Role for a water-soluble form of CoQ10 in female subjects affected by fibromyalgia. A preliminary study

F. Di Pierro[1], A. Rossi[2], A. Consensi[2], C. Giacomelli[2], L. Bazzichi[2]

[1]Scientific and Research Department, Velleja Research, Milan, Italy;
[2]Rheumatology Operative Unit, Department of Experimental and Clinical Medicine, University of Pisa, Italy.

*Francesco Di Pierro, PhD**
*Alessandra Rossi, PhD**
Arianna Consensi, MD, PhD
Camillo Giacomelli, PhD
Laura Bazzichi, MD

**These authors contributed equally to this work.*

Please address correspondence to:
Dr Francesco Di Pierro,
Velleja Research,
Viale Lunigiana 23,
20125 Milan, Italy.
E-mail: f.dipierro@vellejaresearch.com

Received on September 5, 2016; accepted in revised form on October 16, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 105): S20-S27.

Key words: Ubiquinone, micro-emulsion, pain, tender points, DDM Chinone®

Competing interests: none declared.

ABSTRACT

Decreased antioxidant capacity and increased oxidative stress have been observed in fibromyalgia patients. Some trials have also shown that CoQ10 levels are reduced in these patients but that supplementation can restore levels and reduce fibromyalgia symptoms, including pain and fatigue. We evaluated the effect of administration of a finished form of CoQ10 (DDM Chinone®) at a dose of 200 mg×2/day in 22 female subjects with a diagnosis of fibromyalgia in a randomised, open-label, cross-over study. Our results show that, compared to a control group, administration of CoQ10 significantly improved most pain-related outcomes by 24-37%, including fatigue (by ~22%) and sleep disturbance (by ~33%). These results confirm the considerable role played by CoQ10 in reducing pain, fatigue, and sleep disturbance in subjects affected by fibromyalgia.

Introduction

About 2-3% of the world's population have fibromyalgia, with nine times more women than men affected (1, 2). Fibromyalgia is a syndrome of unknown aetiology and is characterised by widespread pain, mainly in the back and neck region, fatigue, and sleep disturbance (3-6). Other frequent disorders include memory impairment, irritable bowel syndrome, temporomandibular joint dysfunction, chronic headache, anxiety, panic attacks, chest pain, irritable bladder, and interstitial cystitis (7). Common treatments include analgesics, antidepressants, anti-epileptics, stimulants, benzodiazepines, and hypnotics (8). Despite this long list of available drugs, really effective pharmacological options have not yet been identified, so multimodal programmes consisting of physical and occupational therapy, sleep and nutrition counseling, and psychological help have also been employed (9, 10). Recently, some studies have suggested that reduced antioxidant capacity correlates with fibromyalgia symptoms, with increased oxidative stress observed in fibromyalgia patients (11, 12). Consequently, the use of antioxidant vitamins and supplements as potential treatment options has been investigated by some authors. However, most of the results of these studies do not support their use (13) with the possible exception of coenzyme Q10 (CoQ10). Some trials have shown that CoQ10 levels are reduced in fibromyalgia patients and that supplementation can restore levels and reduce fibromyalgia symptoms, including pain and fatigue (14, 15). CoQ10 is a lipophilic, high molecular weight, antioxidant molecule which plays an essential role in the mitochondrial electron transport chain; its depletion is described as potentially leading to neuromuscular and/or neurodegenerative disorders (16) and fibromyalgia (17). CoQ10, because of its chemical and physical features, is characterised by low oral bioavailability, which was reported in the rat to be only about 2-3% of the orally administered coenzyme (18). In the case of supplementation with finished dosage forms of CoQ10, absorption is likely also dependent on the chemical characteristics of the formulation, with water-soluble CoQ10 in particular shown to have enhanced bioavailability compared to oily and powder forms (19-21). We have therefore evaluated the effect of administration of a water-soluble finished form of CoQ10 in female subjects with a diagnosis of fibromyalgia.

Materials and Methods

The study. Our study was an open-label, randomised, controlled, cross-over clinical trial performed over 6 months in female patients with fibromyalgia. Written informed consent and the ap-

proval of the ethics committee of the University of Pisa were obtained in accordance with the principles of the Declaration of Helsinki. The study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines.

The patients

Twenty-two female patients aged 53±9.1 years (mean age ± standard deviation) diagnosed with fibromyalgia (time since diagnosis: 7.5±0.5 years) and attending the Rheumatology Operative Unit at the University of Pisa were enrolled in the study after providing informed consent. The inclusion criterion was a diagnosis of fibromyalgia based on current American College of Rheumatology (ACR) diagnostic criteria (22). Exclusion criteria were acute infectious disease within the previous 4 weeks; past or present neurological, psychiatric, metabolic, autoimmune, allergy-related, dermal, or chronic inflammatory disease; undesirable habits (smoking, excess alcohol consumption); medical conditions other than fibromyalgia which required glucocorticoid treatment, analgesics, or antidepressant drugs; past or current substance abuse or dependence; and pregnancy or current breastfeeding. During the 6-month study all patients were asked to follow a standard balanced diet where carbohydrates provided 50–60% of calories, protein 10-20%, and fat 20–30%.

The protocol

After enrolment, the 22 subjects were randomised, by tossing a coin, to arm A (n=12), to be treated for 3 months with a water-soluble CoQ10-based formula, or to arm B (n=10), to be treated, as control, with a comparable CoQ10-free supplement. After 3 months the two arms were reversed and for a further trimester arm A was treated with the CoQ10-free control formula and arm B with the CoQ10-based formula. Treatments were administered twice a day. All outcomes were evaluated at enrolment (T=0), after the first 3 months of treatment (T=1), and after the 3 months of cross-over (T=2).

