Original article

A possible role for essential amino acid supplementation in improving functional recovery and reducing the risk for malnutrition in COVID-19 patients

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Abstract. *Background and aim:* In patients with severe forms of coronavirus disease-19 (COVID-19), prolonged hospitalization and immobilization decrease muscle mass and increase the risk of malnutrition. Moreover, catabolic molecules such as interleukins (IL)-1 and -6 and tumor necrosis factor (TNF) contribute to the reduction of body mass, increasing the risk of sarcopenia. Since sarcopenia represents a negative prognostic factor in COVID-19 patients, protein and/or essential aminoacid (EAA) supplementation has been recommended in these patients, to counteract the loss of muscle mass and strength. Aim of this study was to evaluate the effects of a six-month dietary intervention (including a standardized protein intake and a supplementation of free EAAs) on risk of malnutrition, body composition, muscle strength and physical performance in 74 COVID-19 patients after discharge. *Methods:* All subjects received a balanced diet according to ideal BMI, with protein intake of 1.2 -1.5 gr/kg/day. Each participant received a supplementation of EAAs twice a day during the first three months and once daily for the remaining period. Anthropometric measurements, and assessment of muscular strength, body composition and physical performance were performed during three different visits: immediately after the hospital discharge, after three months and at the end of the six- month observation period. *Results:* Significant changes in body mass index (BMI), Malnutrition Universal Screening Tool (MUST) score, arm circumference and triceps fold values were observed, as well as a significant increase in total body water (TBW), and significant improvements in the S and T scores and in the short physical performance battery (SPPB) score. *Conclusions:* these results suggest that in patients recovering from SARS-Cov2 infection, the dietary intake of 1.2-1.5 gr per kg of protein per day associated with EAA supplementation may contribute to BMI improvement and functional recovery, reducing the risk of malnutrition and osteosarcopenia.

