

REVIEWS

Supplements in Covid-19 patients with chronic symptoms. Is it worth it or not ?

Călina Ciubotariu², Rodica Ana Ungur^{1,2}, Mihai Emil Russu², Paul Cătălin Toboltoc³,
Ileana Monica Borda^{1,2}, Laszlo Irsay^{1,2}, Viorela Ciortea¹, Ioan Onac^{1,2}, Monica Carmen Pop^{1,4}

¹ “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

² Clinical Rehabilitation Hospital Cluj-Napoca, Romania

³ County Clinical Emergency Hospital of Sibiu, Romania

⁴ Clinical Hospital of Pulmonology “Leon Daniello” Cluj-Napoca, Romania

Abstract

The COVID-19 pandemic has taken the medical world by surprise at the beginning of 2020, but, along the way we started to learn much more about this virus. Besides the discovery of a vaccine and better prevention techniques we have found over the course of time that many patients remain symptomatic after the infection.

Among these complaints we can mention fatigue, breathlessness, chest pains, memory and concentration deficits, brain fog, sleep disorders, palpitations, dizziness, joint pains, anxiety, depression, gut problems, taste and smell perturbations and skin rashes.

Concurrently, as long as there is no direct curative treatment for COVID-19, the sales of medical supplements have risen considerably with many people buying these without knowing whether or not they help. We aim to analyze these popular supplements that the general population is using and those used in similar illnesses to see if they manage to have proven results in dealing with the chronic symptoms after SARS-CoV-2 infection. Among these substances we can mention vitamin C, D, quercetin, arginine or turmeric and curcumin.

Keywords: Covid-19, post-Covid 19 syndrome, vitamins, suppliments.

Introduction

Recently, the normal course of modern society has been suddenly changed as a new virus that causes severe pneumonia has emerged at the end of 2019 in the city of Wuhan from the Chinese province of Hubei. After only a few months the outbreak of COVID-19 was declared a pandemic by the WHO and the social and emotional essence of society has drastically changed. To date, there are over 110 million confirmed cases and more than 2.4 million deaths caused by this virus (Chakraborty & Maity, 2020; ***, 2020).

The introduction of vaccines against COVID-19 has brought hope that the pandemic will soon end in the near future, but, in order to achieve this more people need to get immunized to diminish the destructive capabilities of the virus, as the vaccine has proven to be effective in preventing infection. (Polack et al., 2020).

In order to achieve herd immunity we should have at least 50-60% of the population immunized against the infection by getting vaccinated or by catching the disease,

but this number can vary between countries (Fontanet & Cauchemez, 2020). Now that a large number of people have experienced chronic symptoms after developing the infection we are witnessing an increased interest in medical rehabilitation facilities that could help overcome the long-lasting sequelae (van den Borst et al., 2020).

Chronic symptoms and after effects of COVID-19

Some people that get infected with Sars-Cov-2 can present with lasting symptoms even after the infection has resolved and this has nothing to do with the severity of the previous disease. The appearance of symptoms such as fatigue, breathlessness, chest pains, memory and concentration deficits such as “Brain Fog”, sleep disorders, palpitations, dizziness, joint pains, anxiety, depression, GI tract issues, taste and smell disorders and skin rashes have been generically called Post COVID-19 syndrome (1).

A systematic study of the scientific literature that approaches lasting COVID-19 sequelae has pointed that after the disease and in the interval spanning from 2 weeks

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Address for correspondence: Clinical Rehabilitation Hospital Cluj-Napoca, 46-50 Viilor Street, 400437, Cluj-Napoca, România

E-mail: ungurmed@yahoo.com

Corresponding author: Rodica Ana Ungur; ungurmed@yahoo.com

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to 3 months post illness, patients can present fatigue (39-73%), breathlessness (39-74%), reduction in the quality of life (44-69%), abnormal pulmonary function, pulmonary fibrosis (39-83%), myocardial involvement (3-26%), persistent neurological symptoms (55%), a notable rise of psychiatric diseases (5.8% versus 2.5-3.4% in controls) and persistent smell and taste deficits (33-36% of evaluated persons) (Willi et al., 2021).

Furthermore, another prospective study has shown that among 277 cured COVID-19 patients, 141 (50.9%) have post-acute COVID-19 syndrome and 51 (18.9%) of patients still have persistent radiological changes. The respiratory and neurological aftereffects have improved over the course of 16-18 weeks, nevertheless persistent changes were noted in 37 patients (13.3%) (Moreno-Pérez et al., 2021). Another study that has followed-up 179 patients in Italy, who were recovering from Sars-CoV-2 infection, has determined that after 60 days from the onset of the disease, 87.4% of patients had at least one chronic remaining symptom and the quality of life was negatively influenced in 44.1% of the studied population. (Carfi et al., 2021).

General characteristics of health supplements

The market for dietary and health supplements has witnessed an increase during the last year and the lack of a targeted treatment against COVID-19 could have been the major cause of this. A lot of people who got caught in this unforeseen situation have turned to naturist treatments and vitamin supplements used before the advent of modern drugs. For example, the sales of elderflower supplements have seen a 4-fold increase in a single week in march 2020 and Zinc tablet sales have gone up by 255%. The majority of the population used such supplements in order to prevent the actual infection but we should also focus on their effect after the disease is gone, and their role in rehabilitation (Grebow, 2020).

