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The Role of Acetyl-Carnitine and Rehabilitation in the Management of Patients with Post-COVID Syndrome: Case-Control Study

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Abstract: Post-COVID syndrome is characterized by the persistence of nonspecific disabling symptoms, even several months after the resolution of the infection, with clinical characteristics similar to fibromyalgia (FM) and a prevalence of 31%. We evaluated the effectiveness of physical exercise, in association with L-acetyl-carnitine (ALC) therapy, in patients with Post-COVID syndrome, on musculoskeletal pain, dyspnea, functional capacity, quality of life, and depression. We conducted an observational case-control study on patients with Post-COVID syndrome. The patients were randomly divided into two groups: a treatment group that received rehabilitation treatment in combination with ALC 500 mg therapy; a control group that received only rehabilitation treatment. Patients were assessed at the time of recruitment (T0) and one month after the end of therapy (T1), with the administration of rating scales: NRS, Barthel Dyspnea Index (NPI), 12-Item Short Form Survey (SF-12) scale, Fibromyalgia Impact Questionnaire (FIQ), and Patient Health Questionnaire (PHQ-9). The treatment group showed statistically higher variations in pain scores, quality of life, and depression. No statistically significant differences between the two groups emerged regarding changes in dyspnea and functional capacity scores. Combining exercise with ALC is a promising and effective treatment in the management of Post-COVID syndrome, especially for musculoskeletal pain, depression, and quality of life.

Keywords: post-COVID syndrome; chronic pain; acetylcarnitine; rehabilitation



Citation: Scaturro, D.; Vitagliani, F.; Di Bella, V.E.; Falco, V.; Tomasello, S.; Lauricella, L.; Letizia Mauro, G. The Role of Acetyl-Carnitine and Rehabilitation in the Management of Patients with Post-COVID Syndrome: Case-Control Study. *Appl. Sci.* **2022**, *12*, 4084. <https://doi.org/10.3390/app12084084>

Academic Editor: Zimi Sawacha

Received: 17 March 2022

Accepted: 16 April 2022

Published: 18 April 2022

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1. Introduction

The coronavirus pandemic (COVID-19) has affected people around the world and strict lockdown measures have been imposed in order to counter the viral spread, resulting in increased anxiety, depression and suicidal thoughts [1].

The respiratory syndrome caused by Coronavirus SARS-CoV-2 tends to recover completely, in most cases, in two to six weeks with molecular swab test negativization. In about 10–35% of people, however, recovery can continue with a long convalescence, referred to as post-COVID syndrome. The latter is characterized by the persistence of non-specific disabling symptoms, even for several months after infection resolution, with considerable variability among individuals [2].

Nonspecific symptoms occur in about 50–80% of patients recovered from symptomatic COVID-19 infection [3–5]. Ursini et al. [6] observed that after an average of 60 days from the onset of the first COVID-19 symptom, only 12.6% of patients fully recovered; while the

remaining 87.4% had persistent symptoms and 44% reported a worsening quality of life. This “long-term carrier” population is referred to as Long-Haulers. The exact etiological mechanism is not yet fully known, but it is believed that virus-induced immunological imbalances may be at the base [7]. The most common disorders and clinical signs reported by these patients are: muscle pain, fatigue, difficulty concentrating and air hunger. Moreover, in consideration of the numerous organs and systems involved, it can also induce pulmonary, cardiovascular, hematological, renal, gastrointestinal, dermatological, endocrine and neuropsychiatric sequelae [8].

Most of the following, however, can be considered post-traumatic stress disorders: mood and sleep disorders, headache, asthenia, paraesthesia and diffuse musculoskeletal pain [9].

The resolution of this syndrome represents a real challenge for doctors of different specializations and for health systems since, in the near future, it could turn into a very high expense [10].

Studies have shown that clinical features of FM are common after symptomatic COVID-19 infection with an estimated prevalence of about 31% [6], very similar prevalence is detected with other post-COVID chronic pain disorders [11,12].

