Author’s response to reviews

Title: Effect of soy lecithin on fatigue and menopausal symptoms in middle-aged women: a randomized, double-blind, placebo-controlled study

Authors:
Asuka Hirose (a-kacrm@tmd.ac.jp)
Masakazu Terauchi (teragyne@tmd.ac.jp)
Yurika Osaka (120122ms@tmd.ac.jp)
Mihoko Akiyoshi (akiyoshi@shonan.bunkyo.ac.jp)
Kiyoko Kato (kiyoko2226@nifty.com)
Naoyuki Miyasaka (n.miyasaka.gyne@tmd.ac.jp)

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Author’s response to reviews:

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Clare Collins and Sharon Kirkpatrick
Editor-in-Chief
Nutrition Journal

Dear Dr. Collins and Dr. Kirkpatrick:

We wish to submit a revised version of our manuscript “Effect of soy lecithin on fatigue and menopausal symptoms in middle-aged women: a randomized, double-blind, placebo-controlled study” in Nutrition Journal. We truly appreciate the detailed comments and the opportunity to improve our manuscript. We are confident we have addressed all of the reviewers’ concerns/suggestions; we hope the revised manuscript will meet your expectation and that you will consider it suitable for publication. All changes are highlighted in yellow in the text.

Below please find our point-by-point response:
Reviewer reports:

Reviewer #1: This is a nice paper on a relevant issue; I have however some methodological concerns:

abstract:

n cases: 30 or 32??

> I’m sorry, I made a mistake. We corrected the numbers.

introduction:

- please comment on the different types and sources of lipids, expand the paragraph on lipid replacement therapy (including also more references)

> Thank you for your comments. As for the different types and sources of lipids, we explained in the second paragraph of the Backgrounds section as follows: “Lecithin is a complex mixture of phospholipids found mainly in egg yolks, soy, and coles seeds. Phospholipids such as phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, phosphatidyl serine, and phosphatidyl glycerol compose the lipid bilayer of the cellular membrane structure.”

- please state why soy was chosen

> The reviewer’s comment is appreciated. Many previous studies have demonstrated the effects of LRT, but they had used a supplement containing not only phospholipids but also other active ingredients. To the best of our knowledge, this study is the first to examine the effects of soy lecithin on fatigue. This is why we chose soy lecithin in this study. We mentioned about this in the second paragraph of the Backgrounds section.

- please comment on the eventual toxicity

> In this study, safety was assessed by patient-reported treatment-emergent adverse events. During the whole study period, no treatment-emergent adverse event was reported by the participants. It was mentioned in the last paragraph of the Results section.
- the recruitment in a menopausal and general clinic are not comparable, please comment;

> We totally agree with the reviewer. Our purpose in this study was to investigate the effect of soy lecithin on fatigue in middle-aged women, because women in this age group are bothered by fatigue compared to the patients attending a general clinic. We explained about this in the first paragraph of the Backgrounds section.

methods

- major limit: how were the patients selected? how many screened? selected by whom?

> The reviewer’s comment is appreciated. The participants were recruited through advertisements posted in our hospital and in the patients’ social network. The inclusion criteria were Japanese women aged 40 to 59 years and who complained of fatigue, and the exclusion criteria were those who were receiving menopausal hormone therapy, herbal medicine, or psychotropic drugs. Fatigue was evaluated using the item about fatigue in the Menopausal Health-Related Quality of Life (MHR-QOL) questionnaire. We selected the participants according to these criteria. We added a sentence explaining the recruitment in the second paragraph of the Methods section.

- important discrepancy between abstract and methods on numbers

> I’m sorry, I made a mistake. We corrected the numbers.

- how was the tablet composition established?

> Active tablets contained high-dose (1200 mg/day) or low-dose (600 mg/day) soy lecithin. The tablet contained phospholipids in the form of phosphatidylcholine, 24%; phosphatidylethanolamine, 20%; and phosphatidylinositol, 12%.

- very important: I did not find the calculation of the statistical power

> The reviewer’s comment is appreciated. To the best of our knowledge, this study is the first to examine the effects of soy lecithin on fatigue, and we think this is a pilot study. Further studies enrolling more patients which is based on the results of present study are warranted in order to corroborate our findings.
results
- why did some women drop out?

> Thank you for your comments. During the study period, seven women dropped out of the study. Five of them did not continue to take the supplements, and two did not have an examination at our clinic. We added this explanation in the first paragraph of the Results section.

- please gather also the results into a detailed table, such as the baseline one and give all the statistics relative to pre-post (data and delta should be useful)

- please refer to tables and divide the results into sub-chapters

> Thank you for your comments, but we think that the results of the changes from baseline to 8 weeks of treatment are simple and easy to understand. Because a detailed table will be a duplicate, we summarized in the Figure 2.

discussion:

- please supply data on the duration of the studies you cited

-please comment on the ideal duration of a further study

> The reviewer’s comment is appreciated. According to the reviewer’s comment, we supplied data about the duration of studies in the third paragraph of the Discussion section as follows: “Regarding the duration of the treatment, most of the previous studies investigating the effects of dietary LRT supplement on fatigue examined for 8 weeks, meanwhile some examined for 1 or 12 weeks [4].”

collection:

please attenuate on the account of the small number of cases ans short duration.

