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Original Study

Impacts of High-Protein Oral Nutritional Supplements Among Malnourished Men and Women with Sarcopenia: A Multicenter, Randomized, Double-Blinded, Controlled Trial

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A B S T R A C T

Background: Recent evidence suggests that nutritional interventions may improve muscle outcomes in malnutrition and sarcopenia.
Objectives: We evaluated the effects of 2 high-quality oral nutritional supplements (ONS) differing in amount and type of key nutrients in older adult men and women.
Design: A multicenter, randomized, double-blinded, controlled clinical trial.
Participants: Malnourished and sarcopenic men and women, 65 years and older (n = 330).
Intervention: A 24-week intervention period with 2 energy-rich (330 kcal) ONS treatment groups: Control ONS (C_{ONS}, 14 g protein; 147 IU vitamin D_3) versus Experimental ONS (E_{ONS}, 20 g protein; 499 IU vitamin D_3; 1.5 g CaHMB) taken twice daily. Both ONS also contained other vitamins, minerals, and nutrients in varying amounts.
Measurements: Isokinetic peak torque (PT, Nm) leg strength, grip strength (kg), and gait speed ($m \cdot s^{-1}$) were assessed at baseline and 12 and 24 weeks. Left and right leg muscle mass (LMM, kg) were assessed by dual-energy x-ray absorptiometry (DXA). Muscle quality (MQ) was leg strength expressed relative to the tested LMM ($Nm \cdot kg^{-1}$). Subgroup analyses were performed: severe sarcopenia (low skeletal mass index, low grip strength [<30 kg men; <20 kg women], low gait speed [$<0.8\ m \cdot s^{-1}$]) and mild-moderate sarcopenia (low skeletal mass index, normal gait speed, or normal grip strength).
Results: Both ONS groups (E_{ONS} and C_{ONS}) improved PT, MQ, grip strength, and gait speed from baseline with no treatment differences. Those with severe sarcopenia (44%) exhibited lower baseline PT and MQ, with no differences in strength improvements between treatments. However, participants with mild-moderate sarcopenia exhibited higher baseline PT and MQ, with differences in strength improvements at 12 weeks ($E_{ONS} > C_{ONS}$, $P = .032$) in those with normal grip strength. There were no treatment differences based on sarcopenic severity for either grip strength or gait speed.
Conclusion: ONS improved strength outcomes in malnourished older adults with sarcopenia. In those with mild-moderate sarcopenia, but not severe sarcopenia, consumption of the E_{ONS} improved leg muscle strength and quality compared with the standard C_{ONS}.

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Malnutrition and sarcopenia are conditions that are common and overlapping in older adults.[1] Both conditions are strongly influenced by nutrition, where an inadequate nutrient intake is a contributing factor to weight loss and consequently functional impairment. Low lean body mass, a characteristic of sarcopenia, has recently been included in the definition of malnutrition.[2] Another characteristic of sarcopenia, reduced muscle strength, also has been suggested as an indicator of nutritional status.[3] Malnutrition and sarcopenia independently contribute to an increased risk of adverse outcomes, such as falls,[4,5] physical disability,[6] poor quality of life,[7,8] and increased mortality.[9–11] Therefore, interventions for older adults that address both malnutrition and sarcopenia may help reduce these negative outcomes and prolong an older adult's independent lifestyle and improve the quality of life.

The benefits of nutritional interventions for malnutrition-related outcomes are unequivocal.[12] However, the impact of nutrition on sarcopenia is less certain. Most studies report the effects of short-term nutritional interventions on muscle protein synthesis, whereas there are very few high-quality randomized controlled trials.[13] A recent review of the prevalence of sarcopenia and interventions to treat it by the International Sarcopenia Initiative[13] concluded that muscle function impairments in older adults can be improved by exercise interventions, whereas the effects of protein supplementation alone were inconsistent. The authors indicated, however, that calcium β-hydroxy β-methylbutyrate (CaHMB), a metabolite of leucine, showed promise,[13] which was also consistent with a recent meta-analysis examining the benefits of CaHMB on preserving muscle mass in older adults.[14]

The overall expert recommendation was that "Further studies are needed to determine the effect of different nutrition interventions on muscle mass and function using robust, multi-centre and standardised approaches with single or complex nutrition interventions and clinically relevant outcomes (muscle strength, physical performance)."[13]p757

The anabolic signaling of amino acids in skeletal muscle is thought to be primarily triggered by the consumption of essential amino acids, particularly the branched chain amino acid *leucine*.[15,16] It has been shown that higher amounts of protein are needed in older adults compared with young adults to stimulate muscle protein synthesis due to the *anabolic resistance* of aging muscle.[17] Thus, it has been recommended that older adults need at least 1.0 to 1.2 $g \cdot kg^{-1} \cdot d^{-1}$, which is greater than the current US Recommended Dietary Allowance of 0.8 $g \cdot kg^{-1} \cdot d^{-1}$, to maintain muscle function.[18] Because HMB is derived exclusively from leucine in the body,[19] and both leucine and HMB have been shown to stimulate muscle protein synthesis and attenuate muscle protein breakdown,[16] many of the beneficial effects of leucine may be mediated, in part, by HMB.

