Author's response to reviews

Title: Effectiveness of oral nutritional supplementation for older women after a fracture: a randomized controlled pilot study

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Author's response to reviews: see over
Dear Editor,

We herewith send you our revised manuscript “Effectiveness of Oral Nutritional Supplementation for Older Women after a Fracture: Rationale, Design and Study of the Feasibility of a Randomized Controlled Study” for publication in the BMC Geriatrics.

We believe that the subject of this revised manuscript will be of great interest to many readers of your journal as it deals with the complex topic of malnutrition in older people recovering from a fracture. We addressed all the comments of the reviewers and adjusted the text in the manuscript accordingly.

This paper has not been published or submitted to any other journal. There are no financial relationships that can lead to a conflict of interest. The manuscript is read by all authors and the requirements for authorship have been met by all.

We look forward to your reply.

Sincerely yours,

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We thank the reviewers for their detailed and helpful comments. We will address the specific issues to the best of our abilities.

Our main general comment is that the study is a pilot pragmatic clinical trial that aimed to assess the effectiveness, and not the efficacy, of oral nutritional supplements. We were not aiming to address some of the detailed issues related to efficacy and also did not have the financial resources to investigate some issues in greater detail.

Reviewer 1
The authors present an article describing the methods and the problems they found on the performance of an unfinished, randomized controlled study ..... Nevertheless, there are some limitations that should be addressed before publication:

- 1.- The title should be changed to: “Effectiveness of Oral Nutritional Supplementation for Older Women after a Fracture: Rationale, Design and Study of the Feasibility of a Randomized Controlled Study” and focus the interest of the article on the description of methods and study development with the inclusion of some results from the pilot phase and exclude a comparative analysis. The final results and conclusions in the whole population should be presented in a future paper.

We understand the reviewer’s viewpoint. However, we were not able to progress to implement the definitive study because funding applications were unsuccessful. Therefore we believe that it is important to present the pilot data from the randomized trial so that it is available for inclusion in future meta-analyses, and to discuss the possible reasons for the lack of differences between the intervention and control groups.

We have changed the title to that suggested by the Reviewer.

Major revisions recommended:

- 2.- The authors should describe, or represent in a flow-chart, the number of patients >70 years of age admitted to the hospital with a fracture during the study period, % that were approached, % with the inclusion criteria and % that were finally included. Such data would help evaluating the feasibility of the study.

These specific data are not available. We have provided estimates for these data in the text of the revised paper on page 4.

- 3.- the definition of the timing of baseline albumin determination is key, as is the criterion used to define malnutritional status. At least, whether the determination was performed before surgery must be stated. (It is known that serum albumin concentration change with inflammatory situations and surgery.)

The timing of the baseline albumin determination was the first determination after admission to hospital and thus is pre-surgery. This has been added to the text of the revised paper.

- 4.-It is important to describe how the control of the intervention is done and present the data of adherence they have so far:
  o % of patients that took the complete nutritional supplement every day during admission and how many refer to have done it after discharge
  o % of patients that did it without decreasing the usual daily intake.
  o Quantity of milk that patients in the control group received and % of patients that had it every day during admission. These data allow evaluating if a good compliance of this intervention is feasible.
We agree with the reviewer that is important information but it is reported in the results section on page 7 and discussed on page 10 that we do not have this specific information. We have now changed the first paragraph in the Discussion section to emphasize that this information is lacking and this makes it difficult to interpret the results.

- 5.- *The principal end-point must be defined. Which is the operative definition for effectiveness? What is the change in serum albumin determination and when in the follow-up do they consider the intervention to have a nutritional benefit? What is the change in Barthel index during follow-up that they consider relevant and what difference between the groups they hypothesize is considered to be a positive result due to the intervention? Subsequently, they have to estimate the sample size needed to find these differences between groups.*

As we have stated in the last sentence of the Introduction, ‘We investigate the effectiveness of a high calorie, high protein nutritional supplement in terms of changes in recovery rate as measured by abilities in activities of daily living (ADL), and nutritional status.’

