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An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms

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Abstract Fibromyalgia syndrome is characterized by chronic generalized pain accompanied by a broad symptomatologic spectrum. Besides chronic fatigue, sleep disturbances, headaches and cognitive dysfunction that are extensively described in the literature, a considerable proportion of patients with fibromyalgia experience gastrointestinal symptoms that are commonly overlooked in the studies that are not specifically dedicated to evaluate these manifestations. Nevertheless, various attempts were undertaken to explore the gastrointestinal dimension of fibromyalgia. Several studies have demonstrated an elevated comorbidity of irritable bowel syndrome (IBS) among patients with fibromyalgia. Other studies have investigated the frequency of presentation of gastrointestinal symptoms in fibromyalgia in a nonspecific approach describing several gastrointestinal complaints frequently reported by these patients such as abdominal pain, dyspepsia and bowel changes, among others. Several underlying mechanisms that require further investigation could serve as potential explanatory hypotheses for the appearance of such manifestations. These include sensitivity to dietary constituents such as gluten, lactose or FODMAPs or alterations in the brain–gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis. The gastrointestinal component of fibromyalgia constitutes a relevant element of the multidisciplinary pathophysiologic mechanisms underlying fibromyalgia that need to be unveiled, as this would contribute to the adequate designation of relevant treatment alternatives corresponding to these manifestations.

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Introduction

Fibromyalgia syndrome, a chronic musculoskeletal disorder, is characterized by a complex nature and a wide array of symptoms and signs. Chronic generalized musculoskeletal pain, whose underlying cause is unclear, represents the cardinal symptom that defines fibromyalgia [1]. In addition to widespread pain, chronic fatigue and sleep disturbances complement the hallmark triad of the core symptoms of fibromyalgia [2]. Wider range of manifestations can be also seen among patients with fibromyalgia including morning stiffness, headaches, balance problems, cognitive dysfunction (forgetfulness and poor concentration), sexual dysfunction, dysesthesia and psychologic distress (anxiety and depression) [3]. Currently, the diagnosis of fibromyalgia is established based on a clinical evaluation of patients. Diagnostic criteria were first formulated by the American College of Rheumatology (ACR) in 1990 [4] and were later modified in 2010 [5].

While the current evidence does not provide definite conclusions regarding the etiology of fibromyalgia, several biological and psychosocial factors have been suggested [6]. It is known that fibromyalgia develops in genetically predisposed individuals with an evidence of a strong familial aggregation [7]. With respect to the environmental factors, several physical and psychologic triggers are involved such as mechanical and physical trauma, psychologic distress, sexual abuse, and certain infections including hepatitis C virus, human immunodeficiency virus and Lyme disease [8, 9].

The precise pathophysiologic mechanisms underlying fibromyalgia are not fully understood. Alteration in pain

processing reflected in a well-documented decrease of pain threshold among patients with fibromyalgia has been reported [10]; this observation has been associated to the dysfunction of the descending inhibitory pathways [11], central nervous system sensitization and glial cells activation [12]. Alterations in the neuroendocrine function of the hypothalamic–pituitary–adrenal axis (HPA) and dysfunction in the autonomic nervous system [13] have been also identified as essential elements in the composite of underlying mechanisms contributing to fibromyalgia development.

Fibromyalgia is currently classified under the group of syndromes known as central sensitivity disorders [14], which were previously referred to as functional somatic syndromes [15] or medically unexplained somatic symptoms [16]. Central sensitivity syndromes encompass overlapping conditions that share common features of central sensitization which is characterized by abnormal and intense enhancement of pain perception manifested as hyperalgesia, allodynia and receptive field expansion [14]. In addition to fibromyalgia, central sensitivity disorders comprise multiple disorders such as chronic fatigue syndrome, irritable bowel syndrome (IBS), temporomandibular joint dysfunction and tension headache, among others [17].

This common designation describing these disorders is further supported by the high rate of comorbidity among them indicating a sort of mutual association. Increased prevalence of fibromyalgia is reported among patients with chronic fatigue syndrome (55 %), IBS (40.7 %), primary headaches (26.3 %) and temporomandibular disorder (23.7 %) [18]. Conversely, in a large retrospective study, patients with fibromyalgia seemed to be 2–7 times more prone to suffer from headaches, IBS, chronic fatigue syndrome, depression, anxiety, systemic lupus erythematosus and rheumatoid arthritis [19].

In addition to the comorbidity with IBS, many patients with fibromyalgia exhibit nonspecific gastrointestinal manifestations that, despite being very frequent, are commonly overlooked and not granted sufficient attention in the literature as compared to other manifestations of fibromyalgia. Accordingly, the aim of the current review is to explore the gastrointestinal dimension of fibromyalgia and to discuss the underlying mechanisms that might explain the occurrence of such symptoms.

