ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

# A low fermentable oligo-di-mono-saccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits

## *Una dieta baja en oligo-, di- y monosacáridos (FODMAPs) es un tratamiento adecuado para pacientes con fibromialgia, con beneficios clínicos y nutricionales*

Ana Paula Marum[1], Cátia Moreira[2], Pablo Tomas-Carus[3,4], Fernando Saraiva[1] and Catarina Sousa Guerreiro[1,2]

*[1]Faculdade de Medicina de Lisboa. Lisbon, Portugal. [2]Escola Superior de Tecnologia da Saúde de Lisboa. Lisbon, Portugal. [3]Departamento de Desporto e Saúde. Escola de Ciências e Tecnologia. Universidade de Évora. Évora, Portugal. [4]Research Centre for Sports, Health and Human Development. CIDESD, GERON. Portugal*

## Abstract

**Introduction:** Fibromyalgia is a chronic rheumatic disease producing widespread pain, associated to a major comorbidity -irritable bowel syndrome. Low FODMAPS diet (low fermentable oligo-di-mono-saccharides and polyols diet) has been effective in controlling irritable bowel syndrome symptoms. Overweight is an aggravating factor for fibromyalgia. We studied effects of low fermentable oligo-di-mono-saccharides and polyols diets on fibromyalgia symptoms and weight status.

**Methods:** A longitudinal study was performed on 38 fibromyalgia patients using a four-week, repeated assessment as follow: M1 = first assessments/presentation of individual low fermentable oligo-di-mono-saccharides and polyols diet; M2 = second assessments/reintroduction of FODMAPs; M3 = final assessments/nutritional counselling. The assessment instruments applied were: Fibromyalgia Survey Questionnaire (FSQ); Severity Score System (IBS-SSS); visual analogic scale (VAS). Body mass-index/composition and waist circumference (WC) were also measured. Daily macro-micronutrients and FODMAP intake were quantified at each moment of the study.

**Results:** The studied cohort was 37% overweight, 34% obese (average body mass-index 27.4 ± 4.6; excess fat mass 39.4 ± 7%). Weight, body mass-index and waist circumference decreased significantly ($p < 0.01$) with low fermentable oligo-di-mono-saccharides and polyols diet, but no significant effect on body composition was observed. All fibromyalgia symptoms, including somatic pain, declined significantly post-LFD ($p < 0.01$); as well for severity of fibromyalgia [Fibromyalgia survey questionnaire: M1 = 21.8; M2 = 16.9; M3 = 17.0 ($p < 0.01$)]. The intake of essential nutrients (fiber, calcium, magnesium and vitamin D) showed no significant difference. The significant reduction in FODMAP intake (M1 = 24.4 g; M2 = 2.6g; $p < 0.01$) reflected the "Diet adherence" (85%). "Satisfaction with improvement of symptoms" (76%), showed correlating with "diet adherence" ($r = 0.65$; $p < 0.01$).

**Conclusions:** Results are highly encouraging, showing low fermentable oligo-di-mono-saccharides and polyols diets as a nutritionally balanced approach, contributing to weight loss and reducing the severity of FM fibromyalgia symptoms.

**Key words:**

FODMAP. Fibromyalgia. Irritable bowel syndrome. Pain. Diet. Short-chain. Carbohydrates.

## Resumen

**Introducción:** la fibromialgia es una enfermedad reumática crónica, que tiene unas importantes comorbilidades -síndrome del intestino irritable (SII). La dieta baja en FODMAPs (*low fermentable oligo-di-mono-saccharides and polyols diet*) ha sido eficaz en el tratamiento del síndrome del intestino irritable. El sobrepeso es un factor agravante. Se estudiaron los efectos nutricionales del FODMAPs en la fibromialgia.

**Métodos:** estudio longitudinal en 38 pacientes con fibromialgia en el que se utilizó una evaluación repetida, durante cuatro semanas, de lo siguiente: Moment 1 (M1) = primeras evaluaciones/presentación de FODMAPs; M2 = segundas evaluaciones/reintroducción de FODMAPs; M3 = evaluaciones finales/asesoramiento nutricional. Instrumentos de evaluación: *Fibromialgia Survey Questionnaire;* síndrome del intestino irritable (IBS-SSS), escala visual analógica (EVA) y parámetros antropométricos. Cuantificación en todo momento de las ingestas diarias de macro/micro nutrientes y FODMAPs.

**Resultados:** el estudio de cohorte mostró 37% de sobrepeso y 34% obesidad; índice de masa corporal = 27,4 ± 4,6; masa grasa = 39,4 ± 7%. El peso y la circunferencia de la cintura disminuyeron significativamente con FODMAPs, pero no cambió la composición corporal. Los síntomas y la severidad de la fibromialgia (FSQ: M1 = 21,8; M2 = 16,9; M3 = 17,0) se redujeron significativamente después de FODMPAs ($p < 0,01$). No fueron observadas diferencias significativas en el consumo de nutrientes esenciales, especialmente la fibra, calcio, magnesio y vitamina D. El "seguimiento de la dieta" fue del 85% con reducción significativa de la ingesta de FODMAPs ($p < 0,01$: M1 = 24,4 g; M2 = 2,6 g). "La satisfacción con la mejora de los síntomas" (76%) se correlacionó con el "seguimiento de la dieta" ($r = 0,65$; $p < 0,01$).

