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Effects of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine supplementation on the body composition and muscle strength in the elderly

Bülent Saka[1], Sevnaz Şahin[2], Diclehan Kılıç[3], Levent Öztürk[4], Hasan Yılmaz[5], Mutlu Doğanay[6], Serdar Türkyılmaz[7], Selahattin Menteş[8], Ozan Usluer[9], Kürşat Arıkan[10], Selçuk Çomoğlu[11], Levent Güngör[12], Sedat Ziyade[13], Özkan Kanat[14], Duray Şeker[15], Özgür Canoler[16], Eren Gözke[17], Sibel Akın[18], İlker Sücüllü[19], Fatih Tufan[20]

[1]Department of Internal Medicine, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[2]Department of Geriatrics, Ege University School of Medicine, İzmir, Turkey
[3]Department of Radiation Oncology, Gazi University School of Medicine, Ankara, Turkey
[4]Department of Anesthesiology and Critical Care, Atatürk Training and Research Hospital, Ankara, Turkey
[5]Department of Radiation Oncology, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey
[6]Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey
[7]Department of General Surgery, Karadeniz Technical University School of Medicine, Trabzon, Turkey
[8]Department of Radiation Oncology, Erciyes University School of Medicine, Kayseri, Turkey
[9]Department of Chest Surgery, University of Medical Sciences, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey
[10]Department of Ear, Nose and Throat, Adana Numune Training and Research Hospital, Adana, Turkey
[11]Department of Neurology, University of Medical Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[12]Department of Neurology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[13]Department of Chest Surgery, Bezmialem Vakıf Gureba University Hospital, İstanbul, Turkey
[14]Department of Medical Oncology, Uludağ University School of Medicine, Bursa, Turkey
[15]Department of General Surgery, University of Medical Sciences, Dışkapı Yıldırım Beyazıt Research Hospital, Ankara, Turkey
[16]Department of Anestesiology, Eskişehir Acıbadem Hospital, Eskişehir, Turkey
[17]Department of Neurology, Fatih Sultan Mehmet Research Hospital, İstanbul, Turkey
[18]Department of Internal Medicine, Division of Geriatrics, Erciyes University School of Medicine, Kayseri, Turkey
[19]Department of General Surgery, University of Medical Sciences, Gülhane Medical Faculty, Ankara, Turkey
[20]Department of Internal Medicine, Division Geriatrics, Şevket Yılmaz Training and Research Hospital, İstanbul, Turkey

ORCID IDs of the authors: B.S. 0000-0001-5404-5579; S.Ş. 0000-0001-5457-901X; D.K. 0000-0002-6568-0866; L.Ö. 0000-0001-9755-033X; H.Y. 0000-0003-4066-3434; M.D. 0000-0002-3354-2047; S.T. 0000-0002-2619-3336; S.M. 0000-0002-1371-7356; O.U. 0000-0002-5272-3310; K.A. 0000-0002-4941-1236; S.Ç. 0000-0003-2137-7467; L.G. 0000-0002-3016-2137; S.Z. 0000-0002-9549-0633; Ö.K. 0000-0001-6973-6540; D.Ş. 0000-0003-2816-6734; Ö.C. 0000-0002-6697-7055; E.G. 0000-0001-6175-0647; S.A. 0000-0002-6139-7254; İ.S. 0000-0002-5285-3051; F.T. 0000-0003-3245-1618

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ABSTRACT

Objective: Oral amino-acid-combination supplements have become a common intervention to maintain or potentially increase the lean body mass (LBM) in the elderly. Our aim was to determine the tolerance and efficacy of the 8-week beta-hydroxy beta-methylbutyrate/arginine/glutamine (HMB/Arg/Gln) supplementation on anthropometrics, LBM, muscle strength, and gait speed in elderly patients.

Methods: In this longitudinal observational study, a total of 131 elderly patients were evaluated at two consecutive visits, including baseline (Week 0) and single follow-up (Week 8). The use of HMB/Arg/Gln was evaluated in terms of patient compliance, the efficacy on anthropometrics, LBM (kg, measured with bioelectrical impedance analysis-BIA), muscle strength (kg), gait speed, and safety.

