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FOOD ALLERGIES AND INTOLERANCES IN PATIENTS WITH FIBROMYALGIA: THE STATE OF THE ART

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ABSTRACT – The approach to adverse reactions to food represents a difficult task for clinicians due to several unmet needs encompassing all the phases of the medical act. Globally, the prevalence of these reactions shows a progressive increase, but it should be considered that the prevalence of food allergy is largely affected by the diagnostic test used; nonetheless, the lack of accurate tests makes it difficult to calculate the prevalence of food intolerance. In patients suffering from fibromyalgia, food intake is very frequently reported as one of the main responsible for worsening of symptoms, and at diagnosis many patients have already modified their diet, often without a previous nutritional evaluation. Patients frequently start a gluten-free diet and/or a lactose-free diet before the real need is ascertained. Dairy products, incompletely absorbed carbohydrates and gluten-containing foods represent the products the patients consider more frequently the culprit of the onset or worsening of their symptoms. However, the known nocebo effect of foods may induce patients to erroneously associate some foods to symptom onset, also causing a useless elimination diet. The strict association between fibromyalgia and functional gastrointestinal disorders increases the difficulty clinicians have to front during diagnostic approach. Further studies are needed to define the real prevalence of allergy and intolerance in fibromyalgia and to select foods with a negative or positive effect on symptoms.

KEYWORDS: Fibromyalgia, Food allergy, Food Intolerance, Gluten, Lactose, Irritable bowel syndrome.

INTRODUCTION

The approach to adverse reactions to food represents a difficult task for clinicians due to several unmet needs encompassing all the phases of the medical act. First of all, a clear inaccuracy was shown for both symptom reporting and association of symptoms to specific food ingestion by patients. Second, clinician interpretation of the food-symptom association is very difficult. Third, accurate diagnostic tests are available for a minority of these conditions and, finally, the treatment of these conditions is very frequently burdened by objective difficulties causing a low patient compliance. The classification of adverse reaction to foods distinguishes into toxic and non-toxic reactions also called hypersensitivity reactions. Toxic adverse reactions include bacterial contamination, toxin contamination and chemical contamination. These types of reactions will be not analysed in this review, as we shall focalise on hypersensitivity adverse reactions, including both immune-mediated and non-immune-mediated reactions. The first type is associated to a direct activation of immune system and the main model is represented by IgE-mediated reactions such as food allergies. Non-immune-mediated reactions include food intolerances, caused by a defective activity of enzymatic substances, pharmacological activity of food components, or undefined mechanisms, as it happens for food additives[1].

DEFINITIONS FOR FOOD ALLERGIES AND INTOLERANCE

Food allergy is defined as an adverse reaction caused by a specific and reproducible immune response that appears after exposure to a specific food. Food allergens are food-specific components or ingredients, typically proteins, but sometimes also haptens, that are recognized by cells of the immune system, reactive towards that specific component and that induce a specific immunological reaction that causes characteristic symptoms. Sensitization is manifested in the presence of IgE directed against a specific allergen in the absence of symptoms from exposure. Food intolerance is an adverse reaction caused by a food or its component in the absence of involvement of the immune system[2].

There are substantial differences between food allergies and intolerances, in terms of age of onset, time of onset, type of reaction, type of food involved (Table 1). However, due to their low specificity, these differences should be taken into account in the first step of the clinical approach, driving roughly the diagnostic approach which must be confirmed by the next steps. The onset of food allergy is frequent in childhood and is characterized by a prevalence reduction with age. Food allergy is IgE-mediated, it is caused by few foods, it is characterized by immediate or early reactions which are very similar for clinical manifestations, and this makes it possible a direct diagnosis. On the contrary, food intolerance can occur at any age, its prevalence generally increases with age, it is not immune-mediated and generally caused by many different foods with delayed reactions and variable clinical manifestations. Diagnosis is often difficult due to a lack of accurate tests.