Approximately 30.7% of COVID-19 recovered patients meet the American College of Rheumatology criteria for FM, especially if obese and male [6,13].

FM is a complex disease characterized by a wide range of symptoms, notably chronic widespread pain, fatigue and sleep disturbances [14]. The pathogenesis of FM has not yet been fully understood. There is an increase and a disperception of pain associated with neuromorphological alterations and dysregulation between pro-nociceptive and anti-nociceptive pathways. A genetic predisposition has been recognized and its appearance has been associated with stressful life events, psychological characteristics and small fiber neuropathies or neuroinflammation. In addition, the role of some infectious agents, particularly of viral origin, have been hypothesized as being among the triggering factors [15].

The use of ALC has recently been proposed in the treatment of symptoms of fibromyalgia. ALC is an endogenous molecule with an important role in energy metabolism, and, thanks to its antioxidant and brain neurotransmitter modulation properties, it has neurotrophic and analgesic activities, even in the long term, on inflammatory and chronic neuropathic pain [16].

In relation to the clinical correlation between post-COVID syndrome and FM, the present observational case-control study aims to evaluate the effectiveness of physical exercise in association with ALC therapy, in patients with post-COVID syndrome, in terms of improvement of musculoskeletal pain, dyspnea, functional capacity, quality of life and depressive symptoms.

2. Materials and Methods

2.1. Ethical Approval

The study was conducted by the ethical guidelines of the Declaration of Helsinki. The local ethics committee, “Palermo 1”, approved the study, with the reference number 11/2021. The information and data were managed according to the guidelines of Good Clinical Practice (GCP). All participants signed an informed consent form at the time of enrollment to collect clinical data.

2.2. Participants

At the Rehabilitation Unit of the “P. Giaccone” University Hospital in Palermo we conducted a case-control observational study on 60 patients who came to our clinics complaining of symptoms attributable to post-COVID syndrome.

Inclusion criteria were: age \geq 18 years; previous SARS-CoV2 infection with negative swab test for at least one month; presence of at least one FM-like symptom at least 60 days after healing, such as: fatigue, dyspnea, joint and chest pain, difficulty concentrating, sleep disturbance, exercise intolerance, headache, nausea, and cognitive disorders; written informed consent for study participation.

Exclusion criteria were: altered states of consciousness; known FM diagnosis; neoplastic pathologies; neurological, cardiopulmonary, musculoskeletal and gastrointestinal disorders; other autoimmune diseases; lack of consent for study participation.

2.3. Intervention

The recruited patients were randomly divided into two groups using a computer-generated table of numbers: a treatment group comprising 33 patients, who received ALC 500 mg therapy in combination with a rehabilitation protocol including physical exercise and respiratory physio-kinesiotherapy; a control group comprising 27 patients, who underwent the same rehabilitation protocol without drug therapy. Pharmacological therapy was proposed with the following dosage schedule: ALC 500 mg/4 mL vials, 1 intramuscular vial in the morning and 1 intramuscular vial in the evening for 10 days, followed by taking 1 ALC 500 mg tablet per os in the morning and one in the evening for a further 40 days.

The rehabilitation sessions were held three times a week with a duration of 60 min. Each session consisted of 20 min of aerobic exercises, 20 min of postural gymnastics and 20 min of respiratory re-education. Each session was performed under the supervision of a physiotherapist experienced in respiratory physiotherapy.

Aerobic exercises promote the loss of body weight and help reduce the work of the antigravity muscles, with a muscle relaxant and analgesic effect. The aerobic exercises consisted of three parts: joint mobilization, stretching performed at 70–80% of the maximum heart rate and proprioceptive exercises, and neuromuscular coordination exercises [17].

Respiratory physio-kinesiotherapy lasted 20 min and included: (1) respiratory muscle training exercises; (2) coughing exercises; (3) diaphragmatic training exercises; (4) stretching exercises. For respiratory muscle training, participants used a PEP device set to 60% of maximum expiratory pressure. Patients then performed active coughing exercises. This was followed by diaphragmatic training, with maximum voluntary contractions in the supine position, placing an average weight of 1 kg on the anterior abdominal wall. Finally, the session ended with chest muscle stretching exercises assisted by the physiotherapist [18].

