

Once/Day Provision of Essential Amino Acid Enriched Meal Replacement Improves Body Composition and Physical Function in Obese Elderly

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Abstract

Older, obese adults are compromised by muscle atrophy and excess adipose tissue. We have previously demonstrated that the acute ingestion of essential amino acids may augment net protein balance in the elderly. Using a double blind, randomized controlled trial, our objective was to compare an experimental meal replacement enriched with essential amino acids (EMR) compared to a commercial meal replacement (Optifast®) provided once/day (q.d.) for four weeks on body composition and physical function in older, obese participants. Twenty-seven individuals (69 ± 5 yrs; body mass index of 32 ± 4 kg/m²) were randomly assigned to EMR (n=13) or Optifast® (n=15) supplementation. Measurements of body composition, skeletal muscle cross-sectional area (CSA), intrahepatic lipid and physical function were completed pre- and post-supplementation. Body mass, fat mass, and visceral fat mass were reduced with EMR but not altered with Optifast®. Thigh muscle CSA increased ($\Delta 4.1 \pm 1.9$ cm²) with EMR but not Optifast® ($\Delta -1.8 \pm 6.0$ cm²). There was a significant increase in the distance covered during the six-minute walk test with EMR ($\Delta 21 \pm 26$ m) but no change in Optifast® ($\Delta 22 \pm 54$ m). Improvements in body composition and physical function support the efficacious use of EMR-based meal replacements in the obese elderly.

Key Words: skeletal muscle, adipose tissue, aging

1. Introduction

The progressive, deleterious loss of muscle mass that occurs with aging is called sarcopenia [1]. Muscle atrophy that occurs in conjunction with obesity is particularly problematic, as the load required for functional independence is increased, but with depleted contractile machinery [2]. It is therefore predictable that sarcopenic obesity has also been linked to the development of metabolic syndrome and diabetes [3]. While losing weight might seem like the obvious solution, data from epidemiological studies suggest an obesity paradox by which body weight has a protective effect against mortality [4]. The efficacy of weight loss in addressing sarcopenic obesity is further complicated by low fitness levels in the obese elderly [5]; not surprisingly co-mingled with low interest in physical activity as a viable intervention [6]. Moreover, most individuals, particularly the obese elderly prefer dietary modification as their only strategy to potentially improve body composition.

In addition to the health problems associated with sarcopenia and obesity, inadequate nutritional intake can be a significant concern as well [7]. For example, a decline in the quality of the diet can negatively affect optimal body composition and further exacerbate the risks of disability among elderly adults [8]. To address these concerns, many individuals and health care providers utilize meal replacements to help maintain body weight and more importantly functional independence [9]. While the use of standard meal replacements may be effective for weight management in young to middle-aged populations [10], it is quite possible that the overall efficacy of meal replacements may be more complex in the elderly due to the presence of anabolic resistance [11].

Previous work from our laboratory has demonstrated the superiority of a meal replacement enriched with essential amino acids (EAAs) compared to other meal replacements on whole body net protein balance under isocaloric conditions in the obese elderly [12]. These responses were largely due to the provision of specific amounts and profiles of EAAs and non-essential amino acids required for overcoming anabolic resistance in the elderly [13]. Despite the widespread popularity of meal replacements among the elderly and the broad use of dietary strategies to improve overall health throughout modern society, longitudinal evaluations designed to study efficacy of EAA-based meal replacements are limited. Therefore, we have tested the hypothesis that daily consumption of an EAA-enriched meal replacement (EMR) would promote improvements in body composition, skeletal muscle, intrahepatic lipid and physical function compared an isocaloric commercially available meal replacement (ie., Optifast®) in the obese elderly (Table 1).