Key words: sarcopenia, malnutrition, diet, essential amino acids

Introduction

Because of the global emergency caused by the Coronavirus disease-19 (COVID-19) pandemic, governments have been forced to implement social distancing policies, favoring a sedentary lifestyle associated with a loss of muscle mass (1). It is well known that confinement measures promote a reduction in physical activity and sun exposure time, the development of anxiety and stress, and a worsening of the quality of sleep (2). Moreover, appetite dysregulation causes an increase in food intake, and a preference for ultra-processed foods, with a reduction in protein intake. The resulting reduction in vitamin D, anabolic hormones and protein synthesis, and the concomitant increase of insulin resistance, cortisol secretion, oxidative stress, inflammatory cytokines and muscle protein breakdown, lead to a change in body composition: the loss of lean mass and the accumulation of adipose tissue favor the development of sarcopenic obesity, a condition characterized by increased oxidative stress leading to a further aggravation of muscle loss, causing impaired locomotion and disability, especially in the elderly (2). All these changes also contribute to the development or aggravation of chronic conditions such as diabetes, cardiovascular diseases (CVD), osteoporosis, cognitive impairment, and increase the risk of fragility and disability (2). Moreover, CVD, diabetes, and elevated body fat increase the risk of contracting a severe form of COVID-19 (2-4). COVID-19 can have severe clinical manifestations, such as pneumonia with respiratory failure, sepsis and septic shock, which require urgent hospitalization (5,6). Among the complications, acute respiratory distress syndrome (ARDS) (7) generally occurs approximately one week after the first manifestations and necessitates immediate admission to intensive care units (ICU) for ventilatory support (8). In these patients, weight loss and decreased muscle mass may occur, due to symptoms such as ageusia, anosmia, mucositis, dry mouth, dysphagia and inappetence, which lead to a reduction of food intake and increase the risk of malnutrition (9,10). Furthermore, during the so called "cytokine storm" caused by SARS-CoV-2, an increased production of molecules such as interleukins (IL)-1 and -6 and tumor necrosis factor (TNF) is observed, which further contributes to the reduction of body mass through its catabolic action, increasing the risk of developing sarcopenia (11). Sarcopenia, i.e. muscle weakness, is a muscle disease due to adverse muscle changes that develop over time; sarcopenia is common among adults of older age but can also occur earlier in life, because of endocrine or neurodegenerative diseases, physical inactivity, or inadequate nutrition (9). Sarcopenia is defined by low levels of measures for three parameters: (1) muscle strength, (2) muscle quantity/quality and (3) physical performance as an indicator of severity. To assess evidence for sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP) recommends use of grip strength or a chair stand measure with specific cut-off-points for each test (9,12). To confirm sarcopenia by detection of low muscle quantity and quality, Dual Energy X-ray Absorptiometry (DXA) is advised in clinical practice, and DXA, bioelectrical impedance analysis (BIA), computed tomography (CT), or magnetic resonance imaging (MRI) in research studies (9,12). Sarcopenia requires a timely and appropriate nutritional intervention, specifically in patients with COVID-19 (13). In fact, sarcopenia may sustain a vicious circle in these patients, contributing to worsened respiratory and cardiac function, chronic inflammation and insulin resistance (10,11,13), associated with prolonged hospitalization, worse outcomes and compromised well-being of survivors. As sarcopenia represents a negative prognostic factor for the recovery of COVID-19 patients, a preventive nutritional intervention based on caloric/protein supplementation (12) may be useful to avoid malnutrition of these patients during their hospital stay, as well as after discharge. Based on the evidence that deficiency of just one essential amino acid (EAA) is enough to slow down and stop the protein synthetic process (14,15), various expert consensus protocols and guidelines on the optimal clinical approach to malnutrition in the acute phase of SARS-CoV2 infection and during recovery were issued during the COVID-19 pandemic. Many of these guidelines suggested an adequate screening for malnutrition using the Malnutrition Universal Screening Tool (MUST) and encouraged the use of oral supplementation in subjects at risk of being unable to meet nutritional requirements (5,16). However, most of these recommendations left the decision of the type of oral supplementation to the clinician, producing various interventions. Moreover, the difficulty encountered by physicians performing a correct screening for the risk of malnutrition in hospitalized patients during the COVID-19 pandemic because of the emergency complicated their nutritional follow-up, leading to a paucity of published data on the baseline and post-interventional nutritional status of COVID-19 patients. A nutritional approach based on the supplementation with a mixture of EAAs has proven effective in correcting reduced dietary intake and increased degradation of endogenous proteins, showing positive effects on fat free mass (FFM), muscular strength, exercise endurance and physical performance in various conditions associated with impaired nutritional and metabolic state, such as chronic heart failure and chronic obstructive pulmonary disease (17-21), hemodialysis (22), HIV (23), cancer cachexia (24), sarcopenia (25) and Type 2 diabetes (26). On the other hand, consumption of increased dietary protein and/or EAAs are recognized as the two most potent and safest anabolic stimuli to counteract the loss of muscle mass and strength in sarcopenia (27). Given the forced physical inactivity associated with SARS-CoV2 infection and consequent isolation, the most practical and effective means of slowing the loss of muscle mass and function is by optimal nutrition, including adequate intake of free dietary EAAs. An appropriate composition of dietary EAAs has been shown to induce an increase in net protein synthesis compared with an isocaloric protein intake, improving physical performance in older adults (27). Optimal EAA intake leads to greater stimulation of muscle protein synthesis through increased availability of plasma EAAs, which translates in increased muscle mass and function as well as improved muscle quality (force production for a given muscle mass). EAAs can serve as a promising nutraceutical to attenuate the accelerated progression of sarcopenia in the COVID-19 era (27). Aim of this study was to assess the risk of malnutrition in a group of hospitalized COVID-19 patients and to evaluate the effects of a six-month dietary intervention (including a standardized protein intake and a supplementation of free EAAs) on body composition, muscle strength and physical performance.

Materials and Methods

Study design

Patients hospitalized for SARS-CoV2 at the ASST-Bergamo Est hospital were enrolled in our study from November 2020 to November 2021. Smoking status, alcohol abuse and chronic diseases (diabetes, hypertension, heart disease chronic obstructive pulmonary disease), as well as weight before infection were recorded for each patient, and the malnutrition risk was assessed using the MUST scale. Anthropometric measurements, and assessment of muscular strength, body composition and physical performance were performed by the physicians involved in the study during three different visits: the first after the hospital discharge, the second after three months and the third after further three months, i.e. at the end of the observation period (lasting a total of six months). All subjects received a balanced diet according to ideal BMI, with protein intake of 1.2-1.5 gr/kg/day, developed by the dieticians involved in the study. A meal plan was also provided. Each participant received a supplementation of EAAs twice a day (for a total of 8 gr/die) during the first three months and once daily (for a total of 4 gr/die) for the remaining period. Supplementation was carried out using a blend of EAAs in free form, 62.5% of which were branched-chain AAs, according to existing literature (15,28,29). The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Board of Bergamo on May 25, 2020 (Protocol n. 120/20).