A recent pilot study[20] demonstrated that the consumption of 3 g CaHMB daily for 24 weeks positively influenced both leg strength and muscle quality (MQ) in healthy older men and women compared with a placebo. These findings suggested that CaHMB may improve clinically relevant strength parameters associated with the loss of functionality and performance. Despite some earlier limited evidence in healthy older adults,[21–23] it remains unclear whether the magnitude of these effects would be similar or greater for older adults with a combination of malnutrition and sarcopenia, who present elevated risks of morbidity and mortality.[5,6,10]

Vitamin D_3 supplementation is widely recognized to improve bone health, postural stability, and prevent falls and fractures leading to disability.[24,25] Supplementation is especially relevant to older men and women, due to a combination of malnutrition, reduced sunlight exposure, and a decrease in synthesis capacity of skin.[24] Current scientific opinion is 800 IU (20 μg) of vitamin D from all sources should be consumed daily to prevent falls in men and women older than 60 years.[25]

Older adults with malnutrition and sarcopenia may not consume sufficient amounts of high-quality protein and/or other nutrients through diet alone. Finding a convenient and compliant nutritional strategy for the attenuation of both malnutrition and sarcopenia would be advantageous. Oral nutritional supplements (ONS) are ideally suited to provide high-quality nutrition when diet alone is insufficient to meet nutritional needs. Furthermore, because of their energy, protein, and vitamin density, supplementing an older adult's diet with an ONS should not reduce the typical dietary intake, but should improve body weight and several functional outcomes, such as hand grip strength.[3,26] To that end, the purpose of this study was to evaluate the effects of 2 high-quality ONS differing in amount and type of key nutrients in older adult men and women with combined malnutrition and sarcopenia.

Methods

Research Design

This was a 24-week, prospective, randomized, double-blinded, controlled, 2-treatment parallel study design. Men and women 65 years and older from 8 countries across Europe and North America with both malnutrition and sarcopenia were enrolled. Malnutrition was defined as a Subjective Global Assessment rating of B or C.[27] Sarcopenia was defined as low grip strength (<20 kg women; <30 kg men) and/or low gait speed (<0.8 $m \cdot s^{-1}$) in conjunction with low skeletal mass index.[28] Enrolled individuals were stratified for gender and age at each study site and randomized into ONS treatment groups: (1) Control ONS (C_{ONS}) and (2) Experimental ONS (E_{ONS}). The protocol was reviewed by local ethics committees or institutional review boards and all participants signed a written informed consent. This study was a registered on ClinicalTrials.gov with the identifier: NCT01191125.

Participants were instructed to drink 2 servings of the ONS daily between regular meals throughout the duration of the study. Participants also were instructed to continue their usual diet, physical activity, and lifestyle habits, with the following exceptions: (1) consumption of study product daily and (2) the recommended ad libitum diet contained a minimum of 0.8 g protein per kg body weight.

Study participants visited the research facility at baseline (week 0) and every 6 weeks (±1 week) thereafter until the end of the 24-week intervention. At each visit, study staff reviewed product intake forms to assess compliance, dietary intake, recorded medication changes, and adverse events. Fasting blood draw, height (measured only at baseline, m), weight (calibrated stadium scale, kg), body composition, leg strength, grip strength, and gait speed tests were conducted at baseline and at 12 and 24 weeks.

To reduce the potential for learning effects, each participant visited the laboratory for 2 familiarization trials before the baseline assessment (separated by at least 1 day within 4 days before baseline) and 1 familiarization trial ≤4 days before both the 12- and 24-week assessments to practice the strength and functionality tests. Finally, all study staff were trained first by webinar and second in person by a single investigator (JTC) on how to perform the body composition, strength, and functionality tests according to standardized testing protocols.

Study Products

Ready-to-drink 220-mL ONSs were packaged indistinguishably except for a 5-digit code to maintain the double-blind study design. Products were isocaloric, providing 330 kcal per serving (Table 1). Each serving of the C_{ONS} (Ensure Plus; Abbott, Zwolle, Netherlands) contained 14 g protein, 11 g fat, 44 g carbohydrate, 147 IU vitamin D_3, and additional vitamins and minerals. Each serving of the E_{ONS} provided 20 g protein, 11 g fat, 36 g carbohydrate, 1.5 g CaHMB, 499 IU vitamin D_3,