2. Methods

2.1. Recruitment.

We posted informational flyers and newsletters on the University of Alaska Fairbanks (UAF) campus. We held brief informational presentations for the purpose of educating seniors in our community, providing them with an opportunity to participate in the study described herein. Individuals from all racial, ethnic and/or cultural backgrounds between the ages of 60-85 years old with a body mass index of 26-40 kg/m² were encouraged to participate (Table 2). Anyone interested in the trial was encouraged to call our secure, telephone answering service, allowing private and individual telephone conversations to assess eligibility. This study was powered to evaluate changes in body composition in

an older obese cohort. Therefore, no attempt was made to stratify participants according to age or gender. The project (Nutrient Strategies for Muscle Preservation: 986801-17) and all related documents were approved on 17 September 2017 by the UAF Institutional Review Board. All participants provided written informed consent prior to participation.

2.2. Exclusion Criteria

Individuals with a pacemaker or other implanted metal device or object, or who had been previously diagnosed with insulin dependent diabetes, active cancer or malignancy, or a chronic inflammatory condition were excluded. Individuals taking medications, supplements or corticosteroids that might have influenced metabolism or corticosteroids were not enrolled. Finally, any individual with a disease or condition that would have placed them at risk or harm to themselves or others were also excluded.

2.3. Study Participants

Once it was established that individuals were eligible for participation, we enrolled twenty-seven older, obese males and females (69 ± 5 yrs; 32 ± 4 kg/m²) of all races and ethnic backgrounds into a double blind, randomized controlled trial. Participants were weight stable and were not participating in a weight loss or exercise program at the time of enrollment. During pre- and post-supplementation study visits, participants completed the following: a) measurement of body weight and height via electronic scale (Health-o-Meter, St. McCook, IL, USA), b) measurements of body composition using dual energy x-ray absorptiometry (DXA) scans (General Electric iDXA; Madison, WI), c) measurement of the cross-sectional area (CSA) of the skeletal muscles in the upper thigh and intrahepatic lipid utilizing molecular

imaging/spectroscopy (MRI/MRS) (Toshiba Excelart/Vantage 1.5 T MRI/MRS imaging system; Canon, Ōtawara, Tochigi, Japan), c) physical function testing, and d) blood sampling/analysis for hepatic, lipid and metabolic panels. Procedures were performed in the Clinical Research and Imaging Facility on the UAF campus except for blood sampling/analysis performed by LabCorp (1626, 30th Avenue, Fairbanks, AK). Participants were asked to consume their assigned meal replacement (ie., EMR or Optifast®) once each day for four weeks and return each week for refills of their product. Participants returned once each week where research staff recorded their body weight and the weight of any leftover product, and to provide refills of their respective meal replacement. Participants refrained from alcohol consumption (24 h) and intense physical activities (72 h) prior to pre- and post-supplementation study visits.

2.4. Body composition

Determination of fat mass, lean tissue mass, visceral fat mass and bone mineral content was provided by DXA scans (General Electric iDXA; Madison, WI).

2.5. Magnetic Resonance Imaging/Spectroscopy

Measurement of the thigh muscle CSA and intrahepatic lipid were performed in our laboratory as previously described [12].

2.6. Physical Function

Study participants were familiarized with functional tests prior to any performance or measurements of grip strength, floor transfer time or walking distance/speed. Participants were instructed to perform their grip strength measurements three times using the hand-held dynamometer (Lafayette Instrument,

Lafayette, IN) and the final value, in kilograms, was obtained from averaging the second and third attempts. In the floor transfer test, we measured the amount of time required to move from a standing position to a supine position and back up to a complete standing position [13]. For the 6-minute walk test, the participant was instructed to walk as fast as possible without assistance for the entire 6-minute period in an unobstructed hallway. Time was recorded in meters/second obtained using a stopwatch [13].

2.7. Blood Measurements

Sampling and analysis of all blood samples was performed by LabCorp (1626, 30th Avenue, Fairbanks, AK) as previously described [12].

