Author's response to reviews

Title: Weight loss, dysphagia and supplement intake in patients with amyotrophic lateral sclerosis (ALS): Impact on quality of life and therapeutic options

Authors:
Sonja Koerner (koerner.sonja@mh-hannover.de)
Melanie Hendricks (Melanie.Hendricks@stud.mh-hannover.de)
Katja Kollewe (kollewe.katja@mh-hannover.de)
Antonia Zapf (antonia.zapf@med.uni-goettingen.de)
Reinhard Dengler (dengler.reinhard@mh-hannover.de)
Vincenzo Silani (vincenzo@silani.com)
Susanne Petri (petri.susanne@mh-hannover.de)

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Author's response to reviews: see over
Dear Prof. Majithia,

Thank you very much for providing the helpful comments on our manuscript entitled “Weight loss, dysphagia and supplement intake in patients with amyotrophic lateral sclerosis (ALS): impact on quality of life and therapeutic options” by Sonja Körner, Melanie Hendricks, Katja Kollewe, Antonia Zapf, Reinhard Dengler, Vincenzo Silani, and Susanne Petri

We have addressed the reviewer’s suggestions as detailed below.

Reviewer 1:

Major Compulsory Revisions

1. Methods – The influence of respiratory distress and amount of fasciculations on weight loss was evaluated, but the authors did not present any tool to quantify any of those.

According to our experience it is very difficult for patients to exactly quantify the amount of fasciculations and the degree of respiratory distress (as both is variable from day to day and difficult to describe). Therefore we only asked them about presence or absence of fasciculations and respiratory distress. We have now added this information to the Methods section (methods, para 1).

2. It seems that FTD was not a criterion of exclusion, but less than 1% of the ALS population had FTD, which represents a clear bias. Can the authors explain this?

The reviewer is right that the presence of FTD in our study cohort does not reflect a normal ALS population. FTD was not an exclusion criterion but patients with FTD are less likely to participate in a clinical study with questionnaires and are therefore underrepresented in our population. We explained this now in the Methods section (methods, para 1).

3. Significant weight loss was set at 3 Kg, which is a quite arbitrary value. In addition, it would be better to consider a percentage of the body mass index change, as 3Kg does not represent the same for everyone.
The reviewer is right that a percentage of the body mass index change might have been a better measure for weight loss. Unfortunately we do not have the initial and follow up BDI for every patient in the study but only the information we asked for in the questionnaire (weight loss more than 3kg – yes or no). Although 3kg is not the same for everyone we still think that it probably represents significant weight loss for all patients.

4. I am not sure disease duration is statistically equivalent in the 4 groups; in table 1b the p values should be introduced.

Results of the comparison of mean disease duration by t-test were as follows:
No weight loss (54.5 months) vs. weight loss without dysphagia (31.8 months): p=0.066
No weight loss (54.5 months) vs. weight loss with dysphagia (29 months): p<0.01
No weight loss (54.5 months) vs. weight loss (30 months): p<0.01

The disease duration of the groups weight loss (30), weight loss without dysphagia (31.8) and weight loss with dysphagia showed no significant differences.
P values have now been added to table 1.

5. Discussion – This section is too long and repetitive, the detailed discussion on the role of dementia is unnecessary.

The discussion was shortened; the discussion on dementia was deleted (discussion, para 1-3).

6. Vitality is probably related to respiratory distress; we are not sure which independent determinant of weight loss is.

The reviewer is right that vitality is also influenced by respiratory distress as shown by the following regression analysis:

<table>
<thead>
<tr>
<th>Coefficientsa</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Unstandardized Coefficients</td>
<td>Standardized Coefficients</td>
<td>t</td>
<td>Sig.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>43.607</td>
<td>2.376</td>
<td>18.355</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Increased respiratory work</td>
<td>-12.803</td>
<td>3.434</td>
<td>-3.728</td>
<td>.000</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Vitality

But multiple regression analysis taking into account weight loss and respiratory distress shows that both have an independent significant influence on vitality:

<table>
<thead>
<tr>
<th>Coefficientsa</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Unstandardized Coefficients</td>
<td>Standardized Coefficients</td>
<td>t</td>
<td>Sig.</td>
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<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>47.483</td>
<td>2.723</td>
<td>17.439</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>weight loss</td>
<td>-9.457</td>
<td>3.504</td>
<td>-.242</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>Increased respiratory work</td>
<td>-10.093</td>
<td>3.491</td>
<td>-.259</td>
<td>.005</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Vitality

We added this information now in the results section (results, para 1) and in table 2.

