Reduction of Pain, Fatigue, Gastrointestinal and Other Symptoms and Improvement in Quality of Life Indicators in Fibromyalgia Patients with Membrane Lipid Replacement Glycerolphospholipids and Controlled-Release Caffeine

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Abstract
Keywords

1. Introduction

Pain and fatigue are related functionally to cellular energy systems found primarily in mitochondria and specifically in the electron transport chain of the mitochondrial inner membrane. Damage to mitochondrial membranes occurs in various diseases, mainly by oxidation of phospholipid components, and this can result in ion leakage across inner mitochondrial membranes and reductions in the ability of mitochondria to produce high-energy molecules. During aging and most chronic diseases the production of oxidative free radicals, such as Reactive Oxygen and Nitrogen species (ROS/RNS) and other molecules, can cause oxidative stress and cellular damage. ROS/RNS damage often occurs to cellular membranes, and in particular, to the glycerolphospholipids of mitochondrial membranes.
lar lipids with undamaged, unoxidized lipids to ensure proper function of cellular and organelle membranes. Combined with antioxidants, MLR supplements have proven to be effective in reducing ROS/RNS-associated changes in cellular activities and functions and for reducing symptom severity and providing host support in various clinical conditions [8][14][15][16].

In fibromyalgia patients, the MLR supplement NTFactor Lipids has been used to reduce fatigue [8][16]. In a preliminary case report, pain, fatigue and gastrointestinal symptoms were reduced in a small number of fibromyalgia patients (P.A. Breeding and G.L. Nicolson, in preparation).

In fibromyalgia patients another natural approach to reducing the severity of symptoms has been to use low-dose caffeine (equivalent to one or less than one cup of coffee or about 40-50 mg of caffeine) to reduce pain and fatigue [17]. In the study of Scott et al. [17], caffeine consumption had a modest but significant effect on chronic pain reduction compared to an absence of caffeine consumption, but among non-opioid users this effect was not significant [17]. Caffeine is one of the most widely consumed natural food supplements in the world, and it is present in numerous foods and beverages. Caffeine is generally considered safe at doses up to 400 mg per day for adults [18][19].

Here we tested the results of a combination natural supplement that contained a formulation of MLR glycophospholipids (NTFactor Lipids) plus a low dose of controlled-release caffeine in chewable wafers in an open-label study format that used self-reported results on pain, fatigue, gastrointestinal symptoms and quality of life (QOL) indicators in a small group of fibromyalgia patients.

2. Materials and Methods

2.1. Materials and Methods

An open label, Institutional Review Board approved, clinical trial was initiated to study the effects of an all-natural glycerolphospholipid chewable wafer supplement (Patented Energy™ with NTFactor Lipids™) and a chewable wafer containing NTFactor Lipids™ and 184 mg controlled-release caffeine (Brite-Alert™) on fibromyalgia signs and symptoms. The supplement products provided a total of 4.8 g per day of NTFactor Lipids™ and 184 mg controlled-release caffeine per day (released over 8-9 h). The supplement products were provided by Nutritional Therapeutics, Inc. (Hauppauge, NY). The dose of caffeine in the Brite-Alert™ wafers maintains the caffeine blood level equivalent to approximately one cup of coffee over an 8-9 h period. NTFactor Lipids™ is a patented, proprietary lipid complex containing an exogenous source of polyunsaturated phosphatidylcholine, phosphatidylycerol, phosphatidylserine, phosphatidylinositol, and other membrane phospholipids [8]. The participants took the daily dose for 8 days: one Brite-Alert™ wafer plus one Patented Energy™ wafer in the morning and two Patented Energy™ wafers in the afternoon.

To monitor patients we constructed a Combined Fibromyalgia Symptom...
2.2. Subjects

2.3. Study Design

2.4. Statistics
3. Results

3.1. Subjects in the Study

Of the 30 participants recruited to this open-label pilot study, 21 subjects (15 females and 6 males) were fully compliant and completed the study. The main reason for subjects not completing the study was non-compliance with trial instructions. Either subjects did not sign the Informed Consent document, or they did not take all of the study supplements, or they failed to send back all of the fully completed symptom survey forms. Most of the subjects that withdrew from the study did so without taking the test supplements. However, one participant left the trial because of severe headaches that had occurred intermittently before the trial; one participant left because of symptoms unrelated to the trial, and one left due to cardiovascular complaints that had also occurred before the trial. In all of these cases the subjects reported that their symptoms that caused them to leave the study had occurred intermittently before starting the study.