3. Results

Research Participants: Twenty-eight older, obese individuals were randomly assigned to 4 weeks of isocaloric ingestion of either EMR (containing 16 grams of individual EAAs) (n=13) or Optifast® (containing 16 grams of intact protein) (n=15) (Table 1) and completed all aspects of testing related to body composition and physical function. Two participants failed to complete both MRI/MRS scans.

| Table 1. Macronutrients | OF (grams) | OF (calories) | EMR (grams) | EMR (calories) |
|------------------------------------|-----------------------|--------------------------|------------------------|---------------------------|
| EAA's | 0 | 0 | 16 | 66 |
| Protein | 16 | 66 | 6 | 24 |
| Fat | 4 | 32 | 3 | 27 |
| Carbohydrate | 15 | 62 | 11 | 45 |
| Total | 40 | 160 | 36 | 162 |

| Table 2. Clinical characteristics | EMR (pre) | EMR (post) | Optifast® (pre) | Optifast® (post) |
|--|------------------|-------------------|------------------------|-------------------------|
| Age (years) | 67.2±4.9 | | 69.2±5.3 | |
| Sex (m/f) | 6/7 | | 6/9 | |
| Body mass (kg) | 86.6±9.3 | 85.8±9.1* | 92.7±18.8 | 91.8±17.8 |
| Body mass index (kg/m ²) | 30.9±2.3 | 30.5±0.6 | 33.7±5.0 | 33.3±4.8 |
| Waist Hip Ratio | 0.93±0.09 | 0.93±0.10 | 0.93±0.10 | 0.93±0.09 |

*Denotes significant reduction ($P<0.05$).

Body composition: There were no differences in baseline measurements of body composition (Table 3). Body weight, fat mass and visceral fat mass were reduced in EMR but not in Optifast®. Lean tissue mass was preserved in EMR but a trend towards lean tissue mass reduction ($P=0.06$) occurred in Optifast® (Table 3).

| Table 3. Body composition | EMR (pre) | EMR (post) | Optifast® (pre) | Optifast® (post) |
|---|------------------|-------------------|------------------------|-------------------------|
| Body Fat (%) | 40±2 | 39±7 | 41±8 | 41±8 |
| Adipose Tissue Mass (kg) | 33±6 | 32±5* | 36±10 | 33±8 |
| Visceral Adipose Tissue Mass (kg) | 1.8±0.8 | 1.7±0.2* | 2.0±1.5 | 1.5±1.2 |
| Android Adipose Tissue (%) | 48±7 | 48±6 | 47±9 | 45±9 |
| Gynoid Adipose Tissue (%) | 39±9 | 39±8 | 41±10 | 41±10 |
| Android/Gynoid Ratio | 1.3±0.2 | 1.3±0.2 | 1.2±0.3 | 1.1±0.3 |
| Trunk Adipose Tissue (%) | 44±7 | 43±6 | 43±7 | 41±7 |
| Arm Adipose Tissue (%) | 36±10 | 36±10 | 37±10 | 36±10 |
| Leg Adipose Tissue (%) | 33±10 | 33±10 | 38±11 | 38±12 |
| Lean Tissue Mass (kg) | 51±10 | 51±9 | 52±12 | 50±12 [^] |
| Appendicular Lean Tissue Mass (kg) | 24±5 | 24±5 | 25±7 | 24±6 |
| Appendicular Lean Tissue Mass/BMI | 0.7±0.2 | 0.8±0.1 | 0.7±0.2 | 0.7±0.2 |
| Bone mineral density (g/cm ²) | 1.3±0.1 | 1.3±0.2 | 1.3±0.1 | 1.2±0.2 |

*Denotes significant reduction ($P<0.05$). [^]Represents trend towards reduction ($P=0.06$).

There were no changes in appendicular lean tissue mass or appendicular lean tissue

mass/BMI in EMR or Optifast® (Table 3).

