

Coeliac disease – associated disorders and survival

P Collin, T Reunala, E Pukkala, P Laippala, O Keyriläinen, A Pasternack

Abstract

The associated diseases in 335 coeliac patients diagnosed 1980–90 were compared with age and sex matched control patients with various gastrointestinal symptoms. Endocrine disorders were found in 11.9% of coeliac and 4.3% of control patients ($p=0.0003$). Coeliac patients had insulin dependent diabetes mellitus significantly ($p=0.0094$) more often (5.4%) than control patients (1.5%). Connective tissue diseases were found in 7.2% of coeliac and in 2.7% of control patients ($p=0.011$). Sjögren's syndrome occurred in 3.3% of coeliac patients and in 0.3% of controls ($p=0.0059$). Autoimmune thyroid diseases were found in 5.4% and asthma in 3.6% of coeliac patients, but also in 2.7% and 3.6%, respectively, among control patients. The incidences of malignant diseases and the survival rate in coeliac patients were compared with those in the Finnish population. Ten coeliac patients developed a cancer during the follow up (mean 5.3 years, range 1–12) but none had a lymphoma. The risk of malignant diseases in coeliac patients did not differ from that in the Finnish population in general. Eleven coeliac patients died during the follow up. The five year survival rates of coeliac patients did not differ from those in the general population. At least 83% of the coeliac patients adhered strictly to the gluten free diet, which may explain the favourable outcome.

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Department of Internal Medicine, University Hospital of Tampere and Department of Clinical Medicine, University of Tampere, Finland
P Collin
O Keyriläinen
A Pasternack

Department of Clinical Medicine, University of Tampere, Finland
T Reunala

Finnish Cancer Registry, Helsinki, Finland
E Pukkala

Department of Public Health, Biometry Unit, University of Tampere, Finland
P Laippala

Correspondence to: Dr P Collin, Department of Clinical Medicine, University of Tampere, PO Box 607, FIN-33101 Tampere, Finland.

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In a recent review, almost 100 diseases have been described as occurring concomitantly with coeliac disease.¹ An association between coeliac disease and autoimmune diseases has been reported in several studies.^{2–6} An increased risk of malignancy and increased general mortality have also been found among coeliac patients.^{7,8} Coeliac disease is not uncommon, however, and the occurrence of many associated diseases may be coincidental. In this study the frequency of associated disorders and survival of adult coeliac patients were examined.

Patients and methods

PATIENTS WITH COELIAC DISEASE

The study group comprised 335 adult coeliac patients diagnosed at the Department of Internal Medicine, Tampere University Hospital, in the period 1980–90. The annual number of new coeliac patients ranged from 18 to 26 in the period 1980–83 and after that from

29 to 49. There were 86 men and 249 women, and the mean age at diagnosis was 41.4 years (range 16–79) (Table I). Of the total, 274 patients were diagnosed after clinical suspicion of coeliac disease, and 61 were detected by serological screening. The diagnosis of coeliac disease was based on the characteristic histological finding of subtotal or severe partial villous atrophy and crypt hyperplasia in small bowel biopsy.

All 335 patients were prescribed a gluten free diet and asked to attend a control examination after 6–12 months. Two hundred and seventy nine patients (83%) kept to the gluten free diet, 90% of them adhering strictly according to two separate enquiries. Eighteen (6%) failed to maintain the diet at all, and 38 (11%) did not participate in the control examination. A control biopsy specimen during the gluten free diet was available from 258 coeliac patients. Mucosal recovery was seen in 90% of them. Twenty one patients maintaining the gluten free diet refused the control biopsy.

CONTROL PATIENTS

Control patients were selected from among outpatients subjected to upper gastrointestinal endoscopy at the Department of Medicine in 1980–90. They were age and sex matched with coeliac patients. Endoscopy of control patients had to take place within the same year as that in which the diagnosis of the corresponding coeliac patient was established. Abdominal pain or dyspepsia was the reason for endoscopic examination in 257 patients, thoracic pain or symptoms of gastro-oesophageal reflux in 45, and anaemia in 33. Table II shows the endoscopic findings from control patients. Since 1983, a biopsy specimen has been routinely taken from the descending part of the

TABLE I Demographic and dietary data of coeliac patients

Total number	335
Mean age (range)	41.4 (16–79)
Male/female ratio	0.34
Diet:	
Gluten free	279 (83%)
Normal	18 (6%)
Not known	38 (11%)
Control biopsy	258
Mucosal recovery	233 (90%)
No recovery	25 (10%)

TABLE II Demographic data and endoscopy findings in control patients

Total number	335
Mean age (range)	41.7 (16–79)
Male/female ratio	0.34
Endoscopy findings:	
Peptic ulcer or scar	40 (12%)
Oesophagitis	27 (8%)
Non-malignant polyp	5 (1%)
Cancer	3 (1%)
Crohn's disease	2 (1%)
Normal or minor changes	258 (77%)