Table I. Results for the enrolled patients at T=0.

	Arm A (n=12)	Arm B (n=10)	*p*-value
Age	52.5 ± 10.4	53.6 ± 7.8	NS
TP	16.2 ± 2.3	16.9 ± 1.8	NS
SCORE	6.0 ± 2.7	6.4 ± 1.9	NS
FIQ	54.1 ± 16.6	61.5 ± 9.5	NS
WPI	9.6 ± 4.7	11.2 ± 4.0	NS
SS	8.0 ± 2.3	7.8 ± 1.5	NS
Pain	6.4 ± 2.5	7.4 ± 2.1	NS
Stiffness	7.0 ± 3.0	7.9 ± 1.7	NS
Tiredness	7.9 ± 2.7	7.8 ± 1.7	NS
Zung Anxiety	44.2 ± 4.7	49.8 ± 8.7	NS
Zung Depression	43.3 ± 7.7	48.0 ± 6.3	NS
FACIT	19.9 ± 7.4	22.0 ± 3.9	NS
HAQ	0.6 ± 0.4	1.0 ± 0.9	NS
Pittsburgh	8.5 ± 3.8	11.4 ± 3.3	NS
SF-36			
Physical activity	57.7 ± 25.0	55.0 ± 11.5	NS
Physical limitations	34.5 ± 35.7	25.6 ± 11.0	NS
Physical pain	35.4 ± 13.2	31.1 ± 14.3	NS
General health	46.7 ± 19.3	37.9 ± 12.5	NS
Vitality	30.9 ± 17.0	32.8 ± 13.1	NS
Social activity	48.5 ± 21.3	54.0 ± 18.8	NS
Emotional limitations	24.1 ± 36.6	25.9 ± 43.4	NS
Mental health	57.3 ± 16.3	51.6 ± 17.1	NS
Physical health index	35.8 ± 7.7	31.3 ± 4.3	NS
Mental health index	36.5 ± 7.5	36.8 ± 10.5	NS

Note: All values are expressed as the median ± standard deviation.
FACIT: functional assessment of chronic illness therapy; FIQ: Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; NS: not significant; Pittsburgh: Pittsburgh sleep quality index; SCORE: sum of values of tender points divided by number of tender points (18); SS: Symptom severity scale; TP: tender points; WPI: widespread pain index.

During the 6-month study, all enrolled subjects continued their previously prescribed treatment for fibromyalgia with benzodiazepines (18%), antidepressants (50%), cortisone (14%), muscle-relaxants (64%), anticonvulsants (22%), and anti-inflammatory drugs (41%). These therapies did not differ statistically between the two groups (data not shown).

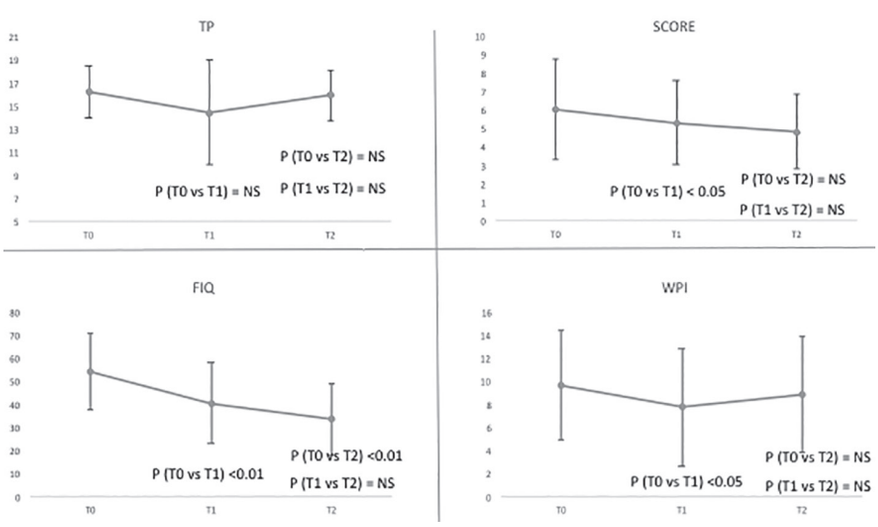

Fig. 1. Trend of TP, SCORE, FIQ and WPI at enrolment, after 3 months (T0-T1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

Table II. Results for enrolled patients at T=1 after 3 months of treatment.