Results: The mean (standard deviation, SD) age was 74.7 (6.8) years (57.3% of participants were males). Of the patients were diagnosed with malnutrition (according to the Subjective Global Assessment test). The main indications for the HMB/Arg/Gln supplementation were sarcopenia (45.8%) and cancer cachexia (42.0%). Only two patients stopped supplementation because of taste problem (1.5%). Overall, 79.4% of patients were still on HMB/Arg/Gln at the follow-up. The mid-upper-arm circumference (MUAC, 25.3–27.0 cm, p=0.017), mid-upper-arm muscle circumference (MUAMC, 21.7–22.2 cm, p=0.006), hand grip strength (16.0–19.0 kg, p=0.0001), and gait speed (0.5–0.7 m/sec, p=0.008) were increased after the HMB/Arg/Gln supplementation. The adverse events were reported in 14 (10.7%) patients. No serious adverse events were reported in association with HMB/Arg/Gln.

Conclusion: Our findings showed that 8 weeks of the HMB/Arg/Gln supplementation applied twice daily were well tolerated and safe in the elderly. The supplementation seems to improve the MUAC, MUAMC, muscle strength, and gait speed.

Keywords: Beta-hydroxy-beta-methylbutyrate, elderly, gait speed, muscle mass, strength, tolerability

Corresponding Author: Bülent Saka; drsakab@yahoo.com

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Introduction

Reaching up to 15% per decade by the age of 70, muscle loss is common throughout the aging process, while sarcopenia or the loss of muscle mass and/or function has been considered to be associated with the functional status, which is directly linked to the health status in the elderly (1, 2). A decline in the lean body mass (LBM) has been associated with decreased physical function, impaired quality of life, poor treatment response, and increased mortality (3).

Based on their capability to increase the protein synthesis in skeletal muscles, the use of amino-acid-combination oral nutritional supplements has become one of the interventions to maintain or potentially increase the LBM in the elderly (3, 4). Beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of leucine, has been shown to stimulate protein synthesis and inhibit proteolysis, while arginine (Arg) and glutamine (Gln) increase collagen and protein synthesis (5-7). Accordingly, the use of the HMB, Arg, and Gln combination in a dietary supplement (HMB/Arg/Gln) has become increasingly studied in terms of its muscle-sparing properties and safety. It seems that HMB/Arg/Gln was more effective in replenishing fat-free mass and reversing weight loss compared to placebo in different populations with various clinical disorders (3, 8, 9).

This non-interventional, prospective, observational multi-center study was designed to evaluate the elderly patients who were applied HMB/Arg/Gln therapy to determine the efficacy of 8-week HMB/Arg/Gln therapy on anthropometrics, LBM, muscle strength, and gait speed.

Patients and Study population

This was a non-interventional, prospective, observational multi-center study. There were 20 centers participating with sufficient experience on adult nutritional supplement therapy across Turkey (already registered at ClinicalTrials.gov; identifier NCT02146612). During the study period, all the patients with HMB/Arg/Gln (2.6 g HMB, 14.8 g Arg, and 14.8 g Gln per sachet) therapy were screened. The exclusion criteria were age <65 years, no indications for the usage of HMB/Arg/Gln, acute medical problem, trauma or severe cognitive impairment (mini-mental state examination score <10), and a history of allergy or hypersensitivity reaction to the HMB/Arg/Gln combination. Patients gave their written informed consent prior to study-specific procedures with the understanding that they had the right to withdraw from the study at any time.

The study was conducted at two consecutive visits, including baseline (Week 0) and single follow-up (recommended at Week 8) visits. A total of 131 patients aged ≥65 years were enrolled into the study.

Data collection

Data on patient demographics (age, gender), primary diagnosis, Subjective Global Assessment (SGA) (10), taste evaluation, and concomitant diseases were collected at the baseline visit. Data on the HMB/Arg/Gln usage patterns (duration [day], amount [package/day], patient compliance [regular use], and persistence [continuation, discontinuation, and reasons for discontinuation]) were collected at the follow-up visit. Data on anthropometrics (height [cm], weight [kg], triceps skin fold [TSF], mid-upper-arm-circumference [MUAC, cm] and calf circumference [CC, cm]), LBM (kg) measured with bioelectrical impedance analysis (BIA), muscle strength measured with a hand dynamometer (kg), and gait speed (m/sec) were collected at both visits.

