Journal of
Food and Nutrition

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Research Article Open Access

Impacts of Oral Nutritional Supplement with EAAS, HMB and Vitamin D Among Patients Recovered from COVID-19: A Pilot Study

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Received Date: November 23, 2020 **Accepted Date:** December 21, 2020 **Published Date:** December 23, 2020

Citation: Martone Anna Maria, Savera Giulia, Landi Francesco (2020) Impacts of Oral Nutritional Supplement with EAAS, HMB and Vitamin D Among Patients Recovered from COVID-19: A Pilot Study. J Food Nutr 6: 1-7.

Abstract

Nutrition is one of the major determinants of health; malnutrition is both a cause and a consequence of immune dysfunction. The intense inflammation triggered by COVID-19 disease leads to malnutrition and consequent negative outcomes both in acute and post-acute phases. The aim of this study was to evaluate the impact of a specific oral nutritional supplement containing essential ammino acids, HMB and vitamin D among patients recovered from COVID19 but still suffering from fatigue.

Twenty patients recovered from SARS-COV-2 infection still suffering from fatigue afferent to a multidisciplinary health care service called "Day Hospital post COVID-19" had received a 6-week treatment with an oral nutritional supplement. Body composition was measured by segmental BIA. At the end of treatment, nutritional parameters serum levels, skeletal muscle mass, handgrip strength and quality of life increased statistically significant.

Nutritional support seems to be effective in meeting the nutritional needs of post COVID19 patients and in improving not only the nutritional parameters but also the physical performance.

Keywords: COVID-19; Personalized Medicine; Essential amino acids HMB; Vitamin D

Introduction

Nutrition is one of the most important determinants of health. In COVID-19, nutritional status is an important factor across all disease stages, from acute to chronic phase [1], especially in subject at higher risk for negative outcomes, such as older adults and those with multimorbidity. It is extensively acknowledged that malnutrition is both a cause and a consequence of immune dysfunction. In addition, in COVID-19 patients, low levels of circulating markers of nutritional status (e.g., albumin, pre-albumin, lymphocyte counts) are associated with worse outcomes [2].

Prolonged in-hospital stay, especially in intensive care unit, is a well-established risk factor for malnutrition, and leads to significant decline in muscle mass and strength and overall physical performance.

It is clearly described that the intense inflammation related to SARS-COV-2 infection may aggravate catabolic processes and anorexia (loss of appetite and consequent less food intake). These phenomena may worsen malnutrition and at the same time they are correlated with longest recovery, impaired physical performance, and reduced quality of life after hospital stay [3].

Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) has proposed a guide for the nutritional management of patients suffering from SARS-CoV-2 infection [4]. According to these recommendations, nutritional screening, assessment and therapy should be considered as an integral part of the continuum of care for COVID-19 patients.

According to the ESPEN guidelines, we implemented a specific comprehensive nutritional assessment in our multidisciplinary post-acute care service [5]. In particular, body composition modifications (assessed by bioelectrical impedance analysis), muscle strength changes, as well as nutritional biomarkers were recorded, and specific nutritional recommendations were provided to support the recovery of post-acute COVID-19 patients. In particular, the aim of the present study was to evaluate the impact of a specific oral nutritional supplement (containing essential amino acids, beta-hydroxy-beta-methylbutyrate and vitamin D) among patients recovered from COVID-19 but still suffering from fatigue.

Methods

The Gemelli Against COVID-19 Post-Acute Care (GAC19-PAC) project is an initiative developed by the Department of Geriatrics, Neuroscience and Orthopedics of the Catholic University of the Sacred Heart (Rome, Italy) aiming to meet the needs of COVID-19 survivals. In this respect, the Fondazione Policlinico Universitario A. Gemelli IRCSS has set up a multidisciplinary health care service called "Day Hospital Post-COVID-19" for all the patients recovered from SARS-CoV-2 infection. The entire GAC19-PAC study protocol has been described in detail elsewhere [5].

Ethical approval and manuscript preparation

The Catholic University/Fondazione Policlinico Gemelli IRCCS Institutional Ethics Committee has approved the GAC19-PAC study protocol [5]. Written informed consent has been obtained from the participants. The manuscript was prepared in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines for observational studies.

