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Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease☆

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Abstract

Background and aims: Patients with inflammatory bowel diseases (IBD) show increased risk for other immune-mediated diseases such as arthritis, ankylosing spondylitis, and some pulmonary diseases. Less is known about the prevalence of other chronic diseases in IBD, and the impact of comorbidity on health-related quality of life (HRQoL).
Methods: The study population comprised 2831 IBD patients recruited from the National Health Insurance register and from a patient-association register. Study subjects completed generic 15D and disease-specific IBDQ questionnaires. The Social Insurance Institution of Finland provided data on other chronic diseases entitling patients to reimbursed medication. For each study subject, two controls, matched for age, sex, and hospital district, were chosen.
Results: A significant increase existed in prevalence of connective tissue diseases, pernicious anemia and asthma. Furthermore, coronary heart disease (CHD) occurred significantly more frequently in IBD patients than in their peers ($p=0.004$). The difference was, however, more clearly seen in females ($p=0.014$ versus 0.046 in males). Active and long-lasting IBD were risk factors. Concomitant other chronic diseases appeared to impair HRQoL. Asthma, hypertension and psychological disorders had an especially strong negative impact on HRQoL, as observed with both the generic and disease-specific HRQoL tools.
Conclusions: In addition to many immune-mediated diseases, CHD appeared to be more common in IBD than in control patients, especially in females. The reason is unknown, but chronic inflammation

Abbreviations: CHD, coronary heart disease; CD, Crohn's disease; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IC, indeterminate/unspecified colitis; SD, standard deviation; UC, ulcerative colitis.

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may predispose to atherosclerosis. This finding should encourage more efficacious management of underlying cardiovascular risk factors, and probably also inflammatory activity in IBD.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing inflammatory diseases of the gastrointestinal tract occurring typically in adolescence or early adulthood. Inflammatory bowel diseases (IBD) are considered to originate from unnecessary or exaggerated inflammatory immune response in a genetically predisposed individual.[1] The overall mortality of IBD patients is equal to or only slightly greater than that of the general population, and patients with IBD live with their disease typically for decades.[2,3] During that time they can develop other chronic diseases associated with IBD or independent of it.

Evidence is convincing of an increased prevalence of immune-mediated diseases in IBD, such as arthritis, ankylosing spondylitis, iritis, uveitis, erythema nodosum, asthma, and psoriasis.[4,5] Regarding pulmonary diseases, an increased incidence of bronchiectasies, bronchiolitis and interstitial pulmonary disease, independent of smoking habits or medication, has been apparent in IBD.[6] Incidence of colon cancer and cholangiocarcinoma is elevated in both CD and UC.[7,8] An association has been found between ischemic heart disease and IBD,[9–11] but mortality for cardiovascular diseases, however, has not been found to be elevated in IBD patients.[12] Data for many other chronic diseases are lacking.

In many surveys, IBD has had a negative impact on HRQoL, especially in its active forms.[13,14] Mental state and social support, age, gender, effects of medical therapy, and complications of treatment may affect their HRQoL.[15,16] It is probable that comorbidity with other chronic diseases has a negative impact on the HRQoL, as well.

The aim of this study was to examine the comorbodity of patients with IBD and compare it to that of a referral population by use of the comprehensive National Health Insurance reimbursement register. Moreover, we wanted to assess how health-related quality of life in IBD, measured with the generic 15D (15 dimensions) instrument and the disease-specific IBDQ (Inflammatory Bowel Disease Questionnaire), is influenced by comorbidity with other chronic diseases.