Anthropometric measurements

Weight was measured to the nearest 0.01 kg using a calibrate balance. Height was measured to the nearest centimetre using a stadiometer at head level. BMI was calculated as weight in kilograms divided by height in meter squared. The circumference of the non-dominant arm was also measured.

Measurement of physical performance

Physical performance was measured by the short physical performance battery (SPPB), a standardized test for the evaluation of physical performance in the elderly (30). The battery consists of a balance test for the evaluation of the balance ability, a chair stand test for the evaluation of coordination and strength, and a gait speed test. The scores for the balance, chair stand and gait speed tests are summed, giving an overall score ranging from a minimum of 0 to a maximum of 12.

Assessment of body composition

Body composition was evaluated using two different methods: i) measuring skinfold thickness triceps, with the Holtain skinfold caliber; ii) through bioimpedance analysis, to estimate fat mass (FM), fat free mass (FFM), total body water (TBW), intracellular water (ICW), extracellular water (ECW), height adjusted skeletal muscle (hSMI) weight adjusted skeletal muscle (wSMI), intramuscular fat (IMAT), adipose tissue (AT), abdominal adipose tissue (AAT), HPA index, S and T score (standard deviation from normal population for muscle mass and bone density). These measures were performed using BIA-ACC Bio-Tekna.

Measurement of muscle strength

Hand grip strength measured by a manual dynamometer (Camry electronic hand dynamometer) was used as an indicator of muscle strength. Three consecutive measurements of the maximum grip pressure were performed for each hand and the mean value of the test was used for statistical analysis.

Statistical analysis

Measured parameters are reported by descriptive statistics (mean, standard deviation) A generalized linear model for repeated measures was applied (GLM repeated measurements) for the inferential comparison of clinical parameters at different times (t1 vs t2 vs t3). This model represents a flexible generalization of linear regression. The SPSS package (IBM Corp, IBM SPSS statistics for Windows, Version 21.0 Armonk, NY: IBM Corp) was used for statistical analysis. The level of statistical significance was set at 5% (a = 0.05). All statistical tests were two-tailed.

Results

A total of 74 patients (26 females, 48 males) were enrolled in the study, with a (mean +/-SD) BMI of 28.37 +/- 5.522 (range 18 to 50.7) The basal characteristics of enrolled patients regarding smoking habit, alcohol consumption and comorbidities are reported in Table 1.

Weight of enrolled patients during the SARS-COV2 infection and during the observation period are reported in Table 2: a consistent weight loss (8.70%) was recorded during hospitalization, whereas a weight gain (2.24%) was recorded in the six months after discharge.

Table 1. Basal characteristics of enrolled patients.

	n	Percentage
Smoking Status		
Former tobacco smoker	7	9.5
Never Tobacco smoker	64	86.5
Current tobacco smoker	3	4.1
Alcohol Consumption		
No	51	68.9
Yes	23	4.1
Diabetes mellitus		
No	55	74.3
Yes	19	25.7
Hypertension		
No	34	45.9
Yes	40	54.1
Cardiac diseases		
No	59	79.7
Yes	3415	20.3
COPD		
No	67	90.5
Yes	7	9.5

Abbreviations: COPD, chronic obstructive pulmonary disease.

Table 2. Recorded body weight before, during and after hospitalization for COVID-19.

Time point	Mean (Kg)	Standard deviation
Hospitalization	81.58	19.69
Discharge	74.48	18.05
Visit 1	79.02	17.44
Visit 2	80.46	18.60
Visit 3	80.79	18.41

The values of MUST, BMI, arm circumference, and triceps fold recorded during each visit are shown in Figure 1. Applying a generalized linear model for repeated measures, significant changes in BMI, MUST, arm circumference and triceps fold values were observed.

The results of the bioimpedance analysis are reported in Table 3: a statistically significant increase in TBW, and significant improvements in the S and T score were recorded.

The results of physical performance and muscle strength assessments are reported in Table 4: a statistically significant improvement in the SPPB score was observed, whereas no changes were recorded for the handgrip test.