Skeletal muscle: Baseline thigh muscle CSA was not different between EMR (136 ± 30 cm²) and Optifast® (142 ± 34 cm²). Thigh muscle CSA increased significantly with EMR but did not change with Optifast® (Figure 1)

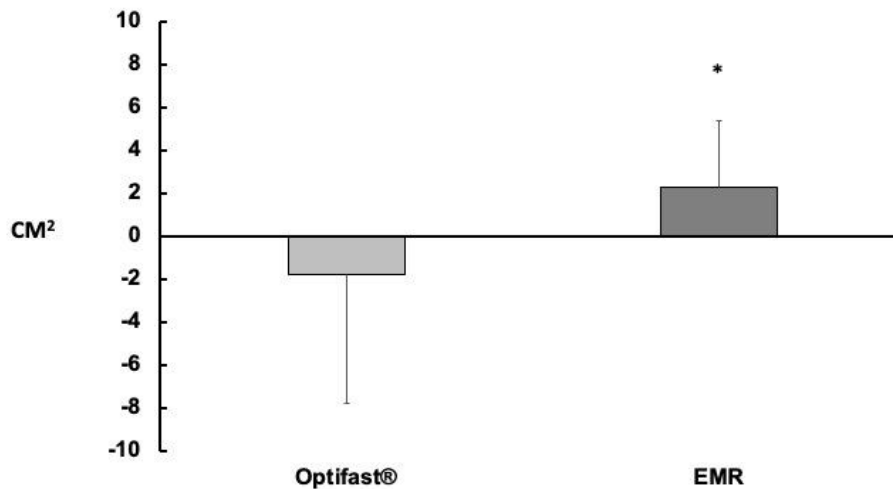


Figure 1. Change in the thigh muscle cross-sectional area with Optifast® and EMR. *Denotes significant increase with EMR ($P < 0.05$).

Liver lipid: There was a significant reduction in MRI/MRS-derived intrahepatic lipid with EMR and no change with Optifast® (Figure 2).

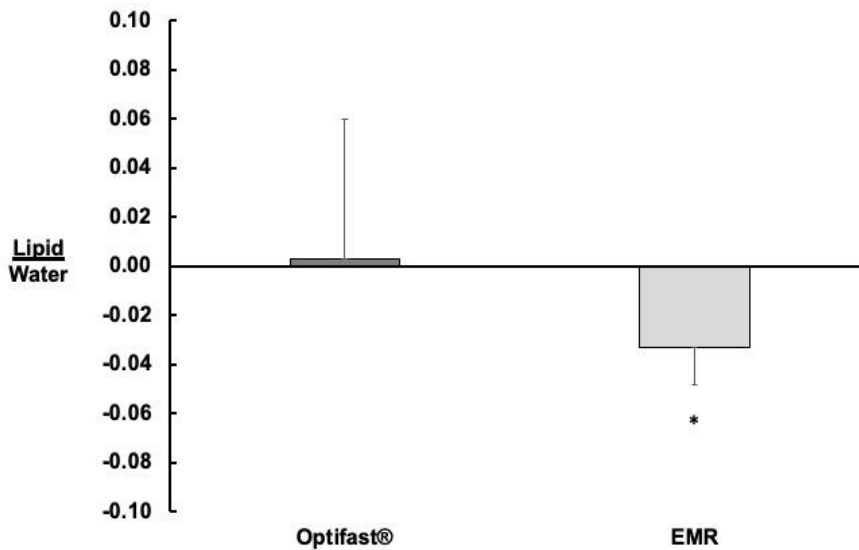


Figure 2. Change in intrahepatic lipid with Optifast® and MR. *Denotes significant reduction with MR ($P < 0.05$).

Physical function: There were no differences in baseline grip strength (kilograms), floor transfer test (seconds) or six-minute walk (meters) between the two groups. No changes in grip strength occurred with EMR or Optifast® (Table 4). The time required to perform the floor transfer test was reduced in EMR but not in Optifast® (Table 4). Also, there was a significant increase in the distance covered during the six-minute walk test with EMR ($\Delta 21 \pm 26$ m) but no significant change in Optifast® ($\Delta 22 \pm 54$ m) (Table 4).