2. Methods

2.1. Survey design and study population

The National Health Insurance, with a register including all permanent residents of Finland, provides coverage for expenses due to sickness and prescribed medication. A patient with a chronic illness can claim special reimbursement for medical expenses with a certificate from a doctor documenting the diagnostic tests needed to confirm the diagnosis. The most important illnesses entitling patients to special refund are shown in Table 1. In addition, some expensive or rare medications or nutritional products can be reimbursed in certain conditions (such as etanercept for severe psoriasis, medications for Alzheimer's disease, and preparations for parenteral nutrition). The majority of patients with chronic diseases claim the special refund, making the National Health Insurance register representative of the total number of patients with a chronic condition.[17]

The study population comprised IBD patients recruited from the National Health Insurance register and from a patient association register. The HRQoL questionnaire packet including the 15D and IBDQ questionnaires, as well as additional questions about patients' demographic characteristics, was mailed to 3852 members of the Finnish Crohn's and Colitis Association and to an additional 1490 patients eligible for reimbursement for IBD medication according to the register of the Social Insurance Institution of Finland. No reminders were sent. Data were collected between September 2006 and February 2008 and included subjects over 18 years of age. For each participant, two control subjects matched for age, gender, and hospital district were chosen from the Social Insurance Institution register including all permanent citizens of Finland. As the aim of the study was to compare patients with IBD with the general population, the reference group included patients with IBD in proportion to their prevalence in that population. No HRQoL data were available for the control group.

2.2. The quality of life questionnaire

2.2.1. 15D

The 15D is a generic, standardized and self-administered measure of HRQoL yielding a 15-dimensional profile and a single index score. Generic HRQoL instruments allow comparisons between various populations and health conditions, a feature essential in directing limited health care resources to treatments expected to bring maximal benefit to patients and society. In its most important properties (reliability, discriminatory power, and responsiveness to change), 15D performance is at least equal to that of similar types of generic HRQoL instruments, and is well validated.[18,19] Having 15 questions with five answer options to each makes it quick and easy to complete; it has been used in studies of HRQoL for various chronic conditions and medical procedures (http://www.15D-instrument.net).

The 15D includes the following 15 dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension involves one question. The single index score (15D score) is calculated from the health-state descriptive system by use of a set of population-based preference or utility weights based on an application of the multi-attribute utility theory. Such a weight for each level of each dimension is obtained by multiplying the level value by

Table 1 The most important diseases conferring entitlement to a special refund under national health insurance.

	Frequency in controls ($n=5662$)	Frequency in IBD patients ($n=2831$)	P (χ^2)	Frequency in females with IBD ($n=1811$)	Frequency in female controls ($n=3622$)	P (χ^2)	Frequency in males with IBD ($n=1020$)	Frequency in male controls ($n=2040$)	P (χ^2)	Frequency in CD ($n=1054$)	Frequency in UC ($n=1661$)	P (χ^2)
Chronic cardiac insufficiency	0.3%	0.5%	NS	0.4%	0.2%	<0.001	0.8%	0.4%	NS	0.4%	0.7%	NS
Connective tissue diseases, rheumatoid arthritis	2.0%	3.9%	<0.001	4.1%	2.4%	<0.001	3,6%	1.5%	<0.001	5.4%	3.0%	0.001
Chronic asthma and obstructive pulmonary diseases	4.3%	7.1%	<0.001	7.7%	4.8%	<0.001	6.1%	3.4%	<0.001	7.0%	7.3%	NS
Chronic hypertension	7.5%	8.1%	NS	7.0%	6.7%	NS	10.1%	9.0%	NS	8.3%	7.7%	NS
Chronic coronary heart disease	1.4%	2.2%	0.004	1.5%	0.8%	0.014	3.4%	2.3%	0.046	2.2%	2.0%	NS
Chronic arrhythmias	0.6%	0.6%	NS	0.4%	0.4%	NS	0.9%	0.9%	NS	0.6%	0.5%	NS
Diabetes mellitus	2.6%	2.3%	NS	1.7%	2.0%	NS	3.2%	3.7%	NS	1.7%	2.3%	NS
Thyroid insufficiency	1.7%	1.9%	NS	2.7%	2.6%	NS	0.5%	0.2%	NS	1.6%	2.0%	NS
Pernicious anemia	0.2%	4.1%	<0.001	4.0%	0.2%	<0.001	4.3%	0.2%	<0.001	10.3%	0.3%	<0.001
Multiple sclerosis	0.2%	0.1%	NS	0.1%	0.2%	NS	0.0%	0.1%	NS	0.0%	0.1%	NS
Epilepsy and comparable convulsive disorders	1.4%	1.1%	NS	0.8%	1.5%	0.024	1.6%	1.2%	NS	0.9%	1.1%	NS
Severe psychotic and other severe mental disorders	2.3%	1.6%	0.023	1.4%	2.2%	0.035	1.8%	2,5%	NS	1.7%	1.4%	NS
Glaucoma	0.7%	0.9%	NS	0.8%	0.8%	NS	1.0%	0.5%	NS	0.9%	0.9%	NS
Cancer or leukemia	0.9%	0.8%	NS	0.8%	0.8%	NS	0.8%	1.1%	NS	0.9%	0.6%	NS