**Conclusiones:** los resultados son muy alentadores, mostrando FODMAPs como un enfoque equilibrado nutricionalmente, que contribuyó a la pérdida de peso y redujo significativamente la severidad de la FM.

**Palabras clave:**

FODMAP. Fibromialgia. Síndrome del intestino irritable. Dolor. Dieta. Hidratos de carbono de cadena corta.

Received: 31/10/2016
Accepted: 03/02/2017

Marum AP, Moreira C, Tomas-Carus P, Saraiva F, Guerreiro CS. A low fermentable oligo-di-mono saccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits. Nutr Hosp 2017;34:667-674

DOI: http://dx.doi.org/10.20960/nh.769

Correspondence:

Ana Paula Marum. Faculdade de Medicina de Lisboa.
Av. Prof. Egas Moniz, 1649-028. Lisbon, Portugal
e-mail: a.p.marum09@gmail.com

## INTRODUCTION

Fibromyalgia (FM) is a functional, diffuse, widespread pain-syndrome classified and recognized by the World Health Organization as a rheumatic pathology with unknown aetiology and currently with no specific effective pharmacotherapy (1). Globally, FM is the third most frequent rheumatic disease, presenting a prevalence of 3.7%, in Portugal (2) and an average age of affliction of 59 years old (3).

FM is a chronic disease having strong impact on the quality of life and, similarly to the majority of chronic diseases, there is a substantial relationship between nutrition, health and well-being (4). Current guidelines consistently recommend a multidisciplinary approach for treating FM (5), wherein nutrition could play a key role.

In addition, obesity is a common factor in patients presenting FM (6). However, it is difficult to determine if obesity associated with FM is a consequence of inactivity imposed by pain, mental state, medication or other factors, or inversely, if obesity directly contributes to FM as an physiopathological aspect. Several studies found that being overweight can affect symptoms of FM (6). Arranz et al. showed a specific body composition in FM patients (high fat mass and low fat free mass) and found that BMI and body composition were correlated with quality of life and symptoms in FM patients (7).

Fava et al. described an increased metabolic risk, with insulin resistance, in FM patients probably due to a relationship between BMI and C-reactive protein, reflecting a micro-inflammation environment, especially in obese FM patients (8). In another study, Alcocer-Gómez et al. showed, *in vitro,* that restricting caloric content to patients fibroblasts, resulted in improved AMP phosphorylation, mitochondrial function and stress response, suggesting diet might have an *in vivo* role in FM treatment (9).

Food sensitivities are also frequently reported by FM patients, indicating a potential dietary link to central sensitization (10). A food awareness survey showed that 30% of FM patients attempted to control symptoms by restricting particular foods (11). Slim et al. proposed dietary interventions for FM treatment using a restricted gluten, lactose or FODMAPs diet; recently, published the results of the pilot trial comparing a gluten free diet (GFD) with a hypocaloric diet (HCD) in FM patients with gluten sensitivity symptoms (NCGS) (12,13); showed no significant difference between the two interventions but with similar benefits in the outcomes. Despite its specificity, GFD wasn't superior to HCD, including the effects in NCGS (14).This study is in accordance with the opinion of other authors as Biesiekiersk: gluten restriction has no effect in patients with non-celiac gluten sensitivity (NCGS), and suggested that "wheat FODMAP" could be the trigger of FM symptoms, instead of gluten (15).

As a whole, the above results suggest that diet can have a potential therapeutic role in the balance of FM syndrome. One possible dietary approach could be to restrict FODMAPs (Fermentable Oligo-Di-Mono-saccharides And Polyols) as part of a multidisciplinary treatment of FM (16). FODMAPs are composed by, poorly absorbed, short-chain carbohydrates, including excess free fructose, lactose, polyols, fructo-oligosaccharides, and galacto-oligosaccharides (17). A low FODMAP diet (LFD) was already found to alleviate GI disorders and symptoms of IBS (16,18) and by comparison, as about 70% of FM patients report IBS symptoms (19), we hypothesized that LFDs may have some therapeutic benefit on FM symptoms.

It's based in the evidence that, patients with IBS could present extraintestinal symptoms (2/3 prevalence of rheumatic disease). Symptoms of IBS usually overlap in 70% of FM patients and 60% inversely. Clinically FM does not differ whether or not it has associated IBS symptoms (19,20,22).

Literature suggests a possible common cause, responsible by both conditions. Common characteristics between IBS and FM: both are characterized by functional pain, not explained by biochemical or structural abnormalities, with predominance in females, associating with life-stressing and complain of sleep disturbances and fatigue. Therapeutic response to the same pharmacotherapy and psychotherapy is described.

Some authors consider contradictory the association between IBS and FM relating it with anti-inflammatory drugs or possible diagnosis of celiac disease in a history of FM.

To date weren't found studies showing the impact of results of LFDs on FM symptoms. This study was a pilot clinical trial on LFDs impact on FM symptoms and nutritional status of participants. Also, was included the objective of demonstrate the nutritional balance of the LFDs.

## MATERIALS AND METHODS

### PARTICIPANTS

A longitudinal study, involving introduction of LFDs to participants suffering from FM. All participants were referred from a qualified rheumatologist having a confirmed diagnosis of FM, according to American College of Rheumatology criteria, 2011 (22). The trial was conducted between January and May 2015, based on a four-week, repeated assessment model.

