The effects of exercise and protein–energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study

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Fighting against inactivity and inadequate nutritional intake are of utmost importance in the elderly. To our knowledge, the few studies which have been performed were conducted for only a short period and the results do not permit formal conclusions to be drawn. We therefore tried to fill this gap in our knowledge by determining whether an intervention combining an acceptable progressive exercise programme and nutritional supplements would be feasible for a long-term period in the very frail elderly, and would bring about concomitant benefits in body composition and muscle power. Accordingly, this exercise and nutritional combination was assessed in the frail elderly in a 9-month randomised trial with a factorial design. Fifty-seven elderly volunteers over 72 years, from sixteen retirement homes in Lyon, France participated in the study. Dietary supplements were compared with placebo, and physical exercise was compared with memory training. Main outcome measures were fat-free mass (FFM) and muscle power. FFM was determined by labelled water, and muscle power was measured by a leg-extensor machine. At 9 months, the compliance was 63 % for exercise sessions, and 54 % for nutritional supplements. In patients with dietary supplements, muscle power increased by 57 % at 3 months (P=0·03), and showed only a tendency at 9 months; although FFM increased by 2·7 % at 9 months, the difference was not significant (P=0·10). Exercise did not improve muscle power at 9 months, but improved functional tests (five-time-chair rise, P=0·01). BMI increased with supplements (+3·65 %), but decreased with placebo (−0·5 %) at 9 months (P=0·007). A long-term combined intervention is feasible in frail elderly individuals with a good rate of compliance. Nutritional supplements and exercise may improve muscle function. Despite no significant results on FFM, due to the limited number of volunteers, combined intervention should be suggested to counteract muscle weakness in the frail elderly.

Protein–energy supplements and exercise: Fat-free mass: Sarcopenia: Frail elderly

Introduction

Loss of skeletal muscle mass and function (sarcopenia) usually characterize ageing (Gallagher et al. 2000). Both physical inactivity and inadequate nutritional intake are the main contributing factors to sarcopenia and reduction in total fat-free mass (FFM) (Campbell et al. 1994; Millward et al. 1997). These changes have been associated with dramatic functional decline, physical frailty, falls and a bad quality of life (Chumlea et al. 1997; Evans,
The potential reversibility of sarcopenia is therefore of utmost importance, especially for frail elderly individuals. Until now, very few studies have investigated both the effects of protein–energy oral supplementation and exercise on various indicators of nutritional status, body composition, and muscular function in this precise population (Meredith et al. 1992; Fiatarone et al. 1994; De Jong et al. 2000). To date, results of available controlled trials investigating potential benefits of combined interventions do not permit a formal conclusion to be drawn. Resistance training improved muscle size but nutritional supplements had no effect on any primary outcome (energy intake, body composition, thigh muscle area) in the Fiatarone et al. (1994) study. A slight improvement of lean body mass and energy intake with exercise and correction of energy intake with nutrient-dense food were observed in the De Jong et al. study (2000). Further, these results were obtained during rather short study periods (Fiatarone et al. 1994; De Jong et al. 2000) and with a monotonous high-intensity resistance training programme requiring heavy unusual equipment that could be neither available to a large population nor well tolerated for a long period. Measurement of muscle strength was investigated only in the Fiatarone et al. (1994) study. No study has assessed muscle power, which is more representative of muscle function since it is directly related to daily activities (Guralnik et al. 1995; Kostka et al. 2000). Therefore, the aims of our study were: (1) to demonstrate in frail elderly individuals over a long period of 9 months the feasibility of a combined intervention using protein–energy oral supplementation together with an acceptable progressive exercise programme without heavy material that could be extended to a large population; (2) to assess its efficacy on body composition and muscle power.