Table 1. The main differences between food allergies and food intolerances.

Food Allergies	Food Intolerances
Onset more frequent in childhood	May occurs at all ages
Shows a trend to decrease with age	Tend to increase with age
Immune-mediated	Not immune-mediated
Generally caused by few foods	Generally reported after many foods
Immediate or early reactions	Delayed reactions
Manifestations are reproducible	Manifestations are variable
Direct diagnosis with specific tests	Difficult diagnosis without specific tests

EPIDEMIOLOGY OF ADVERSE REACTIONS TO FOOD

The prevalence of adverse reactions to food shows a progressive increase. For instance, in 2006, the prevalence of adverse reactions to food was 3-4% in adults and 6% in children, while in 2014 the prevalence had risen to 5% in adults and 8% in children. Similarly, in 2006, the incidence of hospitalizations caused by adverse reactions to food was 0.6 patients in 1000, while in 2014 the incidence had increased to 1.3 patients in 1000[3-5].

Prevalence figures, however, is largely affected by the diagnostic test used. It was previously shown that self-reporting of allergic symptoms by patients after peanuts, milk proteins, eggs, fish and crustaceans' intake is detectable in 12% of pediatric cases and 13% of adult patients, respectively. On the contrary, when "objective" tests drive diagnosis, the prevalence is 3% with both skin prick test and food challenge. Similarly, the prevalence of allergic reactions to fruits, vegetables, legumes, dried fruits, wheat and soy anamnestically reported by patients ranged between 0.02% and 8.5% but skin prick test positivity ranged between 0.02% and 4.2%, and food challenge positivity between 0.1% and 4.3%[6,7].

As far as the prevalence of food intolerance is concerned, accurate diagnostic tests are available only for some component of foods, such as lactose and gluten. Consequently, a reliable prevalence figure for food intolerance is not yet available.

FIBROMYALGIA AND GASTROINTESTINAL SYMPTOMS

In patients suffering from fibromyalgia, food intake is very frequently reported as one of the main responsible for worsening of symptoms. It was recently shown that 37% of patients perceived the presence of allergies as responsible for symptom worsening[8]. Consequently, it is frequent to observe that many patients have already changed their diet to obtain a symptomatic benefit before diagnosis was made[9]. Among 101 fibromyalgic patients who answered to a questionnaire about their dietary habits, 30% of patients reported a previous modification of diet, but only 7 of them suffered from a confirmed intolerance or food allergy, being lactose intolerance the most frequent (4/101). Gastroenterologists are used to dealing with postprandial symptoms as functional conditions, such as functional dyspepsia, functional bloating, functional heartburn, and gastroesophageal reflux disease, which are an important subset of patients seeking ambulatory medical care. However, some recent evidences support also the existence of a large subgroup of irritable bowel syndrome (IBS) suffering from a clear exacerbation of their symptoms after a meal[10]. During a postprandial period of 6 hours, in 67 IBS patients in comparison with 16 healthy controls, the occurrence of abdominal pain, bloating, discomfort, nausea, gas and fullness showed an early peak followed by a progressive regression towards baseline[10]. Two Swedish studies suggested the prevalence of IBS patients with postprandial exacerbation of symptoms was higher than 80% in two different cohorts[11,12] and in our recent experience, even if lower than reported, the prevalence was near to 50%[13].

Fibromyalgia and IBS are strictly associated, and IBS is considered the most common gastrointestinal disorder related to fibromyalgia. Estimates of the prevalence of IBS in fibromyalgia patients range from 32% to as high as 81%[14]. In particular, Sperber et al[14] investigated the prevalence of fibromyalgia in IBS patients and the prevalence of IBS in fibromyalgia patients. Furthermore, they studied implications of concomitant IBS and fibromyalgia on health-related quality of life. By comparing 79 IBS patients and 72 healthy subjects, they reported that 31.6% of IBS patients and 4.2% of healthy subjects fulfilled diagnostic criteria for fibromyalgia. When in IBS patients fibromyalgia was also detected, the worst results in terms of global well-being, sleep disturbance, pain, and anxiety was measured.