All patients signed an Informed consent agreement (2013 Declaration of Helsinki) to participate in the trial. The research project was approved by the Ethics Committee, Medical Academic Centre of Lisbon.

Inclusion criteria for participants were: 18-70 years old; diagnosed with FM at least one year; having received FM therapy for at least 3 months prior to the study enrollment; and having already excluded referrals on a restricted FODMAP diet, or having comorbidities requiring specific nutritional therapy. Exclusion criteria included the co-morbidities requiring specific nutritional approaches such as renal insufficiency, diabetes, celiac disease. Participants with intercurrences as Influenza and respiratory infections were excluded.

### STUDY PROTOCOL

The study consisted in three different assessments "Moments" of four weeks each, at repeated intervals, completing eight weeks

of intervention. A physician and a registered dietician were present at all assessments and available throughout the trial.

At the beginning (Moment 0) participants were introduced to the purpose and protocol of the trial. They signed informed consent agreements and received a booklet containing instructions and recipes for preparing food, as well as tables with the food rich in FODMAPs and a record-keeping section for cataloguing foods and food amounts consumed over a 72 h period.

The recommended diet in Moment 1 (M1) was elaborated reducing lactose, replacing it by lactose free products and dairy alternative drinks; reducing excess of fructose replacing apple, mango, peaches, pear, watermelon, honey, sweeteners as fructose, HFCS, by banana, blueberry, grape, melon, orange, strawberry; reducing fructans rich foods as wheat, rye, onion, garlic replacing them by corn, spelt, rice, oat, gluten free products and garlic-infused oil; reducing galactans rich foods as cabbage, chickpeas, beans, lentils replacing them by vegetables as carrot, celery, green beans, lettuce, pumpkin, potato, tomato; reducing polyols rich foods as apricots, cherries, nectarine, plums, cauliflower, sorbitol xilitol replacing them by fruits as grapefruit, kiwifruit, lemon, lime, passionfruit.

Total FODMAP intake [collective amounts of lactose, fructans, galactans, free fructose and polyols (g/day)], energy (kcal/day), and macronutrients/micronutrients consumed by the participants were quantified for each monitoring period (Moment). Participants reported individual food intake based on standardized dish, cup, and spoon measurements. The estimated dietary intake was calculated from these measurements. Quantities were based upon published amounts of FODMAPs and respective food composition tables (23,24).

At Moment 1 (M1), a clinical/dietary anamnesis was performed to obtain biographic and demographic data, comorbidities, medication requirements, food allergies or intolerances. Anthropometric assessments [weight, body mass index (BMI) and waist circumference (WC)] were performed. OMRON equipment (HBF-511B-E/HBF-511T-E) was used to evaluate fat mass and fat free mass.

All participants completed the questionnaires, which included:

- *Fibromyalgia Severity Questionnaire (FSQ),* validated according to the new ACR criteria, using a "widespread pain index" (19 points) and a "severity score index" (12 points), wherein combined scores ≥ 13 (0-31) indicate positive criteria of FM (22).
- *Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)*- uses a five visual analogue scale to quantify abdominal pain, abdominal distension, intestinal transit and the interference of IBS in daily life (0-500), score-ranked as "mild disease" (75-175), "moderate disease" (175-300) and "serious illness" (> 300) (25).
- *Clinical Outcomes in Routine Evaluation-Outcome Measure (Core-OM)* assessed the mental state and is scored 0-4 (26).
- *Visual Analogic System (VAS)* was applied for calibrating individual symptoms.

All assessment tolls are validated in English language; FSQ, Core-OM and VAS in Portuguese language. Each participant received a personal dietary plan (DP) for restricting foods rich in accordance to FODMAPs. The delivery of the DP was accompanied with accurate instructions and a request for utmost cooperation and compliance. Investigators and participants were totally available to communicate by phone or email in a regular basis.

At Moment 2 (M2) clinical/nutritional data were collected and all questionnaires were filled in, as at Moment 1. In addition, participants completed a questionnaire concerning their satisfaction and adherence to their diet. This questionnaire included questions about overall satisfaction with the study and specific satisfaction with symptoms improvement. Instructions were then given for gradual reintroduction of FODMAPs into their assigned dietary plan (DP). Was chosen a food, representing each FODMAP group, to be reintroduce, increasing the doses along 3 days with a three-day washout period.

Moment 3 (M3) was dedicated to determine any effects resulting from reintroduction of FODMAPs. Clinical and nutritional evaluations were made and assessment questionnaires applied in Moments 1 and 2 were filled in. Lastly, final dietary advice was provided to participants, encouraging them to maintain a balanced diet adjusted to body weight, and to exclude FODMAPs individually identified as being triggers of any negative symptoms.

## STATISTICAL ANALYSIS

The Kolmogorov-Smirnov normality test, with Lillifors correction, was initially used to assess data normality. Changes in values between Moments were tested using analyses of variance (ANOVA) for repeated measures or the non-parametric Friedman test, if data were evaluated as not normally distributed. For the correlations analyses Pearson test or Spearman test were used. All analyses were performed using SPSS (version 22.0; SPSS, Inc., Chicago, IL, USA), and the significance level was set at $p \leq 0.01$ for all tests.

