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EFFECTS OF HIGH-INTENSITY EXERCISE AND PROTEIN SUPPLEMENT ON MUSCLE MASS IN ADL DEPENDENT OLDER PEOPLE WITH AND WITHOUT MALNUTRITION—A RANDOMIZED CONTROLLED TRIAL

M. CARLSSON1, H. LITTBRAND1, Y. GUSTAFSON1, L. LUNDIN-OLSSON2, N. LINDELÖF3, E. ROENDAHL1,2, L. HÅGLIN3

1. Department of Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University, Umeå, Sweden; 2. Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University, Umeå, Sweden; 3. Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Umeå, Sweden. Address for correspondence: Maine Carlsson, Department of Community Medicine and Rehabilitation Geriatric Medicine, Umeå University, SE-901 86 Umeå, Sweden. Phone: +46 90 785 87 69, E-mail: maine.carlsson@germed.umu.se

Abstract: Background: Loss of muscle mass is common among old people living in institutions but trials that evaluate interventions aimed at increasing the muscle mass are lacking. Objective, participants and intervention: This randomized controlled trial was performed to evaluate the effect of a high-intensity functional exercise program and a timed protein-enriched drink on muscle mass in 177 people aged 65 to 99 with severe physical or cognitive impairments, and living in residential care facilities. Design: Three-month high-intensity exercise was compared with a control activity and a protein-enriched drink was compared with a placebo drink. A bioelectrical impedance spectrometer (BIS) was used in the evaluation. The amount of muscle mass and body weight (BW) were followed-up at three and six months and analyzed in a 2 x 2 factorial ANCOVA, using the intention to treat principle, and controlling for baseline values. Results: At 3-month follow-up there were no differences in muscle mass and BW between the exercise and the control group or between the protein and the placebo group. No interaction effects were seen between the exercise and nutritional intervention. Long-term negative effects on muscle mass and BW was seen in the exercise group at the 6-month follow-up. Conclusion: A three month high-intensity functional exercise program did not increase the amount of muscle mass and an intake of a protein-enriched drink immediately after the exercise did not induce any additional effect on muscle mass. There were negative long-term effects on muscle mass and BW, indicating that it is probably necessary to compensate for an increased energy demand when offering a high-intensity exercise program.

Key words: Muscle mass, exercise, nutritional status, residential care facility.

Introduction

The causes of age-associated loss of muscle mass (MM) are multifactorial (1, 2) which includes physical inactivity, malnutrition, as well as the aging process having a strong impact (3). Muscle mass is the largest reservoir of body protein and is important in maintaining nutritional status and physical function (4). The age-related loss of MM increases the risk of disability, morbidity, and mortality (4-6).

Strength exercise 2-3 times per week over at least 9 weeks seems to be effective in increasing MM, in healthy or moderately impaired older people (7, 8). A protein supplement, taken directly after strength exercise, seems to increase the ability to increase MM among older people with severe physical or cognitive impairments living in residential care facilities.

A randomized controlled trial, the Frail Older People—Activity and Nutrition study in Umeå (the FOPANU Study), evaluated the effects of a high-intensity functional exercise program (the HIFE Program) on physical functions as a primary outcome (13). In older people living in residential care facilities the HIFE program showed positive long-term effects on physical functions, although an intake of extra protein immediately after the exercise had no influence. The aim of the present study was to evaluate the effect of a HIFE program and the protein-enriched drink on the ability to increase MM, as a preplanned secondary outcome from the FOPANU study. Our hypotheses were that; 1) a HIFE program would increase MM, 2) an intake of a protein-enriched drink immediately after the exercise program would increase this effect, and 3) the effects from exercise and the protein-enriched drink would be limited among participants with malnutrition.