The relevant difference between groups in Barthel Index (using the 100 point version of this scale) is 10 points. The difference in serum albumin we would consider relevant is 3 g/l.

It is difficult to calculate the required sample size needed to find these differences between groups based on the pilot study due to skewed data, particularly with reference to Barthel Index, and limited adherence in the pilot study. Based on the pilot data there appears to be a slightly greater effect on functioning (as assessed by the Barthel Index) than serum albumin.

We have added comments to this effect at the end of the Discussion section.

We agree with the reviewer that this is an important issue. One of the reasons we performed this pilot study was to evaluate the number of patients that would be necessary to detect any benefit from nutritional supplementation. Therefore no sample size was determined beforehand.

- 6.- *They should also explain if the rehabilitation process is the same in both groups.*

The rehabilitation process was the same for both groups. We have added this statement to the text of the revised paper.

- 7.- *Conclusions should be changed. The current results in this phase of the study and with this small sample do not allow to draw any conclusion about the effect of nutritional supplementation after a fracture.*

We have modified the text of the paper to read “No conclusion can be drawn about the effect of the nutritional supplementation on nutritional status, recovery rate or number of complications for this type of patients due to the limited number of participants and incomplete adherence with use of the supplements.”

Discretionary changes:

- 8.- *To present only descriptive results (table 2) adapted to the definition of outcomes and without comparative analysis. This small sample does not permit to correctly compare the groups adjusting for main confounders.*

See our response to #1 above. We wish to provide data for the two groups because this is the definitive report from this pilot study and we wish the data to be available for future meta-analyses, particularly the Cochrane Collaboration meta-analysis of this topic.

- 9.- *They should discuss the reasons for the long inclusion period in the pilot phase for such a small sample of participants, and whether they think that these reasons could possibly question the feasibility of the trial.*
In the Discussion section on page 10 it was stated:” This is a long recruitment period for such a small number of participants, but we believe that with more staff and funding it would have been possible to include many more eligible participants in a shorter time frame. This could also have helped to overcome the possible issue regarding uncertainty with compliance. A compliance officer to ensure that participants in the intervention group did actually have the set amount of supplement each day could have helped with the accuracy of measuring compliance and also with increasing the compliance to the intervention in itself. Nevertheless, it was difficult to encourage the many cognitively impaired trial participants to consume the supplement”.

We believe that it is feasible to perform such a randomized controlled trial, but it is necessary to have sufficient and staff to include enough eligible participants, and to have a mechanism for encouraging participants to be adherent with the intervention.

Reviewer 2

Major Compulsory Revisions

1. The study has not been designed in a way that will adequately answer the second objective: “to test the effectiveness of oral supplements on malnourished older people with a fracture”. Several important methodological issues exist,
   - The use of albumin alone as an indicator of nutritional status (please see comment to follow);
   - The use of self reported weights;
   - No measure of the proportion of the commercial supplement consumed was incorporated. No assessment of consumption of non-commercial supplements amongst the control group in hospital or at home was provided;
   - There appears to be no assessment of the individual’s nutritional requirements in order to ascertain that the provided supplements are adequate to meet their nutritional needs, or else the volume of commercial supplement required to meet individuals minimum nutritional needs. Some of these difficulties were acknowledged by the authors (ie actual compliance, other dietary intake, the standard provision of high protein milk). The authors have recognized the challenges involved with such as study including ensuring consumption, but the implication of this limitation and the means of assessing the volume of supplement consumed is discussed in a limited way (e.g. a compliance officer). I am of the opinion however, that all the above points need to be addressed before one can be more confident of the results obtained.

We thank the reviewer for these detailed comments and agree with them. As stated in our response to Reviewer 1 this study is a pilot study of a pragmatic randomized trial of the effectiveness (not efficacy) or nutritional supplementation in older people after fractures which was conducted in a climate of limited financial resources. We accept the reviewer’s comments and agree that the issues raised are weaknesses in the study as implemented and have added statements to this effect in the Discussion. We have also altered our interpretation of the results as stated in our response to Reviewer 1.

