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Original article

A Nutritional Supplementation Intervention with Coenzyme Q10, Tryptophan and Magnesium for the Management of Fibromyalgia Symptoms

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Abstract. *Introduction and Objectives:* Management of fibromyalgia syndrome (FMS) is challenging and requires a multidisciplinary strategy. This pilot study aimed to investigate the effects of a dietary supplementation (NSC) containing coenzyme Q10, magnesium and tryptophan on reducing fibromyalgia symptoms, and to assess its tolerability. *Materials and methods:* Patients underwent a 3 month-treatment with NSC followed by 1-month washout and 3 month-treatment with placebo. The Combined Index of Severity of Fibromyalgia (ICAF) was used to evaluate FMS main symptoms. *Results:* Twenty women completed the study, with a mean age of 51.9 (±7.2) years. Mean time since experiencing fibromyalgia symptoms was 7.7 (±6.3) years. Depression and anxiety were reported in 65.0% (13/20) and 30.0% (6/20) of cases, respectively. Fatigue and functional capacity improved after both treatment periods, whereas pain, sleep quality and impact enhanced only after NSC intake. Depression, anxiety symptoms and patients' general health did not improve after treatment. Active coping strategies enhanced after study treatment (not after placebo treatment), while passive coping strategies worsened (even more after placebo treatment). The global ICAF improved after NSC treatment and declined after placebo treatment. No significant differences were found in any of the efficacy outcomes. NSC treatment was well tolerated, with a low incidence of adverse events (5.0%, 1/20). *Discussion and Conclusions:* Supplementation with NSC was effective in improving physical aspects of FMS such as fatigue, pain, sleep quality and functional capacity, as well as global well-being of patients. However, larger studies are needed to confirm the results of this pilot study and whether improvements observed could be statistically significant.

Keywords: fibromyalgia, dietary supplementation, ICAF questionnaire, coenzyme Q10, magnesium, tryptophan

Introduction

Fibromyalgia syndrome (FMS) is a multidimensional chronic disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive dysfunction, depressive episodes, and anxiety (1, 2). Generally, these symptoms may persist over time but fluctuate in intensity from mild to severe (3). Fibromyalgia affects nearly 2%–4% of the global population with a greater prevalence among women, having a negative impact on physical, social, and psychological functioning (4, 5).

Although the etiology and pathogenesis of fibromyalgia are still not fully understood, recognition and diagnosis of FMS has significantly improved over the last years. Furthermore, research examining genetic, neurobiological and psychological mechanisms underlying fibromyalgia symptoms has contributed

to a better understanding of this debilitating disorder (6-8). Nonetheless, due to its sheer complexity, designing interventions to treat FMS continues to be a challenge, and its management requires a multidisciplinary strategy aimed to improve symptoms, function and quality of life.

Despite there is no definitive therapy for FMS, optimal interventions suggested by the recent guidelines include both pharmacological and non-pharmacological approaches (9, 10). Among non-pharmacological treatments, nutrition is a promising tool for FMS patients, given that oxidative stress and/or an imbalance of nutritional components have been demonstrated to play a critical role in the pathophysiology of FMS (11-13). In addition, muscle pain experienced by FMS patients has been associated with deficiencies in essential metal ions, certain vitamins, minerals, and aminoacids (11, 14). Dietary supplements therefore might be critical to improve the overall health status of these patients.

The therapeutic potential of coenzyme Q10 (CoQ10), magnesium, and tryptophan for fibromyalgia can be inferred from some published clinical trials. Oral supplementation with the antioxidant CoQ10 has been shown to decrease fatigue and muscle pain levels in FMS patients (15), and to control depressive symptoms with the regulation of the serotoninergic system (16, 17). Magnesium, which is a trace element commonly deficient in these individuals, has been suggested to improve and prevent not only chronic pain, but also commonly comorbid psychiatric disorders (18). Serotonin substrate supplementation, via L-tryptophan or 5-hydroxytryptophan, has been found to improve symptoms of depression, anxiety, insomnia, pain and eating disorders (19, 20). A dietary and metabolic approach that supports the absorption of tryptophan, has also been shown to be effective in improving FMS symptoms (21). However, the effects of the ingestion of the three above-mentioned components combined have not yet been examined in FMS patients. Hence, the purpose of this pilot study was to investigate the effects of a dietary supplementation with CoQ10, magnesium and tryptophan on reducing fatigue, pain intensity, functional and emotional status, as well as to assess its tolerability in patients with fibromyalgia.