Study Sample

Only the COVID-19 patients who met the WHO criteria for discontinuation of quarantine have been admitted to the follow-up study project [6]. This outpatient service opened April 21st 2020 and it is currently on going. For the present study, we analyzed data from 20 subjects (13 females and 7 males) suffering from fatigue and who had received a prescription for a specific oral nutritional supplement. Prescribing the nutritional supplement was part of normal clinical routine.

Data collection

All subjects who accepted to be screened underwent individual assessment. Demographic information, medical and medication history, laboratory findings, and radiological features were collected. A multidisciplinary approach, including nutritional evaluation, has been put in place for a comprehensive assessment of all the possible damages caused by the SARS-CoV-2 virus. In particular, during the first visit, information and data about the persistence of signs and symptoms COVID-19 related such as fatigue, cough, diarrhea, headache, smell disorders, dysgeusia, red eyes, joint pain, short of breath, loss of appetite, sore throat, and rhinitis were specifically focused and collected.

Body weight was measured through an analogue medical scale. Body height was measured using a standard stadiometer. Body mass index (BMI) was defined as weight (kilograms) divided by the square of height (meters).

The body composition, in particular the skeletal muscle mass, was measured by bioelectrical impedance analysis (BIA). Bioelectrical impedance analysis resistance (ohms, W) was ob-

tained using the in-Body equipment [7]. Segmental bioelectrical impedance analysis views the human body as five cylinders: left arm, right arm, torso, left leg, and right leg. InBody measures each cylinder independently to provide measurements for the entire body and accurate body composition results.

Intervention – Oral nutritional supplement

Twenty patients received 6-week treatment with an oral nutritional supplement based on three essential amino acids (leucine, isoleucine, valine), beta-hydroxy-beta-methylbutyrate (HMB) and vitamin D (Hydroxiram D – ErreKappa Euroterapici, Milano). The composition of each serving is described in Table 1. Patients were advised to take two portions a day away from meals.

Table 1: Characteristics of oral nutritional supplement Hydroxiram D (ErreKappa-Euroterapici, Milano)

Nutritional characteristics	Amount per portion (5.5 grams)
Calories (kcal)	18
Lipids (g)	0
Carbohydrates (g)	2.1
Fiber (g)	1.0
Protein (g)	1.7
L-Leucine (mg)	1250
L-Isoleucine (mg)	625
L-Valine (mg)	625
HMB (mg) *	750
Vitamin D (mcg)	20
Zinc (mg)	5.0

* HMB: beta-hydroxy-beta-methylbutyrate

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD), categorical variables as frequencies by absolute value and percentage (%) of the total. Descriptive statistics were used to describe demographic and key clinical characteristics of the study population according to the gender. The differences in proportions and the means of covariates were assessed using Fisher's Exact Test and t test statistics, respectively.

All analyses were performed in October 2020 using SPSS software (version 11.0, SPSS Inc., Chicago, IL).

Results

Mean age of the participants was 63.5 years (standard deviation 14.6, range from 23 to 81 years), and 13 (65%) were men. Characteristics of the study population according to the gender are summarized in Table 2. Overall, males showed more severe COVID-19 disease than females, considering that in the acute phase of COVID-19 they had a higher percentage of oxygen therapy (100% versus 54%, p=0.04), and non-invasive (71% versus 8%, p<0.01) and invasive ventilation (42% versus 0%, p=0.03). However, the length of hospital stay was similar between males and females. About two months after the onset of the disease, in addition to the fatigue, other symptoms were present without significant differences. Dyspnoea was the most frequent symptom (85%), followed by joint pain (30%), dysgeusia (25%) and sore throat (25%). Conversely, quality of life, measured by the EuroQol visual analog scale, was worse among women than men (63.0 ± 16.2 versus 77.4 ± 11.1, respectively, p=0.05).