Study parameters

The HMB/Arg/Gln supplementation tolerance and its effects on anthropometrics, LBM, muscle strength, and gait speed from baseline to follow-up were evaluated. Safety was also evaluated based on the reports of adverse events (frequency, system–organ classification, severity, relation to study medication, and outcome).

Anthropometric measurements

Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Measurements of MUAC were made in accordance with the National Kidney Foundation's guideline on nutrition in patients with CKD. MUAC was based on the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow between the olecranon process and the acromium. TSF was measured with a Harpenden skin fold caliper (ASSIST Creative Resources Ltd, LL13 9UG, UK). The calculation of MUAMC (cm) was done using the formula MUAC-(3.14 x TSF) (11). The CC (calf circumference) was measured from the largest diameter of the left calf with a flexible tape.

Bioelectrical impedance analysis

LBM (kg) was determined via BIA using the Tanita MC-980MA Multi-Frequency Segmental Body Composition Monitor (Tanita, Tokyo, Japan). For the BIA measurements, the subject stood in an upright position with the bare feet on the analyzer footpads. The impedance between the two feet was measured while an alternating current (50 kHz and ~200 μA) passed through the lower body. Measurement was computed with this impedance value.

Muscle strength and gait speed

The dominant hand grip strength was determined using a Jamar Plus Digital Hand Dynamometer, which is model 2A, hydraulic, analog dynamometer having the anatomical grip with five-position options. This instrument is the recommended and preferred tool, considered to be the gold standard for documenting the grip strength (12). A 4-meter gait speed with ≤0.8 m/sec was associated with low physical activity (2).

Serum prealbumin measurement

Serum prealbumin (PAB) concentrations of the patients (g/dL) were measured by the Cobas Integra 800 Autoanalyser (Roche, Mannheim).

HMB/Arg/Gln regimen

Consistent with manufacturer's instructions, an oral nutritional supplement with a combination of HMB, Arg, and Gln (Abound), and the sachet containing 1.3 g HMB, 7.4 g Arg, and 7.4 g Gln, was recommended to be consumed with 250 mL of water, two times a day.

Statistical analysis

Categorical variables are summarized as n (%), whereas continuous ones are summarized as median (minimum–maximum). The change over time for continuous variable was tested using the Wilcoxon test due to non-normal distribution patterns of continuous variables. Type 1 error was accepted as 0.05. Analyses were performed on the IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethical Committee of Istanbul University, Istanbul School of Medicine (1038/2012). Informed consent was obtained from all individual participants included in the study.

Results

Patient characteristics

Baseline data of the patients were evaluated at Visit 1 (mean [standard deviation, SD] age, 74.7 [6.8] years; 57.3% were males). All patients were diagnosed with malnutrition according to SGA. In those with insufficient oral intake, an energy-/protein-rich diet and/or enteral nutrition supplement was given according to daily needs. Out of 131 patients, 122 (93.1%) attended Visit 2, which was performed for a median 62.0 days after the enrollment (Nine patients were died during the study). Diabetes mellitus (17.6%) and chronic kidney disease (3.1%) were the two most common concomitant diseases encountered in our cohort (Table 1). The main indications for the HMB/Arg/Gln regimen were sarcopenia in 60 (45.8%), cancer in 55 (42.0%) patients, and wounds in 27 (20.6%) (Table 1).

HMB/Arg/Gln use

The HMB/Arg/Gln supplement was used for a median 30.5 days (36 days in cancer patients) at an amount of median 2.0 package/day (58.2% of the cancer patients were still using two packages/day at Visit 2). The taste of HMB/Arg/Gln was identified as very good, good, or neutral by 91.5% of patients. Only two patients (1.5%, one cancer, one sarcopenia) discontinued the supplement because of they had a problem with taste. Overall, 79.4% of patients used HMB/Arg/Gln on a regular basis.