| Table 4. Physical Function | EMR (pre) | EMR (post) | Optifast® (pre) | Optifast® (post) |
|------------------------------|---------------|----------------|-----------------|------------------|
| Right Arm Grip Strength (kg) | 37 \pm 11 | 38 \pm 9 | 34 \pm 10 | 36 \pm 11 |
| Left Hand Grip Strength (kg) | 37 \pm 11 | 36 \pm 11 | 35 \pm 13 | 36 \pm 13 |
| Floor Transfer Test (sec) | 8.9 \pm 2.9 | 7.9 \pm 2.3* | 14.7 \pm 11.7 | 11.2 \pm 7.4 |
| Six Minute Walk distance (m) | 557 \pm 69 | 578 \pm 76* | 541 \pm 128 | 563 \pm 113 |
| Walking Speed (m/sec) | 1.5 \pm 0.2 | 1.6 \pm 0.2* | 1.5 \pm 0.4 | 1.6 \pm 0.3 |

*Denotes significant improvement ($P < 0.05$).

Blood parameters: Blood lipids were represented by total cholesterol, high density

lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides. Hepatic function was characterized by protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The metabolic panel was expressed by glucose, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine and eGFR. All baseline blood parameters were within normal limits in both groups and were not affected by supplementation (Table 5).

| Table 5. Blood parameters | MR (pre) | MR (post) | Optifast® (pre) | Optifast® (post) |
|-----------------------------------|-----------------|------------------|------------------------|-------------------------|
| Total cholesterol (mg/dl) | 178±33.4 | 176±30 | 197±34 | 186±41 |
| HDL cholesterol (mg/dl) | 54±15 | 53±14 | 59±15 | 61±14 |
| LDL cholesterol (mg/dl) | 102±27 | 101±27 | 118±32 | 108±34 |
| Triglycerides (mg/dl) | 115±50 | 111±55 | 98±36 | 87±40 |
| Protein (g/dL) | 6.5±0.3 | 6.8±0.3 | 6.7±0.4 | 6.8±0.4 |
| Albumin (g/dL) | 4.3±0.2 | 4.4±0.2 | 4.2±0.2 | 4.3±0.2 |
| Total Bilirubin (g/dL) | 0.6±0.3 | 0.4±0.3 | 0.5±0.3 | 0.5±0.3 |
| Direct Bilirubin (g/dL) | 0.1±0.0 | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 |
| Alkaline Phosphatase (IU/L) | 70±16 | 69±17 | 71±15 | 70±15 |
| Aspartate Aminotransferase (IU/L) | 21±4 | 22±3 | 24±7 | 24±4 |
| Alanine Aminotransferase (IU/L) | 21±5 | 20±6 | 22±10 | 21±7 |
| Glucose (mg/dL) | 94±14 | 101±30 | 102±50 | 93±10 |
| Blood Urea Nitrogen (mg/dL) | 18±5 | 21±4 | 19±4 | 20±5 |
| Creatinine (mg/dL) | 0.8±0.1 | 0.9±0.2 | 0.9±0.2 | 0.9±0.2 |
| BUN/Creatinine | 21±6 | 24±5 | 21±4 | 22±5 |
| eGFR (mL/min/1.73) | 81±14 | 76±14 | 74±13 | 75±16 |

4. Discussion

The purpose of this study was to evaluate whether one serving/day of EMR for 4 weeks would maintain skeletal muscle and promote the reduction of adipose tissue in

older, obese individuals. Our primary conclusion is that that provision of EMR enabled the preservation of lean tissue mass and increased thigh muscle CSA, while reducing excess adipose tissue and visceral adipose tissue. These beneficial changes occurred in conjunction with increased functional capacity as indicated by improvements in the floor transfer test and the six-minute walk test in with no undesirable side effects with EMR. Therefore, it is apparent that the daily supplementation of a proprietary blend of 16 grams of EAAs included in EMR was more effective than Optifast® in promoting positive changes in body composition and physical function in the obese elderly.