Fibromyalgia and the gastrointestinal component

The frequent presence of gastrointestinal symptoms among patients with fibromyalgia has been reported in several studies that are summarized in Table 1 [4, 5, 19–48]. The initial description of these manifestations in fibromyalgia began as being part of clinical studies exploring the global clinical characteristics of this syndrome where these manifestations were commonly referred to as "IBS symptoms" [20–23]. The suspicion of an underlying role of IBS in fibromyalgia led to the subsequent investigation of the comorbidity between these two conditions in several studies [19, 24–33]. On the other hand, some of the gastrointestinal manifestations experienced by patients with fibromyalgia such as nausea, vomiting and dyspepsia [34] are unrelated with IBS. Thus, other studies have evaluated the frequency of occurrence of other gastrointestinal manifestations in a nonspecific approach [34–37].

Fibromyalgia and irritable bowel syndrome: resemblance and divergence

The resemblance between the two syndromes is not limited to the overlapping manifestations that have been already highlighted. Both fibromyalgia [49] and IBS [50] are linked to an increased prevalence among females. Akkuş et al. [51] attributed this elevated prevalence of IBS among females to coexisting fibromyalgia. However, a meta-analysis conducted by Lovell et al. [52] showed only a modest predominance of IBS among females (OR 1.67, 95 % CI 1.53–1.82). Similarly, in fibromyalgia, the female predominance can be lower and less striking to what has been previously reported; a recently published study found a 2.4 % prevalence of fibromyalgia in females compared to 1.8 % in males [53].

In a review article, Chang [54] details several grounds to support the claim of a common etiology for fibromyalgia and IBS. These include the common features shared by the two syndromes such as the exacerbation of symptoms with stressful life events, the complaints of disturbed sleep and fatigue by the majority of patients, the efficacious treatment of symptoms through psychotherapy and behavioral therapies in addition to the improvement of the IBS symptoms with low doses of tricyclic antidepressants. On the other hand, differences exist between the two conditions, as distinctive responses to somatic and visceral stimuli are reported [54]. While the response to mechanical stimuli is manifested as somatic hyperalgesia in fibromyalgia, patients with IBS without coexistent fibromyalgia exhibit a different response of somatic hypoalgesia [54]. Moreover, differing perceptual alterations between patients with IBS and those with fibromyalgia have been documented in visceral distention studies [54]. This perceptual difference was further confirmed in a study conducted by Caldarella et al. [55], where rectal distensions generated hypersensitivity among patients with IBS and those with coexistent IBS and fibromyalgia; on the contrary, patients presenting with only fibromyalgia tolerated all distensions without discomfort. This finding suggests the presence of multiple mechanisms

Table 1 Summary of clinical studies investigating the gastrointestinal manifestations in fibromyalgia

