vitamin and mineral supplementation, so we were not able to draw conclusions about nutritional markers as predictors of the appearance of the mucosa.

The standard procedure in follow up is still a new biopsy after 6 or 12 months (Cammarota 2005). This is invasive and expensive. Because serological tests have been found in many studies not to be reliable in picking out patients with unrecovered mucosa (Dickey 2000, Vahedi 2003, Tursi 2003A), other opportunities have been discussed.

Tests of small bowel function, such as sugar absorption, for assessing the normalisation of the mucosa, are not in frequent use today. However, sugar absorption tests have shown promising results (Uil 1996). In a study comparing EmA and tTGp with a sorbitol-H₂-breath test in assessing histological recovery after GFD and in assessing dietary transgressions and dietary mistakes, Tursi found the breath test seemed to be better than the antibody tests (Tursi 2003B). Maybe this method could be developed into a useful tool in choosing patients for control biopsy in the follow up of CD patients.

Does CD influence risk of malignancy and mortality rates?

In the Linköping-Örebro cohort of CD patients there was no excess risk in malignant diagnosis as compared with the background population. Earlier reports showed a higher cancer risk in CD patients (Holmes 1976, Cooper 1982, Cottone 1999, Corrao 2001). However, two recent studies report no increased risk of malignancies (Card 2004, Viljamaa 2006). Why do the latest reports differ from the earlier ones? The previous studies were mostly small and not population based. Studies based on routinely collected data have potential weaknesses, because diagnostic data have not been validated. A bias of worse patients who mostly cluster at the referral centres is probable. In a British study in which the General Practice Research Database was used, an increased risk of malignancies of 1.29 (95% CI 1.06-1.55) was reported (West 2004). A Swedish group used the Swedish Inpatient Register and reported the incidence of cancer in CD patients to be 1.3 (95% CI 1.2-1.5) (Askling 2002). In register studies there is, of course, a risk of missing patients who have not been recorded in the register. In our study, based on a carefully scrutinized patient population, we only found 36% of the patients registered as CD patients in the Swedish Inpatient Register.

In spite of the lower risk of malignancies, there was an excess mortality of 38% in the Linköping-Örebro patients. The excess risk of mortality was entirely attributable to cardiovascular disease. Several reports of increased mortality in CD depending on increased rates of malignancies have been published (Nielsen 1985, Logan 1989, Corrao 1995, Cottone 1999, Peters 2003, West 2004). However, our results were found in connection with a lower risk of malignancies, and the excess mortality is due to cardiovascular disease. This is an interesting observation, because we cannot see any overrepresentation of the classical risk factors for cardiovascular disease among our patients. CD patients are smokers to a lesser extent than controls (Snook 1996, Austin 2002, Suman 2003). Any difference in risk of cardiovascular disease, ought to have been in favour of the CD patients. Furthermore, CD patients have lower levels of blood pressure and serum cholesterol than controls

(West 2003).

On the other hand, our group found higher total plasma homocystein levels among CD patients than in the general population (Hallert 2002). Homocystein in plasma is a metabolic marker of folate, vitamin B6 and vitamin B12 deficiency. Hyper-homocysteinemia is an independent risk marker of atherosclerotic disease in men and women (Mahtez 2004). Recently, a British group found that 41% of consecutive, newly diagnosed CD patients had vitamin B12 deficiency (Dahle 2001). The finding of an elevated mortality from cardiovascular disease, especially in the oldest age group, raises questions. Our oldest patients had their CD diagnosed late, and consequently they had been on GFD for a shorter period than patients diagnosed at younger ages. Does a strict GFD for many years protect the patients from cardiovascular disease? Is it possible to prevent cardiovascular disease by additional vitamin intake? These questions remain unanswered. In a recent German publication, reporting from a health research project, men and women with elevated IgA anti-tTG antibodies in serum samples taken 10 years earlier, had an excess mortality of 1.86 and 3.92 respectively (Metzger 2006). To what extent these patients had a CD-diagnosis we do not know, neither how many of them who had been recommended a GFD.