The mean age of participants completing the study was 48.5 ± 9.8 years (16 females, 48.7 ± 10.2 years and 6 males, 48.0 ± 5.6 years, respectively). There was no significant difference in mean age between males and females or between participants completing the study and those that did not complete the study.

3.2. Effects of MLR Supplements on Fibromyalgia Symptoms and QOL

We examined the daily effects of the test supplements on self-reported symptom severity and QOL scores during the 8-day trial and found significant improvements in the individual scores on specific questions (Supplementary Table 1). For example, the overall mean scores (Figure 1(A)) for the 46 questions evaluated in the trial significantly improved during the trial (significantly lower total scores). In the case of QOL, the scale was inverted to show improvements by lower scores (Supplementary Figure 1). Patients positively responded to the test supplements, as shown by significant improvements in total overall scores over the 8-day study period (Figure 1(A), 36.1%, p < 0.001).

In addition, when the scores in the subparts of the combined symptom survey form were examined for reductions in pain (Figure 1(B), 27.2%, p < 0.001), fatigue (Figure 1(C), 37.8%, p < 0.001), and gastrointestinal symptoms (Figure 1(D), 54.7%, p < 0.001) as well as improvements in QOL indicators (Figure 1(E), 39.1%, p < 0.001), by day 8 there were significant differences (ANOVA) from the baseline values obtained before starting the MLR supplements. These significant differences were also obtained on each day monitored during the trial compared to baseline values on all symptoms and indicators.

3.3. Analysis of Data Based on Gender

We examined the trial data to see if there were any differences between the responses to the test supplements between females and males. Both females and males responded to the test supplements, but there were some differences...
Figure 1. Combined and sub-parts of the symptom survey form scores by day for the study. Bars indicate mean ± SEM for overall scores (A), and for pain (B), fatigue (C), gastrointestinal symptoms (D), and QOL indicators (E). Note that the QOL indicator scores are shown in reciprocal format with improvements showing lower scores.

3.4. Model Analysis of the Data
4. Discussion

Oral supplements that contain membrane glycerolphospholipids have been used...
Here we used the MLR supplement NTFactor Lipids with fructooligosaccharides and antioxidants to protect the phospholipids from disruption, degradation and oxidation in the gut. These membrane glycerolphospholipids can be absorbed and transported into tissues and cells without excessive oxidative damage. Once inside cells, the undamaged, replacement membrane phospholipids can exchange with damaged membrane phospholipids, resulting in removal of the latter molecules from cells. They also provide important lipid precursors for specific molecules, such as cardiolipin in the inner mitochondrial membrane. An important addition to the supplements we used was the incorporation of fructooligosaccharides and antioxidants in the MLR glycerolphospholipid mixture to avert oxidation and other types of damage to the phospholipids. This is important for maintaining potency during storage before they can be ingested and while they are ingested and dispersed into small lipid globules that are absorbed by the gut epithelium and transferred to the lymph and blood circulations for transport to various tissues and cells. In animal studies a similar MLR supplement was used to prevent age-associated hearing loss. Hearing loss is normally associated with aging, but addition of MLR glycerolphospholipids to animal chow shifted the threshold hearing from 35-40 dB in control aged laboratory rats to 13-17 dB in the treatment group (p < 0.005). Seidman et al. also found that cochlear mitochondrial function was preserved, and aging-related mitochondrial DNA deletions found in the cochlear were significantly reduced in the animals receiving the glycerolphospholipid supplement in their chow. Most clinical studies using oral MLR supplements have been designed to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage. In some studies NTFactor has been used in a vitamin and mineral mixture (PropaxTM) for cancer patients to reduce the adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting and other side effects. In a double-blind, placebo-controlled, randomized cross-over trial on cancer patients receiving chemotherapy MLR improved fatigue scores, nausea, diarrhea, impaired taste, constipation, insomnia and improved QOL indicators. In several clinical studies MLR glycerolphospholipids have been shown to significantly reduce fatigue. For example, using aged subjects with chronic fatigue in a cross-over format, fatigue scores were significantly reduced from severe to moderate after eight weeks of MLR supplementation with NTFactor. Mitochondrial function also improved with administration of the MLR glycerolphospholipids. After 12 weeks there was a 35.5% reduction in fatigue (p < 0.001), and there was good correspondence between reductions in fatigue and gains in mitochondrial function (p < 0.001). By 12 weeks of supplementation mitochondrial function was found to be similar to that of young, healthy adults. However, when subjects were placed on placebo,
cebo without their knowledge for an additional 12 weeks, their fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on the MLR supplement [32]. Here fibromyalgia patients showed significant reductions in fatigue similar to those found in previous studies with fibromyalgia patients [27].

