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Effect of structured physical activity and nutritional supplementation on physical function in mobility-limited older adults: results from the VIVE2 randomized trial

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Abstract

Objectives: The interactions between nutritional supplementation and physical activity on changes in physical function among older adults remain unclear. The primary objective of this study was to examine the impact of nutritional supplementation plus structured physical activity on 400M walk capacity in mobility-limited older adults across two sites (Boston, USA and Stockholm, Sweden).

DESIGN: All subjects participated in a physical activity program (3×/week for 24 weeks), involving walking, strength, balance, and flexibility exercises. Subjects were randomized to a daily nutritional supplement (150kcal, 20g whey protein, 800 IU vitamin D) or placebo (30kcal, non-nutritive).

SETTING: Participants were recruited from urban communities at 2 field centers in Boston MA USA and Stockholm SWE.

PARTICIPANTS: Mobility-limited (Short Physical Performance Battery (SPPB) ≤ 9) and vitamin D insufficient (serum 25(OH) D < 24 ng/ml) older adults were recruited for this study.

MEASUREMENTS: Primary outcome was gait speed assessed by the 400M walk.

RESULTS: 149 subjects were randomized into the study (mean age=77.5±5.4; female=46.3%; mean SPPB= 7.9±1.2; mean 25(OH)D=18.7±6.4 ng/ml). Adherence across supplement and placebo groups was similar (86% and 88%, respectively), and was also similar across groups for the physical activity intervention (75% and 72%, respectively). Both groups demonstrated an improvement in gait speed with no significant difference between those who received the nutritional supplement compared to the placebo (0.071 and 0.108 m/s, respectively (p=0.06)). Similar effects in physical function were observed using the SPPB. Serum 25(OH)D increased in supplemented group compared to placebo 7.4 ng/ml versus 1.3 ng/ml respectively.

CONCLUSION: Results suggest improved gait speed following physical activity program with no further improvement with added nutritional supplementation.

Keywords

aging; exercise; protein supplement; physical function; mobility limitation

INTRODUCTION

Mobility-limited older adults experience elevated rates of falls, institutionalization, and chronic disease (1). As people over the age of 70 years represent the fastest growing age demographic worldwide (2), there is a substantial need for interventions to address the inevitable increase in mobility limitations and disability in this population.

Inadequate physical activity and poor dietary protein intake are two factors that contribute to the decline in muscle mass and function associated with aging (sarcopenia)(3, 4). Though studies have shown a positive impact of physical activity in this population (5), studies investigating protein supplementation in combination with exercise have been mixed (6–15). Several lines of evidence have suggested that nutritional supplementation (particularly supplements high in protein) can potentiate the increase in skeletal muscle protein synthesis following a single bout of exercise in both young individuals and in healthy older adults (16, 17), though the effects in mobility-limited older adults remains unclear.

More recently, poor vitamin D status has emerged as a potential contributor to poor muscle function among older adults (18). Observational evidence suggests that individuals with deficient or insufficient vitamin D levels are more functionally limited compared to those who are sufficient (19). Additionally, cross-sectional studies have shown that vitamin D status is highly correlated with lower-extremity strength and balance (20–22). Though it has been hypothesized that vitamin D supplementation either with or without exercise may decrease incidence of falls and fractures in the elderly, the results of these trials have been equivocal (22–24). Randomized controlled trials with vitamin D supplementation that have investigated muscle function have had mixed results (25, 26).

To date, few studies have been conducted to determine whether synergistic effects of exercise and nutritional interventions can result in sustained increases in physical performance beyond those produced by exercise alone. **The Vitality, Independence, and Vigor 2 Study (VIVE2)** was designed to compare the effects of an intervention with an experimental liquid oral nutritional supplement to a low calorie placebo drink on exercise

training-induced changes in physical functioning in older adults with demonstrated mobility limitations and vitamin D insufficiency. We hypothesized that a combined high protein, high vitamin D nutritional supplement would induce greater changes in walking speed in conjunction with a structured physical activity program compared to placebo.

METHODS

Participants

This study was conducted in Boston, MA, USA and Stockholm, Sweden. This study was reviewed and approved by the Tufts University Health Sciences Campus Institutional Review Board, and the Regional Ethical Committee of Uppsala, Sweden. Data management and quality control was coordinated by Nestle Health Science, Vevey, Switzerland. This study was sponsored by Nestle Health Science.