Author (year)	Design comparison (gender distribution)	Objective(s)	Diagnostic criteria	*Outcome measure(s)* and main findings
Yunus et al. [20]	Cross-sectional FM: $n = 50$ (43 women/7 men) versus age, sex and race matched healthy controls: $n = 50$ (43 women/7 men)	To describe the clinical features of fibromyalgia	FM—smythe criteria [38]	*GI symptoms*: 34 % of patients with FM versus 8 % of controls ($p < 0.01$)
Campbell et al. [21]	Cross-sectional Fibrositis: $n = 22$ (16 women/6 men) versus age, sex, clinic-matched patients without fibrositis: $n = 22$ (16 women/6 men)	To examine the prevalence and nature of fibrositis symptoms	FM—questionnaire designed by the authors IBS—determined by the examiner	*IBS symptoms*: 50 % of patients with fibrositis versus 5 % in controls
Bengtsson et al. [22]	Cross-sectional PF: $n = 55$ (53 women/2 men) versus RA: $n = 30$ (29 women/1 men)	To investigate the clinical symptomatology of patients with FM compared to those with RA	PF—Yunus et al. criteria [20]	*IBS symptoms*: 44 % of patients with PF versus 43 % of patients with RA
Goldenberg [23]	Cross-sectional FM: $n = 118$ (103 women/15 men)	To evaluate the clinical manifestations of FM and to study the recent efforts to establish diagnostic criteria	FM—criteria set by the author	*IBS symptoms*: 53 % of patients with FM
Weir et al. [19]	Retrospective FM: $n = 2{,}595$ (1,689 women/906 men)	To study the association between FM and other comorbid conditions	FM—identified using the ICD-9-CM code 729.1 IBS—identified using the ICD-9-CM code 564.1	*Risk ratio of IBS*: Women with FM were 4.45 times more likely to have IBS compared to 3.96 times in men with FM
Romano TJ [24]	Cross-sectional PF: $n = 100$ (70 women/30 men) versus SF: $n = 100$ (79 women/21 men) versus patients with arthritic diseases: $n = 100$ (67 women/33 men)	To estimate the prevalence of IBS in primary and secondary fibromyalgia	FM—questionnaire designed by the authors IBS—Kruis et al. criteria [39]	*IBS diagnosis*: 49 % of patients with PF versus 19 % of patients with SF and 9 % of patients with arthritic diseases
Veale et al. [25]	Cross-sectional PF: $n = 20$ (15 women/5 men) versus IBS: $n = 20$ (16 women/4 men) versus IA: $n = 20$ (13 women/7 men) versus IBD: $n = 20$ (10 women/10 men) versus healthy control: $n = 20$ (10 women/10 men)	To compare the prevalence of PF in IBS patients and that of IBS in patients with PF to both healthy and disease control groups	FM—smythe criteria [40] IBS—set by the examiners	*IBS Prevalence*: 70 % among patients with PF versus 10 % in the three control groups *PF Prevalence:* 65 % among patients with IBS versus 12 % in the three control groups
Hudson et al. [26]	Cross-sectional FM: $n = 33$ women	To assess the association of FM with medical (including IBS) and psychiatric disorders	FM—ACR 1990 criteria [4] IBS—supplemental interview for forms of "Affective Spectrum Disorder" [41]	*Current and life-time diagnoses of IBS* were seen in 39 % and 52 % of patients with FM, respectively
Wolfe et al. [27]	Cross-sectional A random sample of 3,006 subjects (2,738 women/268 men)	To determine the prevalence and characteristics of FM	FM—ACR 1990 criteria [4]	*FM prevalence*: 2 % of the general population *IBS prevalence*: 47.5 % of patients with FM

Table 1 continued

Author (year)	Design comparison (gender distribution)	Objective(s)	Diagnostic criteria	*Outcome measure(s)* and main findings
Sivri et al. [28]	Cross-sectional FM: $n = 75$ (65 women/10 men) versus healthy controls: $n = 50$ (39 women/11 men)	To determine the prevalence of GI symptoms suggestive of IBS among patients with FM compared to healthy controls	FM—ACR 1990 criteria [4] IBS—Drossman et al. [42]	*IBS prevalence*: 41.8 % of patients with FM versus 16 % of controls ($p < 0.05$)
Sperber et al. [29]	Cross-sectional (2 studies: IBS study and FM study) IBS study: 79 patients with IBS (61 women/18 men) versus 72 controls of the general population (54 women/18 men) FM study: $n = 100$ women	*IBS study:* To estimate the prevalence of FM among patients with IBS and matched controls by age and gender *FM study:* To estimate the prevalence of IBS among patients with FM	FM—ACR 1990 criteria [4] IBS—Rome I criteria [43]	*IBS study (FM prevalence):* 31.6 % of patients with IBS were diagnosed with FM versus 4.2 % of controls ($p < 0.001$) *FM study (IBS prevalence):* 32 % of patients with FM were diagnosed with IBS
Aaron et al. [30]	Cross-sectional FM: $n = 22$ versus CFS: $n = 25$ versus TMD: $n = 25$ versus healthy controls: $n = 22$	To describe the frequency of comorbid illnesses among patients with CFS, FM and TMD compared with healthy controls	FM—ACR 1990 criteria [4] IBS—Manning 1978 criteria [44]	*IBS prevalence*: 77 % of patients with FM versus 18 % of healthy controls ($p < 0.001$)
Lubrano et al. [31]	Cross-sectional IBS: $n = 130$ (75 women/55 men)	To evaluate the prevalence of FM among IBS patients To assess the possible association between FM with the type and severity of IBS	FM—ACR 1990 criteria [4] IBS—Rome-1 criteria [45]	*FM Prevalence*: Diagnosed among 20 % of patients with IBS *Association between FM and IBS*: Type of IBS: no statistical association ($p = 0.426$) Severity of IBS: significant association ($p = 0.004$)
Kurland et al. [32]	Cross-sectional FM: $n = 105$ (98 women/7 men) versus controls with arthritic diseases: $n = 62$ (43 women/19 men)	To determine the prevalence of IBS among patients with FM	FM—ACR 1990 criteria [4] IBS—Rome I and Rome II criteria [46]	*IBS Prevalence*: 63 % of patients with FM using Rome I and 81 % using Rome II criteria versus 15 % and 24 % in controls, respectively ($p < 0.001$)
Cole et al. [33]	Retrospective IBS: $n = 97{,}593$ (70,475 women/27,118 men) versus non-IBS: $n = 27{,}402$ (14,170 women/13,232 men)	To compare the prevalence of FM between subjects with and without IBS	FM—identified based on medical and prescription claims relating to FM IBS—identified using the ICD-9 CM code 564.1	*Prevalence OR of FM*: 1.8 times greater in IBS compared to that of control subjects (95 % confidence interval: 1.7—1.9)
Pamuk et al. [34]	Cross-sectional FM: $n = 152$ women versus age-matched controls: RA: $n = 98$ women and health subjects: $n = 60$ women	To compare the frequency and severity of GI symptoms To compare disturbances in dyspepsia-related QOL	FM—ACR 1990 criteria [4]	*Frequency of Symptoms*: Higher frequencies of belching, reflux, bloating, sour taste and vomiting were seen among patients with FM ($p < 0.01$) *Disturbances in the dyspepsia-related QOL*: Significantly higher among patients with FM ($p < 0.01$)