However, we don’t agree that albumin alone was the indicator of nutritional status. We used mid upper arm circumference at the primary indicator of nutritional status. In addition, as mentioned above in response to the other reviewer, and stated in the Introduction of the paper we were interested in change in ADL status as a co-primary outcome of the study.

2 The rationale for the selection of the “dose” of supplementation is also unclear. The energy deficit evident from a weight loss of around 1.5-2.5 kg over the initial few weeks (40 days) indicates that the consumption of at least 2 supplements a day (not one) would be required to prevent the decline in weight and potentially achieve maintenance of nutritional status. The 2 Cal/ml supplement provided certainly has the potential to be very filling which is why particular delivery modes have been trialled and to improve consumption. Through non-documentation of consumption, the ability to answer the proposed question regarding the
effectiveness of commercial supplementation is substantially constrained. Neither the intervention nor control groups were meeting goal requirements as evidenced by the ongoing weight loss. Consequently, a conclusion of the study appears to be that there is no additional benefit from use of commercial supplements compared with the use of food as supplements. The step between the act of prescribing a supplement (commercial or food-based) and its final consumption is substantially impacted by many systems and organizational issues including, but not limited to, the service delivery models, assistance with consumption, staff encouragement and perceptions of importance. All of these factors seriously impact consumption. Consequently, such systems and organizational issues are also being investigated through the “intention to treat” approach adopted, which is useful to explore once the stated question concerning the actual effectiveness of commercial supplementation has been addressed.

It is often the case that people eat poorly while in hospital. Even with one supplement a day, nutritional requirements are likely not to be met, as evidenced by continued weight loss. Currently, the study has no means of assessing the proportion of goal requirements being attained, even if consuming the supplement. As commented upon in the paper, ways to confirm consumption would strengthen interpretation of the results. It would be valuable to also record the participants overall consumption of either the commercial or food supplement, the energy or protein intake provided and the proportion of nutritional requirement being met. Not just prescribing or receiving supplements but knowing if people are indeed reaching their nutritional goals is the critical factor. I would suggest the stated aim to “test the effectiveness of oral supplementation” was in fact to “test the effectiveness of oral supplementation compared with the use of regular food as supplements” during a fair portion of the study. Controls received supplementation containing around half the energy and protein of the intervention group. Whether the control group continued additional consumption of food as supplement once home was not ascertained. Both groups were therefore receiving supplementation of energy and protein during their hospital admission, simply different quantities and through different means. Neither the intervention nor control groups were meeting goal requirements as evidenced by the ongoing weight loss. Consequently, a conclusion from the current study appears to be that there is no additional benefit was evident from use of commercial supplements compared with the use of food as supplements.

We agree with these points raised by the reviewer. We chose to design and implement the study in the way that we did because it mirrored clinical practice in the health service at the time that the study was conducted. We have modified the aim of the study as suggested by the reviewer and also adjusted the Discussion to address the points made by the reviewer.

Minor Essential Revisions

3. The use of self-reported weights would not usually be considered acceptable considering it is a key outcome variable. If used, the validity of this approach would need to be assessed and reported with the degree of error factored into the results obtained. Details regarding methods to standardized other weight measurements are not reported.

Self or family reported weights were only used at baseline when it was difficult to weight a participant with a recent hip or pelvic fracture.

We understand the reviewers concern and know there are authors who agree and report that especially for older people accuracy of self-reported weight is not very high:

There are also researchers who report that self-report of weight can be considered as accurate and reliable:


We have now added a sentence to report about accuracy of self-reported weight.

4. Could you please elaborate regarding how the consumption of the supplements was confirmed or estimated in hospital?

Unfortunately we do not have that information. We do know from the research nurses that the majority of participants consumed their supplements as prescribed, but we don’t have actual numbers to confirm this.