The detailed methods of this study have been described elsewhere (27). Direct mailing and newspaper advertisements were the primary recruitment strategies. In brief, men and women aged 70 and above were included in this study who (1) were at risk for mobility-disability, defined as a short physical performance battery (SPPB)(28) score ≤ 9 (2) vitamin D insufficient (serum 25(OH)D ≤ 9 ng/ml and ≤ 24 ng/ml) and not currently using vitamin D supplements (3) no severe cognitive impairment, defined as a Mini-Mental State Examination (MMSE)(29) score ≤ 24 ; (4) undertaking >30 minutes per week of structured physical activity; (5) able to complete the 400 meter walk in <15 minutes without the use of a walker or another person; (6) and were able to safely participate in the nutritional and physical activity intervention.

Randomization—Randomization of subjects to the nutritional supplement or placebo groups was designed to stratify for sex and study site (Sweden or USA). A block size of 10 was employed, which allocated 5 subjects to the supplement group and 5 subjects to the placebo group within each sex and site. A computer-generated randomization determined the order in which the supplements were assigned in each block. Study assessors, data analysts, and investigators were blinded to treatment assignment.

Physical Activity Intervention—All randomized participants were asked to attend 3 sessions per week of a center-based physical activity program (PA) for 6 months. The PA intervention included walking, lower-extremity strength exercises, balance, and flexibility. Participants were asked to walk at a pace where they would rate a 13–14 and perform the strength exercises at a 15–17 on the Borg Scale (30). For each participant, the proportion of the planned six-month visits that were actually attended was computed as an adherence score. For the purposes of secondary “per protocol” analyses (see below), participants were considered adherent to the exercise intervention if they attended at least 60% of the planned exercise visits over the six-month intervention period.

Nutritional Supplementation—Participants were randomized to consume either a nutritional supplement or placebo, once daily for the duration of the trial. The supplement/placebo was consumed immediately after exercise training on scheduled training days. The nutritional supplement contained 20 g of whey protein, 800 IU of vitamin D, 350 mg of

calcium, and an assortment of other vitamins and minerals in a 119 ml, 150kcal beverage (Supplemental table 1). The placebo was a 4 oz non-nutritive sweetened drink providing 30 kcal per serving. Both products were developed and manufactured by Nestle Health Science, Vevey, Switzerland, and were sent directly to the study sites for distribution to the participants. Participants kept a paper log of supplement intake. Each participant's proportionate utilization of doses of the nutritional intervention was used to measure adherence to the nutritional component of the protocol. For the purposes of secondary "per protocol" analyses (see below), participants were considered adherent to the nutritional component if they utilized at least 60% of their intended doses over the course of the six-month intervention period.

Outcomes

Outcomes were assessed at baseline, 3 and 6 months.

400 M walk test—The primary study outcome was a comparison between nutritional supplementation and placebo in 400 M walk performance (expressed as average gait speed during the 400 M walk (m/s)), after 6 months of moderate intensity exercise. Change in 400 M walk time derived from the same test was considered a secondary outcome. The 400 m walk was conducted in a long, straight hallway, where two cones mark a 20 meter course. Participants were instructed to walk 10 laps around the cones at their usual pace, without over-exerting themselves. Participants must have been able to complete all 10 laps in less than 15 minutes at baseline in order to be enrolled in the trial. A straight cane may have been used, and participants were allowed to stop to rest, though leaning on any other object or sitting was not allowed during the test (31).

Short physical performance battery (SPPB)—The SPPB is a summary performance measure consisting of three increasingly difficult standing balance tests, a 4 meter walk at usual pace, and five timed repeated chair stands (32). Each performance measure is assigned a categorical score ranging from 0 (inability to complete the test) to 4 (best performance possible). A summary score ranging from 0 (worst performance) to 12 (best performance) was calculated by summing the three component scores.

Hand Grip Strength—Hand grip strength was measured in the dominant hand with a Jamar Handheld Dynamometer (Patterson Medical, Warrenville, IL)(33). The patients performed the test while sitting comfortably with shoulder adducted and neutrally rotated, the elbow supported on a table and flexed to 90 degrees, and the forearm and wrist in neutral position. The participants were instructed to perform a maximal isometric contraction. The test was repeated after 10 seconds and the highest value recorded.