Table 1 continued

Author (year)	Design comparison (gender distribution)	Objective(s)	Diagnostic criteria	*Outcome measure(s)* and main findings
Triadafilopoulos et al. [35]	Cross-sectional FM: $n = 123$ (113 women/10 men) versus DJD: $n = 54$ (49 women/5 men) versus healthy control: $n = 46$ (40 women/6 men)	To determine the prevalence of GI symptoms in patients with FM compared to patients with DJD and healthy controls	FM—Smythe criteria [47]	*Altered bowel function:* 73 % of patients with FM versus 37 % of patients with DJD and 0 % of healthy controls
Tüzün et al. [36]	Cross-sectional FM: $n = 33$ women versus MPS: $n = 33$ women versus controls with minor illnesses: $n = 33$ women	To compare the quality of life scores of patients with FM and patients with MPS	FM—ACR 1990 criteria [4]	*Gastrointestinal discomfort*: 81.8 % of patients with FM versus 51.5 % and 45.5 % of MPS and controls, respectively
Almansa et al. [37]	Cross-sectional FM: $n = 100$ (93 women/7 men) versus age and sex-matched controls of the general population: $n = 100$ (93 women/7 men)	To evaluate the prevalence of FGIDs in patients with FM To investigate the possible role of psychologic factors in the relationship between FM and FGIDs	FM—ACR 1990 criteria [4] IBS—Rome II criteria [48] Psychologic distress—Symptom Checklist-90 Revised (SCL-90R)	*FGIDs prevalence*: 98 % prevalence of at least one FGID in FM group versus 39 % of controls In FM group, strongest association was seen with IBS (prevalence 39 %, 95 % CI 29.4–48.6) *Psychologic factors*: Significantly higher SCL-90R scores in FM compared to controls Significant association with the presence of different FGIDs

CFS chronic fatigue syndrome, *DJD* degenerative joint disease, *FGIDs* functional gastrointestinal disorders, *FM* fibromyalgia, *GI* gastrointestinal, *IA* inflammatory arthritis, *IBD* inflammatory bowel disease, *IBS* irritable bowel syndrome, *ICD-9 CM* International Classification of Diseases, 9th Revision, Clinical Modification, *MPS* myofascial pain syndrome, *OR* odd ratio, *PF* primary fibromyalgia, *QOL* quality of life, *RA* rheumatoid arthritis, *SCL-90R* Symptom Checklist-90 Revised; *SF* secondary fibromyalgia; *TMD* temporomandibular disorder

that modulate perceptual somatic and visceral responses in these two conditions [55].

Potential responsible pathophysiologic mechanisms

The pathophysiologic mechanisms underlying gastrointestinal symptoms in patients with fibromyalgia remain unexplained. In the following section of this review, two potential mechanisms that could possibly explain the appearance of such manifestations are detailed. These mechanisms include the following: sensitivity to food components and alteration in the brain–gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis.

Hypersensitivity to food components

A considerable percentage of patients with fibromyalgia believe that dietary interventions have a great influence on the disease symptoms and perceive symptomatic aggravation as being secondary to the intake of specific foods [56]. Accordingly, a general tendency exists among these patients toward adopting dietary interventions, such as elimination diets or dietary supplements, in order to attain better symptomatic control. Modifications of the dietary habits have been shown to be adopted by up to 30 % of patients with fibromyalgia [57]; these authors also found that 7 % of the patients reported to have been diagnosed of food allergy or intolerance. Conversely, symptoms suggestive of fibromyalgia were found in the 71 % of a sample of 84 patients experiencing perceived food hypersensitivity (mainly to bread, milk and fruits) [58]. In a recent study investigating food allergy in fibromyalgia, 49 % of cases reported the presence of food allergy and 66 % of them reported the appearance of symptoms with milk, wheat and orange [59]. The most relevant types of food-related disturbances and their potential relationship with fibromyalgia are discussed below.