5. Could you please report what percentage of participants provided their own consent compared with obtaining consent through next of kin? This other measure would give an indication of cognitive status.

Unfortunately we do not have that information.

6. Grip strength was performed on dominant hand, but was recorded after i) how many attempts? ii) using average or the best measure.

There were three attempts and the greatest strength was recorded. This has been added to the paper.

7. Could you please include the reference for equation used to estimate height for knee height?

We have inserted the following reference for the equation used: Han TS, Lean ME. Lower leg length as an index of stature in adults. Int J Obes Relat Metab Disord 1996; 20: 21–7.

8. The method by which malnutrition is defined is very important. Albumin is sensitive and reduces with acute illness or after surgery and so is not a useful discrete indicator of nutritional status. Plasma proteins are sensitive to the severity of illness rather than indicating nutritional status.


As stated in Watterson et al, 2009 “Single parameters, such as CAMA (corrected arm muscle area), BMI (body mass index) and albumin, have some evidence of predictive validity however, screening tools with at least two parameters are recommended because there is evidence that they have higher sensitivity and specificity at predicting nutritional status.” The use of MUAC (Mid upper arm circumference) is appropriate as a monitoring and outcome measures to demonstrate improved patient, clinical and cost outcomes as it takes into account both body fat...
and muscle changes (Watterson et al, 2009). Consequently, it may be worth exploring results of those with low MUAC alone or changes in MUAC alone, as separate from those with low albumin or changes in albumin.


Thank you for this valuable information concerning CAMA, BMI and albumin. We agree that it could be interesting to explore the results of those with low MUAC alone in future studies.

9. Some specific comments regarding results are noted below: Weight was declining and continued to decline, so a serious question exists as to whether the participants nutritional requirements were in deed being met.

We agree with this point of the reviewer and emphasized this issue for future studies on page 11 in the Discussion section.

10. I would suspect the length of stay is skewed data. If this is the case presentation as median and range rather than means and SD would be more appropriate.

This has been changed accordingly.

11. (An Endnote typographical error noted: Miller 17 in the discussion, but listed as 18 in the references)

Thank you this has been corrected.

12. Discussion - Considering the albumin is sensitive to disease severity (and not necessarily a sensitive indicator of malnutrition when used on its own) it may not be a surprise that it predicted hospital stay.

The ongoing weight loss suggests there are in fact 2 malnourished groups, who both continue to be malnourished as it could not be confirmed that the supplement provision was adequate to address the intervention groups actual requirements. Unless enough supplement is consumed to slow or cease weight loss (intermediate outcome measures), the impact of supplementation upon other outcome factors including recovery rates, complications, length of stay and need for assistance cannot be confidently ascertained.

We agree with the reviewer and this point is now emphasized in the Discussion section.

13. Overall comment – this is an important topic implemented in a population deemed to increase with in health service provision. Key limitations or issues for discussion (as well as for consideration in future study includes 1) The definition used to assess malnutrition
2) Proportion of goal nutritional requirements met through prescribed supplementation (commercial or high protein milk) (as weight loss continued)
3) Proportion of nutritional requirements met and the compliance with supplement provision (for both groups, for both home and hospital). Without knowing the consumption and the adherence of intakes, the fundamental question of the value of the supplement provision cannot be answered.

We thank the reviewer for these 3 key issues and agree with them. We have addressed related issues in our reply to Reviewer 1.
We believe that the definition to assess malnutrition was reported in the method section. The proportion of goal nutritional requirements being met are uncertain mainly because we have no information about actual adherence and diet during admission and after discharge. We principally wanted to reduce decline in functioning. We did not have the resources for detailed nutritional assessments and were reliant on weight and MUAC. However, we had a nutrition study who performed more detailed nutritional assessment for a sub group of the participants in this trial. We have added this information to the paper.

Discretionary revisions:

14. Were any power calculations completed to estimate the sample size required?

For this pilot study we did not calculate a sample size estimate.

15. Could I suggest removing the term “only” from the statement regarding one death?

This change has been made.