Bennett et al[8] enrolled 2,569 fibromyalgia patients to complete an internet survey to provide information on symptoms, aggravating factors, triggers, and comorbidities. The most common symptoms were nonrestorative sleep, morning stiffness, pain, fatigue, and concentration. Among co-morbidities, IBS was reported by 44% and bloating by 40% of patients, respectively[8].

In a cohort of 100 fibromyalgia patients, 32% also had IBS and when the two conditions were associated, worse scores for physical functioning and quality of life questionnaire were evident. Thus, Sperber et al[15] suggested that rheumatologists should be aware of the overlap that can affect symptoms and treatment strategies.

Kurland et al[16] studied the prevalence of IBS in 105 fibromyalgia patients and 62 rheumatologic controls. Rome I and Rome II were considered for diagnosis and the prevalence of IBS in fibromyalgia patients was clearly higher in any case than in rheumatologic controls[16].

Since the association between fibromyalgia and IBS is very frequent, the awareness of the relationship between food intake and gastrointestinal symptom onset should be increased among physicians. Figure 1 shows the prevalence of IBS patients reporting a postprandial exacerbation

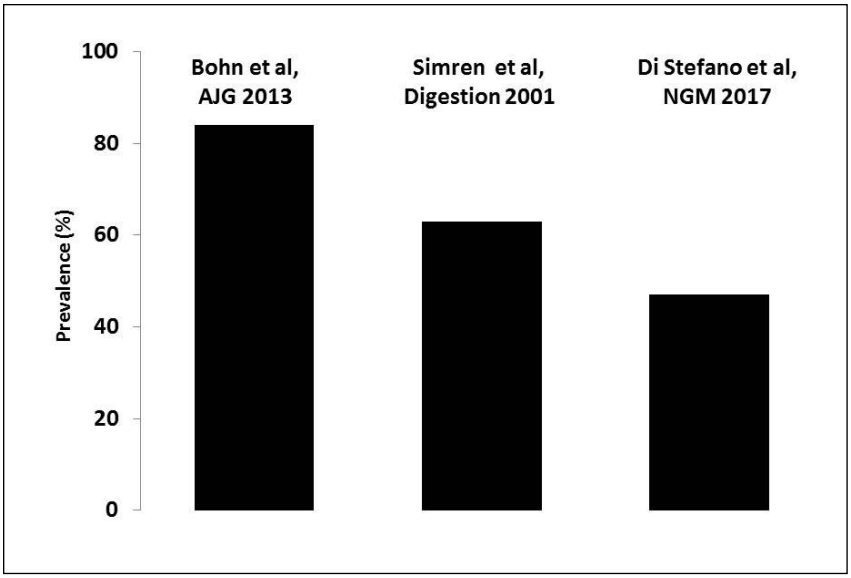

Figure 1. Prevalence of postprandial symptoms in IBS patients[11-13].

of their symptoms[11-13]. Böhn et al[11] recorded a questionnaire fulfilled by 197 IBS patients reporting symptoms from 56 different food items relevant to food intolerance or allergy, but also assessing psychological symptoms and quality of life. The majority of IBS patients (84%) reported symptoms related to at least one of the food items. In 70% of cases, the trigger was considered the intake of food with incompletely absorbed carbohydrates, in 52% of cases the intake of fried foods and fat products, while 49% of IBS patients complained symptoms related to intake of dairy products. The reduction of quality of life was directly related to the number of foods considered as triggers for symptom onset[11].

Simrén et al[12] recorded a questionnaire fulfilled by 330 IBS patients and 80 healthy subjects who reported on their subjective food-related gastrointestinal symptoms after 35 different foods, in addition to anxiety and depression. In IBS patients, in 63% of cases the patients considered their gastrointestinal symptoms to be related to meals, in particular gas problems and abdominal pain. Foods rich in carbohydrates and fat were most frequently reported to cause symptoms[12].