2.4. Clinical Evaluation

Clinical evaluations of patients were performed at the time of recruitment (T0) and 1 month after the end of the proposed therapy (T1). During the clinical evaluations, the presence and frequency of FM-like symptoms was assessed. The following rating scales were also administered: NRS [19], to assess the extent of pain; Barthel Dyspnea Index [20], for the evaluation of dyspnea; SF-12 [21], to evaluate quality of life; FIQ [22], to assess the disability degree in relation to the clinical picture; and PHQ-9 [23], for the evaluation of depression status.

Primary endpoints analyzed were: perceived musculoskeletal pain and degree of dyspnea. Secondary endpoints analyzed were: quality of life, disability degree and depression status.

The NRS scale is a quantitative rating scale by which patients are asked to rate their pain on a defined scale, from 0 to 10 [19].

The NPI evaluates dyspnea in relation to 10 ADLs such as: grooming, bathing, feeding, toilet use, stair use, dressing, bowel movement, bladder discharge, mobility, wheelchair use and transfers (from bed to chair and back). The overall score ranges from 0 (no dyspnea) to 100 (maximum level of dyspnea) [20].

The SF-12 scale is the abbreviated version of the Short Form 36 items Health Survey (SF36) questionnaire and serves as a generic indicator of the quality of life. It consists of 12 questions that investigate 8 different health aspects: physical activity, role limitations due to physical health, emotional state, physical pain, perception of general health, vitality, social activities, and mental health. The lower the score, the greater the degree of disability [21].

The FIQ consists of 10 questions. The first question contains 11 items relating to the ability in the last week to carry out activities of daily life, with a variable score between 0 (always) and 3 (never). The second and third questions ask the number of days in the last week that the patient felt well and was unable to carry out their work (including housework) due to symptoms of FM. Questions from 4 to 10 are horizontal linear scales on which the patient evaluates the difficulty of work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The maximum score of the FIQ is 100; for in-patients with FM, the average values are around 50, while only patients with severe clinical pictures have results above 70 [22].

The PHQ-9 is a nine-item questionnaire designed for depression screening. Each element of the questionnaire is evaluated on a 4-point scale, ranging from 0 (not at all) to 3 (almost every day), with a total score from 0 to 27 with scores ≥ 10 . Higher scores indicated greater symptom severity and a greater probability of major depressive disorder [23].

2.5. Statistic Analysis

All analyzes were performed using R software (R Core Team, 2013).

The sample size was calculated with the formula below:

$$n = \frac{z_{\frac{\alpha}{2}}^2 \sigma^2}{\varepsilon^2} = \frac{z_{\frac{\alpha}{2}}^2 \pi(1 - \pi)}{\varepsilon^2}$$

The type I error is equal to 0.05 (the quantile in the formula is equal to 1.96). The denominator $\varepsilon = 0.13$ is the maximum error acceptable to the researcher, and the choice of ε is arbitrary. Finally, we use the worst-case scenario of the proportion equal to 0.5. The formula gave a result equal to 56.83. Consequently, the number of 60 patients considered was sufficient to prove our thesis.

For the statistical test, we used three different tests: the *t*-test to compare averages for quantitative variables and Mood's median test to compare medians for ordinal variables. Results were considered statistically significant with a *p* value < 0.05 .

3. Result

102 patients with Post-COVID syndrome were evaluated in this study. Of these, 32 did not provide written informed consent to participate in the study, 6 already had a known diagnosis of fibromyalgia and 4 had a history of cancer disease. Only 60 patients were recruited for study participation (Figure 1).