	Arm A* (n=12)	Arm B** (n=10)	*p*-value
TP	14.4 ± 4.5	16.6 ± 1.5	NS
SCORE	5.3 ± 2.3	7.0 ± 1.7	*p*<0.05
FIQ	40.2 ± 17.6	58.4 ± 18.0	*p*<0.05
WPI	7.7 ± 5.1	10.2 ± 4.1	*p*<0.05
SS	6.0 ± 2.4	7.8 ± 2.0	*p*<0.05
Pain	4.6 ± 2.1	7.3 ± 2.2	*p*<0.05
Stiffness	5.4 ± 2.3	6.8 ± 1.9	NS
Tiredness	5.2 ± 2.7	6.8 ± 1.5	NS
Zung Anxiety	36.0 ± 9.4	46.1 ± 8.6	*p*<0.05
Zung Depression	35.0 ± 9.5	44.6 ± 7.6	*p*<0.05
FACIT	14.9 ± 6.9	19.2 ± 7.7	*p*<0.05
HAQ	0.2 ± 0.5	0.9 ± 0.4	NS
Pittsburgh	6.8 ± 3.1	10.2 ± 4.2	*p*<0.05
SF-36			
Physical activity	60.1 ± 21.8	55.0 ± 14.5	NS
Physical limitations	59.7 ± 39.1	20.0 ± 30.7	*p*<0.05
Physical pain	50.7 ± 14.3	36.2 ± 15.3	*p*<0.05
General health	49.3 ± 21.4	37.6 ± 10.3	*p*<0.05
Vitality	56.5 ± 17.9	44.5 ± 14.2	NS
Social activity	60.6 ± 14.2	59.9 ± 18.5	NS
Emotional limitations	71.3 ± 31.6	23.3 ± 41.7	*p*<0.05
Mental health	69.5 ± 19.8	57.6 ± 20	NS
Physical health index	38.0 ± 5.6	32.9 ± 6.1	*p*<0.05
Mental health index	46.8 ± 8.6	39.6 ± 10.3	*p*<0.05

Notes: *Arm A was treated from T=0 to T=1 with the CoQ10-based formula. **Arm B was treated from T=0 to T=1 with the CoQ10-free formula. All values are expressed as the median ± standard deviation. FACIT: functional assessment of chronic illness therapy; FIQ: Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; NS: not significant; Pittsburgh: Pittsburgh sleep quality index; SCORE: sum of values of tender points divided by number of tender points (18); SS: symptom severity scale; TP: tender points; WPI: widespread pain index.

The products

The CoQ10-based product to be tested, DDM Chinone®, was provided in sachets. It was formulated by Labomar (Istrana, TV, Italy) and notified to the Italian Ministry of Health as a nutritional supplement by Omeopiacenza (Pontenure, PC, Italy), according to the provisions of law No. 169 of 2004, on 18 September 2013 (notification number: 66483). This preparation contained CoQ10 (200 mg/dose), vitamin E (15 mg/dose), vitamin B2 (25 mg/dose), vitamin B6 (9.5 mg/dose), vitamin B12 (25 μg/dose), and folic acid (400 μg/dose). As control, a comparable CoQ10-free product, was also provided in sachets. It was formulated by SIIT (Trezzano S/N, Milan, Italy) and notified to the Italian Ministry of Health as a nutritional supplement by Omeopiacenza (Pontenure, PC, Italy), according to the provisions of law No. 169 of 2004, on 27 April 2006 (notification number: 22434).

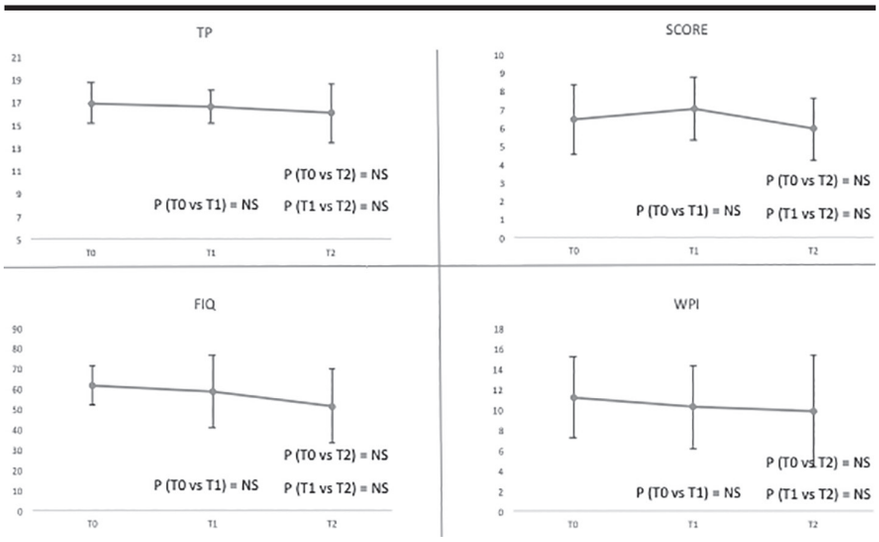

Fig. 2. Trend of TP, SCORE, FIQ and WPI at enrolment, after 3 months (T0-T1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

The endpoints

The primary endpoint of the study was to evaluate the effects of the CoQ10-based formula in subjects with a diagnosis of fibromyalgia and compare these effects to those in the same patients administered a comparable, CoQ10-free formula. The effects of the two products were evaluated at T=0, T=1, and T=2 by: (1) clinical and pharmacological anamnesis; (2) evaluation of the number of tender points (TPs) and their intensity score (SCORE) assessed by digital pressure (the pain threshold was calculated for 18 TPs, and the TP count was determined by the number of TPs that had a pain threshold of ≤4 kg/cm^2; the intensity score was calculated as the ratio between the global TP score divided by 18, as there were 18 TPs) (23); and (3) self-administered questionnaires such as the Fibromyalgia Impact Questionnaire (FIQ) (24), the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system (25), the Health Assessment Questionnaire (HAQ) (26), the Zung Self-Rating Depression Scale (27), and the SF-36 questionnaire (28). Using the SF-36, we evaluated physical activity, physical role limitations, physical pain, general health, vitality, social activity, emotional role limitations, mental health, and indices of physical and mental health. Other instruments used were the Widespread Pain Index (WPI) (29), the Symptom Severity scale (SS) (30), and the Pittsburgh Sleep Quality Index (31), while pain, tiredness, and stiffness were evaluated with a visual analog scale (VAS) (32). Secondary endpoints were tolerability, compliance, and side effects.