**Participants and methods**

Volunteers were recruited in retirement homes in Lyon (France). The study protocol was approved by the ethics committee (Centre Léon-Bérard, Lyon, France). All the residents were invited to an introductory meeting. The residents willing to participate visited their general practitioner for an eligibility check, and gave written consent. Uniform criteria to define frail elderly individuals are still lacking; however, the criteria for inclusion, and the characteristics of our population under study are in agreement with frailty and with the aim of our intervention. The participants mean age was over 83 years, they had multiple diagnoses, and had a length of stay of more than 3 years in retirement homes for the elderly. Exclusion criteria included uncontrolled or rapidly evolving diseases, dementia, type 1 diabetes, severe renal insufficiency (blood creatinine over 200 mmol/l), functional handicap preventing exercising, long-term corticosteroid therapy with receipt of vitamin supplements before the study, and age under 72. Fig. 1 gives an outline of the selection of participants.

### Design, randomisation and follow up

This 9-month clinical trial had a factorial design comparing the effect on the nutritional and functional status of: (1) exercise with a control activity (memory), (2) nutritional supplements with placebo. Patients were randomly assigned to four groups: (1) nutritional supplement plus...
memory; (2) supplement plus exercise; (3) placebo plus exercise; (4) placebo plus memory.

The randomisation was centralised and stratified between the homes and occurred the same day before starting sessions for participants in each home, using a remote data-entry system (Minitel® France Telecom, Paris).

Interventions

Nutritional supplement. The nutritional supplements were provided by Diepal Laboratoires Villefranche sur Saône, France. They were given twice daily at 10.00 and 16.00 hours, and consisted of two nutritional energy drinks of 200 ml supplying 843 kJ (200 kcal) each, with 15 g of proteins (30 % of energy), 25 g of carbohydrates (50 % of energy), and 4.4 g of lipids (20 % of energy). They increased energy intake by approximately 20 % and provided approximately 50 % of the recommended daily allowances for vitamins and minerals. The minerals that were supplied were (mg/d): Ca, 1040; P, 860; Mg, 150; Fe, 7.2; Zn, 7.6. The supplied vitamins were (mg/d): vitamin A, 400 μg; vitamin B1, 0.72; vitamin B2, 0.8; vitamin B3; vitamin B6, 1; nicotinamide, 9; vitamin B12, 0.6 μg; vitamin C, 30; vitamin E, 5; vitamin D3, 24 μg; biotin, 76 μg; folic acid, 100 μg.

Patients had the choice of four different flavours; the placebo for nutritional supplements (also in four different flavours) had an identical packaging but contained neither energy and protein nor vitamins and minerals. The supplements were delivered in unmarked containers and volunteers were unaware of their contents and of the group assignment. The nurse in charge of the study visited each home regularly, in order to check for adverse events, to supervise supplement supply, and assess compliance, by counting of unused units.

Exercise programme. Exercise of moderate, gradually increasing intensity was given by the same trainer, three times weekly for 60 min, with strengthening, balance and flexibility exercises. The programme included: (1) progressive strengthening exercises (using dumbbells and elastic bands) performed in both the seated or kinetic chair position (weight bearing); (2) balance training exercise; (3) flexibility exercise. Strengthening exercises were begun with one set of five repetitions and progressed to three sets of ten. Weights were progressively added. Elastic resistance progressed using a heavier grade of elastic material. Strengthening and standing exercises were also incorporated into group training (ball-games). Each session included a warm-up (10 min), lower-and upper-body strengthening, balance and range of motion (40 min), and cool-down stretching (10 min). The programme was adapted to individual tolerance, and participants were encouraged to do more repetitions. Compliance was checked by recording attendance at the sessions. Three weekly memory sessions served as controls for exercise.