TABLE III Associated diseases in 335 patients with coeliac disease and age and sex matched controls

Disorder	Number of patients					
	Coeliac disease			Control group		
	Women	Men	Total	Women	Men	Total
Endocrine disorders:			40			14
Insulin dependent diabetes mellitus	9	9	18 (0)*	4	1	5 (0)
Autoimmune hypothyreosis	9	2	11 (0)	7	1	8 (0)
Graves' disease	6	1	7 (1)	1	0	1 (1)
Parathyroid adenoma	2	0	2 (0)	0	0	0 (0)
Addison's disease	1	1	2 (0)	0	0	0 (0)
Connective tissue disorders:			24			9
Sjögren's syndrome	11	0	11 (0)	1	0	1 (0)
Rheumatoid arthritis	4	2	6 (0)	6	1	7 (0)
Ankylosing spondylitis	1	0	1 (0)	1	0	1 (0)
Scleroderma	2	0	2 (0)	0	0	0 (0)
Vasculitis	2	0	2 (1)	0	0	0 (0)
Systemic lupus erythematosus	1	0	1 (0)	0	0	0 (0)
Mixed connective tissue disease	0	1	1 (0)	0	0	0 (0)
Pulmonary disorders:			17			12
Asthma	10	2	12 (3)	12	0	12 (0)
Sarcoidosis	4	1	5 (0)	0	0	0 (0)
Neurological disorders:			10			4
Epileptic seizures	2	3	5 (0)	2	1	3 (0)
Dementia	4	1	5 (0)	1	0	1 (0)
Liver diseases	3	1	4 (0)	0	0	0 (0)
Glomerulonephritis	1	2	3 (0)	0	1	1 (0)
Inflammatory bowel disease	0	1	1 (1)	7	0	7 (0)
Psoriasis	4	0	4 (0)	0	0	0 (0)

*Number of diseases diagnosed during the prospective follow up period in 233 coeliac patients and controls.

duodenum of these patients, and thus coeliac disease has been excluded.

ASSOCIATED DISEASES AND SURVIVAL DATA

The hospital records of all patients were examined thoroughly. From these a history of present and past diseases, diagnosed by general practitioners or in hospitals, was registered in the coeliac group at the time of diagnosis, and in the control group at the time of endoscopy. Associated diseases were similarly recorded during the follow up as long as data were available. The time of follow up included in the study was always the same for coeliac and the corresponding control patient. Because 102 (31%) of the control patients had been examined only once in hospital, the follow up data were based on 233 coeliac and respective control patients. The mean follow up time of these subjects was 3.1 years (range 0.5–11 years).

The occurrence of malignant diseases and survival of coeliac patients were assessed up to the end of 1991. The follow up for cancer was made through the files of the Finnish Cancer Registry and for death through the Statistics Finland. The mean follow up time for malignant diseases and survival was 5.3 years (range 1–12). The observed number of malignant diseases and survival was compared with those expected in the age and sex matched Finnish population.

STATISTICAL ANALYSIS

Disease frequencies were compared by Fisher's exact test. The relative occurrence of malignant diseases was presented using standardised incidence ratios (SIR) with 95% confidence intervals. The five year survival of coeliac patients was compared with that in the Finnish population and the survival rates were displayed graphically.

Results

ENDOCRINE DISORDERS

Twelve per cent of the coeliac patients and 4.2% of the control patients were suffering from endocrine disorders ($p=0.0003$) (Table III). Insulin dependent diabetes mellitus was found in 5.4% of coeliac and 1.5% of control patients ($p=0.0094$). Eighteen (5.4%) coeliac patients and nine (2.7%) controls had autoimmune thyroid disease (autoimmune hypothyroidism or Graves' disease) ($p=0.11$).

CONNECTIVE TISSUE DISEASES

Connective tissue diseases were found in 7.2% of coeliac patients and in 2.7% of controls ($p=0.011$). Sjögren's syndrome was diagnosed in 3.3% of coeliac patients and 0.3% of the control patients ($p=0.0059$), the diagnosis being defined according to the Californian criteria.⁹ Rheumatoid arthritis was found in 1.8% of coeliac and 2.1% of the control patients.

OTHER DISEASES

Asthma occurred in 3.6% of both coeliac and control patients; three of 12 such cases among coeliac patients were diagnosed during the follow up. Sarcoidosis was found in 1.5% of coeliac and none of the control patients ($p=0.062$). Four coeliac patients had liver biopsy because of abnormal enzyme concentrations. One patient had primary biliary cirrhosis, one unspecific hepatitis, one cirrhosis of unknown aetiology, and one normal liver histology. No liver biopsy specimens were taken in the case of control patients.