Table 2: Characteristics of study population according to gender *

Characteristics	Total Sample (n=20)	Men (n=7)	Women (n=13)	p
Age (years)	63.5 ± 14.6	73.7 ± 6.5	57.3 ± 14.9	0.01
Acute COVID-19 characteristics				
Pneumonia diagnosed	15 (75)	7 (100)	8 (62)	0.08
Intensive care unit admission	5 (25)	4 (57)	1 (8)	0.03
Oxygen therapy	14 (70)	7 (100)	7 (54)	0.04
Noninvasive ventilation	6 (30)	5 (71)	1 (8)	< 0.01
Invasive ventilation	3 (15)	3 (42)	0 (0)	0.03
Length of hospital stay	13.5 ± 9.7	13.4 ± 9.1	13.6 ± 9.8	0.46
Post acute COVID-19 follow-up				
Days since symptom onset	64.3 ± 12.3	60.8 ± 12.7	66.2 ± 12.2	0.36
Days since hospital discharge	36.1 ± 12.9	37.8 ± 11.7	36.0 ± 10.2	0.54
Persistent symptoms				
Dyspnea	17 (85)	5 (71)	12 (92)	0.27
Joint pain	6 (30)	1 (14)	5 (38)	0.04
Dysgeusia	5 (25)	1 (14)	4 (31)	0.14

Sore Throat	5 (25)	1 (14)	4 (31)	0.14
Anosmia	4 (20)	1 (14)	3 (23)	0.56
Rhinitis	2 (10)	1 (14)	1 (8)	0.58
BMI (Kg/m²)	22.1 ± 3.8	23.4 ± 2.2	21.3 ± 4.3	0.25
Hang grip strength (Kg)	24.0 ± 6.0	29.5 ± 4.5	21.0 ± 4.4	<0.001
Skeletal mass index (Kg/m²)	7.25 ± 1.00	8.35 ± 0.69	6.65 ± 0.52	<0.001
Albumin (g/dl)	4.11 ± 0.32	3.80 ± 0.25	4.25 ± 0.25	0.38
Vitamin D (ng/dl)	23.9 ± 9.2	20.9 ± 5.5	25.2 ± 10.3	0.39
Quality of life (EuroQol scale)	68.0 ± 15.9	77.4 ± 11.1	63.0 ± 16.2	0.05

* Data are given as number (percent) for persistent symptoms and acute COVID-19 characteristics; for all the other variables, means ±SD are reported.
BMI: Body mass index; BP: blood pressure
Quality of life was assessed using EuroQol visual analog scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health)

None of the participants reported difficulty in taking the oral nutritional supplement regarding size, taste, and palatability. The mean treatment was about 6 weeks; treatment compliance was good and no adverse events were reported. Figures 1-6 show the differences between baseline and follow-up values for nutritional and functional outcomes. After a mean of 6 weeks BMI significantly improved among male subjects but not among female participants (Figure 1). Albumin (Figure 2) and serum vitamin D (Figure 3) improved statistically significant both in male and female subjects. Similarly, skeletal muscle mass (Figure 4) and handgrip strength (Figure 5) improved statistically significant at the end of nutritional treatment. Finally, the quality of life (Figure 6) had improved in both males and females, too.