Outcome

The purpose of diagnosing and treating a condition like CD is to restore subjective health and prevent complications. Already in the early 1980s it was shown that CD patients who stick to a strict GFD are characterized by a quick return to normal health and by new found vitality (Swinson 1980, Cook 1984). However, not much was done to find out how the CD patients feel in the long run. We analysed the outcome in patients who had been recommended a GFD 8-12 years earlier. Do CD and its treatment with a GFD influence gastrointestinal symptoms and thus affect quality of life?

In spite of dietary treatment, patients on a strict

GFD had more gastrointestinal symptoms than the general background population. The women had more symptoms than the men (Paper V). In another study we measured the quality of life in patients with a CD diagnosis using the SF-36 questionnaire. CD patients scored significantly lower and thus had worse quality of life than the general population, most marked within the domains of general health and vitality. However, this was only apparent in the female population. In contrast, the male CD population did better than the background population (Hallert 1998). An American study of the impact of a GFD on the quality of life showed the same pattern with a predominance of negative impact on women (Lee 2003). To

explore the reason for the sex difference, Hallert et al performed a descriptive study of ten of our patients. It was obvious that men and women had different coping strategies, which could be a key to understanding the sex differences (Hallert 2003). Reduced quality of life in CD patients was also found by an Italian group. Their patients' scores were roughly equivalent to those of a group of diabetes patients. When looking at anxiety and depression questionnaires, a long time on a GFD indicated a worse score (Fera 2003). A Finnish group has reported normal gastrointestinal symptoms (Lohiniemi 2000), and a normal quality of life (Mustalahti 2002) in CD patients on a strict GFD for one year. One could argue that the results depend on the relatively short time on a GFD. However a recent Finnish study found no difference between CD patients treated for 14 years and the general population (Wiljamaa 2005B).

Why the Finnish results differ from ours and from Italian studies (Addolorato 2001, Ciacci 2003), is unclear. However, Hauser et al. show that despite being on a gluten free diet German CD patients suffer from more symptoms and a worse quality of life than the general population (Hauser 2006). One could speculate as to why female CD patients suffer from more gastrointestinal symptoms and have worse quality of life than male CD patients. A recent American study shows a female: male ratio of 1:1 for other autoimmune diseases and a total extent of 30.7% in CD patients (Bai 2005). It is well known that sex hormones influence the immune system. Women produce more vigorous cellular and humoral immune reactions than men, are more resistant to certain infections and suffer a higher incidence of autoimmune diseases (Bouman rev.2005). From Irritable Bowel Syndrome (IBS) studies we know there is a sex-related difference regarding symptom relief on medication (Novick 2002).

Is it possible that external factors other than gluten play a role in causing symptoms?

An Italian group has shown prevalence of small intestinal bacterial overgrowth in coeliac patients with persistence of gastrointestinal symptoms after gluten withdrawal (Tursi 2003B). However, this finding has not been confirmed in any other study. Many of the gastrointestinal symptoms of CD patients suggest impaired gastrointestinal motility (Corazza 1995). Recently Elli made an overview of all the literature concerning CD, and impaired motility was reported. Although there is sometimes conflicting data, altered intestinal motility in CD patients was also found. However, after introduction of a GFD, motility seems to return to normal and is unlikely to explain our finding of increased gastrointestinal symptoms 10 years after the start of a GFD (Elli 2005).

It is possible that the complaints of indigestion and abdominal pain characterizing the women with CD may represent a coexisting non-organic intestinal disorder. CD shares some clinical features with irritable bowel syndrome. In a British study of 300 IBS patients, six percent were found to have CD

(Sanders 2001). In a similar study Sanders examined patients who sought help for abdominal pain and found out that 10.5% of them were undiagnosed CD patients (Sanders 2002). There has been shown to be a connection both between infection of the gut and IBS (Rodriguez 1999, Spiller 2003), and inflammatory bowel disease and IBS (Simren 2002). In a recent review Quigley stresses the ability of the inflammation in classical inflammatory disorders to disrupt intestinal motor and sensory systems, alter gut function, and thereby produce symptoms that may be difficult to differentiate from those of IBS (Quigley 2005). O'Leary et al. associated IBS-type symptoms with impaired quality of life among their CD patients, regardless of dietary compliance (O'Leary 2002). Therefore, encouraging patients to keep to a strict GFD to obtain restored intestinal mucosa seems not to be sufficient to help all of them to a good life. Living with CD, even well-treated, is far from easy. This seems to be especially true for women, who suffer from more GI-symptoms overall and perceive the disease burden as heavier than do men. Further studies are needed to determine whether the reported GI complaints are causes or effects.