Celiac disease

Celiac disease, a systemic autoimmune disorder caused by permanent gluten intolerance, primarily affects genetically predisposed individuals. It is characterized by chronic inflammation of the small intestine mucosa secondary to gluten intake [60]. According to the recently published Oslo definitions, celiac disease exists in several forms such as the classical, non-classical or monosymptomatic, silent, subclinical, overt, refractory and latent forms [61]. The classical clinical presentation is mostly seen among children, whereas adult celiac patients mainly present with nonspecific gastrointestinal symptoms and "atypical" extraintestinal symptoms such as anemia, chronic fatigue, generalized bone pain, osteoporosis, sleep disorders, cognitive problems, headaches and depression [62, 63]. Nelsen [64] further described these extraintestinal manifestations of adult celiac patients among which he named fibromyalgia-like symptoms in addition to aphthous stomatitis, bone pain and dyspepsia.

Several disorders can mimic the clinical presentation of celiac disease in the absence of histological or serological changes such as microscopic colitis, pancreatic insufficiency, small intestinal bacterial overgrowth and intolerance to certain dietary components (lactose, wheat, gluten) [65]. Other disorders (enteropathies) can even mimic celiac disease pathology such as autoimmune enteropathy, collagenous sprue and nonsteroidal anti-inflammatory drugs injury [65]. Association of severe sprue-like enteropathy with olmesartan (angiotensin-receptor blocker) has been recently reported [66].

Interestingly, a recent study reported the diagnosis of seven (6.7 %) celiac cases among 104 patients with concomitant IBS and fibromyalgia [67]. The significant clinical improvement of fibromyalgia symptoms, gastrointestinal manifestations and health-related quality of life seen among these seven subjects upon the adoption of a 12-month gluten-free diet constitutes another interesting finding of this study [68], which further emphasizes the close relationship existing between these conditions.

The overlap of some manifestations between fibromyalgia and celiac disease raises the possibility that some patients with fibromyalgia might suffer from oligosymptomatic celiac disease. Previous studies suggested an elevated prevalence of fibromyalgia among patients with celiac disease [69, 70], whereas the prevalence of celiac disease in fibromyalgia was shown to be similar to that in the general population [70, 71]. A definite conclusion concerning the prevalence of celiac disease in fibromyalgia is still lacking; hence, larger-scale studies that evaluate such prevalence are needed.

Non-celiac gluten sensitivity

Non-celiac gluten sensitivity (NCGS) is a relatively new entity characterized by the presence of both gastrointestinal and extraintestinal manifestations in the absence of celiac disease or wheat allergy [72]. It is distinct from celiac disease in terms of the absence of anti-transglutaminase or endomysial antibodies and the presence of a normal intestinal mucosa or mild mucosal abnormalities (increased intraepithelial lymphocytes in the absence of villous atrophy) [73]. Patients with NCGS usually experience intestinal and extraintestinal manifestations similar to those of patients with celiac disease which are significantly alleviated upon the exclusion of gluten from the diet [73, 74].

Investigations concerning gluten sensitivity in the absence of celiac disease are still scanty mainly due to diagnostic difficulties as a result of the absence of specific diagnostic biomarkers in addition to the normal serological and histological outcomes that these patients may display [73]. Currently, diagnosis is made by exclusion and by evaluation of the patient's symptomatology after the elimination of gluten from the diet and, later rechallenge with gluten-containing foods, the later being a nonspecific approach that entrains high risk of bias caused by placebo effect [73].

NCGS has been investigated in several disorders such as IBS, autism and schizophrenia [72]. This indicates the potential role that could be played by gluten in the pathophysiology of several disorders. The same reasons that lead to a suspicion of an underlying gluten sensitivity among patients with IBS [72] apply to fibromyalgia where the similarity of the gastrointestinal and extraintestinal manifestations experienced both by patients with fibromyalgia and by patients with NCGS might suggest a possible role of gluten sensitivity in at least a subgroup of patients with fibromyalgia, especially those experiencing nonspecific gastrointestinal symptoms.