The role of undigestible carbohydrate should be accurately discussed with each patient. Even if it is generally considered a positive measure for well-being, the intake of fibers may represent the cause of symptom exacerbation in a subset of patients. In an old paper, Francis and Whorwell[17] detected the effect of different types of fibers in 100 IBS patients and asked with a questionnaire how the severity of symptoms was modified after the intake of these foods. Only 10% of IBS found bran helpful while 55% of IBS patients were made worse by bran. In particular, bran caused bowel disturbance, abdominal distension and pain. Thus, in light of these observations, the authors suggested that the use of bran in IBS should be reconsidered and tailored on each patient[17].

However, it should be noted that beside an increase of bacterial fermentation and alterations of visceral sensitivity, other mechanisms may be responsible for abdominal symptoms in functional patients. We recently showed in 84 IBS patients reporting postprandial moderate to severe abdominal distention that in 47% of cases abdominal distention occurred immediately after meal intake. Postprandial recto-sigmoid tone after meal intake was significantly reduced in patients with severe meal-related abdominal distention and abdominal girth increased immediately after meal intake, suggesting that in IBS patients with severe postprandial abdominal distention an early reflex, rapidly reducing intestinal tone might be considered an adjunctive pathogenetic mechanism for postprandial abdominal distention[13].

Table 2 shows the percentage of IBS patients suffering from moderate, severe, and very severe symptoms after the ingestion of listed foods[12].

Table 2. The percentage of IBS patients suffering from moderate, severe, and very severe symptoms after the ingestion of listed foods (data from Simrén et al[12]).

		Moderate symptoms	Severe symptoms	Very severe symptoms
Animal Products	Cream	17	11	9
	Milk	15	8	7
Fruits and Vegetables	Red/green pepper	16	11	7
	Raw vegetables	20	9	5
	Cabbage	25	19	13
	Onion	25	20	12
	Peas/Beans	26	14	7
Various Products	Hot spices	22	16	7
	Pastries	21	8	4
	Fried food	21	10	2
	Deep-fried food	19	15	10
	Smoked food	15	15	5
	Alcohol	21	9	4
	Coffee	22	9	8
	Pizza	23	13	8

FIBROMYALGIA AND LACTOSE INTOLERANCE

Dairy products are often considered responsible for post-prandial symptoms and lactose withdrawal from diet is frequent even in absence of a clear relationship between intake and symptom onset[18]. It was previously shown that, when patients consider themselves severely lactose intolerant, a large portion of them fail this judgement and, when tested, prove to have a normal lactose absorption[19]. Accordingly, objective tests are needed to better diagnose lactose malabsorption and intolerance.

We have recently shown that patient awareness of the relationship between lactose intake and type of symptom occurrence is also inaccurate. In 268 patients undergoing lactose breath test we recorded the symptoms the patients considered evoked by lactose intake. Among all the reported symptoms, patients considered secondary to lactose intake also the symptoms depending on functional dyspepsia or gastroesophageal reflux disease. When the group of patients was subdivided according to the presence of lactose malabsorption, a higher prevalence of diarrhea, abdominal pain, abdominal distention, bloating, and flatulence was detected in lactose malabsorbers. However, a higher prevalence of epigastric pain, regurgitation, heartburn, and nausea was detected in patients with normal lactose absorption (Table 3)[18]. Accordingly, it is evident that patients are frequently unaware about clinical presentation of this condition, and educational programs are needed to help the general population in the definition of the relationship between food intake and symptom onset.

THE ROLE OF NOCEBO EFFECT OF FOOD

Another important issue, causing confusion in the definition of the relationship between food intake and symptom onset is the known nocebo effect of food. Lactose intake does not represent an exception. In 40 patients with self-reported lactose intolerance, according with a double-blind protocol, we administered lactose or glucose, and we monitored both breath hydrogen excretion and symptom occurrence[18]. In 27 patients the presence of lactose malabsorption was detected by hydrogen breath test and in 13 patients the test proved to be negative.

