



# Benefits of L-Arginine Oral Supplementation in Long Covid Symptoms: Results of a Monocentric Longitudinal Study

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## Abstract

**Background:** Covid syndrome is a complex disease that in some cases can determine symptoms for a long period. This kind of presentation is note today like long Covid syndrome. The causes of long Covid syndrome are unclear, and its treatment is unknown.

**Methods and Results:** Between January 2021 and May 2021, 10 patients (5 Males, 5 Females, mean age  $47.2 \pm 2.3$  years), affected by persistent symptoms of acute COVID-19, were enrolled in a short-term observational follow-up. All patients included were healthy subjects with no risk factors, who after SARS-COV-2 infection, treated at home without hospitalization, reported fatigue in the total absence of fever or other acute symptoms. The molecular swab has been negative for more than 30 days.

A graduated maximum exertion test with respiratory gas analysis and a constant workload endurance test corresponding to 85% of the VO<sub>2</sub> peak at baseline and after 1 month were performed. All had a left ventricular ejection fraction (LVEF) > 60% and a structural normal heart. Treatment with L-Arginine 20 mL of an 8.3% oral solution (1.66 gr) twice a day was initiated in all patients.

**Keywords:** Long COVID; Post-acute COVID-19 syndrome; Endothelial dysfunction; Arginine; SARS-CoV-2

## Introduction

Almost 2 years after the onset of the pandemic, evidence is accumulating that testifies that the natural history of SARS-CoV-2 infection does not end only with the death or recovery of the patient. In fact, many survivors report the persistence of various symptoms for an extended time. The most common and described symptoms are: asthenia, dyspnea, chest pain, joint pain, palpitations, anosmia and dyspepsia, hair loss, impaired cognitive performance (memory and attention deficit) and psychological disorders (anxiety, depression and sleep disorders). A study conducted in China on 1733 patients discharged from a Wuhan hospital, one of the largest available case series, showed that 6 months after the recovery from the infection over 60% of the subjects analyzed had persistent symptoms of fatigue or muscle weakness [1]. Difficulty in sleeping (26%), anxiety or depression (23%) were very common. Other symptoms included lack of

smell or taste, palpitations, joint pain, dizziness, diarrhoea, vomiting and chest pain. This variety of symptoms is called "post-acute COVID-19 syndrome" or "long COVID" [2-5]. More and more studies suggest that endothelial dysfunction may underlie the systemic symptoms of SARS-CoV-2 infection [6-9]. In fact, the vascular endothelium is a key target of the new coronavirus. A recently published study shows how the viral protein S (Spike glycoprotein), through the binding with the ACE 2 receptor, is able to determine a mitochondrial dysfunction, an alteration of the endothelial synthesis of nitric oxide with an antioxidant and protective action for the endothelium and an increase in glycolysis [10]. The same mechanisms could also be at the basis of the long COVID [11-13]. However, no clinical studies have yet shown the usefulness of therapeutic interventions aimed at improving endothelial function. Our experience in a homogeneous and consecutive group of patients with persistent

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post-COVID symptoms treated with oral L-Arginine supplementation was encouraging.

## Methods

Between January 2021 and May 2021, 10 patients (5 M, 5 F, mean age  $47.2 \pm 2.3$  years), suffering from persistent symptoms after acute COVID-19, were enrolled in a short-term observational follow-up. All patients included were healthy subjects with no risk factors, who after SARS-COV-2 infection, treated at home without hospitalization, reported fatigue in the total absence of fever or other acute symptoms. The molecular swab has been negative for more than 30 days, and the acute disease was declared finished. The mean time of the acute disease was  $45 \pm 2.3$  days. A graduated maximum exertion test with respiratory gas analysis and a constant workload endurance test corresponding to 85% of the VO<sub>2</sub> peak at baseline and after 1 month were performed. All had a left ventricular ejection fraction (LVEF) > 60% and a structural normal heart. Treatment with L-Arginine 20 mL (Bioarginina® Farmaceutici Damor SpA) of an 8,3% oral solution (1,66 gr) twice day was initiated in all patients. At the end of the follow-up the performance improvement was evaluated.

## Statistical Analysis

All statistical analyses were performed using SPSS statistical software. Correlation analysis and linear regression were

performed to analyse the relationships between the study variables. The mediation hypotheses were tested according to Baron and Kenny's approach. The total, direct, and indirect effects of comorbidities number on PCS through mMRC were evaluated. The test is statistically significant (at 0.05) if both confident limits have the same sign. This indicates that the null hypothesis of a null indirect effect has to be rejected. A bootstrapping procedure was used (with 5000 bootstrap samples) to estimate the 95% confidence interval for the indirect (mediated) effect.

Finally, to estimate effect size for indirect effects,  $k^2$  was performed. According to Cohen we considered small, medium, and large effect sizes as .01, .09, and .25.

## Results

Exercise capacity increased from  $15.8 \pm 2.1$  to  $31.2 \pm 3.5$  min ( $P < 0.0001$ ) and peak oxygen consumption tended to improve from  $14.6 \pm 1.1$  to  $18, 8 \pm 2.2$  ml / kg per minute ( $P < 0.0001$ ). Oxygen consumption at the anaerobic threshold (AT) increased from  $12.7 \pm 1.4$  to  $16.6 \pm 1.3$  ml / kg per minute ( $P < 0.0001$ ). The positive effects of L-arginine were also associated with an improvement in NYHA functional class and quality of life, and an improvement in the six-minute walk test, which improved from  $135 \pm 16$  meters to  $201 \pm 5$  meters. ( $P < 0.0001$ ) At the end of the follow-up, the L-arginine was discontinued. All resulted are indicated (Table 1).