Four coeliac patients and none of the controls had psoriasis ($p=0.12$). Fifteen (4.5%) coeliac patients were found to have dermatitis herpetiformis shortly after establishment of the diagnosis of coeliac disease. In one coeliac patient the rash developed during the follow up.

MALIGNANT DISEASES

Malignancy had been found before the diagnosis of coeliac disease in four patients (Table IV). In the control group, seven patients had a malignant disease before

TABLE IV Malignant diseases in coeliac patients

Sex	Age		Malignant disease
	(A)	(B)	
F	68	61	Multiple myeloma*
M	76	67	Hodgkin's disease*
F	76	76	Gastric cancer*
F	78	67	Melanoma of the skin*
F	21	21	Melanoma of the skin
F	43	50	Renal cell carcinoma
F	45	48	Breast cancer
F	45	48	Breast cancer
F	45	50	Carcinoid tumour of the pancreas
F	50	50	Meningioma
M	61	62	Lung cancer
M	64	65	Liposarcoma of the abdomen
M	65	65	Renal cell carcinoma
M	75	80	Prostate cancer

(A)=age at diagnosis of coeliac disease; (B)=age when malignant disease was diagnosed. *Malignant disease diagnosed before the diagnosis of coeliac disease.

TABLE V Standardised incidence ratios (SIR) of cancer among coeliac patients during the follow up, compared with the Finnish population

	Observed numbers of cancers	Expected numbers of cancers	SIR	95% confidence intervals
Men (n=86)	4	2.1	1.94	0.53 to 4.96
Women (n=249)	6	4.5	1.34	0.49 to 2.92
Total (n=335)	10	6.5	1.53	0.72 to 2.81

endoscopy. There were three breast cancers, one Hodgkin's disease, one lung, one gastric, and one oesophageal cancer.

During the follow up, 10 coeliac patients developed a malignant disease. The expected number was 6.5 (SIR=1.53, not significant, Table V). Only one patient had cancer of gastrointestinal origin: a woman aged 50 years developed carcinoid tumour of the pancreas five years after the diagnosis of coeliac disease.

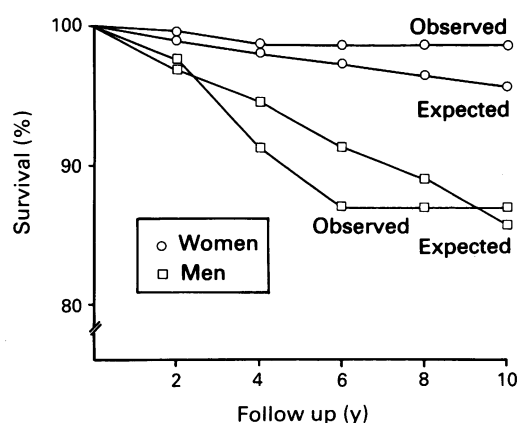
SURVIVAL OF PATIENTS

During the follow up, 11 (3.3%) coeliac patients, eight men and three women, died. Table VI shows the causes of death. The five year survival rate for men was 87.0% and for women 98.6% among coeliac patients. These survival rates did not differ statistically significantly from the rate in the general population (Figure).

Discussion

In this series we found that 5.4% of coeliac patients had insulin dependent diabetes, 5.4% autoimmune thyroid disease, and 7.2% connective tissue disease. The previously reported frequencies of autoimmune diseases have mostly been lower than those now found (Table VII). Cooper *et al*³ examined 314 coeliac patients, a study almost equal in size to ours, and found insulin dependent diabetes in 3.2%, autoimmune thyroid diseases in 3.2%, and connective tissue disease in 6.1%.

Coeliac patients had insulin dependent diabetes mellitus significantly more often than control patients. This may be due partly to the fact that diabetic patients are frequently screened serologically for coeliac disease in our hospital. The association of coeliac disease and insulin dependent diabetes, however, has previously been described both in children^{10 11}



Observed survival of 249 coeliac women and 86 coeliac men compared with that expected in the age matched Finnish population.

TABLE VI Causes of death of coeliac patients

Sex	Age at diagnosis of coeliac disease	Age at death	Cause of death
M	60	60	Vasculitis
M	61	62	Lung cancer
M	61	63	Insulin dependent diabetes mellitus
F	66	69	Intestinal ischaemia
F	68	70	Multiple myeloma
F	69	69	Cor pulmonale
M	70	74	Coronary artery disease
M	73	77	Coronary artery disease
M	75	80	Coronary artery disease
M	76	80	Coronary artery disease
M	78	81	Coronary artery disease

and in adults.¹² Two of our coeliac patients had Addison's disease, an association we have previously published.¹³ Even though the number did not differ statistically significantly from that in the controls ($p=0.50$), the association could be real, because Addison's disease is very rare. The frequency of autoimmune thyroid diseases in this series was comparable with that in previously published studies (Table VII). Nevertheless, the association may be coincidental; the frequency did not differ statistically significantly between coeliac and control patients.