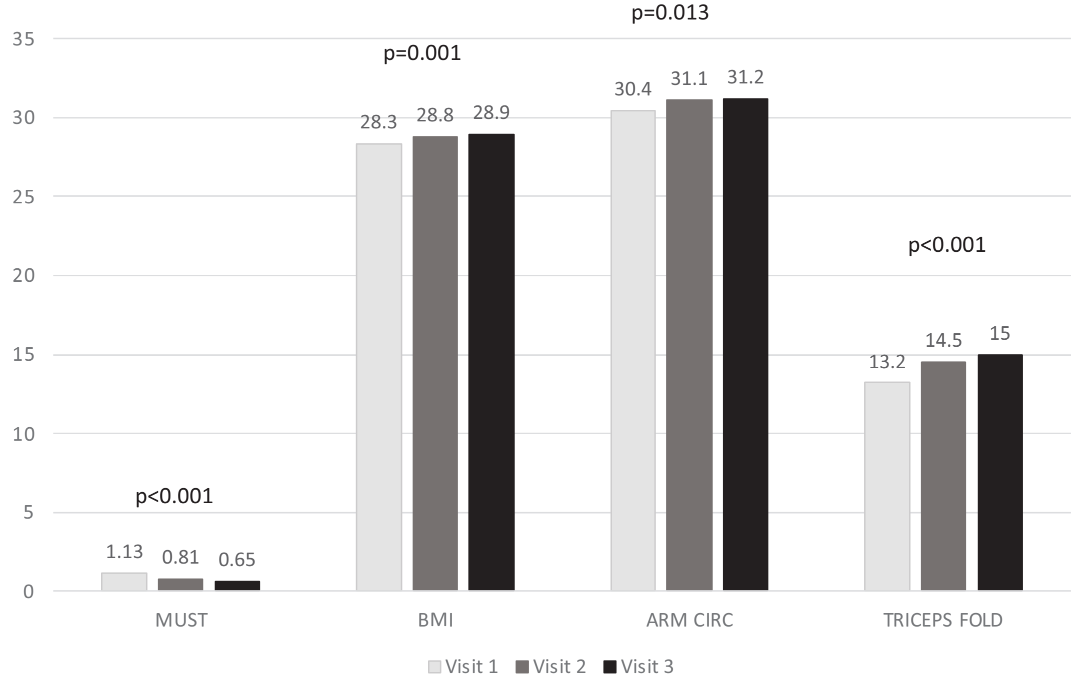

Figure 1. Changes in BMI (Kg/m^2), MUST (n), arm circumference (cm) and triceps fold (mm) values recorded during the observation period. (BMI, body mass index; MUST, Malnutrition Universal Screening Tool)

Table 3. Changes [mean (SD)] in BIA parameters recorded during the observation period.

Parameter	Visit 1	Visit 2	Visit 3	p
TBW	42.9 (6.18)	44.4 (7.17)	46.3 (11.81)	**0.044**
FFM	62.6 (7.11)	63.6 (7.75)	64.2 (8.55)	0.145
FM	37.4 (7.11)	36.4 (7.75)	35.8 (8.55)	0.145
SM	17.4 (7.13)	18.5 (7.70)	19.3 (9.38)	0.062
hSMI	6.1 (2.14)	6.5 (2.28)	7.1 (3.78)	0.054
IMAT	2.1 (0.64)	2.1 (0.67)	2.1 (0.64)	0.883
wSMI	21.3 (6.08)	22.7 (6.26)	23.0 (7.9)	0.150
AT	37.5 (13.42)	37.1 (14.23)	37.2 (13.50)	0.846
AAT	506.2 (195.39)	500.3 (209.39)	500.2 (200.32)	0.844
S score	-0.55 (2.02)	-0.12 (2.10)	0.42 (3.23)	**0.031**
T score	-0.85 (1.20)	-0.63 (1.27)	-0.45 (1.61)	**0.035**
ECW	47 (6.74)	46.6 (6.91)	45.9 (7.44)	0.242
ICW	53 (6.74)	53.4 (691)	54.1 (7.44)	0.242
HPA Index	2.6 (2.18)	3.2 (2.49)	3.0 (2.72)	0.459

Abbreviations: AT, adipose tissue; AAT, abdominal adipose tissue; ECW, extracellular water; FFM, fat free mass; FM, fat mass; hSMI, height adjusted skeletal muscle; ICW, intracellular water; IMAT, intramuscular fat; SM, skeletal muscle; TBW, total body water; wSMI, weight adjusted skeletal muscle.