## RESULTS

### NUTRITIONAL STATUS OF PARTICIPANTS

The cohort consisted of 38 female participants with an average age of 51 years old, and 10 years of diagnosed FM. Thirty-one participants (82%) completed all trial phases. Four types of comorbidities were identified among participants, including gastrointestinal (GI) disorders as diarrhoea, constipation, gastritis, being most common (n = 33; 88%), osteoarthritic disorders (n = 28; 74%), immuno-allergies (n = 23; 60%) and endocrine disorders, such as thyroid dysfunction (n = 7; 18%). 60% of participants (n = 23) reported some form of food intolerance and 11% (n = 4) were allergic to certain foods (documented).

At the outset of the trial, the cohort presented a mean weight of 69 ± 12 kg, BMI of 27.4 ± 4.6 kg/m$^2$, body composition with excess fat mass (39.4 ± 7%) and a fat free mass in the lower limit (25.5 ± 3%), with an average WC of 84 ± 9 cm. Accordingly, a total of 27/38 (71%) of participants had excess of weight, 14

(37%) of them classified as obese. Only 11/38 (29%) were normal weight (Table I).

There was a significant decline in certain anthropomorphic indices among participants between M1 and M2 (restricting FODMAPs). There were significant reductions in mean Weight (> -1 kg; $p < 0.01$), BMI (-0.4 kg/m$^2$; $p < 0.01$) and WC (-2.5 cm; $p < 0.01$). However, no significant changes occurred with body composition (fat mass and fat free mass). The assessment made after reintroduction of FODMAPs, showed no significant changes (between M2 and M3) in all the parameters studied (Table II). Reduction in WC occurred simultaneously with a large reduction in abdominal distension with significant decline (VAS bloating score: M1 = 6.9, M2 = 2.8; M3 = 3.8; $p < 0.01$) (Table III).

## DIETS

During all assessment moments, diet was characterized according to macro- and micronutrients including FODMAPs intakes, with the objective to demonstrate the nutritional balance of the LFDs. Average FODMAP intake declined significantly between M1 and M2, when was followed the FODMAP restrictive period (M1 = 24.4 ± 12 g/day *vs.* M2 = 2.63 ± 5.4 g/day; $p < 0.01$). However there was no significant change in FODMAP intake between M2 and M3, after reintroduction of FODMAPs (M2-M3 = 3.5 g/day; $p > 0.05$). The amounts of FODMAPs consumed by participants at M2, compared with those calculated in assigned dietary plans (DP), did not differ significantly (M2 = 2.63 ± 5.4 *vs.* DP = 0.96 ± 1.14 g/day; p = 0.836) (Table IV). Reported compliance in following the assigned diet plans was 86%.

Mean daily energy need was 1,548 ± 121 kcal based on a normocaloric diet for adjusted weight. Introduction of a normocaloric-LFD (1,552 ± 119) to participants resulted in significant ($p < 0.01$) reduction of caloric intake between M1 and M2 (M1 = 1,958 ± 404 kcal/day *vs.* M2 = 1,625 ± 304 kcal/day, respectively). In this group of patients, there were no significant differences in micronutrient intake as calcium (Ca), magnesium (Mg) and vitamin D (Vit D) between M1, M2 and M3; although the intakes were always lower according the DRI in all assessments [M1 doses: Ca = 703 mg (daily intake recommendation –DRI = 1000 mg), Mg = 249 (DRI = 400 mg), and Vit D = 2,16 ug (DRI = 15 ug)]. About macronutrients, only was found significant changes in the glycosides consume, between M1 and M2 (233.7 g *vs.* 180 g; $p < 0, 01$), and of the lipids, between M1 and M3 (79.4 g *vs.* 57.8; $p < 0, 01$). Fiber and protein intake was not affected by changes in the diets (Table IV).

**Table I.** Participant body composition (n = 38)

| | |
|---|---|
| Weight (kg)* | 69 ± 12 |
| BMI (kg/m$^2$)* | 27.4 ± 4.6 |
| *BMI classes*** | |
| Normal weight | 29% |
| Overweight | 37% |
| Obesity | 34% |
| Waist circumference (cm) * | 84 ± 9 |
| % Fat mass * | 39.4 ± 7 |
| % Fat free mass * | 25.5 ± 3 |
| Energetic needs* | 1548 ± 121 |

**Value expressed as MEAN ± SD; **Expressed as a percentage value.*

## SYMPTOMS

According to the IBS-SSS classification, this cohort presented only 2/38 (4%) of the participants with a score below 75 (without disease), and 33/38 (87%) classified as moderate to severe disease (score over 175); 25/36 of them (70%) presenting the sub-type constipated (IBS-C) (Table V). After introduction of LFDs, there were significant reductions in GI symptoms. The average improvement in IBS-SSS score was 132 ± 117, representing a significant 50% reduction after 4 weeks of LFDs (M1 = 275.3 *vs.* M2 = 137.4; $p < 0.01$) (Table III). The symptoms of Abdominal Pain and Distension also showed significant reductions after introduction of LFDs, between M1 and M2 (M1 = 5.0 *vs.* M2 = 2.4 and M1 = 6.9 *vs.* M2 = 2.8; $p < 0.01$; in pain and distension, respectively) (Table III). But, these declines were no longer significant after reintroduction of FODMAPS. There was also a significant reduction in constipation with LFDs during M1 and M2,