**Table 1:** Exercise capacity, Peak oxygen consumption, NYHA functional class and Six minute walking test evaluated in patients treated with L-arginine.

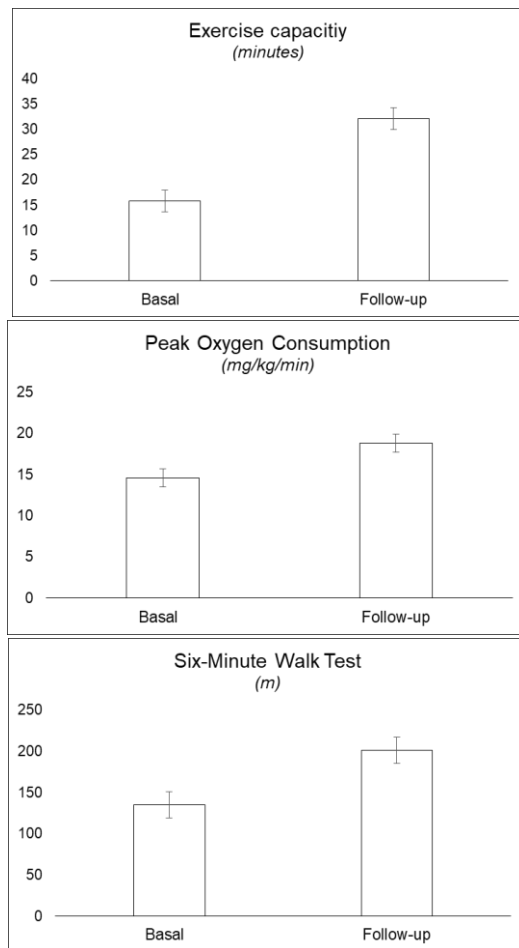
Table 1	Basal	Follow-up	P-value
Exercise capacity	$15.8 \pm 2.1$ min	$31.2 \pm 3.5$ min	<0.0001
Peak oxygen consumption	$14.6 \pm 1.1$ ml/kg/min	$18, 8 \pm 2.2$ ml/kg/min	<0.0001
NYHA functional class	II	I	<0,01
Six-minute walk test	$135 \pm 16$ m	$201 \pm 5$ m	<0,01

## Discussion

Patients with Sars Cov - 2 infection, even after negative swab, may experience persistent symptoms such as fatigue, weakness and pulmonary impairment, which can last for months after recovery from the acute phase. In patients recovered from severe forms, a slow recovery is to be expected. For example, in patients who have been admitted to the intensive care unit (ICU) the symptoms of "post-ICU syndrome" cannot be considered exclusive to COVID-19. However, even non-hospitalized individuals with mild or moderate forms of the disease may experience post-COVID-19 symptoms, sometimes with disabling characteristics and inability to resume a normal life [5]. The pathophysiological mechanisms underlying these manifestations are not clear yet. Persistent endothelial dysfunction, which plays

an important role in the acute phase, could also be at the basis of post-COVID-19 syndrome or long COVID [11-13]. We know, in fact, that the SARS-CoV-2 virus can directly damage vascular endothelial cells, causing systemic endothelial dysfunction. Furthermore, inflammatory cytokines are able to bind specific receptors on the surface of endothelial cells, promoting the activation of platelets, the adhesion of circulating leukocytes and altering the production of nitric oxide [14]. Residual activation of the immune system after the acute phase could be related to persistent endothelial dysfunction during convalescence [11]. Despite the prevalence of persistent symptoms in patients recovered from SARS-COV-2 infection, there are still no specific therapies approved for this condition. We have planned to treat a small group of patients suffering from persistent post-COVID-19 symptoms with a natural amino acid that plays an important role

in the regulation of endothelial function. L-arginine, in fact, is a semi-essential amino acid, substrate of nitric oxide synthase (NOS), an enzyme responsible for the production of nitric oxide, which regulates endothelial homeostasis and vascular tone [15,16]. Some recent studies suggest that amino acid metabolism may play an important role in the pathophysiology of COVID-19; a reduction in plasma levels of L-arginine associated with increased arginase activity has been observed in patients with severe COVID-19 [17-19]. Our data show that oral supplementation of L-Arginine gave an improvement in fatigue and exercise tolerance in all treated patients, in a short time and without any side effects. It is also a natural therapy characterized by low cost, easy availability and the absence of contraindications.



## Conclusions

More and more studies suggest that endothelial dysfunction may underlie the systemic manifestations of COVID, both in the acute and post-acute phases. However, despite a large number of people cured of COVID exhibiting long-term symptoms, so far no clinical studies have demonstrated the usefulness of treatments that aim to regulate endothelial function. Our results suggest that oral L-arginine supplementation could improve the quality of life

of patients with long COVID symptoms. In our opinion, endothelial dysfunction should become one of the priority targets of future COVID therapies in both the acute and post-acute phases. We hope that our research will encourage scientific debate in this direction.

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