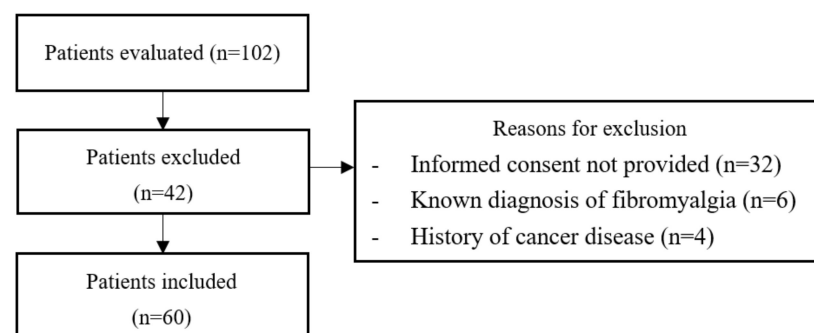


Figure 1. Patients Included.

3.1. General and Clinical Characteristics of Patients

The population under examination had a mean age of 58.7 ± 5.4 years, 43.3% was male and the remaining 56.7% was female. Their mean BMI was 28.2 ± 3.2 Kg/m². 70% had a job, while 30% were unemployed. 65% of the recruited patients had undergone oxygen therapy, while 63.3% had been hospitalized during the SARS-CoV2 infection. No statistically significant difference was found between the two groups at baseline (Table 1).

The symptoms the patients most complained about included: fatigue, dyspnea, joint and/or muscle pain (47%), exercise intolerance (22%), headache (14%), difficulty concentrating (7%) and insomnia (10%).

Table 1. General characteristics at baseline.

Characteristics	Total (n = 60)	Treatment Group (n = 33)	Control Group (n = 27)	p-Value
Age, mean \pm SD	58.7 \pm 5.4	61.3 \pm 4.8	59.8 \pm 4.5	0.22
Gender, n (%)				
Male	26 (43.3)	15 (45.4)	11 (40.7)	0.67
Female	34 (56.7)	18 (54.6)	16 (59.3)	
BMI, mean \pm SD (Kg/m ²)	28.8 \pm 3.2	28.4 \pm 2.9	27.9 \pm 3.3	0.62
Occupation, n (%)				
Working	42 (70)	24 (72.7)	18 (66.6)	0.34
Unemployed	18 (30)	9 (27.3)	9 (33.4)	
Oxygen therapy n (%)				
Yes	39 (65)	22 (66.7)	17 (59.3)	0.48
No	21 (35)	11 (33.3)	10 (40.7)	

3.2. Effects of Combining Functional Rehabilitation with ALC Supplementation in Treatment Group

At T1 treatment group we observed statistically significant improvements in NRS (7.18 \pm 0.9 vs. 4.9 \pm 0.75; $p < 0.05$), FIQ (50.66 \pm 10.6 vs. 41.96 \pm 8.7; $p < 0.05$) SF-12 (26.18 \pm 2.8 vs. 30.45 \pm 2.5; $p < 0.05$) and PHQ-9 (13.03 \pm 3.5 vs. 10.84 \pm 3.1; $p < 0.05$) scale scores. No statistically significant improvement was observed for NPI scores (83.3 \pm 6.5 vs. 85.30 \pm 6.02; $p = 0.21$) (Table 2).

Table 2. Effects of combining functional rehabilitation with ALC supplementation in treatment group at T1.

Characteristics	T0	T1	p-Value
NRS	7.18 \pm 0.9	4.9 \pm 0.75	<0.05
NPI	83.33 \pm 6.47	85.30 \pm 6.02	0.21
FIQ	50.66 \pm 10.63	41.96 \pm 8.68	<0.05
SF-12	26.18 \pm 2.88	30.45 \pm 2.49	<0.05
PHQ-9	13.03 \pm 3.51	9.84 \pm 3.02	<0.05

3.3. Effects of Functional Rehabilitation Alone in Control Group

At T1 in the control group we observed statistically significant improvements in FIQ (49.55 \pm 6.44 vs. 43.03 \pm 5.86; $p < 0.05$) and SF-12 (25.07 \pm 3.2 vs. 27.29 \pm 3.2; $p < 0.05$) scale scores. No statistically significant improvement, in contrast, was found in NRS (7.22 \pm 0.8 vs. 6.8 \pm 0.9; $p = 0.08$), NPI (83.88 \pm 5.1 vs. 86.11 \pm 4.9; $p = 0.10$) and PHQ-9 (13.74 \pm 3.08 vs. 12.34 \pm 2.89; $p = 0.09$) scale scores (Table 3).