Changes in anthropometrics, LBM, muscle strength, gait speed, and laboratory findings

Although the weight, BMI, and LBM values improved or were maintained in 60.9%, 63.9%, and 65.3% of patients at the follow-up visit, respectively, they did not reach statistical significance (weight, 64.6 to 65.0 kg, p=0.25; BMI, 23.7 to 24.2 kg/m^2, p=0.203; LBM, 35.3 to 37.7 kg, p=0.09) (Table 2), which is similar in patients with cancer (LBM, 38.7 to 39.0 kg, p=0.20, 65.5% of the patients with cancer had improved or maintained LBM); sarcopenia (LBM, 38.5 to 39.4 kg, p=0.09); and in the wound group (LBM, 49.7 to 50.2 kg, p=0.40).

A significant increase was noted in the median MUAC (25.3 to 27.0 cm, p=0.017); MUAMC (21.7 to 22.2 cm, p=0.006); and CC (36.5 to 37.7 cm, p=0.001), which were improved or maintained at the follow-up visit in 62.8%, 62.2%, and 73.3% of patients, respectively (Table 2). When cancer patients were taken into consideration, although MUAC (25.5 to 25.9 cm, p=0.124) and MUAMC (21.9 to 21.8 cm, p=0.70) did not change significantly, CC (40.2 to 42.1 cm, p=0.006) was increased in the follow-up visit, which was improved in 69% and maintained in 17.2% of the patients. In sarcopenic patients, MUAC and MUAMC were significantly increased (MUAC, 25.8 to 26.6 cm, p=0.012; MUAMC, 20.2 to 22.1 cm, p<0.001). CC increased from 32.3 to 32.8 cm, which was not significant (p=0.15). In the wound group, MUAMC increased significantly (18.7 to 22.6 cm, p=0.039).

The median hand grip strength (16.0 to 19.0 kg, p=0.0001) and gait speed (0.5 to 0.7 m/sec, p=0.008) were significantly increased, which were improved or maintained at the follow-up visit in 80.0% and 89.4% of patients, re-

Table 1. Patient characteristics and indications for oral nutrition supplement regimen at visit 1 (n=131)	
Age (year), mean (SD)	74.7 (6.8)
Gender (male), n (%)	75 (57.3)
ONS indication (primary diagnosis), n (%)*	
Cancer	55 (42.0)
Sarcopenia	60 (45.8)
Wound	27 (20.6)
Pressure ulcer	19 (14.5)
Burn	3 (2.3)
Surgery wound	3 (2.3)
Diabetic foot ulcer	1 (0.8)
Venous leg ulcer	1 (0.8)
Other	3 (2.3)
Other diagnosis	42 (32.1)
Concomitant diseases	
None	79 (60.3)
Diabetes mellitus	23 (17.6)
Chronic kidney disease	4 (3.1)

*Patients may have more than one disease. ONS: oral nutrition supplement; SD: standard deviation

spectively (Table 2). Although the hand grip strength did not increase significantly in patients with cancer (25.5 to 27.1 kg, p=0.20), it was improved in 66.7% and maintained in 8.3% of patients. In patients with sarcopenia, the median hand grip strength increased significantly (14.8 to 18.6 kg, p<0.001). In wound group, it did not change significantly.

At the follow-up visit, the amount of food consumption (with diet list) was not changed in 59.6%, while it was decreased in 19% and increased in 21.4% of patients. The serum PAB level increased from 20.48±14.59 g/L (Visit 1) to 24.33±12.90 g/L (Visit 2) (p=0.022). In patients with cancer and sarcopenia, the mean serum PAB level of the patients were increased from 18.65±11.28 to 22.88±10.44 g/L and 26.38±29.11 to 29.40±26.78 g/L, but that much difference did not show any statistical significance (p=0.11, p=19). In the wound group, both the mean serum prealbumin and albumin levels increased significantly (PAL, 20.47±20.98 to 25.11±18.37 g/L, p=0.05; albumin, 28.6–31.23 g/L, p=0.03).

