Association of fibromyalgia with cancerous and non-cancerous gastrointestinal comorbidities: a cross-sectional study

E. Savin[1,2], A.M. Tsur[1-3], A. Watad[1,2], O. Gendelman[1,2], U. Kopylov[2,4], A.D. Cohen[5,6], H. Amital[1,2]

[1]Department of Medicine B, Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv; [3]Israel Defense Forces, Medical Corps, Tel Hashomer; [4]Department of Gastroenterology, Sheba Medical Center, Tel Hashomer; [5]Chief Physician's Office, Clalit Health Services, Tel Aviv; [6]Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel.

Abstract

Objective

Several studies have shown a higher prevalence of irritable bowel syndrome (IBS) among patients with fibromyalgia yet, data regarding association between fibromyalgia and other gastrointestinal disorders have been relatively overlooked. Our aim was to investigate the association between fibromyalgia and gastrointestinal disorders including both benign and malignant conditions.

Methods

We conducted a retrospective cross-sectional study based on the comprehensive electronic database of the largest health maintenance organisation in Israel. All subjects with a diagnosis of fibromyalgia in their medical records and age- and sex-matched controls were included in the study. We investigated the association of fibromyalgia with benign gastrointestinal disorders including IBS, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), coeliac disease, Crohn's disease, ulcerative colitis, and with gastrointestinal malignancies including colorectal, pancreatic, stomach, liver, and bile duct cancers.

Results

The study enrolled 18,598 patients with fibromyalgia and 36,985 controls. The mean age was 56.5 years (standard deviation=14) with a female predominance (91%). Fibromyalgia was significantly associated with IBS (OR 4.61, 95% CI 4.09-5.2, p<0.001), GERD (OR 2.62, 95% CI 2.5-2.75, p<0.001), PUD (OR 2.13, 95% CI 1.98-2.3, p<0.001), coeliac disease (OR 2.08, 95% CI 1.63-2.65, p<0.001), Crohn's disease (OR 1.85, 95% CI 1.408-2.32, p<0.001) and ulcerative colitis (OR 1.81, 95%CI 1.4-2.33, p<0.001). Nonetheless, no significant differences were found regarding the prevalence of gastrointestinal malignancies between the fibromyalgia patients and controls.

Conclusion

Our findings suggest that FM is positively associated with various benign but not malignant GI disorders.

Key words

fibromyalgia, pain, irritable bowel syndrome, gastrointestinal diseases

Einat Savin, MD,
Avishai M. Tsur, MD, MHA
Abdulla Watad, MD
Omer Gendelman, MD
Uri Kopylov, MD
Arnon D. Cohen, MD, PHD
Howard Amital, MD, MHA

Please address correspondence to:
Howard Amital
Department of Medicine B,
Sheba Medical Center,
Tel Hashomer 5262100, Israel.
E-mail:
howard.amital@sheba.health.gov.il

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Introduction

Fibromyalgia (FM) is a chronic musculoskeletal disorder, in which pain is the fundamental feature, frequently accompanied by a wide array of additional symptoms such as fatigue, sleep, cognitive and mood disturbances (1, 2). The prevalence of FM is estimated as 2% of the general population with a striking female predominance (3). The pathogenesis of FM is unclear, however a complex interplay between genetic and environmental factors have been postulated as the most plausible mechanism (4).

Gastrointestinal (GI) symptoms are commonly encountered among FM patients (5), as described initially by Triadafilopoulos *et al*. (6), among 123 FM patients 73% reported bowel dysfunction, and 63% had an alternating periods of diarrhoea and constipation, compared with none in the healthy controls ($p<0.001$). Irritable bowel syndrome (IBS) is strongly associated with FM, as it has been reported by Yang *et al*. (7) in a study based on the Taiwan nationwide database, patients with FM had an increased incidence of IBS compared with controls, 7.47 *versus* 4.42 per 1000 person-years (hazard ratio [HR]=1.69 95% confidence interval (CI) 1.59–1.79). Nevertheless, the relation between FM and other non-cancerous GI disorders such as inflammatory bowel disease (IBD) is controversial and underexplored.

Few studies that have investigated malignancies in FM patients observed no significant associations (8,9). Although, McBeth *et al*. (10) demonstrated that patients with widespread pain fulfilling the criteria for FM had an increased incidence of breast cancer (internal rate of return [IRR] 3.67, 95% CI 1.39–9.68), prostate cancer (IRR 3.46, 95% CI 1.25-9.59) and large bowel cancer (IRR 2.35, 95% CI 0.96–5.77) at 9 years follow-up. Given the limited extent of the data, we aimed to investigate the association between FM and GI disorders including benign and malignant conditions by using the database of the largest health maintenance organisation in Israel.

