Reviewer's report

Title: Dietary milk fat globule membrane supplementation combined with regular exercise improves skeletal muscle strength in healthy adults: a randomized double-blind, placebo-controlled, crossover trial

Version: 2
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Reviewer: Wenbo Tang

Reviewer's report:

Overall comments:

This manuscript reports a randomized, double-blind, placebo-controlled, cross-over trial of the effect of dietary MFGM supplementation plus regular exercise vs. regular exercise alone on muscle strength and neuromuscular function in healthy non-athlete male adults.

Several issues in relation to the statistical design, analysis and reporting of the study are listed below.

Major Compulsory Revisions:

1. The Methods section should include the sample size/power evaluations that were performed to support the chosen sample size of 14 subjects, at least for the primary outcome. This should include the assumptions (e.g. expected treatment effect, standard deviation of the outcome variable, etc.) used and the corresponding power that can be achieved with 14 subjects.

2. The estimation of treatment effects in the presence of carry-over effects is problematic. While this study does include a washout period (of comparable duration to the treatment period), a significant difference in the baseline muscle strength between the two periods is still reported by the authors, suggesting the presence of such a carry-over effect. It’s also reported that the baseline muscle strength didn’t differ significantly between the treatment groups. The authors should clarify whether this second test for baseline muscle strength between treatment groups was done for each period (particularly period 2). This is of importance as the absence of such a difference at period 2 baseline could indicate the carry-over effect was non-differential.

3. As a continuation of the above comment, the authors should include the observed carry-over effect and the potentially insufficient washout period as a limitation in the discussion section.

4. The statistical methods (repeated-measures ANOVA and paired t-test of change from baseline) used in the study are not among the preferred methods in the current literature for cross-over designs where baseline data is available. One preferred option is to fit a linear mixed effects model (e.g. Proc Mixed in SAS)
with the dependent variable of either the endpoint (e.g. muscle strength) after 4 weeks or its change from period baseline, the fixed effects of treatment, period, period baseline and the average of period baselines as patient baseline, and the random patient effect. An alternative model that can be chosen a priori when there are concerns of insufficient washout is one similar to the above but with the period baseline and patient baseline fixed effects replaced by the study baseline (i.e. baseline of period 1). In the case of this study, since a carry-over effect is also observed, such a priori decisions between the above two models are no longer possible. Instead, the authors should consider applying one as the primary analysis and the other as a sensitivity analysis so that consistency of results can be assessed.

Minor Essential Revisions:

1. For transparency purposes, is this randomized trial disclosed on public databases such as ClinicalTrials.gov? If so, the registration number of the study should be included in the manuscript.

2. The age range of the study subjects as reported is 31-48 (no mean is provide, see next comment). Although age groups can be defined differently, individuals in this age range are generally considered middle-aged adults rather than young adults.

3. It is good practice in reporting randomized studies to include a table of baseline subject demographics and characteristics (e.g. age, height, smoking status, etc.), as it allows the readers to better assess the randomization and the population under study. The authors should consider adding such a table by the two treatment sequence groups and for the overall sample.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.