Data collection and quality control

Clinical characteristics. Clinical information was recorded by each subject’s general practitioner on the case-report form (i.e. demographic data, medical history, duration of stay in the home, social and former professional status, long-term treatments, blood pressure, heart rate, height and weight). Laboratory results were recorded directly by the laboratories performing the tests (i.e. resting metabolic rate, FFM, muscle power measurements, albumin, pre-albumin). All the volunteers were visited by the nurse from the research staff, to obtain scores for the basic activities of daily living index (Katz et al. 1963), for the instrumental activities of daily living (Lawton & Brody 1969) and for the mini nutritional assessment (Vellas et al. 2000). Volunteers were also visited by exercise trainers, who recorded physical function (time for a 6 m walk, for five-time chair rise, ability to carry 5 kg, gait and balance assessment and risk of falling using the test described by Tinetti et al. 1988).

Quality control. Data were entered using double data entry, and there was computerized quality control regarding presence, likelihood, and consistency.

Body composition

H18O (2.5 %) was obtained from Isotec (St Quentin en Yvelines, France). The labelled water was sterilized before being drunk by the subjects. The subjects came at 7.30 hours to the Human Nutrition Research Centre, voided and then were weighed. After providing baseline urine and saliva samples, they drank 0.88 g H18O kg body weight. Then, urine and salivary samples were collected 3, 4 and 5 h after ingestion of the labelled water to optimize the equilibration plateau determination of the isotope with body fluids. Samples were stored at −80°C in cryogenically stable tubes until analysis. A weighed dilution (dose in Evian water) was prepared from each subject’s dose and analysed with each subject’s sample set. H18O enrichments were measured by isotope ratio MS (OPTIMA; Fisons, Manchester, UK) using the CO2 equilibration technique, as previously described (Blanc et al. 1998).

The total body water was determined from the dilution space of 1H0 after adjusting it by a factor of 1.01 to account for isotope incorporation into other body compartments (Coward, 1990). FFM (kg) was deduced from total body water by FFM = total body water/0.732 where 0.732 is the reported hydration coefficient for FFM (Pace & Rathburn, 1945).

Resting energy expenditure

Resting energy expenditure was measured in the morning (9.00 hours) after a 12 h overnight fast by indirect calorimetry with an open circuit indirect calorimeter, using the ventilated hood method for 1 h after 30 min adaptation (Deltatrac Monitor MBM-100; Datex Instrumentary Corporation, Helsinki, Finland). Measurements were performed in the supine position, at complete rest. Urine samples were collected before the test to determine N excretion by chemiluminescence (Antek 703C; Sopares, Paris, France) as previously described (Arock et al. 1985). The resting energy expenditure was calculated from indirect calorimetry principles using equations derived by Frayn (1983).
Muscle function
Muscular testing of the quadriceps was performed using the recently developed Ergopower dynamometer (Bosco et al. 1995) applied to a leg-extensor machine (Leg Extension Basic; Panatta Sport, Apiro, Italy). The subjects were familiarized with the device during the warming-up phase. The chair of the apparatus was adjusted to give an optimal utilization of the quadriceps. The subjects were asked to perform explosive leg extension against increasing loads, each separated by at least 5 min rest. The test began with a load of 5 kg and increased by steps of 1 kg each. The load displacement was measured every 0·75 mm by means of an optical encoder mounted on an external guide bar. The signal was sampled (200 Hz) and stored on a PC computer (486 DX2; 66 MHz) via a 12-bit interface card. The displacement signal was digitally filtered with a 12 Hz low-pass Butterworth filter with 0-phase lag. The instantaneous velocity, acceleration, force, torques and power produced were obtained by digital derivation. Full details of the calculation and methods are given in Bosco et al. (1995). Accurate measurements of friction and inertia effects during movement were used in the calculation of the torque and power (Rahmani et al. 1998). The instantaneous values were used to determine the average values of velocity, torque and power during each contraction. Average power and velocity were used to draw the power–velocity relationship. Maximal muscle power and corresponding optimal shortening velocity were calculated from a power–velocity curve.

Physical function
Gait velocity over a 6 m course was measured to the nearest 0·01 s at usual pace. Gait velocity was calculated as the average velocity in two trials. For stair walking, subjects were asked to climb up a six-step staircase without stopping, moving at a comfortable pace without using the handrail as support. Measurement was done to the nearest 0·01 s. For the chair rise, the subjects were asked to rise from a chair at a comfortable pace five times consecutively with their arms folded. Gait and balance abnormalities were assessed (Tinetti et al. 1988).