Methods

Settings and study design

The FOPANU study (13), was performed in nine residential care facilities in Umeå in northern Sweden. All facilities comprised private flats with access to dining rooms, alarms, nursing, and care. This study was a stratified cluster-
randomized controlled trial designed in a 2 x 2 factorial model, including an exercise intervention compared with a control activity, and an intake of a protein-enriched drink compared with a placebo. For all measures assessors were blinded to group allocation and previous test results. For the nutrition intervention participants as well as therapists who administered the nutrition intervention and supervised the exercise and control activities, were blinded. The exercise and control activities were introduced to participants and staff at the facilities with no accompanying information about the study hypotheses.

Participants
The inclusion criteria for participation in the main study (13) were:
- aged 65 years or older
- dependent on assistance from one person in one or more personal Activities of Daily Living (ADL) according to the Katz Index (14)
- able to stand up from a chair with armrests with help from no more than one person
- having a score of ten or more on the Mini-Mental State Examination (MMSE) (15).

Out of 489 residents, 191 were assessed as eligible in the FOPANU study (Figure 1).

![Figure 1](image-url)  
Flow of participants through the trial

Bioelectrical Impedance Spectroscopy (BIS) was used in the assessments of body composition in the present sub-study. The exclusion criteria for taking part in the BIS assessments were:
- having a pacemaker or metal implants in the body
- unable to perform BIS measurements on the right hand or foot.

In total 177 persons were included in the present study (Figure 1).

Age, sex, and Katz ADL index score did not differ between those who were included (n=177) and those 71 participants who declined to participate or could not be measured by BIS (n=14).

The residents or their relatives, when appropriate due to cognitive impairment, gave their consent. The study was approved by the Ethics Committee of the Medical Faculty of Umeå University (§ 391/01).

Body composition assessments and outcome measures
Body composition and BMI were assessed at baseline, after the three-month exercise intervention and after six months (three months post intervention).

For Bioelectrical Impedance Spectroscopy (BIS) a Hydra ECF/ICF Spectrum Analyzer model 4200 (Xitron Technologies, San Diego, CA), was used for assessments of Intra Cellular Water (ICW) in liters and Fat Free Mass (FFM) in kg (16). The measures are based on the Cole-Cole parallel model based on the Hanai mixture theory (17).

Intra cellular water and Body Weight (BW) constitute the outcome measures where ICW was the primary outcome. The rationale for using ICW as a proxy for MM is that MM contains mostly ICW (18), and that changes in MM are generally accompanied by changes in ICW (19). Body weight was used in the interpretation of ICW changes. We assumed that there were no essential changes in the bone mass, internal organs, blood or skin during the time that the study lasted.

Geriatric assessments, diagnoses and drugs
The residents’ registered nurses recorded diagnoses, clinical characteristics, and prescribed drugs. The ADL function was assessed using the Barthel Index (0-20 points) (20, 21) and balance using the Berg Balance Scale (BBS) (0-56 points) (22). Visual impairment was noted if the participant was unable to read 5-mm block letters at normal reading distance, with or without spectacles. Cognitive function was assessed using the MMSE (0-30 points) (15), where a score of ≤17 indicates severe cognitive impairment (23). Depressive symptoms were screened for using the Geriatric Depression Scale (GDS-15) (24). The Mini Nutritional Assessment (MNA) was used for grading nutritional status. The scale gives a maximum of 30 points, where < 17 indicates malnutrition, 17-23,5 risk for malnutrition, and ≥24 points a good nutritional status (25). A specialist in geriatric medicine examined the documentation of diagnoses, drugs in regular use, and assessments. Dementia and depression were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV criteria) (26).
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Exercise intervention and control activity
The exercise and control activity were performed in groups of three to nine participants supervised by two physical therapists (exercise) and one occupational therapist (control). The sessions lasted approximately 45 minutes and were held five times during each period of two weeks over three months (13 weeks), 29 sessions in total.