Adverse events

During the course of the study, 14 patients (10.7%) experienced 14 adverse events (10 serious adverse events) (Table 3). In 9 of 10 serious adverse events, the outcome was death of the patient, while none of the deaths and serious adverse events was associated with the HMB/Arg/Gln application (Table 4).

Table 2. Changes in anthropometrics, muscle strength, gait speed, and LBM (n=122)			
	Baseline	**Follow-up**	**p**
Anthropometrics			
Weight (kg)	64.6 (34.8–100.0)	65.0 (35.4–95.0)	0.256
BMI (kg/m^2)	23.7 (14.5–44.4)	24.2 (14.7–42.2)	0.203
MUAC (cm)	25.3 (11.5–38.0)	27.0 (18.5–39.0)	0.017
MUAMC (cm)	21.7 (7.4–28.2)	22.2 (14.7–34.3)	0.0068
CC (cm)	36.5 (25–62)	37.7 (21.5–65)	0.001
Functional tests			
Hand grip strength (kg)	16.0 (1.0–54.0)	19.0 (6.0–60.0)	0.0001
Gait speed (m/sec)	0.5 (0.2–14.8)	0.7 (0.3–4.9)	0.008
Muscle mass (BIA)			
Lean body mass (kg)	35.3 (10.9–67.7)	37.7 (11.5–65.1)	0.092

Data are shown as median (min–max) p-value of the Wilcoxon test. Comparison could only be done for patients with data at baseline and follow-up.
BMI: body mass index; CC: calf circumferences; LBM: lean body mass; MUAC: mid-upper-arm circumference; MUAMC: mid-upper-arm muscle circumference

Discussion

According to the definition by the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is the loss of muscle strength and function with an extensive and progressive reduction in the skeletal muscle mass (2). Sarcopenia accelerates with age. In many studies, the prevalence is 5–25% in people aged between 60 and 70 years, and 11–50% in those aged >80 years (13, 14). Anthropometric measurements were used to predict the muscle mass in the past (15-18). In a recent study, Akin et al. (15) found the MUAMC cut-off values for muscle mass in elderly as 23.8 cm for men and 23.3 cm for women, and the study was conducted in Turkish population. Halil et al. (19) showed 68% of sarcopenia cases in a national nursing home project including 711 elderly residents. They used the handgrip strength for the diagnosis of sarcopenia according to the Cardiovascular Health Study criteria. Sarcopenia was associated with 1-year mortality independently from malnutrition in nursing home residents (20). Sarcopenia treatment included the supplementation of protein–energy needs (1.2–1.5 g/kg/day protein), active exercise, and correction of vitamin D deficiency and functional amino acids such as leucine (21).

Beta-hydroxy-beta-methylbutyrate (HMB) is derived from leucine. It has anti-catabolic effects on skeletal muscles and can reduce muscle damage through the inhibition of muscle protein degradation. It increases the protein synthesis in skeletal muscles through the IGF-1 expression and activation of the mTOR pathway (22-25). Portal et al. (26) showed an increased knee-flexion isokinetic force with HMB. Thomson et al. (27) mentioned an increased muscle strength without any change in the muscle mass. In animal models, the HMB supplementation was shown to increase the muscle mass and functions (28-29). Muscle tetanic force, glycogen and ATP content, resistance to acute muscle fatigue during intense exercise, and citrate synthesis activity were all increased with HMB. Kuriyan et al. (30) showed a negative correlation with age and plasma HMB concentration, which is positively correlated with appendicular lean mass and handgrip strength.

The fat-free mass (FFM) gain was shown in cancer cachexia and AIDS patients with HMB/Arg/Gln supplementation (8, 9). HMB was associated with an increased FFM, muscle strength, and muscle quality in the elderly who participated in a strength training program (31, 32). It was also associated with a decreased muscle breakdown in bed-ridden elderly in a nursing home (33). In a randomized, controlled, double-blind study, Deutz et al. (34) gave HMB to healthy elderly who were confined to complete bed rest for 10 days. The HMB supplementation prevented the decline in LMB (measured with DEXA) when compared to control. In chronic obstructive pulmonary disease, HMB combined to pulmonary rehabilitation improved muscle mass, mus-

Table 3. Adverse events (n=131)