Material and Methods

Study Design and Participants

This was a prospective, double-blind, placebo-controlled, two-period pilot study (FATMIA Study) to evaluate the efficacy and tolerability of a nutritional supplement (NSC) containing a combination of CoQ10 (50.0 mg/capsule), tryptophan (150.0 mg/capsule) and magnesium (296.0 mg/capsule), in FMS patients under a number of ongoing pharmacological treatments for FMS. Patients were recruited from the Department of Rheumatology of the Hospital Universitari Quirón-Dexeus (Barcelona, Spain) and the Hospital Universitari Parc Taulí (Barcelona, Spain), between March and October 2017.

All patients underwent two study periods of 3 months (active treatment with NSC and treatment with placebo), with a 1-month washout period in between. The placebo formulation contained the same excipients as the NSC, without the active components. Both the investigational product and placebo were administered at a dose of two capsules per day, orally, preferably in the morning upon waking. Although the order of administration of the active therapy and the placebo was the same for all patients, both patients and researchers were blind to the treatment allocation.

A sample of 23 patients aged from 18 to 80 years, with a formal diagnosis of fibromyalgia of at least two years, were included in the study. Fibromyalgia was diagnosed according to the revised American College of Rheumatology FMS-2016 criteria (22). Patients were excluded if they had other diseases associated with chronic pain; a score ≥30 on the 21-item version of the Beck Depression Inventory (BDI) (23, 24) and/or a score ≥1 on item 9 (suicide risk assessment); pregnant or breastfeeding women; patients under treatment with other complementary or alternative therapies; subjects receiving more than two serotonin inhibitors; and changes in antidepressant medication and/or other concomitant treatments within 3 months before inclusion. All participants were fully informed and provided signed written informed consent. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Study Procedures and Assessment Tools

During the first visit (baseline), patient demographics and clinical characteristics including age, gender, height, weight, years since the diagnosis of FMS, alcohol intake, smoking status, physical activity, and psychiatric/psychological symptoms were recorded. The presence and severity of depressive symptoms were evaluated with the 21-item self-administered questionnaire BDI, in which each question is graded subjectively from 0 to 3, with higher scores indicating greater severity. Patients also completed the Combined Index of Severity of Fibromyalgia or ICAF (an acronym in Spanish for Índice Combinado de Afectación de la Fibromialgia) (25), a self-administered questionnaire composed of 59 items about the most prevalent clinical manifestations of FMS. ICAF provides information on emotional, physical, and of coping aspects (active and passive) of the patient, and calculates a total score or global score that integrates the four previous factors. The Emotional factor emphasizes the role of emotional aspects such as anxiety and depression. The Physical factor evaluates pain, fatigue, sleep quality and functional capacity. The third factor is referred to as Active Coping, which covers positive strategies for coping with the syndrome, and includes positive expectations of self-efficacy related with the disease. Finally, the fourth factor is referred to as Passive Coping, which addresses ways of coping with the disease centered on inactivity and on the asking for external support (25).

Participants began treatment with NSC after the baseline visit. Telephone monitoring of any adverse event was conducted at 2 months post-treatment. At 3 months, patient demographics and adverse events were recorded, and ICAF was applied. Following a 1-month washout period, patients were prescribed placebo for three additional months. Again, telephone monitoring of any adverse event was conducted at 2 months post-treatment. The last visit was performed three months after having started placebo treatment, and at this point, ICAF was completed and patient demographics and adverse events were recorded.

Statistical analysis

The main variable used to measure the treatment effectiveness was item "fatigue" in the ICAF questionnaire. The other items, as well as the global score of the questionnaire were used as secondary variables. Descriptive statistics were generated for all variables. Continuous variables were described using the mean, standard deviation (SD), median, 25 and 75 percentiles (P25-P75), maximum and minimum. Categorical variables were described as absolute (n) and relative (%) frequencies. Statistical comparisons between visits were performed with the Student's t-test for paired data (p-values lower than 0.05 were considered statistically significant): i) comparison of the main and secondary variables between the end and the beginning of the two 3-month study periods; and ii) comparison of the differences in the evolution of the symptoms during the two treatment periods. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, US).