There are earlier reports on the association between arthritis and coeliac disease.^{14 15} In this series, six coeliac patients and seven control patients had concomitant rheumatoid arthritis, which would suggest that rheumatoid arthritis is not specifically associated with coeliac disease. By contrast, there was a significant association between coeliac disease and Sjögren's syndrome; 11 coeliac patients and only one control patient had Sjögren's syndrome. There are few previous case reports of this association.¹⁶⁻¹⁸ In this study coeliac patients also had various other connective tissue diseases, albeit not in such high numbers as Sjögren's syndrome.

Patients with coeliac disease have an increased frequency of HLA B8 and DR3 and an almost 100% association has been seen with DQw2, which occurs in linkage disequilibrium with DR3. The DQ alleles HLA DQA1*0501 and DQB1*0201 are evidently the most important disease susceptibility genes in coeliac disease.¹⁹ HLA B8 and DR3 can also be found in insulin dependent diabetes mellitus,²⁰ Addison's disease,¹³ Graves' disease,²¹ and Sjögren's syndrome.²² Epithelial HLA DR antigen expression occurs both in the salivary glands of patients with Sjögren's syndrome²³ and in the small bowel of patients with coeliac disease.²⁴ Moreover, antibodies against reticulin and gliadin have been found in serum samples of patients with Sjögren's syndrome,²⁵ suggesting that these patients might have concomitant coeliac disease.

Williams *et al*²⁶ found a history of asthma in 20% of coeliac patients compared with 5% of controls ($p<0.01$). Hodgson *et al*²⁷ found 29% of coeliac patients and 5% of control patients to have a history of atopy, while only 2% of coeliac patients had a history of asthma. In this study, the diagnosis of asthma in all coeliac and control patients was based on a hospital examination at the department of lung diseases. In both groups 3.6% suffered from

TABLE VII Frequency of autoimmune diseases in different adult coeliac patient series

Author, country, reference	Study period	Number of coeliac patients	Insulin dependent diabetes (%)	Autoimmune thyroid disease (%)	Connective tissue disease (%)
Lancaster-Smith <i>et al</i> England ²	1967-74	57	3.5	5.2	1.8
Cooper <i>et al</i> England ³	1958-77	314	3.2	3.2	6.1
Midhagen <i>et al</i> Sweden ⁴	1976-86	139	Not given	10.8	3.6
Snook <i>et al</i> England ⁵	Not given	148	1.4	4.1	0.0
Corazza <i>et al</i> Italy ⁶	1972-89	226	2.2	1.8	2.2
This series	1980-90	335	5.4	5.4	7.2

asthma, suggesting that there is no association between coeliac disease and asthma. By contrast, the finding that five (1.5%) of our coeliac patients but none of the controls had sarcoidosis may be not a coincidence, as Douglas *et al*²⁸ have suggested. Liver diseases²⁹ and chronic inflammatory bowel diseases³⁰ have been connected with coeliac disease. In this series only isolated cases were found. By contrast with previous studies,^{31 32} we found no increased frequency of epilepsy in our coeliac patients. The control subjects in this study were outpatients having gastrointestinal problems similar to those in symptomatic coeliac patients. This selection may increase the occurrence of diseases with gastrointestinal symptoms, for example rheumatoid arthritis and asthma.

An increased risk of malignancy has been definitely established in coeliac disease; these patients are reported to have a 40 to 100-fold risk of developing non-Hodgkin's lymphoma.^{33 34} In this study none of the patients developed non-Hodgkin's lymphoma. The expected number of non-Hodgkin's lymphoma, however, was only 0.2 and the upper limit of the 95% confidence interval 3.6. The frequency of malignant diseases in coeliac patients did not differ significantly from that in the Finnish population in general. Holmes *et al*³⁴ showed that coeliac patients who have adhered to a strict gluten free diet for five years do not run an increased risk of malignancy; this implies that dietary treatment protects against the development of malignant disease. In their series of 210 coeliac patients, 22% did not have a gluten free diet. In this series, only 6% failed to adopt the prescribed diet and over 80% maintained it strictly. The comparatively low malignancy rate found in the present coeliac patients may thus be explained by good adherence to a gluten free diet.

Similarly, there was no statistically significant difference between the five year survival rate among coeliac patients and that in the population in general. By contrast, Logan *et al*⁸ found a 1.9-fold death rate in coeliac patients in Scotland, attributable to the increased rate within five years after the diagnosis of coeliac disease.

In conclusion, this study showed that patients with coeliac disease have an increased prevalence of autoimmune diseases, especially of insulin dependent diabetes and Sjögren's syndrome. No increased rate of malignancy or death was seen in these patients.

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