Adverse event	n	%
Cardio-respiratory arrest	1	0.76
Diarrhea	1	0.76
Nausea	1	0.76
Oropharyngeal pain	1	0.76
Respiratory failure	1	0.76
Aspiration pneumonia	1	0.76
Skin rash	1	0.76
Death	7	5.30
Total	14	10.70

Table 4. Characteristics of adverse events (n=131)

Seriousness	n	%
Non-serious	4	3.1
Oropharyngeal pain	1	
Diarrhea	1	
Nausea	1	
Rash	1	
Serious	10	7.6
Pneumonia aspiration	1	
Death	9	
Cardio-respiratory arrest	1	
Respiratory failure	1	
Other	7	10.7
Total	14	
Causality		
Non-serious	4	3.1
Not reported	2	
Related	2	
Serious	10	7.6
Related	0	0
No relation was reported	10	7.6
Total	14	10.7

cle strength, quality of life, and serum prealbumin levels of the patients (35). Daily administration of HMB/Arg/Gln in older adults aged 65–87 years for 6 months was shown to be associated with an increased LBM and lower-extremity strength as compared with isocaloric placebo (36). Recently, a meta-analysis including data of randomized controlled trials was published about the effect of HMB on muscle loss in the elderly, which indicated the preservation of muscle mass with HMB (37). Limitations of the analysis were small sample sizes, high rate of treatment withdrawal, and the absence of muscle strength measurement.

Our findings revealed a high rate of patient compliance with twice-daily dietary HMB/Arg/Gln supplementation in elderly patients. Withdrawal related to taste problems occurred only in two patients. HMB/Arg/Gln seems to be associated with improvement in terms of MUAC, MUAMC, and CC, as well as the hand grip strength and gait speed with lack of any serious adverse events. Although no significant improvement occurred in BMI and LBM, they were increased or maintained in two-thirds of the patients without any significant change in food consumption. Serum prealbumin levels were found increased at Visit 2, especially in the wound group. An improvement in the upper arm anthropometrics as well as the muscle strength and gait speed might precede the changes in the muscle mass in our cohort. This might be related with the treatment period that was only 8 weeks from baseline to follow-up. Regarding the suggested correlation between the muscle mass and strength in some studies, significant changes in the muscle mass may occur in case of a longer-term use of the HMB/Arg/Gln supplement (38, 39). Lauretani et al. (40) showed a more prominent decrease in muscle strength compared to muscle mass in the elderly, which was also mentioned in the EWGSOP II report (2). On the other hand, the ability to preserve the muscle mass is important, as all of our patients were older and underwent certain treatments for various diseases such as cancer.

In general, the HMB/Arg/Gln supplementation has been considered to be well tolerated by different patient populations (8). Likewise, our findings indicated favorable tolerability and safety profile of the HMB/Arg/Gln supplementation in a cohort of elderly patients with different therapeutic indications.

The first limitation to this study was insufficient data about the serum CRP of the patients to evaluate its relationship with the increase in serum prealbumin levels at Visit 2. Second, we did not give any exercise plans to the patients throughout the study. Various patient groups were included in the study, and it was impossible to maintain a standard physical rehabilitation program in all patients. None of our patients noted resistance exercise training during the study period. The third limitation was the absence of a control population. All of the patients were diagnosed with malnutrition. Although an energy/protein enriched diet or oral nutritional supplement were given to those without sufficient oral intake, most of the patients (78.6%) could not increase their daily food consumption. It would be better to evaluate the effects of HMB/Arg/Gln on the muscle mass and strength, including changes on diet and physical exercise in detail; however, this was an observational study, and it is not easy to maintain a standard diet and physical rehabilitation program to all patients with different diseases and medical problems.

In conclusion, the HMB/Arg/Gln supplementation applied twice a day for 8 weeks seems to improve the MUAC, MUAMC, muscle strength, and gait speed with a favorable tolerability and safety when used for different therapeutic indications among elderly clinical populations. Future larger-scale studies are needed to clarify these promising results with longer-term use.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine (1038/2012).

Informed Consent: Written informed consent was obtained from all individual participants who participated in this study.

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