Table III. Results for enrolled patients at T=2 after cross-over and a further 3 months of treatment.

	Arm A* (n=12)	Arm B** (n=10)	*p*-value
TP	15.9 ± 2.2	16.0 ± 2.6	NS
SCORE	4.8 ± 2.0	5.9 ± 1.7	NS
FIQ	33.3 ± 15.4	51.3 ± 18.3	NS
WPI	8.8 ± 5.0	9.8 ± 5.5	NS
SS	5.8 ± 2.0	6.9 ± 2.0	NS
Pain	3.9 ± 2.2	6.0 ± 2.4	$p<0.05$
Stiffness	5.0 ± 3.4	6.6 ± 1.8	NS
Tiredness	3.8 ± 2.5	7.3 ± 2.0	$p<0.05$
Zung Anxiety	34.4 ± 7.0	44.8 ± 9.8	$p<0.01$
Zung Depression	34.2 ± 7.2	46.1 ± 11.1	$p<0.05$
FACIT	13.6 ± 6.7	19.1 ± 7.0	NS
HAQ	0.6 ± 0.5	0.7 ± 0.3	NS
Pittsburgh	6.7 ± 4.0	10.8 ± 3.5	$p<0.05$
SF-36			
Physical activity	68.6 ± 20.4	51.9 ± 27.5	NS
Physical limitations	55.0 ± 35.0	21.9 ± 36.4	$p<0.05$
Physical pain	50.0 ± 17.5	42.3 ± 14.7	NS
General health	55.4 ± 23.0	39.5 ± 13.1	NS
Vitality	56.7 ± 18.5	45.6 ± 18.4	NS
Social activity	62.7 ± 20.6	53.0 ± 19.7	NS
Emotional limitations	57.2 ± 36.5	33.3 ± 43.6	NS
Mental health	65.4 ± 11.7	51.5 ± 23.9	NS
Physical health index	40.7 ± 8.2	35.4 ± 5.2	NS
Mental health index	44.8 ± 7.8	37.4 ± 13.6	NS

Notes: *Arm A was treated from T=1 to T=2 with the CoQ10-free formula. **Arm B was treated from T=1 to T=2 with the CoQ10-based formula. All values are expressed as the median±standard deviation. FACIT: functional assessment of chronic illness therapy; FIQ: Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; NS: not significant; Pittsburgh: Pittsburgh sleep quality index; SCORE: sum of values of tender points divided by number of tender points (18); SS: symptom severity scale; TP: tender points; WPI: widespread pain index.

Statistical analysis

The non-parametric Mann-Whitney test was used to compare differences between group outcomes during the same period. The non-parametric Wilcoxon signed rank test for matched pairs was used compare outcomes in the same group during different periods. The statistical software JMP 10 for Mac OsX was used and statistical significance was set at $p<0.05$.

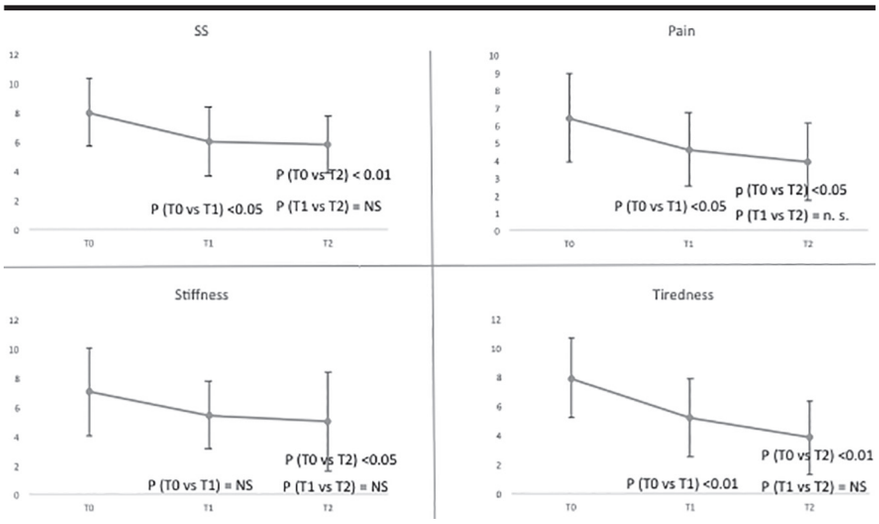

Fig. 3. Trend of SS, Pain, Stiffness and Tiredness at enrolment, after 3 months (T0-T1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

Results

The main aim of our open-label, randomised, cross-over study was to evaluate the effect of a water-soluble finished form of CoQ10 in subjects with a diagnosis of fibromyalgia. We measured 23 different parameters in the two groups during the same period (Tables I-III) and in the same group during different periods (Fig. 1-12). Table I provides the median results for subjects in arm A (n=12) and arm B (n=10) at T=0. The 23 parameters evaluated did not show any statistical difference between the two groups, demonstrating that the groups were comparable.