In 21 patients, it was not possible to ascertain the relationship between carbohydrate intake and symptoms; in some patients, in fact, abdominal symptoms were reported also after glucose or when hydrogen breath test after lactose was negative. Therefore, monitoring symptom onset after unblinded lactose administration represents an inaccurate method to select intolerant patients, even if a double-blind protocol is used to avoid nocebo effect[18].

FIBROMYALGIA AND GLUTEN INTAKE

Celiac disease is an autoimmune disorder which occurs in genetically predisposed individuals when gluten is introduced with the diet. An altered immunological response causes intestinal lesions responsible for intestinal malabsorption. Wheat allergy is a different condition, being an IgE-mediated condition, triggered by gluten intake. Recently, Non-Celiac Gluten Sensitivity (NCGS) was proposed, an entity with an incompletely clear pathogenesis, improved by withdrawal of gluten from diet[20]. Symptoms of patients with celiac disease and NCGS frequently overlap those present in fibromyalgic patients[21]. In 178 fibromyalgic patients and 131 healthy subjects, besides anemia, the frequency of celiac-type symptom was significantly higher in fibromyalgic patients compared to healthy subjects (Figure 2)[21]. Accordingly, it was supposed that gluten intake is a promoting factor for gastrointestinal symptoms in fibromyalgic patients. There are no study dealing with the prevalence of non-celiac gluten sensitivity in fibromyalgia; on the contrary there are several studies dealing with the prevalence of celiac disease in fibromyalgia.

The prevalence of celiac disease was tested in 104 IBS patients with fibromyalgia and 125 IBS patients without fibromyalgia and an active case finding for CD was conducted[22]. In 6.7% of IBS patients with fibromyalgia high anti-tTG serum levels were detected and HLA-DQ2/HLA-DQ8 genotype and duodenal villous atrophy were consistent with a diagnosis of CD. After a gluten-free diet (GFD), these seven patients showed a remarkable improvement in their symptoms. The Authors demonstrated that in CD patients with fibromyalgia, GFD improves also fibromyalgic symptoms[22].

Tovoli et al[23] enrolled 90 fibromyalgia patients and serologically tested them for CD and then positive patients underwent duodenal biopsies. The authors also enrolled 114 celiac disease patients to investigate the presence of fibromyalgia-like symptoms among them through a questionnaire.

Table 3. Prevalence of symptoms in patients with self-reported lactose malabsorption[18].

	Diarrhea	Pain in Abdomen	Bloating	Distention	Flatulence	Satiety	Fullness	Epigastric	Epigastric Pain	Regurgi-Burning	Heartburn tation
All the patients	45.1	50.0	95.9	79.1	72.4	21.3	22.4	14.6	6.4	2.3	2.3
Patients with lactose malabsorbtion	53.5	64.5	95.9	97.1	95.3	11.6	8.1	8.1	6.6	2.4	2.4
Patients without lactose malabsorbtion	30.2	24.0	95.8	46.9	31.3	38.5	47.9	26.0	17.7	17.7	15.6