The exercise program was based on the HIFE Program (27). The objective of the HIFE Program was to improve lower-limb strength, balance, and gait ability. The program was based on exercise in functional weight-bearing positions and included lower-limb strength and balance exercises while standing and walking. The physical therapists selected exercises for each participant according to their functional deficits and encouraged the participants to exercise at a high intensity. The load in lower-limb strength exercises and the degree of difficulty in the balance exercises were progressively increased. It was recommended in each session that the participants performed at least two lower-limb strength exercises and two balance exercises in two sets. The intention was for participants to perform strength exercises at 8-12 repetition maximum (RM) (28), and the load was increased as soon as they achieved more than 12 repetitions. For the first two weeks (build-up period) 13-15 RM was recommended. Physical tasks integrated into daily life activities were recommended individually regarding type, number, and frequency at the end of the exercise period, with the aim of maintaining physical function.

The control activity program consisted of theme-based sitting activities such as watching films, reading, singing and conversation.

Protein and placebo drink
The nutritional supplement consisted of a milk-based protein-enriched drink (200 ml) containing 7.4 g protein, 15.7 g carbohydrate, and 0.43 g fat, corresponding to 408 kJ per 100 g. The placebo drink contained 0.2 g protein and 10.8 g carbohydrate, corresponding to 191 kJ per 100 g. The drinks were provided within five minutes after each session of either exercise or control activity. If the participant was unable to participate in the activity the drink was still offered when possible. The two drinks had a similar taste and identical design. Each carton was weighted after the intake to assess the amount that had been consumed. No nutritional supplements were offered after the three-month exercise period.

Statistical Analyses
One-way analysis of variance (ANOVA) or the chi-square test was used to determine differences between groups at baseline.

To investigate the incidence of outliers in the outcome of ICW, a box plot of distribution of the absolute differences between baseline and the follow-ups was used. An outlier was defined as a value with a difference of 1.5-3*interquartile range (IQ) from the upper or lower edge of the box, and an extreme outlier was defined as >3*IQ. Between baseline and 3-month follow-up eight outliers and six extreme outliers, and between baseline and 6-month follow-up two outliers and six extreme outliers, were found according to the box plot analysis. In a consensus meeting, in which the four participating researchers were blinded for group allocations, it was judged that the figures for two outliers at three months, one outlier at six months, and all extreme outliers were due to measurement errors. These 15 participants were, therefore, excluded from further analysis (Figure 1).

To evaluate between-group effects in ICW and BW, analysis of covariance (ANCOVA) was performed at three and six months based on the intention-to-treat principle (i.e. everyone who is randomized is considered to be part of the trial, regardless of level of attendance). The dependent variable was the post-intervention value. The independent variables were activity (exercise or control) and nutrition (protein or placebo). Baseline value of the outcome measure, age and sex were used as covariates to control for individual differences at baseline. Adjustments were also made for differences (p <0.15) between the groups at baseline regarding the Barthel ADL index, impaired vision, angina and treatment with proton pump inhibitors. An interaction analysis was performed to evaluate whether the intake of a protein-enriched drink influenced the effects of the exercise.

An interaction analysis was also performed for ICW and BW to evaluate whether malnutrition (MNA below17) and sex influenced the effects of the exercise, at three and six months.

Additional between-group analyses, were conducted among those 133 participants who had ICW measurements at all three time points (baseline, three, and six months). Differences between exercise and control groups in ICW, BW, FM and Berg Balance Scale were analyzed at three and six months using an ANCOVA, with the same dependent and independent variables, and adjustments as in the analysis described above. The rationale for this additional analysis was to facilitate a comparison of the three- and six-month results of the outcome measures (ICW and BW) and, in addition, to relate the changes in the outcome measures to changes in FM and the Berg Balance Scale.

Within-group effects were analyzed in each group, activity and nutrition, to describe the change over time, by paired sample t-tests, comparing outcome measures at baseline with those at three and six months, respectively.

All statistical tests were 2-tailed; and p < 0.05, was considered to indicate statistical significance. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software (Version 17.0 for Windows SPSS Inc, Chicago, IL).