The results obtained after the first 3 months of treatment are shown in Table II. Fifteen of the 23 outcomes were better in arm A (CoQ10-based formula) than in arm B (Coq10-free formula). Treatment with the CoQ10-based formula improved:

1. SCORE by 24.3% (SCORE is the intensity score of TPs calculated as the sum of the values of tender points divided by the number of TPs);
2. FIQ scores by 31.2% (the 10-question FIQ scores the well-being of fibromyalgia patients from 0 to 100);
3. WPI scores by 24.5% (the WPI scores the perception of widespread pain from 0 to 19);
4. SS scores by 12.8% (the SS scores the severity of symptomatology from 0 to 12);
5. Pain by 37% as measured by a 0–10 VAS;
6. Anxiety and depression by 21.7% and 21.5%, respectively, as measured by the Zung scale scoring from 20 to 80;
7. FACIT scores by 22.4% (the FACIT scores the quality of life in relationships limited by a chronic pathology from 0 to 44);
8. Quality of sleep scores by 33.3% as measured by the Pittsburgh Sleep Quality Index from 0 to 21.

In addition, the SF-36 questionnaire, which evaluated eight different health domains plus two general indices and where higher scores indicate better outcomes, revealed a considerable improvement for physical limitation, physical pain, general health, emotion-

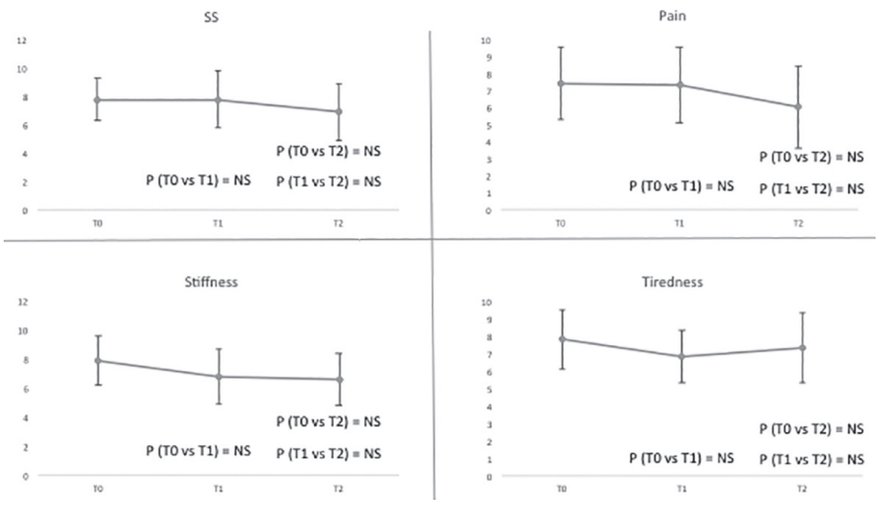

Fig. 4. Trend of SS, Pain, Stiffness and Tiredness at enrolment, after 3 months (T0-T1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

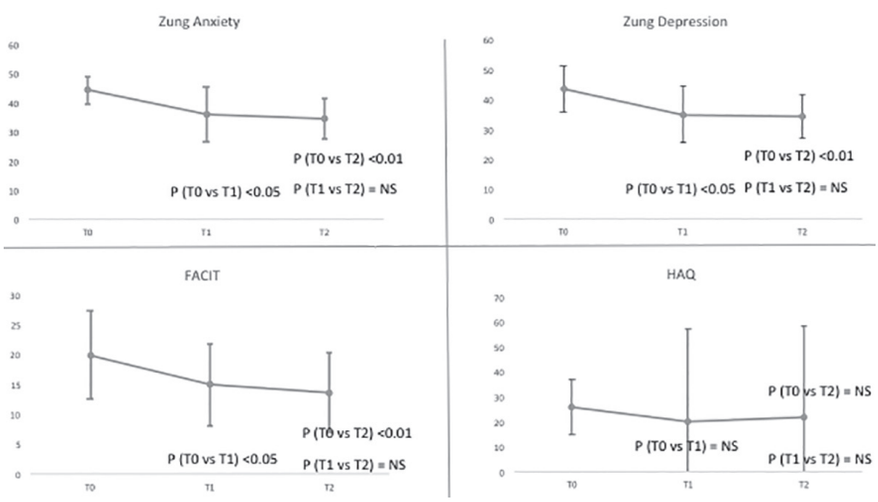

Fig. 5. Trend of Zung, Anxiety, Zung Depression, FACIT and HAQ at enrolment, after 3 months (T0-Y1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

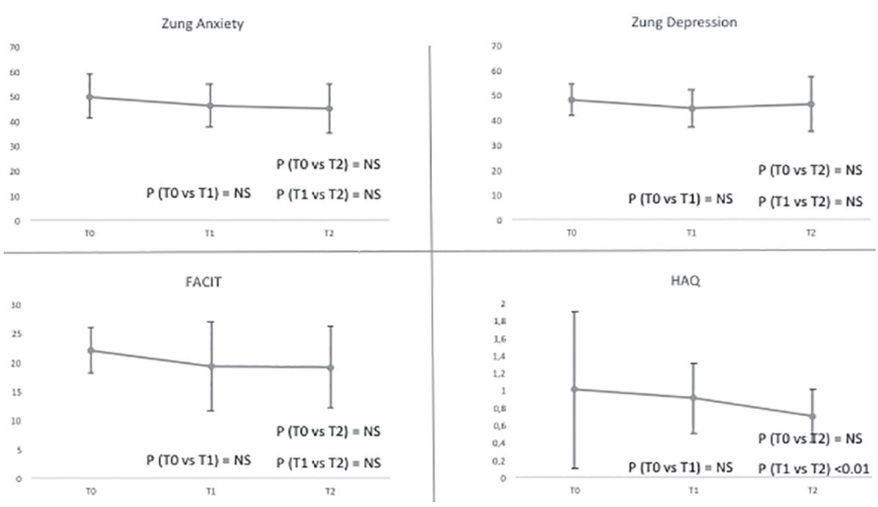

Fig. 6. Trend of Zung, Anxiety, Zung Depression, FACIT and HAQ at enrolment, after 3 months (T0-Y1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