Results

This pilot study included 23 patients. Twenty of them completed the study while three (13.0%) dropped out because they failed to attend all clinical visits (n=2) or presented an adverse event (n=1). Baseline characteristics of participants are presented in Table 1. All participants were female, with a mean (SD) age of 51.9 (7.2) years (range, 41.0-63.0). The mean BMI was within the overweight range (26.9 [4.5] kg/m^2; range, 19.8-36.8). The mean time since experiencing fibromyalgia symptoms was 7.7 (6.3) years. Fifty percent of the group (10/20) had a paid employment. None of the patients reported an alcohol intake habit; 40.0% of them (8/20) were smokers (≥1 cigarette per day); and 85.0% (17/20) were not performing any kind of physical activity. Depression and anxiety were reported in 65.0% (13/20) and 30.0% (6/20) of cases, respectively. All patients were under pharmacological treatment for FMS symptoms. The most commonly reported medication was paracetamol in 60.0% (12/20) of patients, followed by selective

Table 1. Demographic and clinical characteristics of patients with fibromyalgia syndrome (FMS) at baseline

Parameter	**Value (n=20)**
Age, years [mean (SD)]	51.9 (7.2)
Sex (F/M)	20/0
BMI, kg/m^2 [mean (SD)]	26.9 (4.5)
Years since first FMS diagnosis [mean (SD)]	7.7 (6.3)
Occupational status, n (%)	
Working full-time or part-time	10 (50.0)
At home	3 (15.0)
Not working due to FMS or receiving disability pension	5 (25.0)
Retired	1 (5.0)
Unemployed	1 (5.0)
Smoking, n (%)	
Yes	8 (40.0)
No	12 (60.0)
Alcohol consumption, n (%)	
Yes	0 (0.0)
No	20 (100.0)
Physical activity, n (%)	
Yes	2 (10.0)
No	17 (85.0)

F/M: female/male; BMI: Body Mass Index.

serotonin reuptake inhibitors (SSRIs) in 45.0% (9/20), and tramadol in 40.0% (8/20) of patients. In addition, tryciclic antidepressants and dual-action antidepressants were taken by 10.0% (2/20) and 35.0% (7/20) of individuals, respectively; anxiolytic medication by 35.0% (7/20); antiepileptic drugs by 15.0% (3/20); and nonsteroidal anti-inflammatory drugs (NSAIDs) by 30.0% (6/20) of patients.

Table 2 shows the mean ICAF score of the different emotional, physical, and coping factors reported by patients, as well as the global ICAF score across visits. For all studied variables, there were no statistically significant differences between the start and the end of treatments, nor between the two treatments. Mean values of the main variable fatigue were lower at the end of the NSC and the placebo treatment periods (from 14.0 to 13.0, and from 14.5 to 13.2, respectively). Pain intensity scores subtly diminished at the end of the treatment with NSC (difference: 0.3 points), whereas they increased after treatment with placebo (difference: 0.2 points). Similar results were obtained when assessing the rest of the physical factors sleep quality, impact and functional capacity of patients. These variables seemed to improve at the end of the study treatment (i.e., score values decreased), whereas they mainly declined at the end of the placebo treatment. Emotional factors (including depression and anxiety symptoms) did not improve after NSC treatment ($p>0.05$). Active coping strategies enhanced after study treatment (score values increased from 43.8 to 45.0) and mini-

Table 2. ICAF punctuation of emotional, physical, and coping aspects of patients, and global score across visits