Statistical analysis
Statistical analysis was performed using SAS® (SAS Institute, Cary, NC). The target sample size (120 elderly) was chosen to be able to detect a 1 SD difference in the primary criteria, with a power of 90%. Intention to treat analyses were used for the primary and secondary outcome variables, i.e. patients were analysed in the group in which they were randomized regardless of compliance. Missing data were not replaced. Comparisons of baseline characteristics were performed by t test or χ² test depending on the nature of variables. FFM and muscle power measurements were transformed on a log scale to normalize their distribution. A two-factor ANOVA was used to determine the effects of physical exercise vs. memory training and of dietary supplements vs. placebo at 3 and 9 months with adjustment to the baseline value, and to determine the interaction between the two interventions. In the case of significant interaction, analyses were performed for each intervention on each subgroup of the other intervention.

Results
Among 800 residents of sixteen retirement homes, fifty-seven were included, 50% of the target sample size (Fig. 1). The mean age was 83 years, 88% were women, 84% had one or more chronic diseases, (37% had three or more), and 58% received more than four long-term medications. During the preceding year 26% acknowledged at least one fall, 37% an infectious disease, and 30% a depressive episode. Of the participants, 47% were dependent for at least one of the activities of the basic activities of daily living index, 54% for at least one of the instrumental activities of daily living, and 37·5% had a mini nutritional assessment score below 24. The mean baseline quadriceps power was 83 W; there was no statistically significant difference between groups. Participants’ baseline characteristics are shown in Table 1. The compliance to exercise sessions was 70% at 3 months, 63% at 9 months; it was 61% and 54% respectively for supplements of the subjects, fifteen (26·3%) dropped out: one died; five had clinical events; six retracted their consent immediately after randomisation; three dropped out because of lack of interest.

Primary outcomes
The primary analysis compared the dietary supplement to the placebo supplement, and the exercise training to the memory training. Results are given in Table 2.

Changes in quadriceps muscle power. No statistically significant difference was observed between groups with exercise at 3 or 9 months. With supplements an improvement in muscle power was observed at 3 months (+ 56·8%; P=0·03).

Changes in fat-free mass. Variations of FFM did not reach statistical significance with exercise or with supplements even though FFM showed a tendency to increase in the supplemented group and to decrease in the placebo group at 3 and 9 months.

Secondary outcomes
As shown in Table 3, exercise significantly improved the timing for the five-time chair rise at 9 months (P=0·014). Other favourable changes in muscle function and nutritional status (albuminaemia, mini nutritional assessment, resting energy expenditure) at 3 or 9 months were not significant.

A significant increase in BMI either at 3 or 9 months was observed with supplements.

There was a significant negative interaction between the timing for the five-time chair-rise time and the resting metabolic rate at 3 months but differences between groups were not significant.
Discussion

To the best of our knowledge, the present study is the first trial that investigates over a long-term period the effects of complete liquid supplements in frail elderly individuals combined with a progressive and moderately intense exercise programme. After a 9-month intervention, our results show that in individuals with a high burden of chronic diseases, such a combined intervention is feasible (compliance of 50 to 60%), even though this could be improved. The greatest difficulty is to motivate elderly individuals to volunteer for such a study or to perform any effort to improve their health. Supplements improved muscle power, at least at 3 months, and exercise somehow improved mobility.

Most of the drop-outs withdrew before or immediately after baseline measurements, indicating that the non-participation was unrelated to the type of intervention. Once activities had started, the participants enjoyed attending the sessions (exercise as well as memory activities).