**Table II.** Comparison of repeated assessment of nutritional status between different assessment periods (M1, M2 and M3) of the trial (n = 31)

| Parameter | M 1 | M2 | M3 | p-value | (M1-M2) | (M2-M3) |
|---|---|---|---|---|---|---|
| Weight, kg | 68.36 | 67.08 | 67.1 | $p < 0.01^b$ | * | ns |
| BMI, kg/m$^2$ | 27.2 | 26.8 | 26.8 | $p < 0.01^b$ | * | ns |
| WC (cm) | 83.9 | 81.4 | 81.4 | $p < 0.01^b$ | * | ns |
| Fat mass, % | 39.4 | 38.8 | 38.9 | $0.20^b$ | ns | ns |
| Fat free mass, % | 25.5 | 25.7 | 25.9 | $0.33^b$ | ns | ns |

*FODMAP: low fermentable oligo-, di-, mono-saccharides and polyols); BMI: body mass index; WC: waist circumference; *Significant. [a]p-value of Friedman test. [b]p-value of analysis of variance (ANOVA).*

**Table III.** Repeated assessments of symptoms scores (n = 31)

| Parameter | M1 | M2 | M3 | P value | M1-M2 | M2-M3 |
|---|---|---|---|---|---|---|
| FM Severity Score | 21.8 | 16.9 | 17.0 | $p < 0.01^a$ | * | ns |
| IBS Severity Score | 275.3 | 137.4 | 158.1 | $p < 0.01^b$ | * | ns |
| Distress Score | 1.8 | 1.6 | 1.5 | $p < 0.01^b$ | * | ns |
| VAS generalize pain | 6.6 | 4.9 | 5.4 | $0.000^a$ | * | ns |
| Muscle tension | 6.1 | 4.6 | 4.7 | $0.002^a$ | * | ns |
| Asthenia | 7.3 | 5.8 | 5.6 | $0.024^b$ | ** | ns |
| Depression | 5.1 | 4.2 | 4.0 | $0.043^a$ | ** | ns |
| Sleep quality | 6.6 | 5.1 | 5.0 | $0.017^b$ | ** | ns |
| Memory | 6.9 | 5.0 | 5.5 | $0.001^a$ | * | ns |
| Headache | 4.9 | 3.8 | 4.0 | $0.046^a$ | ** | ns |
| Abdominal pain | 5.0 | 2.4 | 3.0 | $0.000^b$ | * | ns |
| Constipation | 5.7 | 3.3 | 3.8 | $0.012^b$ | ** | ns |
| Diarrhoea | 2 | 0.8 | 1.5 | $0.019^b$ | ** | ns |
| Bloating | 6.9 | 2.8 | 3.8 | $0.000^b$ | * | ns |

*[a]p-value ANOVA. [b]p-value of Friedman test. *Statistically significant differences between M1 and M2 ($p < 0.01$). **Statistically significant differences between M1 and M2 ($p < 0.05$).*

**Table IV.** Comparisons of nutritional intake between different assessment periods (M1, M2 and M3) of the trial (n = 31) and between LFD and DP

| | M1 | M2 | M3 | p-value | M1-M2 | M2-M3 | DP | M2-DP |
|---|---|---|---|---|---|---|---|---|
| FODMAPs, g | 24.4 | 2.6 | 6.1 | $p < 0.01^a$ | * | ns | 0.96 | ns |
| Energy, kcal | 1973 | 1615 | 1566 | $p < 0.01^b$ | * | ns | 1556 | ns |
| Glycosides, g | 233.7 | 180.0 | 178.5 | $p < 0.01^b$ | * | ns | 203 | ns |
| Protein, g | 74.1 | 71.8 | 68.1 | $p = 0.295^b$ | ns | ns | 70.7 | ns |
| Lipids, g | 79.4 | 65.2 | 57.8 | $p < 0.01^{a¥}$ | ns | ns | 53.9 | ns |
| Fiber, g | 22.7 | 21.1 | 20.7 | $p = 0.29^b$ | ns | ns | 22.3 | ns |
| Calcium ,mg | 703 | 717 | 708 | $p = 0.90^a$ | ns | ns | 817 | ns |
| Magnesium, mg | 249 | 223 | 242 | $p = 0.30^a$ | ns | ns | 252 | ns |
| Vitamin D, ug | 2.16 | 3.06 | 2.71 | $p = 0.96^a$ | ns | ns | 2.5 | ns |

*DP: dietary plan; LFD: low FODMAP diet. *Statistically significant difference between M1 and M2 ($p < 0.01$). ¥Statistically significant difference between M1 and M3 ONLY ($p < 0.01$). [a]p-value of Friedman test. [b]p-value of analysis of variance (ANOVA).*

**Table V.** Characterization of gastrointestinal symptoms of FM among participants prior to initiation of the trial

| | | |
|---|---|---|
| *Score IBS-SSS[a]* | 275.3 ± 101 | 0 a 500 |
| No disease/remission | 4% (2/38) | < 75 |
| Mild disease | 9% (3/38) | 75-175 |
| Moderate disease | 50% (19/38) | 175-300 |
| Serious illness | 37% (14/38) | > 300 |
| IBS-C | 70% (25/36) | |
| IBS-M | 22% (8/36) | |
| IBS-D | 8% (3/36) | |

*[a]Expressed as mean ± SD. IBS-SSS: Irritable Bowel Syndrome symptom severity scale; IBS with constipation (IBS-C), with diarrhoea (IBS-D) and mist (IBS-M).*

and a non-significant increasing after reintroduction of FODMAP, as assessed at M3 (M1 = 5.7, M2 = 3.3, M3 = 3.8; $p < 0.05$) (Table III).