In addition to fatigue, in the present study we also examined subjects for reductions in widespread pain and gastrointestinal symptoms, common complaints of fibromyalgia patients, as well as changes in QOL indicators. We found significant reductions in pain (p < 0.001) and gastrointestinal symptoms (p < 0.001) as well as improvements in QOL indicators (p < 0.001). The changes in fatigue, pain, gastrointestinal symptoms and QOL indicators were found to be significant on each day of the study (p < 0.001).

Although there were differences between the responses of males and females in the study, consistent with previously studies, these differences were generally not statistically significant.

Using a mixed-effects statistical model and calculating Marginal and Conditional R² values indicated that the data were consistent and occurred with a low degree of variance. Although the number of subjects and time of the study were quite limited, the statistical analysis suggested that increasing the number of participants or the time of the study would be unlikely to change the conclusions. In fact, the results suggested that further reductions in overall scores, pain, fatigue, gastrointestinal symptoms and improvements in QOL were likely to occur with further time on the combination supplement.

Recently a case study with fibromyalgia patients using the MLR glycerol-phospholipids (Patented Energy™ wafers) without added control-led-release caffeine demonstrated that individual fibromyalgia patients evaluated in a clinic setting by specialists also showed reductions in pain, fatigue and gastrointestinal symptoms in the same time frame as the current study (Breeding, P. A. and Nicolson, G. L., in preparation). This indicated that the effects seen here were not due to caffeine alone.

The formulation used in this clinical study contained controlled-release caffeine that delivered a modest dose of caffeine over eight hours. Caffeine in low to moderate doses has been used previously to reduce pain and other symptoms in patients with various diagnoses [34]. Thirty clinical studies involving more than 10,000 patients have been conducted with combinations of drugs and caffeine to assess the value of caffeine as an added adjuvant [34]. For example, Verovoy et al. [35] found that fibromyalgia patients benefited when a low dose of caffeine was added to a combination mixture of carisoprodol and paracetamol (acetaminophen) to reduce pain and other symptoms. When caffeine was in the mixture, the combination was more effective (p = 0.015) [35]. Here we did not compare caffeine alone to NTFactor Lipids alone or to the combination of NTFactor Lipids plus control.
5. Conclusion

Acknowledgements

Disclosures

Conflicts of Interest

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Supplementary

Name __________________________ Day (circle): 0 1 2 3 8

IMM COMBINED SYMPTOM SURVEY FORM—FIBROMYALGIA

1. Rate the level of your pain at the present moment.
   0 1 2 3 4 5 6 7 8 9 10
   No pain Very intense pain

2. In general, how much does your pain problem interfere with your day-to-day activities?
   0 1 2 3 4 5 6 7 8 9 10
   No interference Extreme interference

3. Since the time you developed a pain problem, how much has your pain changed your ability to work?
   0 1 2 3 4 5 6 7 8 9 10
   No change Extreme change
   ___ Check here, if you have retired for reasons other than your pain problem.