Methods

Study design

This is a retrospective cross-sectional study based on the comprehensive electronic database of Clalit Health Services (CHS), which is the largest health maintenance organisation in Israel, serving approximately 4.6 million people. CHS holds a centralised computerised database continuously collecting pharmaceutical, clinical, and administrative data of hospital and primary care physicians' encounters of all members. The diagnoses are documented by either a primary care physician or specialist using the International Classification of Diseases (ICD). The data is systematically verified and was found to be highly creditable in previous studies (11, 12), including study that investigated the association between FM and diabetes mellitus (13). The Ethics Committee of the CHS approved this study and waived the requirement for informed consent.

Study population

All subjects with a diagnosis of FM in their medical records, ICD 9th revised (ICD-9) code 729.1, either given by a specialist or community physician, included in the study. Controls were randomly matched from the CHS electronic database in a 1:2 ratio by age and sex.

Study variables

Demographic data including age, sex, body mass index (BMI), smoking status, and socioeconomic status (SES) were obtained from the CHS electronic database. SES was defined based on the location of residence and was obtained from records of the Israeli Ministry of Interior, as previously described (12). GI diagnoses were identified using the following ICD-9 codes: IBS (564.1), gastroesophageal reflux disease (GERD) (530.81, 530.11, 530.10), peptic ulcer disease (PUD) (531, 532, 533), coeliac disease (579.0), Crohn's disease (555.0-555.2, 555.9), ulcerative colitis (556), colorectal cancer (153, 154), stomach cancer (151), liver and bile duct cancer (155) and pancreatic cancer (157).

Statistical analysis

Data analysis was performed using R version 4.0.2 (R Core Team, Vienna, Austria). Categorical variables were presented as n (%) and compared using the chi-square test of independence,

continuous variables as mean (standard deviation [SD]) and compared using student's t-test. Logistic regression models were used to determine the odds ratio (OR) between FM and GI disorders. All tests used were two-tailed, with *p*-values <0.05 considered to be statistically significant. The models were adjusted for age, sex, BMI, SES, and smoking status.

Results

The study included 18,598 patients with FM and 36,985 age- and sex-matched controls. The mean age was 56.5 years (SD=14) with a female predominance (91%). Smoking status was significantly higher among FM patients compared with the controls (37% *vs*. 30% respectively, *p*<0.001) as well as BMI (29.07 *vs*. 28.14 respectively, *p*<0.001). Most patients in FM and control groups were at low (45%) or medium (39%) SES (Table I).

Non-malignant GI disorders

FM patients had a higher prevalence of IBS (4.8 *vs*. 1.1%, *p*<0.001), GERD (24.9 *vs*. 11.2%, *p*<0.001), PUD (8.2 *vs*. 4.0%, *p*<0.001), coeliac disease (0.7 *vs*. 0.4%, *p*<0.001), Crohn's disease (0.8 *vs*. 0.4%, *p*<0.001), and ulcerative colitis (0.6 *vs*. 0.4%, *p*<0.001), compared with matched controls (Table II). In univariate and adjusted multivariate logistic regression, FM was significantly associated with IBS (OR 4.61, 95% CI 4.09–5.2, *p*<0.001), GERD (OR 2.62, 95% CI 2.5–2.75, *p*<0.001), PUD (OR 2.13, 95% CI 1.98–2.3, *p*<0.001), coeliac disease (OR 2.08, 95% CI 1.63–2.65, *p*<0.001), Crohn's disease (OR 1.85 95% CI 1.48–2.32, *p*<0.001) and ulcerative colitis (OR 1.81, 95% CI 1.4–2.33, *p*<0.001) (Table III and Fig. 1).

Malignant GI disorders

There was no difference between the groups in the occurrence of GI malignancies including, colorectal, stomach, liver, bile duct and pancreatic cancers (Table II). Univariate and multivariate adjusted logistic regression did not demonstrate statistical differences between FM patients and controls (Table III and Fig. 1).

Table I. Characteristics of study population stratified by fibromyalgia and control groups.

Characteristic	FM (n=18,598)	Control (n=36,985)	*p*-value
Age	56.5 (14.1)	56.5 (14.1)	0.758
Female gender (%)	16,920 (91)	33,651 (91)	0.975
BMI	29.07	28.14	<0.001
Smoking (%)	6,913 (37)	11,106 (30)	<0.001
SES (%)			0.973
Low	8,414 (45.3)	16,770 (45.4)	
Medium	7,168 (38.6)	14,235 (38.6)	
High	2,985 (16.1)	5,918 (16)	

Data are n (%) or mean (standard deviation).
FM: fibromyalgia; BMI: body mass index (kg/m^2); SES: socioeconomic status.

Table II. Prevalence of the investigated gastrointestinal disorders among fibromyalgia and control groups.