al limitations, physical health index and mental health index. After crossing-over (Table III), the number of parameters with results significantly different between the two arms declined to six out of 23, again demonstrating a trend in favour of arm A, even though arm A had been treated with the CoQ10-free formula. Results showed considerable reduction for pain tiredness, anxiety, depression, sleep, and physical limitations. We then evaluated the results obtained in the same group in different periods (Fig. 1-12). As shown in Figure 1, treatment with the CoQ10-based formula between T=0 and T=1 improved three out of four outcomes with significant results shown for SCORE, FIQ, and WPI; TP also showed a tendency to improve between T=0 and T=1 but the difference was not significant. In contrast, no significant results were observed between T=1 and T=2 when a CoQ10-free formula was administered. As shown in Figure 2, when the first administered product was the CoQ10-free formula, neither TP, SCORE, FIQ, or WPI were improved. A tendency to improvement in SCORE and FIQ was only observed between T=1 and T=2 when the CoQ10-based formula was given. Similarly, between T=0 and T=1 when the CoQ10-based formula was administered (Fig. 3), the outcomes SS, pain, and tiredness were statistically improved but none of these outcomes were improved when the treatment started with the CoQ10-free formula (Fig. 4). Figures 5 and 6 show the trends for anxiety, depression, FACIT, and HAQ. Again when the treatment started with the Coq10-based formula (Fig. 5), 3 out of 4 outcomes were statistically improved versus T=0, with no significant results seen between T=1 and T=2 when the CoQ10-free formula was administered. When the treatment started with the CoQ10-free formula (Fig. 6), no significant results were observed except in the case of HAQ between T=1 and T=2 when the CoQ10-based formula was given. Figures 7 and 8 show the trends for physical activity, physical limitations, physical pain, and general health as evaluated by the SF-36 questionnaire. Significant improvements were seen only when the

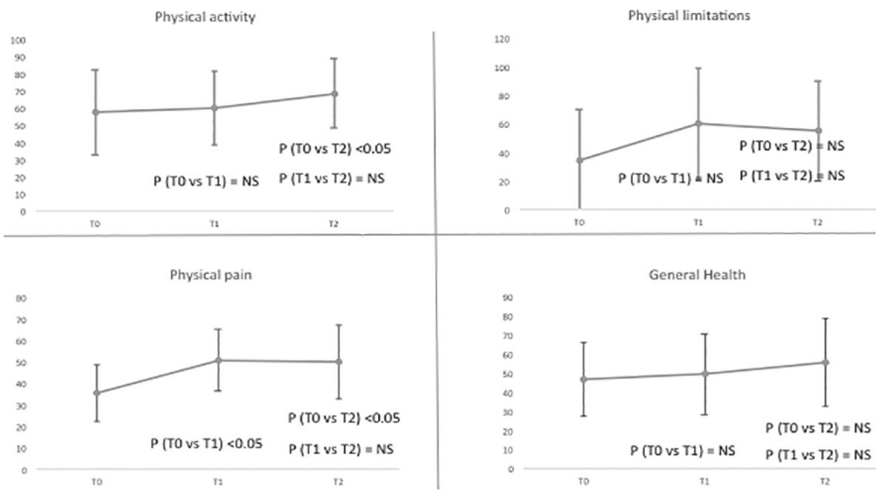

Fig. 7. Trend of Physical activity, Physical limitations, Physical pain and General health at enrolment, after 3 months (T0-T1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

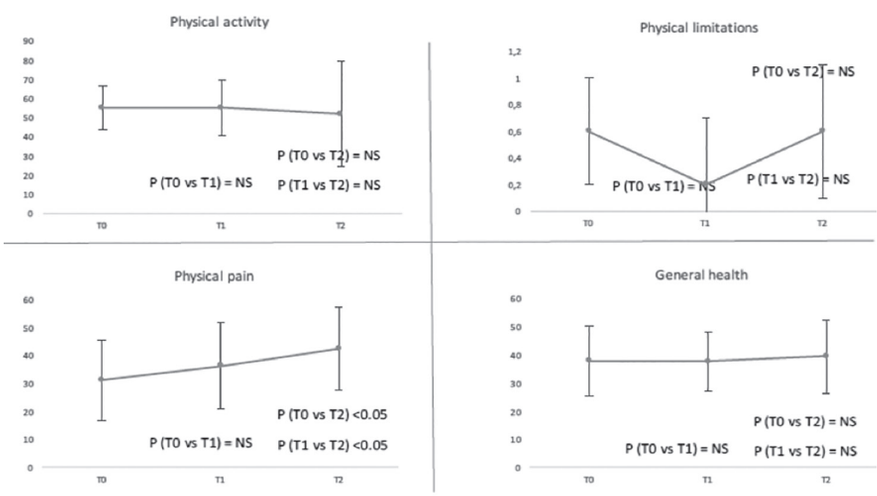

Fig. 8. Trend of Physical activity, Physical limitations, Physical pain and General health at enrolment, after 3 months (T0-T1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