Serum vitamin D status—Serum 25(OH)D was analyzed at screening using a standard immunoassay (*DiaSorin RIA kit (DiaSorin, Stillwater, MN, USA)*) or a chemiluminescence method (CLIA, Roche Diagnostics, Basel, Switzerland) at the US and Swedish site, respectively. All samples (baseline, 3, and 6 months) were re-analyzed using a standard immunoassay (*DiaSorin RIA kit (DiaSorin, Stillwater, MN, USA)*) following completion of the trial and are reported in the present paper.

Appendicular Lean Mass (ALM)—To inform pre-specified subgroup analyses (see below), appendicular lean mass at baseline was obtained using DXA (Hologic, Discovery A (Hologic, Bedford MA) used at Tufts; GE Lunar (Madison, WI) used at Stockholm) (34). Appendicular lean mass (arm plus leg lean mass) was assessed for this study by blinded assessors using standard anatomical cut points.

Statistical Considerations

Sample size—The planned enrollment (N=150) was intended to provide 90% power to detect a clinically significant mean difference (intervention minus control) of 0.1 m/s in average walking speed over 400 m, assuming: walking speed has a standard deviation of 0.19 m/s, as estimated by preliminary data in this population; Pearson correlation between baseline and follow-up measurements at least 0.5; and cumulative missingness of walking speed measurements no greater than 20% at 6 months. Estimation was by mixed-effects linear regression incorporating control for stratifying factors (study center and participant sex) and baseline walking speed. Study center was included as a random effect. The primary analysis incorporated data on all individuals with follow-up outcomes measures at six months.

Safety—Total number of serious adverse events (SAEs) and the number of participants reporting at least one SAE were tabulated. Non-serious adverse events (AEs) were classified by System Organ Class (SOC) as delineated in the Medical Dictionary for Regulatory Activities.

Sensitivity and Subgroup Analyses—As a complement to primary assessments, secondary “per-protocol” (PP) analyses were conducted including only those participants adherent to both the exercise and nutrition components of their randomized assignment.

Pre-specified subgroup analyses divided the analytic sample on four dichotomized measures taken at baseline: 1) **circulating vitamin D levels**, with participants whose 25(OH)D levels did not exceed 24 ng/ml deemed vitamin D insufficient (a total of 19 participants had a 25(OH)D level above 24 ng/ml when their samples were reanalyzed in batch following completion of the trial); 2) normal **gait speed**, for which participants with gait speed less than 0.8 m/s were considered slow walkers; 3) summary **physical function**, with participants whose SPPB less than 8 considered functionally limited; and 4) **appendicular lean mass index** (ALMI) - ALM divided by height-squared - for which women with ALMI less than 5.5 and men with ALMI less than 7.26 were classified as sarcopenic (35). Evidence for effect modification by these factors was assessed using stratified analyses and interaction terms.

Results

Study Participants and Enrollment

From December 2011 to February 2014, we screened a total of 2,694 individuals (Figure 1). Of these, a total of 149 participants were randomized (75 to control). Baseline characteristics were similar among the randomized groups (Table 1). Twenty subjects were sarcopenic.

Eighty five participants were recruited in Boston and 64 in Stockholm. Except for serum vitamin D concentrations there were no significant differences between the two study sites. The trial was completed in November 2014.

Analytic Samples

N = 137 (91%) of randomized individuals had evaluable follow-up data at six months. Of these, 120 (60 per arm) were adherent on both the nutritional and PA components of the design, qualifying for the per-protocol analysis.

Intervention Delivery and Adherence

The mean (SD) session attendance for PA was 75% (22%) in the nutritional supplementation group and 72% (24%) in the placebo group (Table 2). Proportionate supplement intake was 88 (22%) in the nutritional supplementation group and 86 (28%) in the placebo group.

Effective delivery of the intervention was reflected in differential change in vitamin D levels by randomization. Mean serum 25(OH)D increased by approximately 36% (7.1 ng/ml) in the group receiving the nutritional supplement but only 14% (2.5 ng/ml) among those receiving placebo; the estimated mean (95% confidence interval; **CI**) difference in six-month change attributable to the nutritional intervention, controlling for sex and site, was 4.6 (2.2, 7.1) ng/ml. In the PP sample, results were essentially identical [mean (95% CI) difference 3.9 (1.2, 6.5) ng/ml at six months].