Discussion

Nutritional status and diet modulate inflammation and immune function and may be adjusted to impact COVID-19 outcome (31). Malnutrition has been documented in up to 53% of patients with COVID-19, probably because of the catabolic state induced by the inflammatory response to SARS-CoV-2

Table 4. Changes in physical performance and muscle strength parameters recorded during the observation period.

Parameter	Visit 1	Visit 2	Visit 3	p
Hand grip right (Kg)	31.3	31.3	31.5	0.933
Hand grip left (Kg)	30.7	29.9	30.4	0.610
SPPB score	9.35	10.53	11.10	<0.001

Abbreviations: SPPB, short physical performance battery.

infection, leading to the utilization of albumin and even muscle protein to synthesize the acute-phase proteins. Moreover, digestive tract malfunction can exacerbate the poor nutritional status in older patients with COVID-19, increasing the risk of sarcopenia (31). Considering these observations, the main result of our study was a significant reduction of the risk of malnutrition, as assessed by MUST, recorded after six months of diet therapy and EAA supplementation in patients discharged after hospitalization for COVID-19. This result was further supported by the concomitant increase of BMI, reflecting a weight gain mainly due to the increase of FFM and TBW, as documented by BIA analysis, and associated to a significant increase of the triceps fold and of the circumference of the arm. Although muscle mass, muscle strength and physical performance at enrolment were not indicative of sarcopenia, the statistically significant improvement in the S score during the observation period is suggestive of a reduction in the risk of developing this condition. This is an important achievement, since many studies have described that sarcopenia is a predictor of the risk of pneumonia in the elderly, and it is associated with mechanical ventilation, hospitalization time, and mortality in ICU patients (31). The concomitant increase of the T score similarly indicates a reduced risk of bone loss and osteoporosis, probably associated with an improved nutrition status.

Although the prevention of sarcopenia in COVID patients generally requires an aggressive approach based on specific nutritional support protocols and physical activity programs (32), the critical situation of the COVID-19 pandemic did not allow to prescribe personalized preventive exercise protocols. Many studies have shown that physical exercise increases muscle size and strength in older individuals (33,34): in our study, despite the lack of a specific motor rehabilitation program, a nutritional intervention based on EAA supplementation was able to improve muscle performance after COVID-19, as documented by the statistically significant increase of the SPPB score observed after six months. Unexpectedly, such increase was recorded in the absence of any change of the handgrip strength, which is a well-known indicator of muscle performance (9): although lower limbs are more relevant than upper limbs for gait and physical function, hand grip strength has been widely used and is well correlated with most relevant outcomes (9). The short period of observation may explain the discrepancy observed between the results of the handgrip test and the SPPB score in the present study. The results of our study confirm the importance of appropriate nutritional assessment and treatment during COVID-19 hospitalization and after discharge, to reduce complications and improve clinical outcomes (5). According to the practical guidance for nutritional management of individuals with SARS-CoV-2 infection, recently published by the European Society for Clinical Nutrition and Metabolism (ESPEN), malnutrition is to be avoided during COVID-19 hospitalization and recovery, because of its negative impact on patients' survival, especially in the presence of older age and comorbidity (5). The recommended approach includes the use of the MUST scale to screen for malnutrition, and the optimization of the nutritional status through diet counselling from an experienced professional, with personalized calculation of energy needs (from 27 to 30 kcal per kg body weight and day, according to age, weight and comorbidities), protein requirements (1 or >1 gr protein per Kg body weight and day, according to age and comorbidities) and fat and carbohydrate ratio (from 30:70 in subjects with no respiratory deficiency to 50:50 in ventilated patients). Part of the general nutritional approach for the prevention of viral infections is supplementation and/or adequate provision of vitamins to potentially reduce disease negative impact (5). The dietary intervention proposed to patients enrolled in the present study was in line with ESPEN recommendations and proved to be effective in favouring recovery and functional improvement. The association of EAA supplementation with a high protein diet may have contributed to further support protein synthesis and overcome the catabolic state typically associated with SARS-COV-2 infection, leading to increased muscle mass and function, as previously suggested (22).