Results
The baseline characteristics of the 177 participants are presented in Table 1. The age range was 65 to 99 years and 74% were women. The mean BMI was 24.9 kg/m² and 28 participants (16%) had a MNA score <17, 114 (65%) >17 to
Table 1
Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Activity</th>
<th>Exercise n=42</th>
<th>Placebo n=41</th>
<th>Control n=47</th>
<th>Placebo n=47</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>84.4 ± 6.3</td>
<td>85.3 ± 5.5</td>
<td>85.4 ± 7.2</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>133 (79)</td>
<td>28 (68)</td>
<td>34 (72)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Anthropometry and nutritional assessments, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW (kg)</td>
<td>63.9 ± 12.2</td>
<td>65.3 ± 14.3</td>
<td>64.8 ± 12.1</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>161 ± 9.3</td>
<td>161 ± 9.3</td>
<td>161 ± 9.3</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>FFM (kg), (n = 174)</td>
<td>34.7 ± 7.6</td>
<td>34.8 ± 7.4</td>
<td>35.4 ± 7.8</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>ICW (l), (n = 174)</td>
<td>12.4 ± 3.3</td>
<td>12.6 ± 3.1</td>
<td>13.1 ± 5.0</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>BMIc</td>
<td>30.2 ± 9.4</td>
<td>30.7 ± 9.3</td>
<td>29.4 ± 9.9</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Mini Nutritional Assessment (0-30), (n = 175)</td>
<td>20.4 ± 3.8</td>
<td>20.8 ± 3.4</td>
<td>20.7 ± 3.2</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Intra Cellular Water, SD = standard deviation. For all assessments, except Geriatric Depression Scale, higher scores indicate better status. Number after a characteristic indicates that there are missing assessments,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. a = FM=BW-FFM, b = Information from the Mini Nutritional Assessment, c = Noted if the participant was unable to hear a conversation in a normal voice at a distance of one meter, or used a hearing aid, d = Only systemic treatment, BH = Body Height, BMI = Body Mass Index, BW = Body Weight, FM = Fat Mass, FFM = Fat Free Mass, calculated from BIS, ICW = Intra Cellular Water, SD = standard deviation. For all assessments, except Geriatric Depression Scale, higher scores indicate better status. Number after a characteristic indicates that there are missing assessments.

Compliance with intervention

Attendance level was 79% for the exercise group and 72% for the control group among the 149 participants with both a baseline and follow-up outcome value. In the exercise group, the attendance level was 72% for participants with MNA under 17 and 80% for those who had a MNA ≥ 17, and 75% for women and 86% for men. The participants in the exercise group performed lower-limb strength exercises at high-intensity (8-12 RM) in a median of 60% of the attended exercise sessions and in a median of 93% at medium (13-15 RM) or high intensity. The protein-enriched drink was taken in 84% and the placebo drink in 79% of all occasions. The protein-enriched drink package was completely emptied on 82% and the placebo drink on 80% of these occasions.

3-month follow-up

The between-group analyses at the 3-month follow-up revealed no significant differences in ICW and BW in the exercise group compared to the control group, nor in the protein group compared to the placebo group. No interaction effects

23.5, and 33 (19%) ≥24. At three months, 149 of the 177 participants (84%) were followed up and the corresponding figure at six months, was 139 (79%) (Figure 1).
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Outcome analyses in mean (SE) for group values, and for between-group differences mean (95% CI)* at 3 and 6 months based on the intention-to-treat principle