4. How much has your pain changed the amount of satisfaction or enjoyment you get from participating in social and recreational activities?
   0 1 2 3 4 5 6 7 8 9 10
   No change Extreme change

5. How supportive or helpful is your spouse (significant other) to you in relation to your pain?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all supportive Extremely supportive

6. Rate your overall mood during the past week.
   0 1 2 3 4 5 6 7 8 9 10
   Extremely low mood Extremely high mood

7. On the average, how severe has your pain been during the last week?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all severe Extremely severe

8. How much has your pain changed your ability to participate in recreational and other social activities?
   0 1 2 3 4 5 6 7 8 9 10
   No change Extreme change

9. How much has your pain changed the amount of satisfaction you get from family-related activities?
   0 1 2 3 4 5 6 7 8 9 10
   No change Extreme change
10. How **worried** is your spouse (significant other) about you in relation to your pain problem?

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11. During the past week, how much **control** do you feel that you have had over your life?

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12. How much **suffering** do you experience because of your pain?

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13. How much has your pain changed your **marriage and other family relationships**?

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14. How much has your pain changed the **amount of satisfaction or enjoyment** you get from **work**?

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_Check here, if you are not presently working._

15. Do you have an urgent feeling of need to vomit but it does not occur or have **nausea**?

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16. Do you have **vomiting** of mucus and stomach contents or strong unproductive retching?

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17. Do you feel **bloated** or congestion of food without prior food intake?

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18. Do you have **abdominal cramps or stomach pain** without specific localization?

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19. Do you feel that your stomach is **overfilled** soon after starting to rest or not able to finish your meal?

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20. Do you have **belching** with acid taste, heartburn, burning sensation in the esophagus or food pipe?
21. Do you experience discomfort or sickness combined with the need to vomit?
None
Very severe

22. Do you have loss of appetite?
None
Very severe

23. Do you have an unpleasant feeling or pain behind the sternum or breastbone?
None
Very severe

24. Do you have pain localized in the upper abdomen below the sternum or breastbone?
None
Very severe

25. Rate your level of fatigue on the day you felt most fatigued during the last week.
None
Very severe

26. Rate your level of fatigue on the day you felt least fatigued during the last week.
None
Very severe

27. Rate your level of fatigue on the average during the last week.
None
Very severe

28. Rate your level of fatigueright now.
None
Very severe

29. Rate how much in the last week fatigue interfered with your general level of activity.
None
Very severe

30. Rate how much in the last week fatigue interfered with your ability to bathe and dress.
None
Very severe

31. Rate how much in the last week fatigue interfered with your normal work activity
(includes both work outside the house and housework or work around the home)
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**32.** Rate how much in the last week fatigue interfered with your **ability to concentrate.**

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**33.** Rate how much in the last week fatigue interfered with your **relations with other people.**

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**34.** Rate how much in the last week fatigue interfered with your **enjoyment of life.**

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**35.** Rate how much in the last week fatigue interfered with your **mood.**

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**36.** Indicate in the last 8 days **how many days** you felt fatigued for any part of the day.

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**37.** Rate **how much of the day,** on the average, you felt fatigued in the last week.

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<td><strong>Entire Day</strong></td>
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**38.** Indicate which of the following best describes the **daily pattern** of your fatigue in the last week.

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<tbody>
<tr>
<td><strong>None</strong></td>
<td>Worst in morning</td>
<td>Worse in afternoon</td>
<td>Worse in evening</td>
<td>No consistent daily pattern</td>
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**39.** Do you have any difficulty combing your hair?

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<td><strong>Very severe difficulty</strong></td>
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**40.** Can you walk continuously for 20 minutes?

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**41.** Can you prepare a homemade meal?

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</table>
None

42. Are you able to vacuum, scrub or sweep floors?
   0  1  2  3  4  5  6  7  8
   None

43. Can you lift and carry a bag full of groceries?
   0  1  2  3  4  5  6  7  8
   None

44. Can you climb one flight of stairs?
   0  1  2  3  4  5  6  7  8
   None

45. Can you change bed sheets?
   0  1  2  3  4  5  6  7  8
   None

46. Can you sit in a chair for 45 minutes?
   0  1  2  3  4  5  6  7  8
   None

47. Can you go shopping for groceries?
   0  1  2  3  4  5  6  7  8
   None