NS, no significant difference between groups; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis. Each P value refers to significancy of differences between the groups in the two previous columns; significances have been calculated with the chi-square method. "Controls" are age and gender matched individuals picked from the National Health Insurance register.

the importance weight of the dimension at that level. The maximum score is 1 (no problems on any dimension) and minimum score 0 (deceased). Subjects with 12 or more completed answers on individual dimensions can be included in the analysis by replacement of missing data with predictions from linear regression analysis based on the other dimensions, with age and gender as independent variables. A difference of ≥ 0.03 in 15D score is considered clinically important in the sense that a person can, on average, feel the difference.[18]

2.2.2. Inflammatory Bowel Disease Questionnaire (IBDQ)

The disease-specific HRQoL was assessed with the IBDQ, a widely used, standardized 32-item questionnaire providing scores describing four different aspects of life (digestive symptoms, social function, emotional status, and systemic symptoms). The IBDQ has good validity for various IBD populations[20–22] and correlates well with clinical activity indices and changes in disease activity.[23,24] Responses are graded on a 7-point scale, with 7 referring to no problems and 1 to extensive problems in that domain. A total IBDQ score, ranging from 32 to 224, is calculated by summing all items, with a higher score indicating better quality of life. The questionnaire was translated into Finnish and into Swedish, Finland's two national languages. Furthermore, a back-translation to English was done by Helsinki University Language Services to confirm the linguistic accuracy of the translation. The IBDQ was used under licence from McMaster University, Hamilton, Canada.

Patients who left five or more questions unanswered were omitted from analysis. Likewise, those who left two or more questions unanswered in one particular domain (bowel symptoms, emotions, social function, or systemic symptoms) were excluded. If only one question in a particular domain went unanswered, the mean score for the other items of the subscore and total IBDQ score were calculated according to answers obtained.

2.3. Statistical analysis

The data were analyzed by the Statistical Package for Social Sciences, Windows version 16.0 (SPSS Inc., Chicago, IL, USA), with results presented as percentages, means, and standard deviations (SD), or medians. Differences in categorical variables between groups were tested with the Chi-square test, and differences of means with ANOVA. The Cox regression model served for examining differences in the occurrences of chronic diseases between IBD patients and their controls, and linear regression for studying the patient characteristics/risk factors for CHD in IBD. Furthermore, partial correlation with matching for age was used for estimating the impact of various chronic diseases on HRQoL scores. A p-value <0.05 was considered significant.

2.4. Ethical considerations

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (registration number 94/E5/06), and it was carried out in accordance with the Declaration of Helsinki. All participants with IBD gave written informed consent. Control patients could not be identified by the data obtained from the national register.

3. Results

3.1. Patient characteristics

Of the 5342 questionnaires mailed, 3 071 (57%) were completed and returned. Of those, 240 were invalid: Two came from patients under 18 years, 20 reported not having IBD (these came from subjects chosen from the patient organization), and 30 had not signed the informed consent. An additional 188 subjects had omitted their social identity numbers, making their reimbursement data unobtainable from the Social Insurance Institute, or had failed to complete the HRQoL questionnaire adequately for calculating the scores. In sum, data from 2831 questionnaires (53% of those mailed) were available for the study. For these, 5662 control patients, matched for age, gender, and hospital district, were selected from the Social Insurance Institution register.