<table>
<thead>
<tr>
<th>Time after baseline assessment</th>
<th>Activity</th>
<th>Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise</td>
<td>Control</td>
</tr>
<tr>
<td>3 month, n=149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICW, l</td>
<td>12.4 (0.2)</td>
<td>12.6 (0.2)</td>
</tr>
<tr>
<td>BW, kg</td>
<td>64.8 (0.3)</td>
<td>65.5 (0.3)</td>
</tr>
<tr>
<td>6 month, n=139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICW, l</td>
<td>12.2 (0.2)</td>
<td>12.6 (0.1)</td>
</tr>
<tr>
<td>BW, kg</td>
<td>65.3 (0.4)</td>
<td>66.5 (0.4)</td>
</tr>
</tbody>
</table>

Note. BW = Body weight, ICW = Intra cellular water. *Between-group effects analysed by 2 x 2 factorial ANCOVA in which the post-intervention value was the dependent variable. Independent variables were the allocation to activity (exercise/control) and nutrition (protein/placebo) groups, pre-intervention value, age, sex and covariates adjusting for differences (p<0.15) between the groups at baseline (Barthel ADL index, impaired vision, angina, proton pump inhibitors). p†-value for test of interaction effect between the activity and nutrition interventions.

Within-group differences between post- and pre-intervention values at 3 and 6 months, based on the intention-to-treat principle, mean (SD)

<table>
<thead>
<tr>
<th>Time after baseline assessment</th>
<th>Outcome measure</th>
<th>Activity</th>
<th>Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Exercise</td>
<td>p</td>
</tr>
<tr>
<td>3 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICW, l</td>
<td>66</td>
<td>0.07 (1.4)</td>
<td>0.686</td>
</tr>
<tr>
<td>BW, kg</td>
<td>66</td>
<td>-0.6 (2.7)</td>
<td>0.080</td>
</tr>
<tr>
<td>6 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICW, l</td>
<td>63</td>
<td>-0.3 (1.2)</td>
<td>0.068</td>
</tr>
<tr>
<td>BW, kg</td>
<td>63</td>
<td>-0.6 (3.1)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Note. BW = Body Weight, ICW = Intra Cellular Water.

Table 2

No interaction effects were revealed for ICW and BW between activity groups and MNA below 17 (p = 0.170 vs. 0.320) and sex (p = 0.671 vs. 0.698) respectively. The within-group analyses in people with MNA below 17 showed no significant changes in ICW and BW, either in the exercise group (0.3 l, p = 0.411 vs 0.3 kg, p = 0.185) or in the control group (0.3 l, p = 0.673 vs -0.5 kg, p = 0.548). For participants with a MNA ≥ 17 BW decreased (-0.8 kg, p = 0.048) but not ICW (-0.4 l, p = 0.141) in the exercise group, while no significant changes were seen in the control group (0.06 l, p = 0.782 vs. 0.3 kg, p = 0.418).

Additional analysis

Between-group changes in ICW, BW, FM, and BBS for the 133 participants who had measurements from all three time points (baseline, three and six months) are visualized in Figure 2.
The main clinical implication of this study is that despite the negative long-term effect on MM the high-intensity exercise is beneficial regarding physical function (13) and the effect on physical impairments living in residential care facilities. Three months represents end of intervention period. The zero line indicates no difference between the two study groups at baseline, and the control group at 3 and 6 months.

Figure 2
An additional analysis based on 133 participants i.e., all participants with ICW data for all three occasions. Differences in change in ICW, BW, FM and Berg Balance Scale at 3 and 6 months from baseline, between exercise and control group. Three months represents end of intervention period. The zero line indicates no difference between the two study groups at baseline, and the control group at 3 and 6 months.

Discussion
This study revealed that a HIFE program during a period of three months did not lead to an increase in the amount of MM among older people with severe physical or cognitive impairments living in residential care facilities. Three months after the exercise period had ended (6-month follow-up) the MM was significantly lower in the exercise group than in the control group. The protein-enriched drink that was taken immediately after the exercise, did not influence the ability to maintain or increase the amount of MM. Notably, the effects of the exercise on MM did not seem to be worse for those who were malnourished.