Study Limitations

The main limitations of the study are the small sample size and the short follow-up period: the observed results need therefore to be confirmed by further studies evaluating a larger number of patients for a longer period. In addition, inflammatory markers, such as IL-1 or -6, were not measured, so it was not possible to explore possible correlations between inflammation and the nutritional status. Furthermore, we did not consider in the analysis pre-existing risk factors, such as lifestyle, eating habits and physical activity levels, that may have influenced the nutritional status and clinical outcomes of enrolled patients. No details on the physical activity during the observational period was recorded, so a possible effect of exercise on the observed changes in body mass and physical performance cannot be excluded. Finally, in the absence of a control group no definitive conclusions can be drawn on the actual role of EAA supplementation as a part of the proposed dietary intervention in the observed recovery after SARS-CoV2 infection.

Conclusions

The results of our study suggest that in patients hospitalized for SARS-Cov2 infection, the dietary intake of 1.2-1.5 gr per kg of protein per day associated with EAA supplementation may have contributed to BMI improvement and functional recovery, reducing the risk of malnutrition and osteosarcopenia.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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References

1. Breen L, Stokes KA, Churchward-Venne TA, et al. Two weeks of reduced activity decreases leg lean mass and induces “anabolic resistance” of myofibrillar protein synthesis in healthy elderly. J Clin Endocrinol Metab. 2013 Jun;98(6): 2604-12. doi: 10.1210/jc.2013-1502.
2. Kirwan R, McCullough D, Butler T, Perez de Heredia F, Davies IG, Stewart C. Sarcopenia during COVID-19 lockdown restrictions: long-term health effects of short-term muscle loss. Geroscience. 2020 Dec;42(6):1547-1578. doi: 10.1007/s11357-020-00272-3.
3. Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine. 2020 Apr;68(1):2-5. doi: 10.1007/s12020-020-02294-5.
4. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 2020 Dec;21(4):495-507. doi: 10.1007/s11154-020-09569-2. Erratum in: Rev Endocr Metab Disord. 2021 Mar;22(1):145.
5. Barazzoni R, Bischoff SC, Breda J, et al; endorsed by the ESPEN Council. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020 Jun;39(6): 1631-1638. doi: 10.1016/j.clnu.2020.03.022.
6. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA. 2020 Apr 28;323(16):1545-1546. doi: 10.1001/jama.2020.4031.
7. Dushianthan A, Grocott MP, Postle AD, Cusack R. Acute respiratory distress syndrome and acute lung injury. Postgrad Med J. 2011 Sep;87(1031):612-22. doi: 10.1136/pgmj.2011.118398.
8. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). 2023 Aug 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010 Jul;39(4):412-23. doi: 10.1093/ageing/afq034.