Category	Variables	Start visit T1 Mean (SD)	End visit T1 Mean (SD)	Start-End T1 Mean	p-value	Start visit T2 Mean (SD)	End visit T2 Mean (SD)	Start-End T2 Mean (SD)	p-value	T2-T1 p-value
Physical factor	Fatigue	14.0 (3.6)	13.0 (4.4)	1.0	0.242	14.5 (3.8)	13.2 (5.0)	1.3	0.812	0.837
	Pain intensity	12.8 (3.3)	12.5 (3.7)	0.3	0.693	12.4 (3.7)	12.6 (3.9)	-0.2	0.902	0.799
	Sleep quality	7.1 (2.2)	6.2 (2.4)	0.9	0.117	6.5 (2.9)	7.2 (2.4)	-0.7	0.330	0.263
	Impact	22.1 (4.6)	20.5 (6.8)	1.6	0.237	21.3 (5.1)	21.7 (5.5)	-0.4	0.284	0.469
	Functional capacity	5.7 (3.1)	4.9 (3.1)	0.8	0.179	5.8 (3.0)	5.5 (3.3)	0.3	1.000	0.689
Emotional factor	Depression and anxiety	9.3 (3.6)	10.1 (2.5)	-0.8	0.353	10.2 (4.0)	10.3 (4.3)	-0.1	0.555	0.408
	General health	12.3 (5.3)	13.6 (6.3)	-1.3	0.386	14.5 (6.1)	13.7 (7.0)	0.8	0.333	0.054
Active coping factor	Self-efficacy	18.9 (7.0)	17.8 (7.2)	1.1	0.626	15.1 (6.7)	16.4 (8.0)	-1.3	0.871	0.292
	Active coping strategies	43.8 (14.8)	45.0 (13.6)	-1.2	0.781	45.5 (16.2)	45.0 (16.5)	0.5	0.616	0.982
Passive coping factor	Passive coping strategies	38.8 (11.4)	40.3 (11.6)	-1.5	0.554	37.5 (11.6)	41.8 (13.7)	-4.3	0.580	0.594
Global punctuation	Global punctuation	185.2 (33.2)	184.1 (31.1)	1.1	0.855	183.5 (31.3)	187.6 (33.3)	-4.1	0.785	0.866

T1: treatment with nutritional supplement containing coenzyme Q10, magnesium and tryptophan; T2: treatment with placebo

mally lessen after placebo treatment (from 45.5 to 45.0); while self-efficacy aspects decreased after NSC therapy (from 18.9 to 17.8) and increased after placebo treatment (from 15.1 to 16.4). Score values regarding passive coping strategies increased after NSC therapy (from 38.8 to 40.3; difference: -1.5), although these strategies worsened even more after placebo treatment (from 37.5 to 41.8; difference: -4.3) ($p>0.05$). The global ICAF score was 185.2 at the beginning of the study and decreased 1.1 points at the end of the NSC treatment ($p>0.05$). After the second treatment period, the global ICAF score increased 4.1 points, indicating a worsening of the FMS symptoms after placebo treatment ($p>0.05$).

None of the twenty patients that completed the study reported any adverse event across all clinical visits and telephone follow-up, except for one patient (5.0%) that described one mild adverse event (gastrointestinal discomfort) at the last visit, after placebo treatment.

Discussion

This pilot study was aimed to investigate the effects of a dietary supplementation containing CoQ10, magnesium and tryptophan on FMS symptoms. We used the ICAF questionnaire to evaluate emotional and physical symptoms, and the way in which patients coped with the disease. The NSC intake for three months resulted in a perceptible reduction of the severity of all physical symptoms, although no statistically significant differences were found among the studied variables (fatigue, pain intensity, sleep quality, impact and functional capacity of patients). After the 3-month placebo treatment, physical symptoms except for the variable fatigue did not show the same trend. Such tendency was expected after NSC treatment, since oral supplementation with CoQ10 has been shown to significantly reduce pain, fatigue and morning tiredness in patients with fibromyalgia (16, 17). Furthermore, based on the review of different studies, supplementation with magnesium, which plays an important function in ATP synthesis and muscle metabolism (26), has been considered to be a viable treatment choice for chronic pain (18).

On the other side, the effect of the supplement intake did not significantly alter the levels of the main relevant emotional factors. Depression and anxiety and the patient's global health seemed to slightly worsen at the end of the NSC treatment as compared to the placebo treatment. Interestingly, although all three components of the NSC individually (CoQ10, tryptophan, and magnesium) have been shown to control and/or prevent the depressive symptoms associated with FMS (16-19, 21, 27), we did not observe the same tendency in their combined ingestion.