There were significant declines (patient improvement) in all individual FM symptoms between M1 and M2, especially with scores on somatic pain (VAS) (M1 = 6.6, M2 = 4.9; $p < 0.01$) and muscle tension (M1 = 6.1, M2 = 4.9; $p < 0.01$) in accordance with the reduction in severity of FM (M1 = 22; M2 = 17; $p < 0.01$). No significant differences were noted after reintroduction of FODMAPs. The distress score throughout the trial and was not aggravated by reintroduction of FODMAPs (M1 = 1.8; M2 = 1.6; M3 = 1.5) (Table III).

It was found notable, positive correlations between improvements of somatic pain (declined VAS scores) with a number of

GI symptoms, including abdominal pain (rs = 0.443; $p < 0.01$), abdominal distension (rs = 0.386; $p < 0.05$) and with the improvement of IBS-SSS score (rs = 0.406; $p < 0.01$). Of particular note was "rate of satisfaction with improvement in symptoms" being strongly correlated (r = 0.650; $p < 0.01$) with "diet compliance rate", suggesting patients were conscious of LFDs lowering severity of symptoms. In concordance, was reported 77% of satisfaction with the diet in general and was observed 85% of compliance to diet plans.

## DISCUSSION

This was the first clinical trial wherein a LFD intervention was experimented as a potential therapeutic approach for FM. The results of this pilot intervention with LFD, suggest beneficial influence on the outcome of somatic and visceral symptoms of FM (27). The study could prove that, the dietary plan implemented restricted in FODMAPs, was nutritionally balanced and provided a healthy diet, with benefits on weight status, at least for the period of the duration of the trial (4-8 week). Was found a very significative compliance to the assigned diets, comparing the participants FODMAPs intake with DP content.

There are some concerns regarding safety and nutritional balance of LFDs (28). LFDs prescribed in our study were helpful in providing a balanced intake of energy, macro- and micronutrients.

Our cohort exhibited nutritional status profiles similar to previous studies describing FM body composition (6) with a high prevalence of overweightness and high fat mass (29,30). The majority of research already done on FM, presents the weight loss as being crucial on alleviating its impact (7,31). We found a nutritional benefit provided by the prescribed LFDs, resulting in weight-loss without significant decrease in essential nutrient intake (protein, fiber, calcium, magnesium, vitamin D. The nutritional counselling promoted a tendency to improve the intake of important nutrients as calcium and vitamin D without, however, to be sufficient to achieve the recommended levels for the needs of these patients. The micronutrient intake was generally low in all assessed moments, which agrees with the data of publications describing the same pattern of nutritional deficiencies in FM (32,33).

The results of this trial have notable commonalities with other study's, where was implemented a LFD therapy for IBS treatment (16,18,28). LFD was found to alleviate symptoms of IBS in all published studies, providing an improvement of 75% in IBS cases. In IBS, LFD was found to be especially effective in relieving abdominal pain and distension, but was less effective in mitigating constipation (16,28). Also, we found this response among our cohort of FM patients, with alleviation of GI symptoms by LFD therapy and the most prominent response in abdominal pain and distension. These results reflect those published by Perez et al. where 31 IBS patients were treated with LFD for 21 days (34). Additional comparison between ours and Perez et al. results, shows reductions in VAS abdominal pain scores (6 to 2.8 *vs.* 5 to 2.4, respectively) and VAS distension scores (7.0 to 4.2 *vs.* 6.9 to 2.2, respectively).

The results of the intervention in the subgroup of FM constipated patients, are consistent with the Rao et al. opinion (28), about IBS patients treated with LFD. The study also found reduction in the global IBS score in IBS-C sub-type, when treatment of LFD was implemented. Thus, LFD can to be a potential therapy in FM patients suffering from constipation but, such therapy, needs to be accompanied by educating patients to strictly adhere to recommended levels of dietary fiber and water intake. Other studies report a large predominance of constipation (IBS-C sub-type 90%) in patients with FM (19,34). Our trial showed a 70% prevalence of constipation (25/36, IBS-C), 8% with diarrhoea (3/36, IBS-D) and 22% with mixed symptoms of diarrhoea and constipation (8/36, IBS-M). The prevalence of IBS-C in FM sufferers appears to be higher than in patients with only IBS, in general, where it is reported to be about 50% of cases (35). Another study of LFD therapy for IBS showed this same profile: 64.5% IBS-C, 22.6% IBS-D and 12.9% IBS-M (32). Authors (28) discuss the possibility that the reduced fiber intake of the LFD may contribute to constipation aggravation. Regarding the data from our study, we found that fiber intake was not significantly different throughout the trial and fiber consumption was always sufficient in relation to the daily needs in this trial. Based on these observations, we concluded fiber content did not contribute to any changes in FM symptoms in our study.