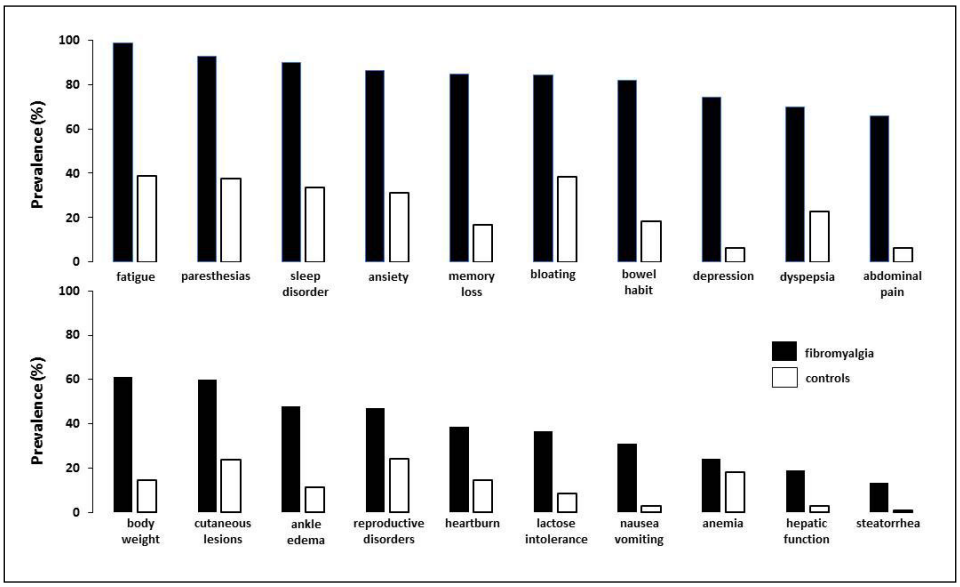

Figure 2. Prevalence of celiac-type symptoms in fibromyalgic patients and healthy controls (data from García-Leiva et al[21]).

The prevalence of celiac disease in the 90 fibromyalgia patients was identical to that from general population (1%). A total of 14.9% of celiac disease patients reported chronic widespread pain and 11.4% satisfied the ACR 1990 criteria for fibromyalgia. Their symptoms, however, were not modified by gluten-free diet (GFD). Thus, the authors suggested a case-finding strategy among fibromyalgia patients and avoid GFD in fibromyalgic patients without a well-established diagnosis of celiac disease.

Elhami et al[24] studied the prevalence of celiac disease in 300 Iranian patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or fibromyalgia (each group 100 patients). Serum IgA Anti-tTG levels were assessed, and seropositive patients underwent duodenal biopsy. Seropositivity for celiac disease was found in 1% of SLE patients, in 3% of RA patients and in no-one of fibromyalgia patients. Only RA patients had three times higher prevalence rate than normal population for celiac disease[24].

Nisihara et al[25] enrolled 94 fibromyalgia patients to investigate the prevalence of celiac disease, and none of them was positive to endomysial antibodies (IgA-EmA). According to these results, the authors suggested that it is not worthwhile to screen every fibromyalgia patient for celiac disease.

EFFECTS OF GLUTEN-FREE DIET IN FIBROMYALGIC PATIENTS WITH CELIAC DISEASE

Rodrigo et al[26] enrolled 7 celiac disease patients with severe IBS and fibromyalgia to assess the effectiveness of a gluten-free diet. They monitored the changes of scores in the tender points' test, fibromyalgia impact questionnaire, quality of life questionnaire, visual analogue scales for gastrointestinal complaints, pain and tiredness, anti-tTG serum levels and drug prescriptions. Before starting the gluten-free diet all patients showed villous atrophy in duodenal biopsies and they had a poor quality of life, and a high number of tender points, tTG levels and drug prescriptions. After 1 year of gluten-free diet, all patients significantly improved, with a 51-60% decrease in tender points, fibromyalgia impact questionnaire, visual analogue scales, and in the number of prescribed drugs, accompanied by a 48-60% increase in quality of life, and a tTG decrease to normal serum levels. According to this pilot study, Rodrigo et al[26] suggested that a gluten-free diet for celiac disease patients with severe IBS and fibromyalgia can simultaneously improve celiac disease and IBS and fibromyalgia symptoms.

GLUTEN FREE DIET IN PATIENTS WITH FIBROMYALGIA

Due to the similarity of clinical presentation of fibromyalgia and gluten-related disorders, the effect of a gluten-free diet was compared with a hypocaloric diet[27]. A cohort of 75 fibromyalgia patients were randomly allocated to receive a gluten-free diet (n=35) or a hypocaloric diet (n=40) over a 24-week period.