The demographic characteristics of the patients are shown in Table 2. The mean age of the patients was 44.1 (SD 13.4). Weekly symptoms of IBD were reported by 37% of the patients and monthly symptoms by 21%. Forty-one percent reported having symptoms less frequently. Altogether, 29% of the patients had comorbid diseases. The study population was divided into three subgroups by diagnosis: UC, CD, and indeterminate or unspecified colitis (IC). As some of the patients did not report their exact diagnosis, they were classified in the group IC. As the group of IC was considerably smaller than the other two groups, no significant differences between them and their controls existed in frequency of other chronic diseases, and their results are therefore not shown.

3.2. Comorbidity in IBD patients and in controls

The percentages of patients and controls entitled to a special refund for the most important chronic diseases are shown in Table 1. The percentage of control patients having IBD was 0.7%, a percentage proportional to actual occurrence of IBD in the population. A significant increase occurred in prevalence of connective tissue diseases, asthma, and pernicious anemia in IBD patients compared with that of controls, a feature seen especially in patients with CD. The rates of malignant diseases were similar in IBD patients and in their peers.

The most pronounced difference, in addition to connective tissue diseases, chronic pulmonary diseases, and pernicious anemia, appeared for CHD, which occurred significantly more frequently in IBD patients ($p=0.004$). Especially females with IBD appeared to be at increased risk compared with their peers, with a 1.6-fold prevalence of CHD ($p=0.014$). In male IBD patients, the comparable risk for CHD was just significantly increased ($p=0.046$), but it was still over twofold compared to female IBD patients (1.4% versus 3.4%, $p=0.043$ after controlling for age). No significant difference emerged in ages of female CHD patients with or without IBD. In patients diagnosed with IBD at over 50 years of age ($n=299$, current mean age 64 years), the CHD prevalence was 9.7%, with only just significant difference from their peers having prevalence of 6.0% ($p=0.045$). Patients with both IBD and CHD were slightly younger than patients with only CHD (66.2 versus 64.5 years),

Table 2 Patient characteristics.

	All patients ($n=2831$) [a]	Ulcerative colitis ($n=1661$)	Crohn's disease ($n=1054$)
Age (years)			
Range	18–96 [b]	18–84	18–85
Mean (SD)	44.1 (13.4)	44.3 (13.0)	43.7 (13.6)
Median	42	42	41
Gender			
Female	64% ($n=1811$)	62% ($n=1035$)	66% ($n=698$)
Male	36% ($n=1020$)	38% ($n=626$)	34% ($n=356$)
Duration of disease (years)			
Range	0–50	0–50	0–40
Mean (SD)	10.4 (8.2)	10.3 (8.5)	10.7 (7.8)
Median	8	8	9
Frequency of any additional chronic disease	29% ($n=831$)	26% ($n=429$) [c]	35% ($n=367$) [c]
Active disease (symptoms at least weekly) [d]	37% ($n=865$)	36% ($n=427$)	40% ($n=366$)

[a] Includes patients with ulcerative colitis, Crohn's disease and indeterminate colitis ($n=116$).
[b] The oldest patient belonged to the group of indeterminate colitis, data not shown here.
[c] $P<0.001$ for difference between disease groups.
[d] Percentage calculated according to number of the patients answering this question.

but not significantly. The differences in frequencies of chronic diseases between IBD patients and their peers measured with the Cox regression model are shown in Table 3. A linear regression model of patients characteristics as risk factors for CHD showing increased risk for those with active disease and IBD diagnosed at an older age is shown in Table 4. IBD activity was related to prevalence of chronic cardiac insufficiency ($p=0.030$), pernicious anaemia ($p=0.022$), epilepsy ($p=0.010$), and glaucoma ($p=0.007$), as well.