Table 3. Effects of functional rehabilitation alone in control group at T1.

Characteristics	T0	T1	p-Value
NRS	7.22 \pm 0.87	6.8 \pm 0.92	0.08
NPI	83.88 \pm 5.15	86.11 \pm 4.96	0.10
FIQ	49.55 \pm 6.44	43.03 \pm 5.86	<0.05
SF-12	25.07 \pm 3.19	27.29 \pm 3.16	<0.05
PHQ-9	13.74 \pm 3.08	12.34 \pm 2.89	0.09

3.4. Comparison between the Results of the Two Groups

Finally, Table 4 shows the comparison between the variations in the scores of the different evaluation scales used between the two groups. Compared to the control group, the treatment group showed statistically higher variations in NRS (2.28 ± 0.63 vs. 0.42 ± 0.63 ; $p < 0.05$), SF-12 (4.27 ± 1.91 vs. 2.22 ± 2.53 ; $p < 0.05$) and PHQ-9 (3.19 ± 2.04 vs. 1.4 ± 1.33 ; $p < 0.05$) scale scores. No statistically significant difference between the two groups emerged when comparing the variation in NPI (1.97 ± 3.8 vs. 2.23 ± 3.9 ; $p = 0.79$) and FIQ (8.7 ± 5.72 vs. 6.52 ± 2.68 ; $p = 0.07$) scale scores.

Table 4. Comparison of the variations in the score of the evaluation scale between the two groups.

Characteristics	$\Delta T1-T0$	$\Delta T2-T0$	<i>p</i> -Value
NRS	2.28 ± 0.63	0.42 ± 0.63	<0.05
NPI	1.97 ± 3.88	2.23 ± 3.92	0.79
FIQ	8.7 ± 5.72	6.52 ± 2.68	0.07
SF-12	4.27 ± 1.91	2.22 ± 2.53	<0.05
PHQ-9	3.19 ± 2.04	1.4 ± 1.33	<0.05

4. Discussion

Recently, considerable interest has been given to important and frequent sequela after SARS-CoV-2 infection, represented by a chronic post-infectious syndrome, called Long-COVID syndrome, which can occur in hospitalized and non-hospitalized patients [24].

Post-COVID syndrome presents with non-specific symptoms, most commonly characterized by diffuse musculoskeletal pain, fatigue, headache, dyspnea, anosmia, and memory impairment, which are FM-like disorders [6,24]. This syndrome occurs more frequently in patients with a more severe form of COVID-19, including a higher hospitalization rate and more repeated supplemental oxygen treatment [6,24].

SARS-CoV-2 virus is highly immunogenic, which is why it can induce a significant post-viral musculoskeletal syndrome [13,24] underlying which could be endothelial or neuromuscular lesions, immunological imbalance and inflammation. Regarding the latter, it is interesting to note that some of the pro-inflammatory cytokines involved in COVID-19 and PACS manifestations, such as interleukin (IL) -1 and IL-6,2 39, may contribute to the FM pathogenesis [6].

The therapeutic management of patients with post-COVID syndrome remains rather controversial, as to date no pharmacological treatment has been shown to improve or mitigate post-COVID syndrome symptoms [10]. Data in the literature suggest that rehabilitation may play an important role in the treatment of post-COVID syndrome by performing low-intensity aerobic exercises with gradual increase in difficulty, according to the patient's tolerance, as well as breathing exercises aimed at improving respiratory muscle efficiency, especially of the diaphragm [25]. Some studies have shown that a personalized multidisciplinary rehabilitation approach, involving breathing, musculoskeletal system and psychological interventions, is able to improve symptoms such as pain, fatigue, endurance and anxiety, but not depression [26–28].