Figure 1

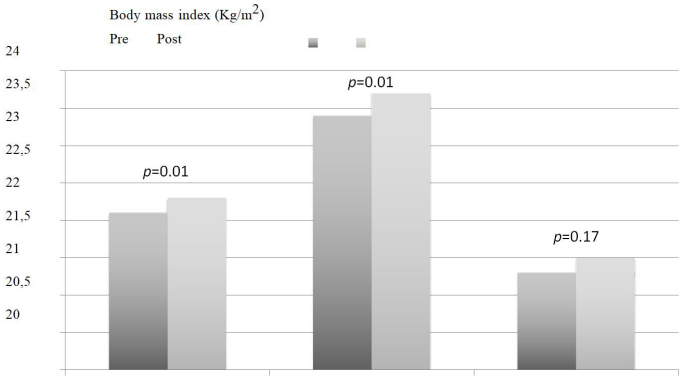


Figure 2

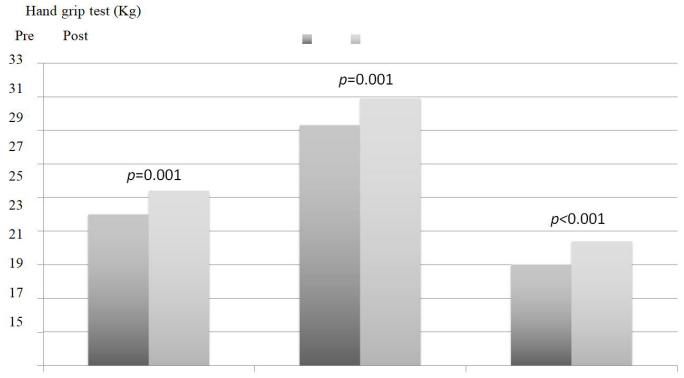


Figure 3

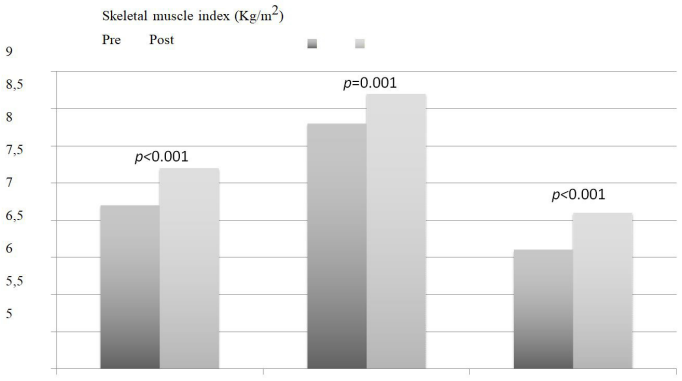


Figure 4

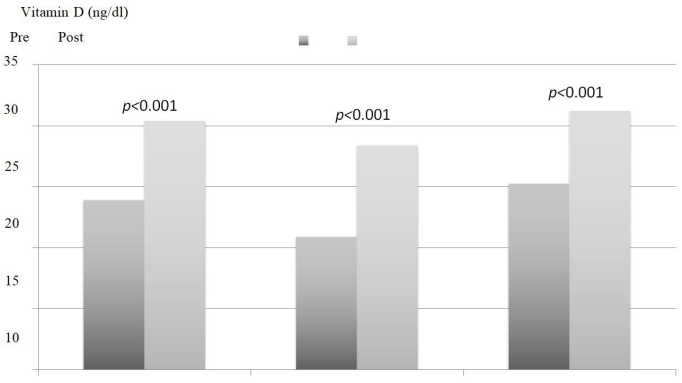


Figure 5

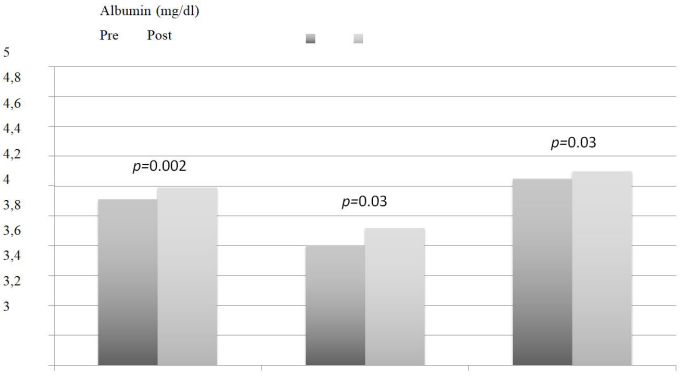
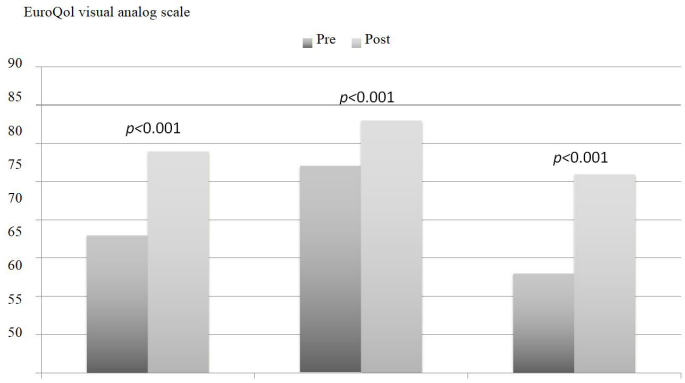


Figure 6



Discussion

Expert consensuses recommend accurate and timely nutritional assessment and interventions to improve clinical outcomes in people at risk of malnutrition, including persons with chronic/severe diseases [8,9]. The present study confirms the importance of nutritional support in patients suffering from a catabolic disease such as COVID-19. A nutritional supplement based on essential amino acids (leucine, isoleucine, valine), beta-hydroxy-beta-methylbutyrate (HMB) and vitamin D supported the improvement of nutritional parameters and physical performance among subjects recovered from COVID-19 but still suffering from persistent symptoms, such as fatigue. Furthermore, particularly in female participants, nutritional support contributed to better quality of life.