Assessment of the active coping factor yielded conflicting results. Despite the fact that differences were not statistically significant, the use of active coping strategies enhanced after study treatment and were not maintained —even lessened— after placebo treatment, while self-efficacy aspects decreased after NSC therapy and increased after placebo treatment. Passive coping strategies for dealing with FMS symptoms did not improve after NSC intake, although these strategies worsened even more after placebo treatment ($p>0.05$).

Nevertheless, the overall evaluation of the multidimensional aspects of FMS patients after NSC consumption showed a positive trend on the physical factor of the disease. Furthermore, when analyzing the global punctuation of the ICAF questionnaire, the global score decreased at the end of the first treatment period, indicating that patients might have a tendency to experience positive changes in FMS symptoms after NSC treatment. On the contrary, after treatment with placebo, the ICAF global scores increased, revealing an appreciable decline in the overall health status of patients.

NSC treatment was well tolerated, with a low incidence of adverse events (5.0%, 1/20 patients). In fact, the only adverse event that occurred was reported at the end of the placebo treatment period.

Although the results of this study suggest that supplementation with CoQ10, tryptophan, and magnesium might improve fatigue, pain, functional capacity and other physical aspects of FMS, as well as the global well-being of patients, the sample size was small. Further studies are needed to test the reliability of the results and whether improvements could be statistically significant. Another limitation of the current

study is that dietary habits of patients have not been considered, and they might have negatively influenced the effectiveness of the NSC treatment. It has been described that some molecules, such as fructose, can reduce tryptophan absorption and, as a consequence, its availability as substrate for serotonin synthesis (28). CoQ10 optimal absorption is also related to diet, improving when it is taken with dietary fat (29, 30). Reduction of magnesium absorption can also be caused by a dietary aluminum intake, contributing to magnesium deficiency (31). Thus, dietary habits might have influenced the observed results and should be taken into account in future studies. An additional aspect that should be also considered in forthcoming investigations is the pharmacologic basal treatment for FMS. Amitriptyline, for example, a commonly prescribed antidepressant, is known to induce CoQ10 deficiency in patients with depressive episodes (32). However, when combined with magnesium citrate treatment, amitriptyline has been shown to improve depressive symptoms [33]. Tryptophan supplementation taken in conjunction with medications such as monoamine oxidase inhibitors, or in combination with selective serotonin reuptake inhibitor medications should also be used with caution, since it could increase the risk of serotonin syndrome. However, more research is needed to understand the dose-dependent side effects of tryptophan supplementation both alone and in combination with other drugs [34]. Preliminary data have shown an early antidepressant effect and a slow-wave sleep protective effect when tryptophan (2 g/daily) is added to fluoxetine (20 mg/daily) in the treatment of major depressive disorder, with very low side effects [35]. These results would suggest that low tryptophan levels may have synergistic effects when used with other serotonergic drugs. According to this, the use of NSC in conjunction with other serotonergic compounds in some patients might have been favorable, since the daily dose of tryptophan was lower (0.3 g) than the levels reported in the aforementioned trial. Overall, effectiveness of oral supplementation with NSC could vary depending upon the basal FMS medication, and this consideration should be examined in future research.

It is important to highlight the exploratory nature of the study, since it was designed as a pilot study to explore the potential extent in terms of effectiveness and tolerability of the NSC treatment in patients with fibromyalgia, prior to undertaking a larger study. The results herein presented serve as a basis for broader exploration of the possible benefits of NSC intake in reducing fibromyalgia symptoms.

Conclusions

The results of this study constitute the first investigation of the effect of a nutritional supplement containing CoQ10, magnesium and tryptophan on FMS. Although the results should be confirmed in larger studies, they suggest that NSC treatment for 3 months, in addition to pharmacological therapy, could be of interest for improving FMS symptoms and well-being of patients. This treatment appeared to primarily improve physical symptoms such as fatigue, with a low occurrence of adverse events.

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Conflict of Interest Disclosure

No potential conflict of interest relevant to this article was reported by the authors.

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