In light of the well-known similarities between post-COVID syndrome and FM, during our investigation we evaluated the effectiveness of physical exercise associated with LAC in patients with post-COVID syndrome in terms of improvement of musculoskeletal pain, dyspnea, functional capacity, quality of life and depressive symptoms.

Our study was the first to evaluate drug therapy with ALC in the management of patients with post-COVID syndrome. We have observed that physical exercise alone is shown to improve functional capacity and quality of life. However, if it is combined with ALC therapy, an improvement in musculoskeletal pain and depression is also achieved. Finally, by comparing the variations of the different outcomes examined, we observed how physical exercise, associated with ALC supplementation, also leads to improvements in quality of life.

ALC also acts on the muscle level and the effectiveness of oral ALC supplementation in humans has been evaluated. A study evaluated its effectiveness in improving glucose tolerance in insulin-resistant individuals. The authors used a dosage of 2000 mg of acetyl-carnitine per os per day, observing an increase in the levels of acetylcarnitine in the resting muscle and an increase in its formation during physical activity, with consequent beneficial effects on metabolic flexibility [29].

Recent studies have shown the potential role of carnitine as a therapeutic option for COVID-19, in consideration of its antioxidant, immunomodulatory, and cellular energy production functions [30]. One of the serious effects of SARS-CoV-2 infections is cytokine storms that are responsible for hospitalizations, ICU concentrations, and mortality in COVID-19 patients [31]. ALC could be a potential therapeutic option to protect against damage caused by COVID-19, as it could help prevent the cytokine storm that typically occurs in these patients. Elevated LAC levels appear to be associated with decreased susceptibility and severity of COVID-19. However, its role in post-COVID syndrome is unclear [30].

Our results agree with data in the literature on the efficacy of ALC in FM symptoms. Rossini et al. [31], in a randomized trial, evaluated the efficacy of ALC in FM patients compared to placebo, observing a decrease in total myalgic score and in the number of positive tender points higher in the ALC group after the tenth week of treatment. Furthermore, the ALC group showed a statistically significant improvement in musculoskeletal pain, depression and quality of life. Another study [32] observed significant improvements in mood/depressive state, disease severity, physical well-being and quality of life in both patients receiving Duloxetine 60 mg/day and those receiving ALC 1500 mg/day. However, no significant reduction in pain and anxiety levels were found.

The most relevant data highlighted in our study is the effectiveness of ALC, in association with exercise, in improving the depressive state of patients with post-COVID syndrome. Depression and anxiety are particularly relevant problems in these patients. Neuroplasticity impairments [33] and alterations in fatty acid and lipid metabolism appear to be involved in the pathophysiology of depression [33]. ALC is an endogenous molecule with important neurotrophic and neuroprotective properties, as well as having an antidepressant action. ALC in fact modulates the neurotrophic levels at the level of the spinal cord, hippocampus and prefrontal cortex, stimulating neurogenesis. It also regulates the activities of neurotransmitters, such as serotonin and dopamine [34], and improves brain energy metabolism [35].

However, our study is not without limitations. Among these, the small sample size and the lack of long-term follow-up are the main ones, resulting from the short duration of the study, which does not allow generalizing the results provided, but is justified by the historical period of the pandemic.

5. Conclusions

The proper management of post-COVID syndrome is still unclear today, given a lack of knowledge about it. We believe that the combination of physical exercise with ALC intake is a promising and effective treatment in the management of post-COVID syndrome, especially for the management of musculoskeletal pain and depression, as well as for improving quality of life.

Author Contributions: Conceptualization, D.S.; methodology, F.V.; software, V.E.D.B.; validation, D.S. and G.L.M.; formal analysis, V.F.; investigation, F.V.; resources, S.T.; data curation, L.L.; writing—original draft preparation, F.V.; writing—review and editing, V.F.; visualization, D.S.; supervision, G.L.M.; project administration, D.S.; funding acquisition, G.L.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Local Ethics Committee “Palermo 1” (protocol code 11/2021 on 15 December 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflict of interest.

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