Several studies investigated the effects of gluten-free diet in IBS given its close correlation with NCGS. In an uncontrolled study, diarrhea dominant-IBS (d-IBS) patients were shown to display more frequent celiac-related IgG antibodies (37 %) and HLA-DQ2 expression (39 %) as compared to patients with inflammatory bowel disease (18 and 23 %, respectively) [75]. In this study, the adoption of a gluten-free diet among IBS patients over a period of 6 months lead to a significant improvement in gastrointestinal symptomatology (especially among those who were positive for HLA-DQ2) and to a significant decrease in IgG antigliadin concentrations among HLA-DQ2-positive subjects. In a randomized, double-blind study carried out in 40 patients with celiac disease and 44 patients with NCGS, the suppression of gluten from the diet over a 6-month period lead to the disappearance of antigliadin IgG antibodies in 89 % of NCGS patients classified as good responders ($n = 39$) and in 60 % of those classified as mild responders ($n = 5$); the persistence of IgG antibodies following adopting a gluten-free diet in NCGS was significantly correlated with the low degree of compliance; on the other hand, IgG antibodies persisted in 43.3 % of celiac patients classified as good responders ($n = 30$) and in 30 % of those classified as mild responders ($n = 10$) [76]. The effects of gluten challenge in IBS patients who were symptomatically controlled on a gluten-free diet were investigated in a randomized double-blind controlled study and a more frequent and significant deterioration of symptoms was seen upon gluten challenge as compared to placebo (68 vs. 40 %, respectively) [77]. Given the increased comorbidity between fibromyalgia and IBS, these data could be relevant for the future treatment of the subgroup of patients with concomitant IBS and fibromyalgia.

Preliminary results in a group of selected patients with FM suggest that an improvement after gluten elimination from the diet can be seen [78]. Well-designed randomized clinical trials testing for this hypothesis are needed.

Lactose intolerance

Intolerance to lactose results from the inability to digest this carbohydrate as a result of the deficiency in the lactase enzyme that is responsible for its hydrolysis in the small intestine. As a result of maldigestion, lactose is malabsorbed in the small intestine and subsequently flows to the colon where, among intolerant individuals, it elicits a wide range of symptoms such as abdominal pain, bloating, flatus, diarrhea, borborygmi, nausea and vomiting [79].

In addition to the principal role of lactase activity, several other factors can affect the degree of digestion and tolerability to lactose such as gastrointestinal transit, visceral sensitivity, functional bowel disorders and colonic microflora composition [80]. Lactose intolerance has been investigated in IBS where 45 % of IBS patients presented lactose malabsorption and 30 % reported the appearance symptoms with the ingestion of milk products [81]. However, some IBS patients without lactose maldigestion report the occurrence of symptoms similar to lactose intolerance [79].

The potential mechanisms through which lactose intolerance could elicit symptoms in IBS have been studied. Increased gas production and visceral hypersensitivity following lactose ingestion in IBS patients are thought of as contributors to the appearance of digestive symptoms [82]. It is also worth highlighting the "bacterial toxin" hypothesis suggested by Campbell et al. [83]; these authors consider that lactose and other undigested carbohydrates, via effects on gene expression and growth, affect the balance of microflora in the large intestine and the various cell types such as neurons, skeletal, smooth and cardiac myocytes and mast cells; all of which contributing to the systemic symptoms seen in patients with lactose intolerance and patients with IBS [83]. The role of a lactose-free diet in IBS is not yet established.

Lactose intolerance is a frequent form of food intolerance. Clinicians are aware that it is also a common clinical finding among patients with fibromyalgia who frequently state that they do not tolerate milk. However, to our knowledge, no data are reported in literature concerning its exact prevalence in these patients. In a recent study (manuscript under revision), our group found, among 178 patients with fibromyalgia, that 36.5 % of them reported to suffer lactose intolerance [84].

FODMAPs

Fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) are short-chain carbohydrates poorly absorbed in the small intestine. They include fructans, galactose, lactose, fructose and sugar alcohols that are found in a wide variety of dietary sources such as certain fruits (apple, pear, peach, watermelon, etc.), cereals (wheat, rye and barley), milk, and yogurt, among others [85]. The fructans oligosaccharides are the specific carbohydrates present in wheat whose various constituents have been linked to distinct pathologic effects [86]. FODMAPs have been proposed to play a role in the pathophysiologic mechanisms underlying NCGS. It has been recently postulated that the triggers of NCGS symptoms are not limited to the gliadin, non-gliadin parts of gluten or gluten contaminants but rather they might include other wheat components such as amylase-trypsin inhibitors or FODMAPs [86]. Accordingly, their dietary reduction in patients with IBS and NCGS was linked to a significant symptomatic relief as reported in the placebo-controlled, crossover study conducted by Biesiekierski et al. [87]. Following the initial phase of reduced FODMAPs, patients displayed significant worsening to a similar degree upon the challenge of varying amounts of gluten or placebo which indicates the lack of specific or dose-dependent effects for gluten in NCGS secondary to FODMAPs reduction [87].