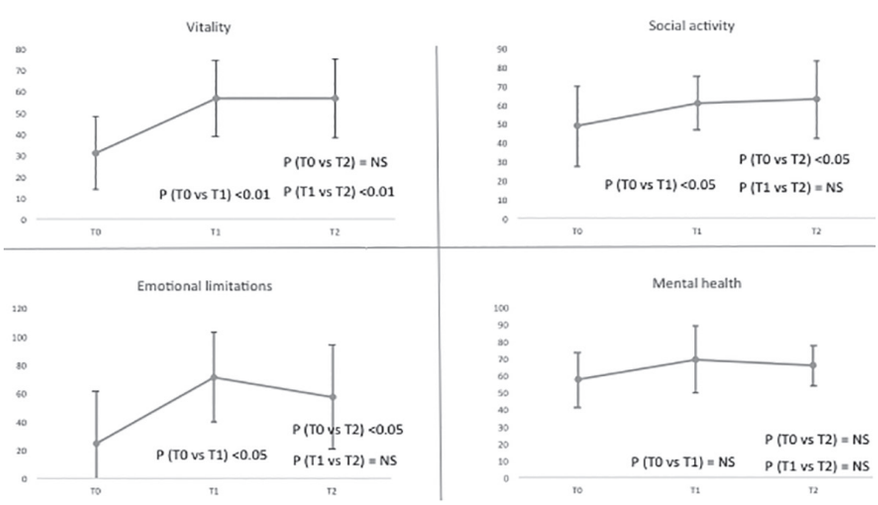

Fig. 9. Trend of the Vitality, Social activity, Emotional limitations and Mental health at enrolment, after 3 months (T0-T1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

CoQ10-based formula was given first (physical activity and physical pain; Fig. 7). No significant results were observed when the CoQ10-free formula was administered first (Fig. 8) except for physical pain where a significant result was seen between T=1 and T=2 when the CoQ10-based formula was given. Figures 9 and 10 show trends for vitality, social activity, emotional limitations, and mental health. Again when the CoQ10-base formula was given first, vitality, social activity, and emotional limitations were all significantly improved (Fig. 9). However, when the CoQ10-free formula was given first, the results were not significant, except for vitality (Fig. 10). Finally, Figures 11 and 12 show trends for the physical health index, the mental health index, and the Pittsburgh Sleep Quality Index. When the CoQ10-based formula was administered first, all three outcomes were significantly different (Fig. 11). In contrast, when the CoQ10-free formula was administered first, no effects were observed (Fig. 12).

Statistical analysis of the results got performed taking into account all confounders such as the different class of drugs, comorbidities and disease duration shown no correlation with findings (data not shown). Regarding compliance, all subjects reported they had used products as instructed. No particular side effects were observed and the few episodes of gastric pain and gut discomfort reported were equally distributed between groups and treatments (data not shown). No patient drop-outs were reported and all subjects completed the study.

Discussion

As several reports have claimed CoQ10 may have a possible beneficial role in fibromyalgia, we enrolled 22 women with a diagnosis of fibromyalgia in a 6-month study. Subjects were administered a water-soluble form of CoQ10 or a comparable CoQ10-free formula. We randomised participants to arm A or arm B. Arm A started with the CoQ10-based formula, while arm B started with the CoQ10-free formula. After 3 months the treatments were reversed for a further 3 months. Although definitive con-

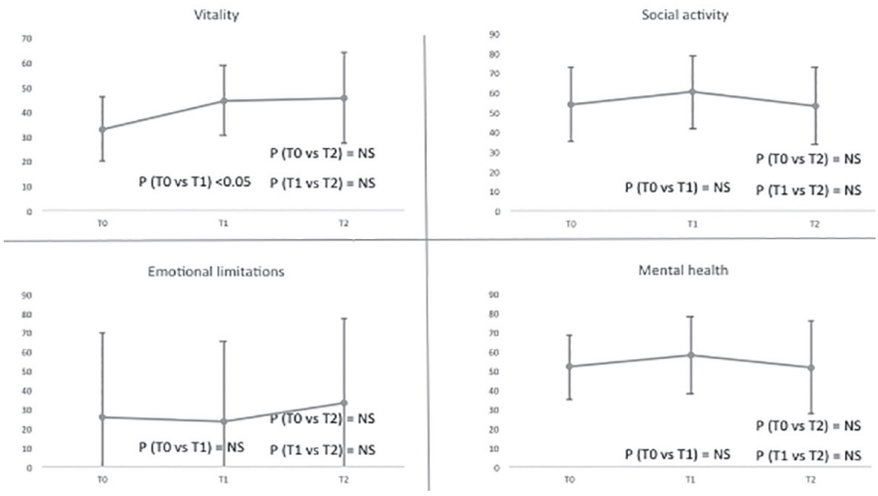

Fig. 10. Trend of the Vitality, Social activity, Emotional limitations and Mental health at enrolment, after 3 months (T0-T1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