Treatment strategies for frail elderly individuals are usually aimed at the restoration or maintenance of function. Beneficial effects on functional capacity and muscle strength have already been detected with such a programme (McMurdo & Rennie 1994; Lazowski et al. 1999). In view of the fact that energy balance is critical

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Effect of exercise</th>
<th>Effect of supplement</th>
</tr>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Females: n</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>83</td>
</tr>
<tr>
<td>Length of stay (years)</td>
<td>4.02</td>
</tr>
<tr>
<td>Three chronic illnesses: n</td>
<td>16</td>
</tr>
<tr>
<td>Four long-term medications: n</td>
<td>25</td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27·6</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>39·00</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>41·20</td>
</tr>
<tr>
<td>Pre-albumin (g/l)</td>
<td>0·27</td>
</tr>
<tr>
<td>MNA score</td>
<td>24·31</td>
</tr>
<tr>
<td>Resting metabolic rate (KJ/24 h)</td>
<td>1142</td>
</tr>
<tr>
<td>Muscle function and mobility</td>
<td></td>
</tr>
<tr>
<td>Muscle power (W)</td>
<td>92·14</td>
</tr>
<tr>
<td>Gait and balance abnormalities</td>
<td>1·94</td>
</tr>
<tr>
<td>6-m walk time (s)</td>
<td>8·17</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>13·88</td>
</tr>
<tr>
<td>Six-stair climb time (s)</td>
<td>6·25</td>
</tr>
</tbody>
</table>

MNA, mini nutritional assessment.

Table 2. Primary outcome variables, measured at 3 months and at 9 months, expressed as relative variation (%)*

<table>
<thead>
<tr>
<th>Effect of exercise†</th>
<th>Effect of supplement†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise (n 20)</td>
<td>Memory (n 25)</td>
</tr>
<tr>
<td>Supplement (n 30)</td>
<td>Placebo (n 27)</td>
</tr>
<tr>
<td>Mean SEM</td>
<td>Mean SEM</td>
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<tr>
<td>Mean SEM</td>
<td>Mean SEM</td>
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<tr>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>Variation in fat-free mass</td>
<td></td>
</tr>
<tr>
<td>3-month fat-free mass (n 45)</td>
<td>1·39</td>
</tr>
<tr>
<td>9-month fat-free mass (n 42)</td>
<td>0·77</td>
</tr>
<tr>
<td>Muscle power variation</td>
<td></td>
</tr>
<tr>
<td>3-Month muscle power variation (n 43)</td>
<td>30·12</td>
</tr>
<tr>
<td>9-Month muscle power variation (n 43)</td>
<td>56·87</td>
</tr>
</tbody>
</table>

* For details of subjects and procedures, see Table 1 and p. 732.
† No interaction between the two interventions was found.
Muscle function and mobility at 9 months

- Six-stair climb time: a significant increase in muscle power (+18 %; $P<0.003$). These authors have also reported that 45 % of the variance in the gain in strength was predicted by the independent contribution of changes in energy intake ($P<0.003$). This finding and our results suggest that nutritional status is critical for muscle function.

The lack of a favourable effect of exercise on the FFM in our study deserves several explanations. Most of the studies have shown direct beneficial effects only on the muscle size of the quadriceps area (Frontera et al. 1988; Sipila & Suominen 1995; McCartney et al. 1996 and were not performed in the very old institutionalized frail elderly. Fiatarone & Suominen (1994) failed to demonstrate an effect of dietary modification during strength training and Fiatarone et al. (1994) found that nutritional supplements had no primary or interactive effect on muscle strength. Conversely in a further study, Fiatarone Singh et al. (1999) observed after a 10-week combined intervention that the greatest changes in strength were correlated with the largest increases in energy intake ($P<0.003$). These authors have also reported that 45 % of the variance in the gain in strength was predicted by the independent contribution of changes in energy intake alone ($P<0.003$). This finding and our results suggest that nutritional status is critical for muscle function.