3.3. Chronic diseases, disease activity, and HRQoL

Disease activity had a significant influence on HRQoL scores. Mean IBDQ score for those reporting weekly symptoms of IBD was 138, while it was 178 for those reporting symptoms less frequently than monthly ($p<0.001$). The difference for 15D scores was as marked, 0.824 versus 0.905 ($p<0.001$). Those with most active disease (weekly symptoms) had a higher risk of having other chronic diseases than patients with less active disease ($p=0.028$ between the groups). Even after controlling for disease activity, having other chronic diseases in addition to IBD appeared to impair HRQoL ($p=0.001$). Especially asthma, hypertension, or psychological disorders had a strong negative impact on HRQoL, observed with both the generic and disease-specific HRQoL tools. Table 5 shows the HRQoL scores for diseases with prevalence of 0.5% or more in the study population.

4. Discussion

The data obtained from the reimbursement register can be considered reliable, as the diagnoses of the patients are based on nationally and internationally accepted principles, and it includes practically all patients entitled to reimbursement. The data acquired from this comprehensive national health register showed significantly increased prevalence of CHD in IBD patients compared with their age- and gender-matched peers. One explanation may be the chronic inflammation that accelerates atherosclerosis, a mechanism suspected to lie behind the increased CHD risk in rheumatoid arthritis, as well.[25,26] In some studies, however, no relationship between chronic inflammation and atherosclerosis has been evident after appropriate correction for traditional risk factors.[27–29] We had data for some of the traditional risk factors for atherosclerosis such as hypertension, whereas no data of smoking habits or individual lipid values in index patients or their peers were available due to the nature of the study. In females, lower risk for and later onset of CHD has been evident in large population-based studies.[30,31] According to our findings, risk for CHD was significantly higher in females with IBD than in their peers, but still lower than in males. In males, the relative risk was only just significant, partly explained by the smaller number of male responders. Long-lasting and active IBD was a risk factor for CHD in both sexes.

In some cases, ischemic colitis has been suspected to be diagnosed incorrectly as IBD in elderly patients with underlying atherosclerotic disease.[32] In that case, one would expect the rate of CHD to be significantly higher in those patients diagnosed with IBD in their late middle- or old age. We saw no convincing evidence of this, however.

Table 3 Differences in frequencies of the most important reimbursed chronic diseases in IBD patients and in age and gender matched controls (Cox regression model).

Disease	B	SE	*P*	OR	95% CI	
					lower	upper
Diabetes	−0.218	0.162	0.179	0.804	0.585	1.105
Chronic hypertension	0.132	0.097	0.176	1.141	0.943	1.380
Coronary heart disease	0.633	0.190	0.001	1.883	1.297	2.733
Asthma	0.526	0.100	<0.001	1.693	1.392	2.059
Connective tissue diseases	0.657	0.139	<0.001	1.928	1.468	2.534
Pernicious anemia	3.080	0.317	<0.001	21.757	11.685	40.509
Severe mental disorders	−0.427	0.183	0.020	0.652	0.456	0.934

Table 4 Impact of patient characteristics on risk for coronary heart disease in patients with inflammatory bowel disease (linear regression model).

	B	SE	t	*P*	95% CI for B	
					Lower	Upper
Constant	−0.051	0.008	−5.981	<0.001	−0.067	−0.034
Female gender	−0.005	0.003	−1.530	0.126	−0.010	0.001
Time from diagnosis	0.001	0.000	4.741	<0.001	0.001	0.001
Age at diagnosis	0.002	0.000	14.507	<0.001	0.002	0.002
Disease activity [a]	0.007	0.003	2.356	0.018	0.001	0.013
Diagnosis [b]	0.006	0.003	2.219	0.027	0.001	0.012

Table presents the impact of patient characteristics on coronary heart disease risk, showing increased risk in patients with longer-lasting disease, in patients diagnosed at an older age, in patients with active disease and in patients with Crohn's disease.

[a] Weekly symptoms of inflammatory bowel disease.

[b] Crohn's disease versus ulcerative colitis.

The Social Insurance Institution register comprised 31,703 patients (both children and adults) eligible for reimbursement for IBD medication in 2008; while the total population of Finland is 5.3 million.[17] The 2831 subjects surveyed represent about 9% of Finland's IBD population. The study population comprised patients from all over the country, followed up in various hospitals, instead of a single centre. The response rate of 53% can be considered satisfactory for a postal survey in which no reminders went out.