It should be noted that the reduction of prebiotic fiber, resulted from the fructo-oligosaccharide LFD restriction, is described as a possible risk factor to colon health and can contribute to constipation and colorectal cancer (28,36). However, these risks appear to be contradictory to the evident improvement of IBS symptomatology treated with LFD, as described by authors (16) and confirmed in our study with FM patients suffering from concomitant IBS. This contradiction has been described by authors as the "paradox of the LFD" (3). Furthermore, the eventual risk of lowering prebiotic fiber content could be avoided by concomitant inclusion of probiotics in LFD therapy. This hypothesis has already been proposed (16) but has yet to undergo study.

The more remarkable results of our study were the alleviation of FM symptoms as somatic pain, muscle tension and impact in the daily life of FM, after treatment with LFDs. Moreover, gradual improvement of distress score, throughout our study, was an added contribution of LFD therapy to symptomatic improvements. The positive correlation between reductions in somatic pain and GI disorders, in our study, is also notable. More extensive research is needed to discern the interconnection between these symptoms in FM patients.

There are many other aspects of LFD therapy open to future research. One is determining what role, if any, LFD-therapy plays in the neuro-enteric axis of FM patients. Also, cost/benefit analysis of implementing LFD-therapy for treating FM needs to be investigated, similar to what has already occurred for IBS.

## CONCLUSION

FM is a disease that requires a treatment with multidisciplinary approach and nutrition approach has a strong potential. Our study is the first clinical trial that evaluate LFD-intervention integrated

into FM patient treatment. The diet therapy, LFD, prescribed in this study was shown to have positive impact on FM symptoms, especially with painful hypersensitivity, a mechanism commonly mediating symptoms of FM and IBS. Also, LFD contributed to weight loss in the cohort studied, an advantage in FM sufferers with a high prevalence of overweightness. Moreover, LFD demonstrated to be a balance diet without nutritional risk described in addition to symptomatic improvement of FM.

Overall, this pilot study shows that a LFD could be one option to use as a potential dietary approach to FM treatment but these limited results imply cautious optimism towards use of LFD therapy for FM and, at a minimum indicate, more extensive studies must be conducted to verify its efficacy and safety.

## ACKNOWLEDGMENTS

We thank to Santa Maria Hospital, Department of Rheumatology, and Myos Association the consent and logistic support for the field research. We also thank Prof. Elisabete Carolino Drª Alice Gonçalves and Dr. Bruce Campbell for statistical assistance and the English revision.

## STATEMENT OF AUTHORSHIP

Ana Paula Marum contributed to conception and design of the study, generation, collection, assembly, analysis and interpretation of data, and drafting article; Cátia Moreira contributed to dietary plans and nutritional quantifications, Pablo Tomas-Carus contributed to recruitment, critical revision of article, Fernando Saraiva contributed to recruitment and critical revision of article, Catarina Sousa Guerreiro contributed to concept/design, revising it critically for important intellectual content and final approval of the version to be submitted.