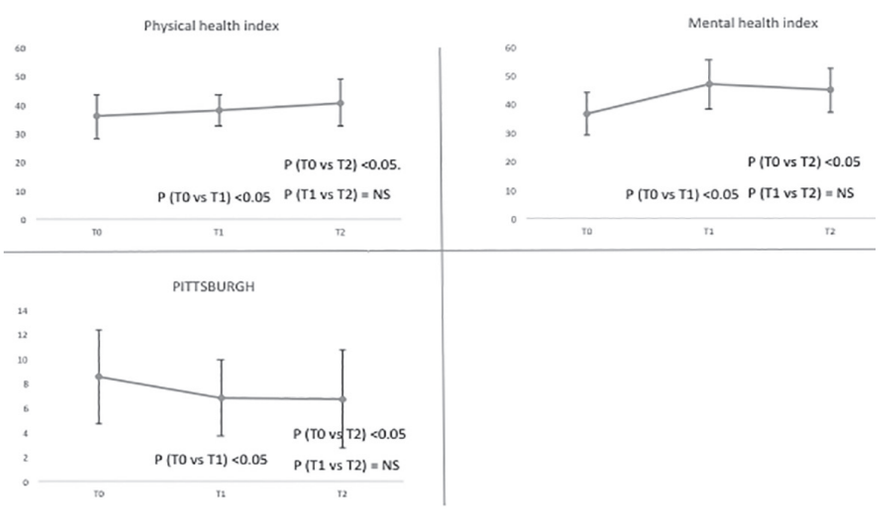

Fig. 11. Trend of Mental health index, Physical health index and PITTSBURGH at enrolment, after 3 months (T0-T1 with CoQ10 formula) and after 3-months cross-over (T1-T2 with CoQ10-free formula) on Arm A (n=12).

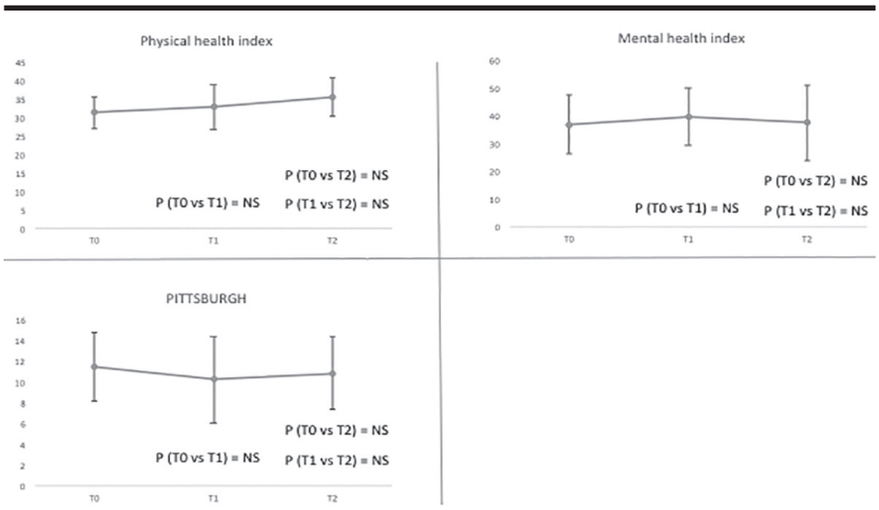

Fig. 12. Trend of Mental health index, Physical health index and PITTSBURGH at enrolment, after 3 months (T0-T1 with CoQ10-free formula) and after 3-months cross-over (T1-T2 with CoQ10 formula) on Arm B (n=10).

clusions cannot be drawn due to the low number of subjects (22) enrolled to analyse a high number of parameters (23), the lack of a blinded condition, and the absence of a placebo, we propose, in agreement with previous suggestions (11-15), that the use of CoQ10 could be beneficial in patients with fibromyalgia. Fibromyalgia is mainly characterised by pain, fatigue, and sleep disturbance. Its use in our study significantly reduced most pain-related outcomes including the overall TP score (SCORE), the perception of widespread pain (WPI), pain as measured by the VAS, and physical limitations, physical pain, and the physical health index measured using the SF-36 questionnaire (Table II and Fig. 8). The use of the CoQ10-based product also seemed to statistically relieve the fatigue experienced by most patients with fibromyalgia as the results of FACIT and HAQ questionnaires indicated (Table II and Fig. 5), as well as improving parameters like vitality and social activity, which were evaluated with the SF-36 questionnaire (Fig. 9). Similarly, the CoQ10-based product improved sleep as shown by the results of the Pittsburgh Sleep Quality Index (Table II and Fig. 11). CoQ10-treated subjects also seemed to experience better mental health: anxiety and depression improved according to the Zung questionnaire (Table II and Fig. 5), as did emotional limitations (Table II and Fig. 9) and the mental health index (Table II and Fig. 11) according to the SF-36 questionnaire. Comparison of results between the two groups receiving different treatment at the same time showed six outcomes were improved (Table III) immediately after cross-over in patients previously treated with the CoQ10-based formula. Five of six outcomes had already been improved by the CoQ10 treatment with only one (tiredness) apparently improved by treatment with the CoQ10-free formula. Our suggestion that CoQ10 is beneficial is confirmed by the fact that, as shown in Table II, no results were significant when the CoQ10-free formula was given as first treatment. Similarly, if we consider the same groups at different times, no outcomes were better with treatment with the CoQ10-free

formula. We have also analysed (data not shown) the results by pooling all subjects whether or not they were treated with the CoQ10-based formula and without taking into account the cross-over design without finding any substantial differences with the presented results, highlighting again the statistically significant effects of the CoQ10-based formula on most of the outcomes considered (mainly those related to pain), with no effect seen on any outcome from treatment with the CoQ10-free formula. In our opinion this is the first time in which a systematically evaluation of CoQ10 in improving fibromyalgia-related clinical outcome is performed. The data got could be potentially useful for physicians and surely prompt to further mechanistic studies. In conclusion, despite the previously mentioned study limitations, we believe that the results of our pilot study confirm the beneficial effects exerted by CoQ10 in counteracting pain, fatigue, sleep disturbance, and mental difficulties in female subjects affected by fibromyalgia.

Acknowledgment
The authors thank Dr Paolo Risso for the statistical analysis.

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