In our study, exercise increased mobility but not muscle power. Several randomised controlled studies have shown the effectiveness of physical activity programmes in retirement homes including range of motion, or seated exercise on muscular strength or function (McMurdo et al. 1994; Lazowski et al. 1999). In fact, most authors have studied changes in muscle strength (Fiatarone et al. 1990, 1994; Fischer et al. 1991), and only a few investigators have examined changes in muscle power in the elderly (Skelton et al. 1995; Jozsi et al. 1999). Power is the product of the force generated by the speed of muscle contraction. Muscle power in very old adults has been found to be more important than strength for performing daily activities such as stair climbing, rising from a chair and walking (Bassey et al. 1992; Skelton et al. 1995; Foldvari et al. 2000). Frontera et al. (1988) investigated the effects of a high-intensity resistance exercise programme and showed a substantial improvement (>100 %) in isotonic strength, with no significant change in power. Skelton et al. (1995) examined the effect of a 12-week programme of resistance exercise in elderly individuals. Despite a significant increase in muscle strength, there was no statistically significant improvement in muscle power (+18 %; $P=0.11$).

An important finding from our study is the observation of a significant increase in muscle power with supplements. Meredith et al. (1992) failed to demonstrate an effect of dietary modification during strength training and Fiatarone et al. (1994) found that nutritional supplements had no primary or interactive effect on muscle strength. Conversely in a further study, Fiatarone Singh et al. (1999) observed after a 10-week combined intervention that the greatest changes in strength were correlated with the largest increases in energy intake ($P<0.003$). These authors have also reported that 45 % of the variance in the gain in strength was predicted by the independent contribution of changes in energy intake alone ($P<0.003$). This finding and our results suggest that nutritional status is critical for muscle function.

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in the *vastus lateralis* and the mean age is observed (Fiatarone Singh *et al.* 1999). Thus, age and frailty may weaken the adaptive mechanisms to loading.

No significant change in FFM was observed with supplements. The nutritional intervention also failed to be effective in the other two studies carried out to date that have investigated the combined effect of exercise and nutritional supplementation in frail elderly (Fiatarone *et al.* 1994; De Jong *et al.* 2000). In the first study, a significant reduction in dietary energy intake with supplements may explain the negative results (Fiatarone *et al.* 1994). In the second (De Jong *et al.* 2000), the lack of improvement of the FFM is probably due to the use of non-energetic supplements. In view of the difficulties in assessing energy intake, the evolution of the BMI is an objective assessment of the energy intake. The significant increase in BMI in the supplemented group clearly indicates that the energy-dense supplements used in our study did not result in a reduction in the spontaneous dietary energy intake.

There are some limitations to the present study. Indeed, the small sample size may account for the lack of any significant favourable effect of exercise on the FFM and muscle weakness in the frail elderly.

This suggests that combined intervention may counteract the energy-dense supplements may explain the negative results (Fiatarone *et al.* 1994). In the second (De Jong *et al.* 2000), the lack of improvement of the FFM is probably due to the use of non-energetic supplements. In view of the difficulties in assessing energy intake, the evolution of the BMI is an objective assessment of the energy intake. The significant increase in BMI in the supplemented group clearly indicates that the energy-dense supplements used in our study did not result in a reduction in the spontaneous dietary energy intake.

There are some limitations to the present study. Indeed, the small sample size may account for the lack of any significant favourable effect of exercise on the FFM and muscle function. The proportion of home residents who where randomised among 800 elderly subjects who received information is low. Therefore the population included in the study is a rather highly selected one, and the results may not apply to the general elderly population. However Pacala *et al.* (1996) have depicted in detail this important methodological problem and no solution is readily apparent.

Social advantages of such interventions have not been measured in the present study, but the participants showed great psychological and social benefits of the intervention. Some of the participants continued the sessions after the end of the study.

In conclusion, our results show, for the first time, the feasibility of physical exercise combined with nutritional supplementation in frail elderly individuals in a long-term study. Muscle power is improved in the supplemented group while functional gains are obtained with exercise. This suggests that combined intervention may counteract muscle weakness in the frail elderly.

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