10. Damanti S, Cilla M, Tuscano B, et al. Evaluation of Muscle Mass and Stiffness with Limb Ultra-sound in COVID-19 Survivors. Front Endocrinol (Lausanne). 2022 Feb 17;13: 801133. doi: 10.3389/fendo.2022.801133.
11. Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent Inflammation, Immunosuppression and Catabolism Syndrome. Crit Care Clin. 2017 Apr;33(2):245-258. doi: 10.1016/j.ccc.2016.12.001.
12. Cruz-Jentoft AJ, Bahat G, Bauer J, et al.; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019 Jul 1;48(4):601. doi: 10.1093/ageing/afz046. Erratum for: Age Ageing. 2019 Jan 1;48(1):16-31.
13. Narici M, Vito G, Franchi M, et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: Physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. Eur J Sport Sci. 2021 Apr;21(4):614-635. doi: 10.1080/17461391.2020.1761076.
14. Munro HN. Second Boyd Orr Memorial Lecture. Regulation of body protein metabolism in relation to diet. Proc Nutr Soc. 1976 Dec;35(3):297-308. doi: 10.1079/pns19760050. PMID: 800653.
15. Wischmeyer PE. Clinical applications of L-glutamine: past, present, and future. Nutr Clin Pract. 2003 Oct;18(5): 377-85. doi: 10.1177/0115426503018005377.
16. Cawood AL, Walters ER, Smith TR, Sipaul RH, Stratton RJ. A Review of Nutrition Support Guidelines for Individuals with or Recovering from COVID-19 in the Community. Nutrients. 2020 Oct 22;12(11):3230. doi: 10.3390/nu12113230.
17. Aquilani R, Opasich C, Gualco A, et al. Adequate energy-protein intake is not enough to improve nutritional and metabolic status in muscle-depleted patients with chronic heart failure. Eur J Heart Fail. 2008 Nov;10(11):1127-35. doi: 10.1016/j.ejheart.2008.09.002.
18. Aquilani R, D'Antona G, Baiardi P, et al. Essential amino acids and exercise tolerance in elderly muscle-depleted subjects with chronic diseases: a rehabilitation without rehabilitation? Biomed Res Int. 2014;2014:341603. doi: 10.1155/2014/341603.
19. Macchi A, Franzoni I, Buzzetti F, et al. The role of nutritional supplementation with essential amino acids in patients with chronic heart failure. Mediterr J Nutr Metab 2010. doi: 10.1007/s12349-010-0010-2.
20. Baldi S, Aquilani R, Pinna GD, Poggi P, De Martini A, Bruschi C. Fat-free mass change after nutritional rehabilitation in weight losing COPD: role of insulin, C-reactive protein and tissue hypoxia. Int J Chron Obstruct Pulmon Dis. 2010 Feb 18;5:29-39. doi: 10.2147/copd.s7739.
21. Dal Negro RW, Aquilani R, Bertacco S, Boschi F, Micheletto C, Tognella S. Comprehensive effects of supplemented essential amino acids in patients with severe COPD and sarcopenia. Monaldi Arch Chest Dis. 2010 Mar;73(1):25-33. doi: 10.4081/monaldi.2010.310.
22. Sukkar SG, Gallo F, Borrini C, et al. Effects of a new mixture of essential amino acids (Aminotrofic(®)) in malnourished haemodialysis patients. Med J Nutrition Metab. 2012 Dec;5(3):259-266. doi: 10.1007/s12349-012-0098-7.
23. Manfrin P, Vecchio C, Minisci D, Muzio F. Effects of an amino acid formula administered orally to malnourished HIV-positive patients: short-term results. Nutr Ther Met. 2013; 31: 40-44.
24. Madeddu C, Macciò A, Astara G, et al. Open phase II study on efficacy and safety of an oral amino acid functional cluster supplementation in cancer cachexia. Mediterr J Nutr Metab 2010. 3: 165-172.
25. Solerte SB, Gazzaruso C, Bonacasa R, et al. Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. Am J Cardiol. 2008 Jun 2;101(11A): 69E-77E. doi: 10.1016/j.amjcard.2008.03.004.
26. Solerte SB, Fioravanti M, Locatelli E, et al. Improvement of blood glucose control and insulin sensitivity during a long-term (60 weeks) randomized study with amino acid dietary supplements in elderly subjects with type 2 diabetes mellitus. Am J Cardiol. 2008 Jun 2;101(11A):82E-88E. doi: 10.1016/j.amjcard.2008.03.006.
27. Park S, Chang Y, Wolfe RR, Kim IY. Prevention of Loss of Muscle Mass and Function in Older Adults during COVID-19 Lock-down: Potential Role of Dietary Essential Amino Acids. Int J Environ Res Public Health. 2022 Jul 1;19(13):8090. doi: 10.3390/ijerph19138090.
28. Brosnan JT. Interorgan amino acid transport and its regulation. J Nutr. 2003 Jun;133(6 Suppl 1):2068S-2072S. doi: 10.1093/jn/133.6.2068S.
29. Kadowaki M, Kanazawa T. Amino acids as regulators of proteolysis. J Nutr. 2003 Jun;133(6 Suppl 1):2052S-2056S. doi: 10.1093/jn/133.6.2052S.
30. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995 Mar 2;332(9):556-61. doi: 10.1056/NEJM199503023320902.
31. Silverio R, Gonçalves DC, Andrade MF, Seelaender M. Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link? Adv Nutr. 2021 Jun 1;12(3): 682-692. doi: 10.1093/advances/nmaa125.
32. Wang PY, Li Y, Wang Q. Sarcopenia: An underlying treatment target during the COVID-19 pandemic. Nutrition. 2021 Apr;84:111104. doi: 10.1016/j.nut.2020.111104. Epub 2020 Dec 5.

33. Martín Del Campo Cervantes J, Habacuc Macías Cervantes M, Monroy Torres R. Effect of a Resistance Training Program on Sarcopenia and Functionality of the Older Adults Living in a Nursing Home. J Nutr Health Aging. 2019;23(9):829-836. doi: 10.1007/s12603-019-1261-3.
34. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol (1985). 1988 Mar;64(3):1038-44. doi: 10.1152/jappl.1988.64.3.1038.

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