Overall, gluten-free diet was not superior to hypocaloric diet in reducing the number of gastrointestinal, extra intestinal and gluten sensitivity symptoms[27].

Isasi et al[28] administered a gluten-free diet to 20 fibromyalgia patients with duodenal intraepithelial lymphocytosis without villous atrophy. After a mean follow-up period of 16 months, the authors considered as clinical improvement the remission of pain, return to normal life, suspension of opioids or return to work. For some patients the improvement was surprising and observed after few months, but for other patients the improvement was slow and observed over many months. These results suggest that if fibromyalgic patients show duodenal lymphocytosis may have a better response to gluten-free diet[28].

GLUTEN TOXICITY

Even if gluten may cause enteropathy in predisposed subjects, uncertainty still characterizes whether gluten is toxic in normal subjects. Studies *in vitro*, using the human colon carcinoma cell line Caco-2, have shown the effect of a medium containing a peptic-tryptic gliadin digest on cell growth[29]. After 24 h and 48 h of gliadin exposure, an inhibition of cell growth of 20% was observed, associated to the reduction of intracellular glutathione, the increase of cellular lipid peroxidation and the impairment of intestinal barrier with increase of permeability. Another *in vitro* study on CACO-2 cells showed that the addition of gliadin led to a reduction in transepithelial electrical resistance up to 40% in 100 minutes and a consequent increased in the flux of FITC destran was observed confirming the involvement of the paracellular pathway[30]. In addition, variations in the localization of the tight junction proteins before and after gliadin treatment were also detected[30]. In Caco-2 cell monolayers exposed to gliadin, added to the apical side of monolayers, a decrease of claudins-3, -4 and occludin in plasma membrane and an increase in cytosol was evident. Gliadin induced a reorganisation of F-actin and an increase in polymerisation as stress fibres to the cell subcortical compartment. Zonulin-1 was expressed at the tight junction in the nucleus in untreated Caco-2 cells, while gliadin addition made the expression in the nucleus undetectable[30]. Unfortunately, this protocol did not consider a control protein making the specificity of the result very low. Studies *in vivo* have shown that in healthy volunteers the administration of a gluten-containing meal in comparison with a gluten-free meal is not associated to modifications of gastric and gallbladder emptying rate, onset of symptom, alteration of the secretion of gastrointestinal hormones[31]. Similarly, hydrogen and methane breath excretion are not modified by the presence of gluten in the test meal[31]. Further studies in both patients and healthy volunteers are needed to clarify whether gluten administration should be considered as a risk factor for the onset of symptoms.

HYPOCALORIC DIET IN PATIENTS WITH FIBROMYALGIA

The effect of a hypocaloric diet on fibromyalgia symptom severity was analysed in two studies[32,33]. In a randomized controlled trial, in comparison with an isocaloric diet, the administration of a hypocaloric diet induced a significant reduction of the severity of pain, fatigue and depression. Moreover, after hypocaloric diet, inflammatory markers, such as IL-6 and PCR, were significantly lower[32]. An open trial in fibromyalgic patients showed a significant reduction of pain severity, an increase of quality of life and acceptance of body image, a reduction of anxiety and depression severity[33]. A recent review on seven papers on dietary intervention in fibromyalgia underlined the very low overall certainty of evidence of 12 and a moderate certainty of 2 out 14 analyzed outcomes and suggested that a psychological component of the disease could be responsible, at least in part, for the effect of diet[34].

CONCLUSIONS

The true prevalence of food allergies and intolerances in fibromyalgia is not yet well defined. The close association between fibromyalgia and functional gastrointestinal conditions often makes it difficult to define the origin of the symptoms in the individual patient. Selected subgroups of patients may benefit from a gluten-free diet, but further studies are still needed to define the relationship between the effect of food intake on fibromyalgia.

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