Diagnosis of CD today

Twenty years ago only the people at the tip of the CD iceberg were diagnosed (Logan 1992). Longer ago, only patients with overt gastroenterological symptoms, most common in combination with signs of malabsorption, were recognized. Today we have learned that CD can occur with only subtle symptoms, and this new knowledge seems to be one of the factors that has raised the prevalence figures.

In the 1960s nearly 100% of the CD patients presented with diarrhoea, but this figure is less than 50% today (Lo 2003).

In our study (Paper I) gastrointestinal symptoms constituted the reason for investigation in about half of the patients, while 47% had no gastrointestinal complaints at all. This was similar to previous findings in the UK (Logan 1983). In spite of more patients with silent CD being diagnosed over time, the proportion of patients with gastrointestinal symptoms was still about 50% in the late 1990s (Collin 1997). However, in a more recent paper a British group found gastrointestinal symptoms in only 28.4% of the cases (Sanders 2002).

The high prevalence figures for CD today are related to the use of serological methods in the diagnostic work-up. The sensitivity of EmA is 85-98% (Chorzelski 1984, Hällström 1989, Farell 2002). Similar figures have been achieved for tissue transglutaminase, both derived from guinea pig

(Sulkanen 1998) and recombinant human tissue transglutaminase (Burgin-Wolf 2002).

To date, serology is not sufficient in itself for diagnostic purposes, and the diagnosis of CD still relies on a histological confirmation (Murray 1999, Dewar 2005). However, a recent study shows that 12% of the specimen preparations from a well reputed pathology unit were not orientated well enough for a diagnosis. In the future, CD diagnosis will probably become more reliant on serological methods (Collin 2005A), although histological methods are also developing. Villous tip intraepithelial lymphocytes might be a more definite sign for distinguishing early CD from non-specific changes (Järvinen 2004). To support histological borderline findings the presence of coeliac specific antibodies, immunogenetical markers, HLA DQ2 or DQ8 compatible with CD are needed. The demonstration of gluten dependence (the recovery of symptoms and inflammation by GFD or histological deterioration following gluten challenge) is needed to support histological borderline gluten sensitivity (Collin 2005A).

What will be the consequences of diagnosing more patients with silent and even latent CD? Most authors agree that CD patients with mild symptoms benefit from obtaining a diagnosis (Sjöberg 2004, Treem 2004). Recently, limited screening programs in well-defined regions with continuous and prospective evaluation of their costs and benefits were proposed (Mearin 2005). The Tampere group has followed up CD patients who were diagnosed by screening of risk groups 14 years earlier. Both quality of life and bone mineral density were comparable to those in the general population (Wiljamaa 2005B). Today there is no consensus suggesting mass screening, but increased alertness should be observed when we see patients at risk of developing the condition (Collin 2005C).

CONCLUSIONS

The prevalence of coeliac disease in adults was 95.5/100,000 (1986). The highest prevalence, 178/100,000 inhabitants, was found in the age group 65-74 years. The lowest prevalence was found in patients aged 15-24 years. Among associated diseases, an especially high incidence of thyroid disease was observed, 13% of our patients had either hypo-or hyperthyreosis.

After recommendations of a strict GFD there is an excess mortality risk but no excess risk of developing a malignant disease in a 15 year follow-up.

Since the titres in the serologic tests used to confirm the diagnosis of CD fell rapidly and continued to decline following initiation of a gluten free diet, it is important to inquire about the possibility of a self-prescribed diet before the patient sought medical advice.