In contrast to the present three-month intervention, other studies among healthy or moderately impaired old and very old people have shown increased MM after high-intensity strength exercise programs (9, 29, 30). Perhaps, a longer intervention period than three months would have been necessary, since it is possible that several factors could have limited the muscle building capacity in this group of older persons. Their severe physical impairments as well as the co-morbidities, with probably high proportion of inflammatory cytokines and polypharmacia, may have limited the effects of the exercise (4). Furthermore, the participants in the present study, because of their high age, may have been affected by decreased levels of anabolic stimuli hormones, enzyme activity and insulin sensitivity which could have contributed to the lack of effects from the exercise (4). In addition, women dominated the study sample. This may also have limited the effects since men seem to have a greater ability to generate MM than women (30, 31).

At the 6-month follow-up (3-months after the exercise period had ended) the exercise group had significant losses of MM and BW. However, improvements in physical functions (BBS) were seen and correspond to results reported from the FOPANU study (13). The loss of MM indicate that the improvement in physical function is caused by improved neuromuscular function (32). The ability to improve physical function despite loss of MM has also been shown in a study among older people with obesity (33). The loss of MM and body weight indicates that a negative energy balance, which might be caused by the exercise and its effects, affected many participants. The long-term effects on physical functions, and ADL (27), indicate that the participants in the exercise group used their improved physical capacity in daily life after the 3-month exercise period, which might have resulted in a higher metabolic rate and higher energy needs. This may not have been compensated for by a higher food intake. Unfortunately, we did not measure the participant’s total nutritional intake and energy expenditure.

The protein-enriched drink that was taken immediately after the high-intensity exercise during three months did not influence the MM among the participants in our study. This result is in accordance with a study by Candow et al (34), but is in contrast to a study by Esmarck et al (9). Notably, both these studies included only healthy, older men. A body weight loss due to a putative negative energy balance was seen in the present study, in contrast to the study by Esmarck et al (9) where the participants seem to have been well nourished. Consequently, the lack of increasing effect of the protein-enriched drink in the present study may be explained by the participants consuming too little energy. Thus, the protein may have been metabolized as energy instead of contributing to the muscle building. However, caution should be taken when interpreting the results from Esmarck’s study since the within-group result indicates that the comparison group did not develop any muscle hypertrophy after 12 weeks of resistance exercise, which contradicts other studies among healthy older men (31, 35).

Previous studies have used a variety of direct and indirect methods for measuring body composition, making it difficult to compare the results (9, 29-31, 34). The BIS instrument used in this study has been shown to be valid for measuring the whole body’s ICW (36, 37) and reliable for measurements of body composition in old people with physical and cognitive impairments (38). The HIFE program mainly focused on lower limb training, nevertheless the whole body’s ICW was measured. Today it is possible to measure MM in the lower limbs with BIS so-called segmental measurements (39) which would have given even more valid results.

One limitation of this study was that the number of participants was determined through a prior power analysis based on the BBS and not on the ICW as outcome variable. Even though 148 participants were included, there might be type II errors in the study.

The main clinical implication of this study is that despite the negative long-term effect on MM, the high-intensity exercise is beneficial regarding physical function (13) and the effect on...
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MM did not differ for those with malnutrition. It seems necessary when offering exercise to compensate for the higher energy expenditure with increased nutrition intake, presumably also after an exercise period, to counteract the decline in MM.

Conclusion

No increase in muscle mass was seen among older ADL dependent persons, living in residential care facilities, after three months of high-intensity functional weight-bearing exercise despite long-term improvements in physical function demonstrated in the main study. The intake of a protein-enriched drink immediately after the exercise, had no additional effect on the ability to increase muscle mass. The presence of malnutrition at baseline seems not to influence the effect. There were negative long-term effects on muscle mass, and BW, which indicates that it is probably necessary to compensate for an increased energy demand when offering a HIFE program.

Further studies are needed over a longer period to evaluate the causes and consequences of the loss of muscle mass.

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Conflict of interest: None.

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