## REFERENCES

1. Borchers AT, Gershwin ME. Fibromyalgia: A Critical and comprehensive review. Clin Rev Allergy Immunol 2015;49(2):100-51. DOI: 10.1007/s12016-015-8509-4.
2. Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M, et al. Prevalence of fibromyalgia: a survey in five european countries. Semin Arthritis Rheum 2010;39(6):448-53. DOI: 10.1016/j.semarthrit.2008.12.003.
3. Laroche F, Guérin J. Fibromyalgie: où en est-on en 2015? Douleur et Analgésie. 2015;28(1):31-9. DOI: 10.1007/s11724-015-0407-2.
4. Nishida C, Uauy R, Kumanyika S, Shetty P. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. Public Health Nutr 2004;7(1A):245-50. DOI: 10.1079/PHN2003592.
5. Ángel García D, Martínez Nicolás I, Saturno Hernández P. Clinical approach to fibromyalgia: synthesis of evidence-based recommendations, a systematic review. Reumatol Clínica 2015;803:4-7. DOI: 10.1016/j.anpedi.2012.06.005.
6. Rossi A, Lollo AC, Guzzo MP, Giacomelli C, Atzeni F, Bazzichi L, et al. Fibromyalgia and nutrition: what news? Clin Exp Rheumatol 2015;33(Suppl.88):S117-25.
7. Arranz LI, Canela MA, Rafecas M. Relationship between body mass index, fat mass and lean mass with SF-36 quality of life scores in a group of fibromyalgia patients. Rheumatol Int 2012;32(11):3605-11.
8. Fava A, Plastino M, Cristiano D, Spanò A, Cristofaro S, Opipari C, et al. Insulin resistance possible risk factor for cognitive impairment in fibromialgic patients. Metab Brain Dis 2013;28(4):619-27.
9. Alcocer-Gómez E, Garrido-Maraver J, Bullón P, Marín-Aguilar F, Cotán D, Carrión AM, et al. Metformin and caloric restriction induce an AMPK-dependent restoration of mitochondrial dysfunction in fibroblasts from Fibromyalgia patients. Biochim Biophys Acta 2015;1852(7):1257-67.
10. Holton KF, Kindler LL, Jones KD. Potential dietary links to central sensitization in fibromyalgia: past reports and future directions. Rheum Dis Clin North Am 2009;35(2):409-20.
11. Arranz LI, Canela MÁ, Rafecas M. Dietary aspects in fibromyalgia patients: results of a survey on food awareness, allergies, and nutritional supplementation. Rheumatol Int 2012;32(9):2615-21.
12. Slim M, Calandre EP, Rico-Villademoros F. An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms. Rheumatol Int 2014;35(3):433-44. DOI: 10.1007/s00296-014-3109-9.
13. Slim M, Molina-Barea R, García-Leiva JM, Rodríguez-Lopez CM, Morillas-Arques P, Rico-Villademoros F, et al. The effects of gluten-free diet versus hypocaloric diet among patients with fibromyalgia experiencing gluten sensitivity symptoms: protocol for a pilot, open-label, randomized clinical trial. Contemp Clin Trials 2015;40:193-8. DOI: 10.1016/j.cct.2014.11.019
14. Slim M, Calandre EP, García-Leiva JM, Rico-Villademoros F, Molina-Barea R, Rodríguez-López CM, et al. The Effects of a gluten-free diet versus a hypocaloric diet among patients with fibromyalgia experiencing gluten sensitivity–like symptoms. J Clin Gastroenterol 2016 DOI: 10.1097/MCG.0000000000000651
15. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 2013;145(2):320-8. DOI: 10.1053/j.gastro.2013.04.051.
16. Marsh A, Eslick EM, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. Eur J Nutr 2016;55:897-906. DOI: 10.1007/s00394-015-0922-1.
17. Barrett JS, Gibson PR. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? Therap Adv Gastroenterol 2012;5(4):261-8. DOI: 10.1177/1756283X11436241
18. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. J Gastroenterol Hepatol 2010;25(2):252-8. DOI: 10.1111/j.1440-1746.2009.06149.x;
19. Helfenstein M, Heymann R, Feldman D. Prevalence of irritable bowel syndrome in patients with fibromyalgia. Rev Bras Reum 2006;46(11):16-23. DOI: 10.1590/S0482-50042006000100005.
20. Chang L. The association of irritable bowel syndrome and fibromyalgia. Eur J Surg 1998;164(583):8-1032-36.
21. Veale D, Kavanagh G, Fieldding JF, Fitzgerald O. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. Rheumatology 1991;30(3):220-2.
22. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 2011;38(6):1113-22. DOI: 10.3899/jrheum.100594.
23. Biesiekierski JR, Rosella O, Rose R, Liels K, Barrett JS, Shepherd SJ, et al. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. J Hum Nutr Diet 2011;24(2):154-76.
24. Muir JG, Rose R, Rosella O, Liels K, Barrett JS, Shepherd SJ, et al. Measurement of short-chain carbohydrates in common Australian vegetables and fruits by high-performance liquid chromatography (HPLC). J Agric Food Chem 2009;57(2):554-65.
25. Almansa C, Sánchez RG, Barceló M, Díaz-rubio M, Rey E. Traducción, adaptación cultural y validación al español del cuestionario de gravedad del síndrome de intestino irritable (Irritable Bowel Syndrome Severity Score). Rev Esp Enfermedades Dig 2011;103(12):612-8.
26. Sales CMD, Moleiro CM, Evans C, Alves PCG. Versão Portuguesa do CORE-OM: tradução, adaptação e estudo preliminar das suas propriedades psicométricas. Rev Psiquiatr Clínica 2012;39(2):54-9.
27. Marum AP, Moreira C, Saraiva F, Tomas-Carus P, Sousa-Guerreiro C. A low fermentable oligo-di-mono saccharides and polyols (FODMAP) diet reduced pain and improved daily life in fibromyalgia patients. Scand J Pain Scandinavian Association for the Study of Pain 2016;1-7.

28. Rao SSC, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. Aliment Pharmacol Ther 2015;41(12):1256-70. DOI: 10.1111/apt.13167
29. Lobo MT, Paiva E, Andretta A, Schieferdecker ME. Composição corporal por absorciometria radiológica de dupla energia de mulheres com fibromialgia. Rev Bras Reumatol 2014;54(4):273-8.
30. Aparicio VA, Ortega FB, Carbonell-Baeza A, Gatto-Cardia C, Sjöström M, Ruiz JR, et al. Fibromyalgia's key symptoms in normal-weight, overweight, and obese female patients. Pain Manag Nurs 2013;14(4):268-76.
31. Senna MK, Sallam RA-ER, Ashour HS, Elarman M. Effect of weight reduction on the quality of life in obese patients with fibromyalgia syndrome: a randomized controlled trial. Clin Rheumatol 2012;31(11):1591-7.
32. Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. Rheumatol Int 2008;28(11):1117-21.
33. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain 2014;155(2):261-8.
34. Pérez y López N, Torres-López E, Zamarripa-Dorsey F. Respuesta clínica en pacientes mexicanos con síndrome de intestino irritable tratados con dieta baja en carbohidratos fermentables (FODMAP). Rev Gastroenterol México 2015;80(3):180-5. DOI: 10.1016/j.rgmx.2015.06.008
35. Schmulson M, Vargas JA, López-Colombo A, Remes-Troche JM, López-Alvarenga JC. Prevalence and clinical characteristics of the IBS subtypes according to the Rome III criteria in patients from a clinical, multicentric trial. Rev Gastroenterol México 2010;75(4):427-38.
36. Staudacher HM, Lomer MCE, Anderson JL, Barrett JS, Muir JG, Irving PM, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr 2012;142(8):1510-8.
37. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut 2015;64(1):93-100.