Disease	FM (n=18,598)	Control (n=36,985)	*p*-value
IBS	896 (4.8%)	404 (1.1%)	<0.001
GERD	4,637 (24.9%)	4,157 (11.2%)	<0.001
Peptic ulcer disease	1,522 (8.2%)	1,470 (4.0%)	<0.001
Coeliac disease	138 (0.7%)	137 (0.4%)	<0.001
Crohn's disease	154 (0.8%)	157 (0.4%)	<0.001
Ulcerative colitis	118 (0.6%)	133 (0.4%)	<0.001
Colon and rectal cancer	177 (1.0%)	362 (1.0%)	0.759
Stomach cancer	18 (0.1%)	29 (0.1%)	0.482
Liver/ Bile duct cancer	7 (0.0%)	22 (0.1%)	0.287
Pancreatic cancer	18 (0.1%)	23 (0.1%)	0.156

Data are n (%). FM: fibromyalgia; IBS: irritable bowel syndrome; GERD: gastroesophageal reflux disease.

Table III. Univariate and multivariate logistic regression of the association between fibromyalgia and gastrointestinal disorders. Adjusted for age, sex, body mass index, smoking and socioeconomic status (n=55,583).

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p*-value
IBS	4.58	4.07-5.17	<0.001	4.61	4.09-5.2	<0.001
GERD	2.62	2.5-2.75	<0.001	2.62	2.5-2.75	<0.001
Peptic ulcer disease	2.15	2-2.32	<0.001	2.13	1.98-2.3	<0.001
Coeliac disease	2.01	1.59-2.55	<0.001	2.08	1.63-2.65	<0.001
Crohn's disease	1.96	1.57-2.45	<0.001	1.85	1.48-2.32	<0.001
Ulcerative colitis	1.77	1.38-2.27	<0.001	1.81	1.4-2.33	<0.001
Colon and rectal cancer	0.97	0.81-1.16	0.759	0.95	0.79-1.14	0.567
Stomach cancer	1.23	0.67-2.2	0.483	1.15	0.62-2.08	0.642
Liver/bile duct cancer	0.63	0.25-1.41	0.291	0.62	0.24-1.39	0.272
Pancreatic cancer	1.56	0.83-2.88	0.160	1.59	0.84-2.94	0.144

OR: odds ratio; CI: confidence interval; IBS: irritable bowel syndrome; GERD: gastroesophageal reflux disease.

Discussion

This study found that FM patients have a higher prevalence of benign, but not malignant, GI disorders compared with matched controls. Moreover, FM was found to have a positive association with the benign GI disorders, these findings persisted after adjusting for potential confounders. The FM cohort in our study is consistent in terms of age, female to male ratio, BMI and smoking status with previous reports (3, 14, 15).

Previous studies that investigated the association between FM and chronic disorders, found that FM patients were more likely to suffer from the following conditions: Rheumatoid arthritis, systemic lupus erythematosus, anxiety, depression, chronic fatigue syn-

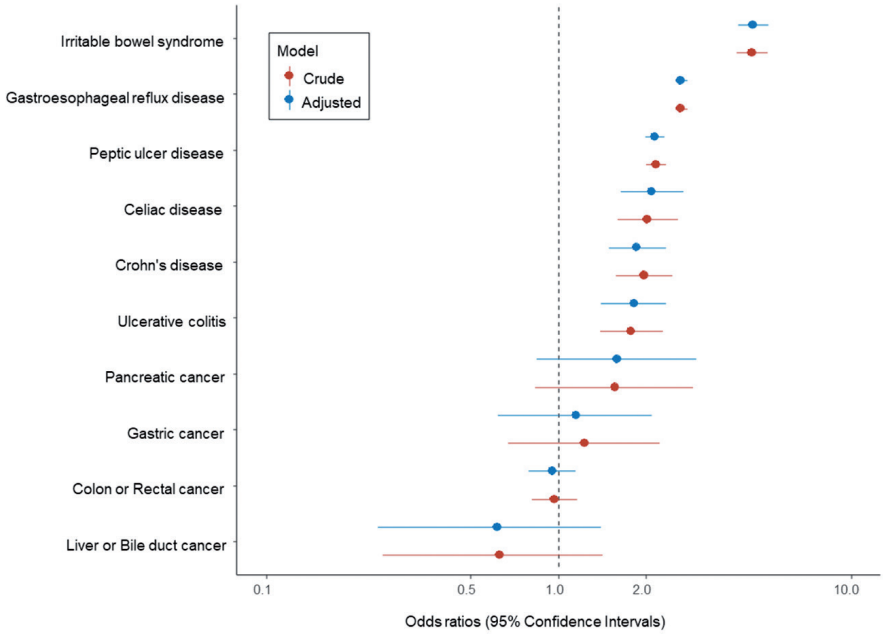

Fig. 1. Forest plot of fibromyalgia odds ratio for gastrointestinal disorders. Adjustment included age, sex, body mass index, smoking and socioeconomic status.