Persistent fatigue could be originated by a sort of "acute sarcopenia"- acute muscle mass and strength loss – which in turn recognizes selective malnutrition a key etiological factor [1].

Patients with combined COVID-19 and malnutrition usually presented elevated inflammatory response, which may represent the biological substrate of malnutrition itself observed in these patients [10]. In addition, the altered nutritional status may be related to the presence of some characteristic symptoms of COVID-19, such as gastrointestinal disorders, diarrhoea, altered taste and smell, loss of appetite. Malnutrition is significantly associated with poor outcome of COVID-19, while the prognosis of patients with normal nutrition status is better. Therefore, nutritional status of the patients with COVID-19 should be carefully evaluated [11].

Even in COVID-19 pandemic era every patient should have access to nutritional care as a part of healthcare services. In this respect, it is important to recommend practical protocols for nutritional assessment and prescription of nutritional supplements that should be available for all health care professionals and, in particular, primary care physicians. Furthermore, specific protocols for assessment and nutritional care for COVID-19 outpatients and those in the recovery phase of the disease are needed. It has been clearly demonstrated that even two months after the onset of the disease, more than 50% of patients continue to have fatigue and about 15-20% still have smell disturbances, altered taste and loss of appetite [1,12].

Calculation of energy, protein, micronutrient and oral nutritional supplement needs should be performed taking into consideration all the specific requirements of the older persons and/or polymorbid patients. Nutritional therapy should be tailored according to the patient's needs; they could be met by food and oral supplements. For most patients, energy needs are between 25 and 35 kcal per kilogram of body weight per day, and at least 1 grams of protein per kilogram of body weight per day should be warranted. For obese patients or those with sarcopenic obesity, ideal body weight should be used to calculate requirements.

The nutritional supplement (mainly based on leucine, isoleucine, valine, beta-hydroxy-beta- methylbutyrate and vitamin D) administered to patients in this pilot study, seems to be effective in meeting the nutritional needs of post COVID-19 patients and in improving not only the nutritional parameters, but also the physical performance.

However, some important limitations of the study need to be highlighted. First, in view of the small number of patients treated, the study should be considered as a pilot study. Second, this is an observational study and therefore the results obtained cannot be directly correlated to the nutritional treatment. It is possible that the improvement in physical performance is merely related to the longer time since the onset of the disease. However, these improvements may at the same time be related to the higher serum albumin and vitamin D levels.

Despite these limitations, it is important to highlight that combined nutritional intervention comprising controlled diet, nutritional supplementation containing HMB and vitamin D can induce weight gain, decrease functional limitations, and reduce the incidence of clinical complications, which could have important cost implications [13]. Furthermore, essential amino acids are important for the proliferation and differentiation of innate and acquired immune cells. Essential amino acids supplementation was associated with reduced inflammation in both inflamed and infected patients. In addition, such supplementation has been demonstrated to be associated with increased circulating lymphocytes in inflamed patients [14]. Finally, vitamin D deficiency has been reported in several chronic conditions to be associated with

increased inflammation and deregulation of the immune system. These observations, together with experimental studies, suggest a critical role for vitamin D in the modulation of immune function [15]. In this respect, the hypothesis that the nutritional supplement based on leucine, isoleucine, valine, HMB and vitamin D may have had a positive effect on nutritional status and functional recovery is supported by a robust biological plausibility [16,17].

Further studies, possibly controlled clinical trials, are needed to confirm these results.

However, the evaluation of nutritional status and the prescription of adequate nutritional support is mandatory in patients in the acute phase of COVID-19 and even in the post-acute phase.

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