In addition to a diet history, any one of the antibody analysis as well as a zinc analysis was clinically satisfactory (>90%) to verify restitution of the mucosa, as well as identifying patients with un-restored mucosa.

Adult CD patients on a gluten free diet for several years experienced significantly more gastrointestinal symptoms than the general population. This may be attributable to some extent to the composition of a gluten free diet. The symptoms were more pronounced in women. This may raise questions about an association with their subjective health status, which has been shown to be less good than that of men with coeliac disease.



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Populärvetenskaplig sammanfattning på svenska (Comprehensive summary in Swedish)

Historik

Celiaki beskrevs första gången av en grekisk läkare andra århundradet efter Kristi födelse. Upptäckten föll sedan i glömska och den första moderna beskrivningen daterar sig till London 1888. Man visste inte då att sjukdomen berodde på en skada på tarmslemhinnan, ännu mindre vad den i sin tur kom sig av. I slutskedet av andra världskriget noterade en holländsk barnläkare, Dr Dicke att hans celiakipatienter blev mycket bättre. Pga kriget rådde stor brist på spannmål. Efter att svenska flygplan, som ett led i en hjälpinsats, bombat Holland med spannmål blev barnen sämre igen. Dr Dicke drog då slutsatsen att mjölet var en negativ faktor för hans patienter. Några år senare på femtiotalet, kunde man för första gången genom att titta i mikroskop visa att tunntarmslemhinnan var skadad. Kort härefter utvecklades metoder för att ta prov från tunntarmslemhinnan och förutsättningarna för både diagnostik och behandling var klara. Längre betraktades celiaki mer eller mindre som en barnsjukdom som var mycket sällsynt hos vuxna. När de diagnostiska metoderna spreds och de medicinska gastroenterologerna blev talrikare på 1970- och 80-talen visade det sig att celiaki var långt ifrån ovanlig även hos vuxna.

Studien

Mitt första arbete var en kartläggning av celiakipatienterna inom Örebro sjukhus upptagningsområde. Förekomsten var cirka 1/1000, vilket var bland de högsta på den tiden (1986). Dels genom ökad medvetenhet hos läkarna och dels genom att man nu kan "screena" för celiaki med enkla blodprov som mäter antikroppar, har celiakidiagnosen blivit allt vanligare och man räknar nu med att närmare 1/100 har celiaki. Detta har medfört att den kliniska bilden av en celiakipatient är annorlunda nu än för några decennier sedan. Många patienter som får diagnos idag har få eller inga symptom. Redan 1986 hade nästan hälften inga symptom från mag-tarmkanalen. Sedan dess har denna andel minskat ytterligare. I det första arbetet finner man också en mycket hög samtidig förekomst av sjukdomar i sköldkörteln, ett resultat som senare har kunnat verifieras av andra forskare.

I mitt andra arbete följer jag upp dessa patienter efter 15 år med avseende på eventuellt insjuknande i cancersjukdom och för att se om de fortfarande är i livet. Statiska centralbyrån och Socialstyrelsen var behjälpliga med jämförelser mot kontrollpersoner, bakgrundsbefolkningen, dödsorsaks- och

cancerregistret. Förutom Örebropatienterna inkluderade jag motsvarande patienter i Linköping. Några skillnader mellan de båda sjukhusen fanns ej. Insjuknandet i cancersjukdom var lägre än förväntat. Risken att dö var däremot högre än förväntat. Ökningen utgjordes till största delen av ökad dödlighet i hjärt-kärlsjukdom i de högsta årsklasserna. Detta är något överraskande då man vet från andra studier att celiakipatienter har *färre* klassiska riskfaktorer, t.ex. de röker mindre, har bättre blodtryck och kolesterol jämfört med folk i allmänhet. Fler intressanta uppslag finns till ytterligare studier för att förklara de påvisade skillnaderna.