Primary and Secondary Efficacy Analyses

Gait speed during the 400 M walk improved significantly in both groups (Figure 2); mean (95% CI) increase was 0.08 (0.05, 0.10) for intervention and 0.11 (0.08, 0.14) for placebo. At six months the difference between the two groups was statistically nonsignificant; mean (95% CI) difference -0.03 (-0.07, 0.005), $p = 0.09$; differences were of similar magnitude in the PP sample. Analyses of pre-specified subgroups indicated modest but statistically nonsignificant evidence that treatment effects differed by baseline vitamin D status (Figure 2); results for the PP sample were similar.

SPPB scores improved substantially in both groups (mean six-month increase 2.1 and 2.6 units in intervention and placebo, respectively). At six months, the mean (95% CI) model-estimated difference in SPPB scores was 0.55 (-1.01, 0.01); $p = 0.052$. Results were similar in the PP sample (mean difference -0.045; 95% CI (-0.93, 0.14), $p = 0.15$). Pre-specified subgroup analyses demonstrate little evidence of variation in effects across population subcategories (Figure 2); results for the PP sample were similar.

Safety

A total of seven serious adverse events (SAEs) were reported by five (7%) of the participants assigned to the nutritional supplement, while eight SAEs were reported by 7 (9%) individuals assigned to placebo. There was one death in the control arm. All SAEs were deemed by the medical safety officer as Not or Unlikely to be Related to trial procedures (supplementary table 2).

Discussion

The primary aim of this study was to compare the effects of a high protein, high vitamin D nutritional supplement with a placebo on exercise-induced changes in physical functioning in community dwelling older adults. Although we observed significant and clinically meaningful improvements in physical function measured by gait speed and the SPPB, no further beneficial effect of the nutritional supplement was observed. Multiple studies have examined the impact of protein supplementation on strength, muscle size, and muscle quality when combined with resistance training in older adults.(9, 36–39) However, this study was the first to examine the long term effects of a low volume liquid nutritional supplement providing whey protein in a proprietary concentrated form (20 g/4 fl. oz) in combination with vitamin D and other nutrients and a more moderate intensity exercise training intervention, in mobility-limited older adults.

The decision to study older individuals with demonstrated functional limitations is multifactorial. Reduced muscle mass and loss of muscle strength and power are strong independent predictors of the ability to perform several mobility-related tasks, such as walking and stair climbing(40, 41). Targeting individuals prior to the onset of clinically evident disability may have important public health implications for designing function promoting therapies to prevent mobility disability with advancing age. In addition, these “at risk” individuals may represent a cohort of older individuals where functional limitations in walking and other tasks are closely related to impairments such as sarcopenia, reduced muscle strength and power, which may maximize the benefits from nutritional and/or exercise interventions.

The synergistic effect of protein supplementation on muscle anabolism and function following both acute and chronic exercise in young and middle-aged adults has been demonstrated (16, 42). However, in mobility-limited more frail individuals these synergies have been less robust (9, 39, 43, 44). In a recent systematic review evaluating studies that had examined the combined effects of protein/amino acid supplementation and exercise training on changes in physical functioning in older adults the authors concluded that no additional improvements were observed in physical functioning above those obtained from exercise training alone (45). However, a more recent study was conducted examining combined multi-nutritional supplementation in conjunction with exercise training in frail older adults with poor nutritional status at baseline. Rondanelli et al. observed a significant increase in fat free mass, handgrip strength, and physical functioning in response to 12 weeks of a daily nutritional supplement (22 g whey protein, 10.9 g essential amino acids, 100 IU vitamin D) combined with structured physical activity intervention in sarcopenic older men and women (15). This study differs from our study in several key areas. Subjects in the study of Rondanelli et al. were screened from hospitalized patients and were enrolled only if they had objectively measured sarcopenia. It is likely that this population was also at greater risk for malnutrition and thus benefitted from both the physical activity intervention and the nutritional supplement compared the community dwelling older adults with no signs of malnutrition examined in the present study.