The weakness of our study is any unknown differences between non-responding and responding IBD patients. Those who returned the questionnaire may have been more aware of their symptoms and of issues concerning HRQoL or have had disease profiles differing from those of non-responders. For example, severe psychological problems may have made completing the questionnaire impossible, which would explain the differing frequency of chronic psychoses or other severe psychological disorders between IBD patients and their controls.

Comorbidity with many other chronic diseases appeared to affect generic, but also disease-specific HRQoL. Active IBD was a risk factor for some of the chronic diseases, which partly explains the impairment of HRQoL in them. Low HRQoL in many dimensions seemed to result from severe psychological disorders in particular. Hypertension is not usually considered to be a heavy burden on one's life, but in this survey, patients suffering from hypertension had even lower 15D scores than had patients with a history of cancer. One confounding factor may be that some patients receiving a special reimbursement for cancer may have completely recovered, and our data gave no details on the state of their disease. Pernicious anemia seemed to be significantly more common in CD than in UC. However, patients with impaired absorption of vitamin B12 (in the National Health register

Table 5 Impact of the most important chronic diseases with reimbursed medication on HRQoL in IBD patients.

	Mean 15D score (SD)	*P* [a]	Mean IBDQ score (SD)	*P* [a]
All patients with IBD (*n*=2831)	0.88		164	
IBD patients with no other chronic disease (*n*=2000)	0.89 (0.085)	<0.001	168 (34.3)	<0.001
IBD with any other chronic disease (*n*=831)	0.84 (0.110)	<0.001	157 (36.2)	<0.001
Chronic cardiac insufficiency (*n*=15)	0.85 (0.095)	NS	165 (25.5)	NS
Connective tissue diseases, rheumatoid arthritis and comparable diseases (*n*=111)	0.86 (0.094)	0.027	165 (33.1)	NS
Chronic asthma and similar obstructive pulmonary diseases (*n*=202)	0.84 (0.109)	<0.001	157 (37.3)	0.004
Chronic hypertension (*n*=230)	0.83 (0.110)	<0.001	152 (35.0)	<0.001
Chronic coronary heart disease (*n*=62)	0.81 (0.107)	0.004	159 (32.2)	NS
Chronic arrhythmias (*n*=16)	0.82 (0.119)	NS	160 (35.0)	NS
Diabetes mellitus (*n*=64)	0.82 (0.120)	0.002	160 (37.1)	NS
Thyroid insufficiency (*n*=54)	0.85 (0.102)	NS	154 (37.0)	NS
Pernicious anaemia (*n*=116)	0.84 (0.111)	0.001	150 (35.5)	<0.001
Epilepsy and comparable convulsive disorders (*n*=31)	0.87 (0.092)	NS	158 (36.7)	NS
Severe psychotic and other severe mental disorders (*n*=44)	0.77 (0.137)	<0.001	139 (35.4)	<0.001
Glaucoma (*n*=25)	0.86 (0.112)	NS	173 (27.4)	NS
Cancer or leukemia (*n*=22)	0.84 (0.139)	0.015	148 (43.1)	NS
Severe hypofunction of reproductive glands (*n*=26)	0.83 (0.115)	NS	155 (38.2)	NS

[a] Partial correlation estimated with matching for age. Comparison has been made between all IBD patients and IBD patients with the disease referred to. HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire.

equivalent to pernicious anemia) may in fact be patients with a history of intestinal resections causing postoperative impairment of B12 absorption.

The increased prevalence of CHD in IBD patients is an interesting finding in IBD encouraging more efficacious management of underlying cardiovascular risk factors (e.g. smoking and hypertension) and probably also of the inflammatory activity. Especially in females, the increased risk for cardiovascular diseases should be borne in mind. Furthermore, health-care personnel should be aware of the negative impact of comorbid diseases on HRQoL in IBD patients.

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