We have previously demonstrated the beneficial influence of EMR on whole body protein synthesis, protein breakdown and net protein balance compared to a high protein meal replacement (ie., Bariatric Advantage) in older, obese adults using stable isotope methodology [14]. Our acute metabolic study utilizing a randomized, cross-over design provided the initial “proof of concept” upon which we based the physiological outcome study described herein. The profile of EAAs in EMR was formulated to optimize translation of protein synthesis and overcome anabolic resistance in the context of aging [15, 16]. The daily provision of EMR over the course of 4 weeks promoted an increase in skeletal muscle in older, obese individuals. The beneficial alteration in body composition occurred without any change in physical activity or additional dietary manipulation. Unlike the use of growth hormone, testosterone or other pharmaceutical approaches that are complicated by potential adverse side effects [17], EMR did not elicit any serious adverse events or side effects. In fact, markers of hepatic and kidney function were within normal limits at baseline and did not change over the course of the 4-week study with the consumption of either EMR or Optifast®.

MRI, or computed tomography (CT), derived measurement of thigh muscle CSA represents the gold standard for the evaluation of muscle mass, as this method is near identical when compared to cadaveric data [18]. Therefore, the significant increase in thigh muscle CSA in EMR compared to a slight but not significant reduction in Optifast® is particularly compelling. It is our assertion that EMR provides the requisite EAAs required to overcome anabolic resistance in the elderly, presumably facilitated by the optimization of intracellular translation, associated with the amino acid precursors in the profile needed to support accelerated muscle protein synthesis [16,19]. The improved muscle CSA in those receiving EMR translated to improvements in the six-minute walk test and the floor transfer test; both of which have been tightly linked to independent living and/or functional capacity in the elderly [20,21].

The reduction in whole body and visceral adipose tissue in the EMR group may have been tied to the energy cost of accelerated protein synthesis [22]. For example, we know that 20 kcals are used every 1 mol of amino acids incorporated into muscle protein [23]. Based on a theoretical calculation using data from our previous study, the stimulation of protein synthesis resulting from a single serving of EMR, multiplied by 30 days, would only account for an increased expenditure of 1596 ± 143 kcals. Therefore, it is likely that the provision of EMR several times throughout the day and/or as part of a caloric restriction strategy would be more beneficial in promoting impressive reductions in visceral and whole-body adipose tissue.

In addition to our concerns related to sarcopenic obesity in the elderly, we are also aware that non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions in the obese elderly [24]. Closely associated with insulin resistance and

metabolic syndrome, NAFLD not only contributes to metabolic dysregulation and can also lead to nonalcoholic steatohepatitis putting individuals at an increased risk for fibrosis, cirrhosis and liver failure [25]. While the precise effects of increased amino acid intake upon NAFLD are still unclear, previous work has demonstrated that 11 grams of essential amino acids provided twice daily reduced intrahepatic lipid and plasma lipids [26]. Pre-clinical studies suggest that energy requirements for amino acid metabolism may enhance the oxidation of intrahepatic lipid [27]. While some studies have suggested an association between elevated branched chain amino acid concentrations and insulin resistance [28-30], we demonstrated a significant reduction in intrahepatic lipid with once/day supplementation of essential amino acids in the form of EMR over the course of one month in obese elderly (Figure 2). Our results are consistent with considerable literature where BCAAs have been given to subjects without inducing insulin insensitivity [31].

5. Conclusions

The EMR approach is unique in that the anabolic influence of the EAAs can be maximized within the context of a single meal instead of multiple feedings throughout the day. The positive benefits of EMR consumed daily for four weeks by our obese, elderly participants occurred with no changes in physical activity or additional dietary manipulation. Alternatives to the utilization of EMR are time-consuming and tedious with limited pragmatic application in this cohort, offering relatively modest if any benefits despite exceptionally high financial costs and the need for clinical supervision [32]. On the other hand, daily provision of EMR for just one month promoted a net gain of thigh

muscle CSA determined by MRI scans, as well as significant reductions in total fat mass, and more importantly, visceral fat mass. EMR represents a new concept in modification of body composition and metabolic health that can be achieved with minimal inconvenience or stress to the user.

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Conflicts of Interest: Coker and Wolfe are Managing Partners and Co-Owners of Essential Blends, LLC that have received funding through the Small Business Innovations in Research from the National Institutes of Health to develop clinical nutrition products. We declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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