Sedan 80-talet har flera antikroppsmetoder för att väcka misstanken om celiaki tillkommit. Det är frågan om antikroppar mot gliadin som är en beståndsdel i gluten, och numera även antikroppar mot vävnadstransglutaminas, ett enzym som finns i tunntarmsslemhinnan som vanligen finns hos den obehandlade celiakipatienten. I mitt tredje arbete redovisas vad som händer med nivåerna av 4 utvalda antikroppar från diagnostillfället och efter 1, 3, 6 och 12 månaders glutenfri kost. Det visade sig att nivåerna började sjunka ganska direkt. Denna iakttagelse var upphov till slutsatsen att antikroppsdiagnostik av celiaki hos patienter som på egen hand påbörjat en glutenfri kost är vansklig redan mycket kort tid efter dietomläggning.

Andra har tidigare visat det är värdefullt att hitta och behandla en patient med celiaki för att minska risken för cancer, benskörhet, infertilitet och förbättra utsikterna för en lyckad graviditet. Hörnstenen är en tunntarmslemhinna som är läkt. Kan man genom att använda kostutfrågning och blodprov få en tillräckligt god bild av om tunntarmslemhinnan är läkt eller inte? Det var frågeställningen inför det fjärde arbetet. Det visade sig att bland svenska celiakipatienter som varit rekommenderade gluten fri kost i 10 år höll 91% en strikt glutenfri kost. Det är en hög siffra vid internationell jämförelse. I 88% av fallen kunde några enkla kostfrågor förutsäga att slemhinnan var läkt. Läger man till en antikroppsanalys ökas säkerheten ytterligare. Hundraprocentig säkerhet kan man förstås bara få med biopsi, men det är ju trots allt ett mindre ingrepp för patienten och dessutom en fråga om hur sjukvårdens resurser skall fördelas.

En fråga som blivit mer aktuell på senare år är hur patienten ”mår egentligen”. I det femte arbetet har patienter som haft celiaki i 10 år, och är i bevisad remission fått fylla i frågeformulär om symptom. Det visar sig att många mår långt ifrån bra, med symptom från magen. Speciellt är det kvinnorna som mår sämre.

ABSTRACT

Coeliac disease (CD) is considered to be the result of a complex interplay of intrinsic (genetic) factors and variable extrinsic (environmental) factors. The complex background of CD explains its wide spectrum of clinical manifestations.

For a very long time CD was considered more or less a disease of childhood, which was extremely rare in adults. Nowadays we know that CD is one of the most common food intolerance disorders.

An epidemiological study of CD in a geographically defined area of Sweden (Paper1) showed a prevalence of 95.5/ 100 000 inhabitants. Among the associated diseases an especially high incidence of associated thyroid disease, 10.8% was observed.

In a fifteen-year cohort follow up study of all CD-patients residing in the counties of Örebro and Linköping (Paper 2) the total mortality was increased with 38% (SMR 1.38 95% C.I. 0.31-0.83). This was mainly explained by a 48% increased death rate in ischemic heart disease, significant in patients over 65 years (SMR 1.58 95% C.I. 1.00-2.06). However, there was a 47 % lower risk of all malignancies (SIR 0.53 95% C.I. 0.31-0.83).

A cohort of 22 consecutively biopsy-proven adult CD patients (Paper 3), were followed in respect of antibody titres from diagnosis and after 1, 3, 6, and 12 months on a gluten free diet (GFD). All antibody titres fell sharply within one month. Thus excluding a CD diagnosis serologically on a patient who has initiated a GFD by herself is not to recommend.

In another cohort with CD patients(Paper IV) who were diagnosed 8-12 years earlier recommended and who were recommended, the reliability of diet history, serological and biochemical markers to predict the appearance of the small intestinal mucosa were analysed (Paper IV). The history of a strict GFD gave a predictive value of 88% of a mucosa in remission. The values of serological tests (AGA, EmA and tTG) to predict a mucosa in remission were 93% for all.

In CD patients in remission gastro-intestinal symptoms were evaluated with the GSRS questionnaire. Subjects with CD reported significantly more GI-symptoms than a general population sample ($p<0.01$). This was particularly true for women with CD who scored worse than female controls .By contrast men with CD reported no more symptoms than male controls.