drome, and IBS (16-20). Indeed, IBS is strongly associated with FM, as it has been reported by Yang *et al*. (7), FM patients had an increased incidence of IBS compared with the controls, 7.47 *vs*. 4.42 per 1000 person-years (HR= 1.69, 95% CI 1.59–1.79). IBS was found to be firmly associated with FM in our study (OR 4.58) with an overall prevalence of 4.8%. This finding is somehow lower compared to previous cross-sectional studies, ranging from 20% to 80% (21-23). Such differences are attributed to the methodological differences across studies and the classification criteria applied for the diagnosis of IBS.

Consistent with our results, previous studies that investigated the correlation of FM with GERD and PUD, based on Taiwanese nationwide database, demonstrated a bidirectional relationship between FM and GERD (24), as well as higher incidence of PUD in FM patients compared with the controls (25). Controversy exists regarding the association between FM with IBD or coeliac disease. Palm *et al*. (26) observed no difference in the prevalence of FM in IBD patients compared to the general population while Buskila *et al*. (27) demonstrated a higher prevalence of FM (30%, p=0.001) in Israeli patients with IBD compared with healthy controls. IBD was also found to be a risk factor for develop FM based on a large population cohort study, with a higher risk found in male IBD patients and the greatest risk occurred in age below 39 years (28). A previous small study showed that the overall prevalence of coeliac disease in FM patients was identical to the general population (~1%) (29), nevertheless patients with coeliac are prone to develop FM (30). Given the insufficient and non-consistent previous data, our cross-sectional study including 18,598 FM patients indicate a significant association between FM and these benign GI disorders.

Few studies have investigated malignancies in FM patients with limited conclusions. McBeth *et al*. (10) demonstrated that widespread pain according to the American College of Rheumatology 1990 criteria for FM (31) is associated with an increased incidence of large bowel cancer in a 9 years follow-up, among men 0.9 per 1,000 person-years, and among women 0.6 per 1,000 person-years (IRR 2.35, 95% CI 0.96–5.77). In addition, Eyigor *et al*. (32) reported a higher prevalence of FM diagnosis (10.7%) among hospitalised cancer patients compared to the general population. However, the GI malignancies that were investigated in our study were not found to be associated with FM. Similar to our results, Wolfe *et al*. (8) observed no significant association between FM and malignancies, and Dreyer *et al*. (9) concluded there is no higher incidence of cancer among patients fulfilling the criteria for FM.

We suggest that the observed association between multiple benign GI disorders and FM is best explained by multifactorial mechanisms involving psychosocial factors and bi-directional gut-brain interactions. Psychosocial factors and previous stressful life events have been associated with FM pathogenesis (33). Acute and chronic stressful life events were also associated with the onset or exacerbation of GI disorders including IBD, IBS, GERD and PUD (34-36). The pathophysiology is assumed with Gut-Brain axis and hypothalamic pituitary adrenal (HPA) axis. Stress input to the brain activates the HPA axis, which produce secretion of corticotrophin releasing factor (CRF) in the hypothalamus, with receptors expressed in the brain and the gut. CRF has a potent effect on the gut including enteric peristalsis, increased gut permeability, elevated visceral hypersensitivity, and increased perception of pain. Stressful life events have been shown to cause permanent hypersecretion of CRF as well as alternation in sympathetic and HPA axis (34, 37, 38). Gut-Brain axis is bi-directional; the gut communicates with the central nervous system (CNS), affecting pain regulation and inhibiting hypersensitivity. The gut flora communicates with the CNS via the enteric nervous system using direct or indirect interactions by alterations of neurotransmitters and cytokines levels (35). Significant alternation in gut microbiome of FM patients compared with controls have been described by Minerbi *et al*. (39), which also observed an association between several taxa and FM severity. Clos-Gracia *et al*. (40) found reduced gut microbiome diversity in FM patients and alters serum metabolomics.

Our study has several strengths; to our knowledge, this is one of the largest studies that investigated GI comorbidities in FM patients. In addition, the population-based design and the choice of match controls reduce the risk of bias.

However, this study does have several limitations given its retrospective cross-sectional nature, which limits any conclusions about the relative risk of developing GI disorder in FM patients. Moreover, this study lacks information regarding temporality, and the information concerning the criteria for diagnosing the various diseases was unavailable. However CHS data are systematically verified and was found to has high validity in earlier studies (11-13).

Conclusion

Our findings suggest that FM is positively associated with various benign but not malignant GI disorders, further prospective studied are required to explore this association and validate our results.

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