However, we should find legitimate reasons for their use by doing an objective retrospective analysis of their effects, as the medical supplements industry has gained a huge profit by selling their products, the majority of those using them having no idea whether they have any benefits in treating the disease. The Council for Responsible Nutrition in Washington has developed a questionnaire for dietary supplements users and has established that 91% of them have changed their routine of administration by increasing the dosage since the pandemic has begun. The most popular choices seem to be Vitamin C and Vitamin D (2).

Considering the fact that a large number of people have been buying these supplements in order to prevent or treat the infection, we should foresee that a high proportion of those suffering from post-COVID syndrome and needing rehabilitation will also buy them.

Supplements for the fatigue after COVID-19

The general complaint of fatigue is often encountered after viral infections such as Ebola or Mononucleosis, but also after bacterial infections (Wilson et al., 2018; Katz et al., 2009). One study performed in Australia on 253 patients suffering from Epstein-Barr infection (glandular

fever), *Coxiella burnetii* (Q fever) or Ross River infection (epidemic polyarthritis) has shown that 28 of them had chronic fatigue syndrome after 6 months post-infection (Hickie et al., 2006). The definition of chronic fatigue syndrome given by Fukuda et al. is "a persistent or relapsing fatigue that cannot be explained by other medical or psychiatric conditions, which has been present for at least six months, is not alleviated by rest, and causes substantial reduction in daily activities" (Fukuda et al., 1994). Therefore, it is not surprising that fatigue is one of the most common long term symptoms after COVID-10 infection, and it can manifest in patients with no prior comorbidities who have healthy lifestyles.

Regarding the etiology of fatigue there are many hypotheses. Chronic fatigue is usually encountered after conditions that injure lungs, the heart or the kidneys but we need prospective studies in order to verify the effect of Sars-CoV-2 on such organs. Furthermore, psychiatric conditions like post-traumatic stress disorder (PTSD) or depression could also lead to fatigue-like symptoms especially in patients that have been respiratory assisted (Komaroff & Bateman, 2021). Another hypothesis is circulated in case there are no lesions on these aforementioned organs and it is associated with neuroinflammation. In this case, there are a number of cytokines that are secreted and they cause a decrease in energy consuming activities so that the organism can devote its energy to the healing process (Poon et al., 2015; VanElzakker, 2013).

Lutein and quercetin are flavonoids that inhibit the neuroinflammation caused by mast cells and therefore they can reduce the mental fatigue that is also known as "Brain Fog" in Long-Covid-19 infection (Theoharides et al., 2020). They are easy to find, are generally considered safe and can lead to an increase in cognitive performance (Harwood et al., 2007; Taliou et al., 2013). Mast cells and macrophages together with T lymph cells are stimulating the fibroblasts and therefore the overall fibrosis process. As a result, the inhibition of mast cells can offset this effect and could diminish the pulmonary fibrosis seen in COVID-19 and also the cognitive fatigue arising from the infection (Kazama, 2020).

One of the most popular supplements used to treat fatigue in Korea is ginseng (*Panax ginseng*). A meta-analysis that addresses 155 scientific papers about this compound has underlined that there are 4 randomized controlled studies that include 429 people and prove that ginseng reduces fatigue in a modest to moderate way. Therefore, the evidence is insufficient to ascertain that this compound is beneficial in improving fatigue and physical performance (Bach et al., 2016).

Arginine is an amino acid with antioxidative and vasodilating properties which is also known for its ergogenic effect and it is involved in many essential chemical processes (Campbell et al., 2004). Moreover, it is proven that diet supplementation with 6 grams of L-arginine for 3 days has increased the physical performance of patients with stable angina (Bednarz et al., 2000). The same positive effect on physical performance and some other hemodynamic parameters was witnessed on patients with precapillary pulmonary hypertension (Nagaya et al., 2001). Also, one study has shown that a 4-week diet

with arginine and grape seeds has increased the onset of neuromuscular fatigue in untrained men (PWCFT) while doing cycle ergometry (Camic et al., 2010). Consequently, arginine could be considered for administration in patients that suffer from neuromuscular fatigue after COVID-19 infection, but we should further assess the dose needed because the typical daily intake is between 3.5 and 5 grams (***, 2001).

The effect of a polynutrient supplement has been studied in a randomized, placebo-controlled, double-blind trial on 53 patients suffering from chronic fatigue syndrome. These patients were not taking any supplements prior to this study. Over the course of the 10 week study, the subjects were assigned on taking polynutrient supplements that contained Casein, Cysteine, Na, K, Cl, Ca, Mg, P, Vitamin A, D, E, B6, B12, C, Folate, Carnitine, Biotin, Coenzyme Q10. However, at the end of the study there was no significant difference between patients that were taking the supplements and the placebo arm of the study. Moreover, patients reported no significant change in the magnitude of complaints and no one reported complete recovery at the end period suggesting that the prescription of supplements may be of no use in treating chronic fatigue syndrome (Brouwers et al., 2002).