> We agree with the reviewer. According to the reviewer’s suggestion, we added the following sentence in the Conclusion section: “Further studies with longer duration enrolling more patients with severe fatigue are warranted in order to corroborate our findings.”
Reviewer #2: The current manuscript describes the effect on soy lecithin on menopausal symptoms in middle-aged women.

Authors used proper English language and a solid methodology. Nevertheless, this reviewer has some points to address that may improve the manuscript.

TITLE: only fatigue is mentioned, while also other menopausal symptoms were studied. Suggestion to add this to the title: ... fatigue and menopausal symptoms in ....

> The reviewer’s comment is appreciated. According to the reviewer’s suggestion, we added to the title.

ABSTRACT

Confusion arose on the number of participants. 3 x 30 = 90, while 96 participants were enrolled?

Again, confusion about the duration of the treatment, and the moments when data was collected. After reading the full text, I guess that the treatment was 8 weeks, and that data were collected before, half-way and at the end/immediately after treatment. This should be properly described.

> I’m sorry, I made a mistake. We corrected the numbers.

About the duration of the treatment and the moments when data was collected, the reviewer’s understanding is correct. As mentioned in the abstract, “the participants were randomized to receive active tablets … or placebo, for 8 weeks. The following parameters were evaluated: age, …before and 4 and 8 weeks after treatment.”

INTRODUCTION

Good job!

Maybe good to mention that phospholipids are part of all membranes, including the cell membrane and the organelles.

AIM: why did you choose soy lecithin and not lecithin from egg yolk or another source? This may be added to the discussion.
Methods

As already mentioned, strong methodology, but because of the randomization, the groups differed for some baseline characteristics that may have had their influence on the results. This should be addressed in the discussion. An attempt to make 'matched samples'' could have prevented this.

We agree with the reviewer. According to the reviewer’s suggestion, we added the following sentences in the fifth paragraph of the Discussion section: “In the present study, there was statistically significant differences in the baseline characteristics among the study groups, that is weight, body mass index, and body fat mass were significantly higher in the high-dose group. On the other hand, there was no significant difference in the POMS-vigor score, diastolic blood pressure, and CAVI that changed significantly after the 8-week treatment, therefore we consider that the differences in the baseline characteristics would have a small influence on the results of the present study.”

line 171: height, weight and BMI are not parameters from body composition. Suggestion to rephrase: Height, weight, BMI and body composition including fat mass and ...

The reviewer’s comment is appreciated. According to the reviewer’s suggestion, we modified the sentence.

line 172: this reviewer strongly believes that not muscle mass but fat free mass was estimated by the BIA device. Please check and correct throughout the manuscript and tables.

The reviewer’s comment is appreciated. According to the reviewer’s suggestion, we rephrased.

line 184: please also describe how you defined sleep latency and sleep efficiency.
We investigated physical activities and objective sleep states using the actigraphy system that is loaded with a miniature triaxial acceleration sensor. It measured motion with accelerometers and sleep–wake identification was automatically performed by using the Cole–Kripke algorithm. We defined sleep latency as the time from time in bed to the start of identification of sleep. Sleep efficiency is calculated as pure sleep time (time in bed minus awake time) divided by time in bed. We added these explanations in the “Physical activities and objective sleep states” paragraph of the Methods section.

STATISTICS

Please be more detailed for which analyses the different tests were used. If you do it here, it is not necessary anymore in the results section.

> According to the reviewer’s comment, we added sentences in the Statistics paragraph as follows: “The baseline characteristics of the participants who completed the 8-week treatment were compared. Then, the changes from baseline to 8 weeks of treatment in all of the collected data were evaluated.”, and removed the sentences from the Results section.

RESULTS

Did you do a drop out analysis? Please add.

> Thank you for your comments. See above.

line 203: suggestion to rephrase: The group mean age ranged from .... (instead of participant mean age)

> The reviewer’s comment is appreciated. According to the reviewer’s suggestion, we rephrased.

line 209-210: this is actually part of the methods - statistical analysis section.

> See above.
DISCUSSION

line244: do you mean that you can find mitochondria in the cell membrane? Or do you mean that the cell membrane also encloses mitochondria? please be clear and correct.

> Thank you for your comment. We agree with the reviewer that it was hard to understand, therefore we modified as follows: “The cell membrane including mitochondrial membrane is composed of phospholipids, forming a dynamic structure represented by the fluid mosaic model proposed by Singer and Nicolson in 1972.”

What is the clinical relevance of a lower diastolic blood pressure? Systolic blood pressure was not altered by lecithin...

> We agree with the reviewer. Our results showed that lecithin decreases the diastolic blood pressure and CAVI, but it is difficult to explain details of the mechanisms. Because some studies showed that lecithin or LRT lowered cholesterol and reduced atherosclerotic plaques, we only indicate the possibility as follows: “There is a possibility that lecithin lowers cardiovascular risks, although the mechanisms are yet to be elucidated.”

FIGURES: please define the y axes and add units.

> Thank you for your comments. We added the units.

Sincerely,

Masakazu Terauchi,
Department of Women’s Health,
Tokyo Medical and Dental University,
Yushima 1-5-45, Bunkyo,
Tokyo 113-8510,
Japan
Telephone: +81-3-5803-4605
Facsimile: +81-3-5803-4605
E-mail: teragyne@tmd.ac.jp