Sensitivity to FODMAPs might constitute the common base for the sensitivity to various food components, as this broad family includes the sensitivity to lactose and wheat (gluten). To our knowledge, the specific role of FODMAPs in fibromyalgia and the possible underlying mechanisms associated to its possible effects in fibromyalgia are not yet investigated. The current experience with FODMAPs restriction diet in IBS has revealed promising outcomes, as it has been linked to improved IBS symptomatology of pain, bloating, flatulence and nausea in addition to improved quality of life [88]. These outcomes encourage undertaking the adequate investigations to explore any possible role of these nutritional constituents in fibromyalgia.

Microbiota–gut–brain axis alterations

The bidirectional communication between the gastrointestinal tract and the brain is regulated through multiple pathways at the neural, hormonal and immunological levels [89]. This gut–brain bidirectional signaling ensures the preservation of the gastrointestinal homeostasis and exerts multiple effects on affect, motivation and higher cognitive function, constituting what is termed as a top-down and bottom-up construct [90]. The contribution of the enteric flora to these interactions has been lately recognized and its fundamental role has led to the more inclusive nomenclature of the brain–gut–enteric microbiota axis [89]. In the top-down communication, the brain can exert its effects on the enteric microbiota via changes in the gastrointestinal motility and secretion, intestinal permeability and signaling molecules released in the gut lumen [91]. For the bottom-top model, the signaling from enteric microbiota to the brain is mediated through epithelial-cell, receptor-mediated signaling and via direct stimulation of the *lamina propia* cells when the intestinal permeability is increased [91]. Alterations in the gut microbiota (dysbiosis or small intestinal bacterial overgrowth) can influence this bidirectional communication and recent evidence suggests that several health conditions such as visceral pain, autism spectrum disorders, obesity, anxiety/depression and multiple sclerosis can be affected by intestinal microbiota alterations [92].

Small intestinal bacterial overgrowth

Small intestinal bacterial over growth (SIBO) represents one the forms of alteration of the normal gut microbiota. It is characterized by qualitative and quantitative change of the bacterial colonies that inhabit the small intestine [93]. Under normal conditions, the upper tract of the small intestine is mainly colonized by gram-positive bacteria whose counts do not exceed 10^3 organisms/mL; however, in the case of SIBO, the count of these colonies increases to exceed 10^5–10^6 organisms/mL [94].

The human body retains several defense mechanisms that efficiently maintain a controlled growth of enteric bacterial populations. These mechanisms include the following: the gastric acid capacity of eradicating swallowed microorganisms, intact ileocecal valve, the antegrade peristalsis (especially the migratory motor complex) ability of sweeping the bacteria into the colon [95] and the tight epithelial cells lining ability to prevent the access of pathogenic agents and to secrete immunoglobulins, mucous, defensins and other antimicrobial products [96].

Factors that predispose patients to develop SIBO are usually associated with an impairment of one or more of those homeostatic defense mechanisms or alternatively they can originate from certain anatomic abnormalities. Several disorders are commonly associated with SIBO such as scleroderma, diabetes mellitus, chronic pancreatitis, chronic intestinal pseudo-obstruction, celiac disease, Crohn's disease, chronic atrophic gastritis, small intestinal obstruction, diverticula, fistulae, surgical blind loop and previous ileocecal resections [93, 95]. The long-term use of proton pump inhibitors provokes gastric achlorhydria and, consequently, predisposes patients to develop SIBO [97].

Clinically, patients with SIBO usually present nonspecific symptoms consistent with the manifestations occurring secondary to the microbiota–gut–brain axis alterations.

These symptoms include bloating, abdominal distension, abdominal pain or discomfort, diarrhea, fatigue, anxiety/depression and weakness [94, 98].Thus, a substantial similarity can be noticed between the nonspecific intestinal manifestations experienced by patients with fibromyalgia and those characterizing SIBO; an observation that suggests a possible role for the latter in fibromyalgia. In addition, the leaky gut reported in fibromyalgia [99] has also been seen in SIBO [100].

Pimentel et al. [101] reported the diagnosis of SIBO in 78 % of the 123 subjects with fibromyalgia who underwent lactulose hydrogen breath test, an evaluation used for the diagnosis of SIBO. Of those, 25 patients underwent an antibiotic eradication therapy, and as a result, complete eradication was achieved in 11 patients who also reported a significant improvement of symptoms such as bloating, gas, diarrhea, constipation, abdominal pain and joint pain on follow-up. This study supports a possible role for SIBO in the occurrence of the intestinal symptoms experienced by patients with fibromyalgia. In another study that aimed to compare the prevalence of SIBO between patients with fibromyalgia and those with IBS, 100 % of patients with fibromyalgia ($n = 42$) were diagnosed with SIBO compared to 84 % of subjects with IBS ($n = 111$) and 20 % of the controls ($n = 15$) ($p < 0.05$) [102]. Another interesting finding was the significant correlation found between somatic pain in fibromyalgia and the degree of hydrogen levels recorded in the breath test ($r = 0.43$, $p < 0.01$) [102].