Dietary supplements in long-term respiratory symptoms

Symptoms such as chest pains and breathlessness are among the more lasting effects in those that are cured from COVID-19. These manifestations could be caused by changes like pulmonary fibrosis that can appear in some cases after the infection (Spagnolo et al., 2020). The targeted antifibrotic treatment could be taken into account for some patients that present with this disease. Drugs like Nintedanib and Pirfenidone are currently used to treat idiopathic pulmonary fibrosis and could have a future in this pathology (Spagnolo et al., 2020).

A series of plant based supplements have been studied on animal models (mice) in which pulmonary fibrosis was induced using bleomycin; these are skins of *Citrus reticulata*, Grape seed extracts and Curcumin. *Citrus reticulata* blanco was used in Chinese medicine for a long time, being known for its beneficial effects in respiratory diseases. The skins of the *Citrus reticulata* inhibit collagen production and its accumulation in animal models, therefore attenuating the effects of pulmonary fibrosis (Li et al., 2021). The same plant was studied for its antifibrotic properties in hypertrophic scar tissue, as it inhibited fibroblasts by increasing their apoptosis and it accelerated the degradation of collagen fibers (Qi et al., 2006).

Also, the grape seed extracts contain polyphenols like flavonoids, proanthocyanidins and procyanidins, together with vitamins and minerals and it could therefore be used as a dietary supplement (Weber et al., 2007). It works by inhibiting the expression of MMP-9 and TGF- β 1 and could lead to an increase in quality of life for patients with pulmonary fibrosis, many studies pointing that it has a protective effect against bleomycin-induced fibrosis and fibrosis induced by silica or amiodarone (Hemmati et al., 2008; Liu et al., 2017; Madkour & Ahmed, 2013).

Additionally, this type of extract was mentioned in articles about fatigue, so it could be an interesting subject to study on COVID-19 patients, considering the fact that it could address more than one chronic symptom of this disease (Camic et al., 2010).

Curcumin has been shown to have a beneficial, antioxidative and antifibrotic effect in mice that had bleomycin-induced fibrosis. This effect is attributed to a number of mechanisms:

- by reducing the influx of inflammatory cells;
- by decreasing the activation of alveolar macrophages and further release of toxic mediators, and;
- by decreasing excess collagen deposits in the lungs (Punithavathi et al., 2020).

Likewise, it had the same result in amiodarone and radiotherapy-induced pulmonary fibrosis (Cho et al., 2013).

Vitamin D is known for its role in the well-being of the musculo-skeletal system, by being the steroid pro-hormone that regulates the homeostasis of calcium and phosphorus in the body. Besides this well known role, this vitamin has an anti-inflammatory, anti-bacterial, anti-proliferative and citoprotective influences and it counteracts endogenous and exogenous stress (Basit., 2013).

There are numerous studies that demonstrate that Vitamin D deficiency is a risk factor for developing COPD and cystic fibrosis and is also correlated with the degree of fibrosis shown in other organs (Janssens et al., 2020; Alvarez et al., 2017; Dadabhai et al., 2017). Vitamin D has a cancelling effect upon signals related to fibrosis such as the inhibition of PGE2 and therefore the reduction in the number of fibroblasts that induce fibrosis (Liu et al., 2014). It was experimentally shown that Vitamin D has a role in preventing bleomycin-induced fibrosis and it could therefore be used together with other therapeutic agents because it does not have any notable side effects. The degree of its positive influence is also related to the degree of Vitamin D deficiency that the patient which is receiving this treatment has (Tzilias et al., 2019).

Dietary supplements for long term neurological and psychiatric symptoms after COVID-19

Although they have a much rarer occurrence than breathlessness or fatigue, symptoms that belong to a neurological or psychiatric spectrum can be found in some patients. For these, curcumin was approached for its neurological and psychological modulating effects in the context of COVID-19. This natural supplement, found commonly as a spice in South East Asian cuisine has immunomodulating and antidepressive properties that positively act on one's cognitive and mental well-being (Lopresti & Drummond, 2017). There is also a much lower case fatality rate in South East Asia among people that get infected with COVID-19, and for this reason their diet and traditional medicine practices are being evaluated (Soni et al., 2020). Furthermore, this compound has effects in modulating the monoaminergic group of neurotransmitters such as dopamine, glutamate, serotonin and noradrenaline and it has a positive impact in pathologies related to stress (Zalachoras et al., 2020).

Conclusions

1. More and more people throughout the world are getting infected with Sars-CoV-2 and a large proportion of people still battle with its long term effects.

2. To this date, there is no approved treatment for this spectrum of symptoms but there is a wide array of medical and dietary supplements that have a proven effect in countering these symptoms found in similar diseases. Their effect was not thoroughly studied in the setting of COVID-19, but it could be an interesting subject to approach in the near future considering the rise in the sales of medical supplements during the pandemic.

Conflict of interests

There are no conflicts of interests.

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