Vitamin D supplementation has been studied for a variety of outcomes in many populations, including falls (46, 47) and fracture (48, 49). However, a recent randomized trial in community dwelling older men and women with a prior fall history who received monthly low-dose 24,000 IU of vitamin D3 (24,000 IU group), high dose receiving 60,000 IU of vitamin D3 (60,000 IU group), or 24,000 IU of vitamin D3 plus 300 µg of calcifediol (24,000 IU plus calcifediol group) monthly showed no effect of 60,000 IU vitamin D on changes in the SPPB at 6 and 12 months (50). In the present study, we were able to significantly increase serum vitamin D status in the group receiving the nutritional supplement. However, we cannot evaluate the effects of improving vitamin D status alone in the present trial as this was not our primary outcome

In a recent study conducted by Pahor et al., it was found that structured, moderate intensity physical activity alone can prevent mobility loss in mobility-limited older adults (5). The present study adds further novelty by illustrating the effects of additional nutritional supplementation to enhance the potent function promoting effects of physical activity in this population.

The present study is not without some limitations. First, although we specifically recruited subjects with demonstrated vitamin D insufficiency, the study participants were not malnourished. Thus the effects of a nutritional supplement may have been blunted. There are inherent cultural differences when sites are located in different countries and this may have contributed to some of the variability in response. We also did not measure dietary intake and thus do not know if the nutritional supplement provided was truly supplemental or acted as a meal substitute.

In conclusion, we demonstrated that a multi-nutrient high protein nutritional supplement had no additional benefits on the exercise-induced improvements in physical function in mobility limited older adults with vitamin D insufficiency. Evidence from this trial suggest nutritional supplementation can improve vitamin D status but offers little additional benefit with respect to physical functioning in mobility limited non-malnourished older adults. These results were consistent when per protocol analysis or pre-specified subgroups were analyzed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
CONSORT diagramming showing participant flow through screening and trial procedures.

* Participants could fail multiple exclusion criteria

** Including one participant who missed the 3 month visit but remained enrolled

Figure 2. 400 Meter walking speed and SPPB by study visit. Means and 95% confidence intervals (line segments) are shown in upper panels, with model-estimated mean difference presented in text. Similar estimates for each pre-planned subgroup analysis are given in lower panels.

Table 1:Baseline Characteristics of Study Participants¹

	Supplement (n=74)	Placebo (n=75)
Age, y	78.1 (5.8)	76.9 (4.9)
Female sex	34 (46)	35 (47)
Body Mass Index, kg/m²	27.9 (3.3)	28.4 (3.9)
MMSE Score	27.3 (1.7)	27.4 (1.9)
Number of Medical Diagnoses	2.8 (2.5)	2.8 (2.7)
MNA-SF Index		
25(OH)D, ng/ml	19.7 (6.8)	17.7 (5.9)
25(OH)D ≥ 24 ng/ml	60 (81%)	62 (83%)
400 M Walking Speed, meters / second	0.89 (0.16)	0.92 (0.15)
Walking Speed < 0.8 m/s	21 (28%)	12 (16%)
SPPB Score	7.8 (1.3)	8.0 (1.1)
SPPB < 8	23 (31%)	19 (25%)
Appendicular Lean Mass Index, kg/m²	7.1 (1.0)	7.4 (1.1)
ALMI < 5.5 (women) or 7.26 (men)	11 (15%)	14 (19%)
400 M Walk Time, seconds	463 (90)	446 (82)
Handgrip Strength, kilograms	25.0 (8.0)	28.3 (9.7)

¹ Data are means (SD), or % of sample; MMSE, Mini-Mental State Exam; MNA, Mini-nutritional assessment; SPPB, Short physical performance battery.

Table 2:Adherence to Protocol by Trial Arm and Components of Intervention^I

	Supplement (N = 74)	Placebo (N = 75)
Exercise Adherence Score	0.75 (0.22)	0.72 (0.24)
Participants Exercise Adherent (at least 60% attendance)	62 (84%)	62 (83%)
Product Adherence Score	0.88 (0.22)	0.86 (0.28)
Participants Adherent on Nutritional Intake (at least 60%)	65 (88%)	65 (87%)
Per Protocol Sample	60 (81%)	60 (80%)

^I Data are means (SD) or counts (%)