Considering these findings, the suspicion of a possible role of SIBO in fibromyalgia is reasonable, mainly among those who experience nonspecific gastrointestinal symptoms suggestive of SIBO. If confirmed, this finding would support investigating the effect of an antibiotic course which targets the SIBO spectrum of microorganisms or probiotics in the management of SIBO manifestations. The American College of Gastroenterology, in its 2009 guidelines for the management of IBS has recommended, with IB grade of evidence, the use of a short-term course of a non-absorbable antibiotic such as rifaximin [103]. Two additional studies further supported this recommendation, as rifaximin use was shown to be associated with a significant improvement of IBS symptoms such as bloating, abdominal pain and loose stools among patients who had IBS without constipation [104]. Additionally, *bifidobacteria* and certain combinations of probiotics demonstrated some efficacy in IBS when used alone (IIC grade of evidence) [103] or when combined with an antibiotic therapy [105] and the use of *Lactobacilli* in chronic fatigue syndrome has been associated with significant decrease in anxiety [106]. Thus, these findings further advocate conducting randomized controlled clinical trials that investigate the potential role of probiotics and/or a short-course of antibiotics among patients with fibromyalgia who are diagnosed with SIBO.

Giardiasis

In addition to SIBO, recent observations suggest a role for *Giardia* infection in provoking alterations of the intestinal microbiota and subsequent production of chronic symptoms [107]. When present, the clinical presentation of giardiasis infection range from an asymptomatic profile to the presence of several symptoms such as diarrhea, nausea, weight loss, bloating and abdominal pain [107]. In addition to muscular complications, infections with *Giardia* species are believed to precede the occurrence of several disorders such as arthritis, skin allergies, impaired cognitive function, chronic fatigue syndrome and functional gastrointestinal disorders (including post-infectious IBS) [107], all of which are closely related with fibromyalgia. The development of these complications may require 2–3 years following the infection and in the absence of any detectable parasitic loads [107].

Several environmental factors have been linked to the etiology of fibromyalgia including infections such as parvovirus B19, mycoplasmosis, hepatitis B or C viruses, human immunodeficiency virus and Lyme disease [9, 108]. To our knowledge, the influence of the exposure to *Giardia* sp. infections on the possible development of fibromyalgia is not yet investigated. The overlap of some of the manifestations of fibromyalgia with giardiasis and the hypothesized influence of such type of subclinical infections on the microbiota–gut–brain axis indicates the need for studying any possible role for this type of infections in fibromyalgia.

Further understanding of the underlying interaction of the microbiota and enteric pathogens with the gut–brain axis is still needed. This in turn will facilitate the understanding of the pathogenetic mechanisms underlying several disorders.

Conclusions

Gastrointestinal symptoms, similar to the IBS manifestations, are highly prevalent among patients with fibromyalgia. However, they are generally overlooked in studies that are not specifically dedicated to evaluate these manifestations, as they are usually focused on the most typical fibromyalgia associated symptoms such as fatigue, sleep disturbances and psychologic distress. Considering the high prevalence and disabling nature of the gastrointestinal manifestations which contribute to an impaired quality of life among patients with fibromyalgia, studies directed to evaluate the relevant impact of such manifestations in the context of healthcare costs and utilization are needed.

The high frequency of food intolerance in fibromyalgia suggests a possible role for hypersensitivity to certain dietary components such as gluten, lactose or FODMAPs in the occurrence of the gastrointestinal manifestations. This suspicion can be also taken into consideration given the facts that intolerance to these dietary components is frequently reported in IBS (highly comorbid with fibromyalgia) and are associated to symptomalogic profile similar to the one described by patients with fibromyalgia. Another suggested pathophysiologic mechanism is the alteration in the brain–gut axis occurring via SIBO, which is frequently seen in fibromyalgia, or subclinical infections such as giardiasis. Future studies that aim to confirm or reject these explanatory hypotheses are warranted. The gastrointestinal component of fibromyalgia constitutes an important element of the multidisciplinary pathophysiologic mechanisms underlying fibromyalgia that need to be unveiled, as this would contribute to the implementation of potential treatment alternatives corresponding to these manifestations.

Conflict of interest The authors declare that they have no conflict of interest.

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