7. The discussion on dietary supplements is confusing.

The discussion on dietary supplements was shortened and focussed (discussion, para 3 and 5).
8. The many drawback of this study should be stressed by the authors.
The main drawback of the present study is that it is retrospective and based on subjective information of the patients. We now highlighted this limitation in the conclusion section (conclusion, para 1). In the conclusion we already stated that further prospective studies are required to confirm our results regarding high calorie nutritional supplements and PEG insertion (conclusion, para 2) and to substantiate the characteristics of ALS patients with weight loss without dysphagia (conclusion, para 3).

Minor Essential Revisions
1. Abstract – the results section is unclear
   We tried to clarify the results section in the abstract.
2. Introduction – regarding study main aims the authors mention “to investigate the extent of weight loss in ALS and potential underlying causes beyond dysphagia”. Reading results and discussion it seems that the main were moved to correlated weight loss with clinical features and changes in QoL evaluation, as well as to test weight loss and survival. The authors should re-address the main objectives of this study.
   The respective section of the introduction was re-structured (introduction, para 3).
3. Methods – It is important to expand the statistical section to explain the multiple regression analysis method applied. The second paragraph of Subjects and methods should be re-styled.
   The multiple regression analysis has now been explained in the method section (page 5, para 2). The second paragraph of Subjects and methods was rephrased.
4. Results – The information on the positive impact of PEG is important. On the other hand the results of weight loss on survival are based on poor statistics. The authors should apply Kaplan-Meier survival curves and the log-rank test to verify that weigh loss is independent from bulbar-onset as determining short survival.
   We now have added Kaplan-Meier survival curves in Figure 2C. Respective changes were also made in the manuscript (results, para 4; figure legend, para 2). In the patient group we were able to follow up, the amount of patients with bulbar or spinal onset was not significantly different in the patient groups with and without weight loss (Chi²Test=0.328), hence the bulbar onset can not be held responsible for the difference.
5. The last paragraph of page 6 is not well written.
   This paragraph was re-structured (results, para 3)
6. Table 2 is a SPSS output. The authors should present it in a more conventional way.
   The design of table 2 was changed.

Reviewer 2
1. The number of patients is rather difficult to follow since the authors didn’t offer numbers just percentages during the text. I would suggest that the authors mention number and percentage as well.
   We have now provided numbers and percentage in the results section (results, para 1-4).
2. I am a little bit confused since the authors mentioned at page 3: “....and benefit of highcalorie supplements and PEG. Further...in other dietary supplement intake...”. The authors shall define the 2 distinct types of dietary supplements. The high calorie nutritional supplements should be defined as well other dietary supplement intake.
   High calorie supplements mean calorically dense drinks or shakes, which are to counteract weight loss; other dietary supplements mean supplement medication with e.g. vitamins, antioxidants or homeopathic
medication. The two terms were no explained by examples when first mentioned on page 3 (introduction, para 3).

3. Table 1 deal with “…with and without dietary supplement intake/weight loss” while Figure 1 deal with “…and impact of high calorie supplements/PEG”. The authors shall define the number of the patients with “dietary supplement” and those with “high calorie supplements”.

The number of both are now added in the results section and it has been precisely distinguished between the two types of supplements throughout the results section (results, para 2 and 5).

4. In the collected information (Suppl 1) there were mentioned “supplement intake” and “high calorie food intake”. There were no further informations related to the high calorie food intake.

We investigated the influence of high calorie supplements and dietary supplements (see comment on 2.). High calorie supplement intake and high calorie food intake was meant to be equivalent. To avoid confusion we changed “high calorie food intake” to “high calorie supplement intake” in table 1.

5. The information offered at page 10 could be confusing: “Given the fact that some patients (according to our study) invest between 2 and 3 Euro per day in supplements, one must postulate that ALS patients receive sound and substantial information about the lack of evidence for any relevant benefit as well as potential side effects”. The authors shall answer to the title if the supplement intake” are beneficial or not. It seems that the answer is yes, being Figure 3 C as the patient related outcome measure positive. Please provide an answer and a more appropriate explanation.

The paragraph mentioned by the reviewer was deleted and replaced by a concluding statement regarding intake of dietary supplements.

We hope that the manuscript is now suitable for publication in BMC Neurology.

Yours,
Sincerely,
Sonja Körner