

Post Covid Differences between Long-Covid and Covid Sequelae Treatment Options for Both Conditions

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Abstract

SARS COV2 pandemic has become the most formidable challenge modern Medicine has ever encountered. Newly released pharmacological compounds and sera have shown deceptive outcomes, while repurposed drugs are still waiting their generalized admittance. Vaccines, though always the most preferable option, have shown decreasing efficacy in the new COVID variants. In the meantime, millions of lives are being unnecessarily lost. Confusion still prevails over certainty and that may be applied not only to illness but also (and mainly) to convalescence. Post COVID, long COVID, and COVID sequelae, are entities which happen to be mixed-up, taken for one another, and mostly misunderstood. So are the pharmacological options to manage them. In this article, we develop the clinical, pathophysiological and statistical differences between them, and also include therapeutic options that have proved their efficacy in each case, such as ivermectin + a combination of magnesium, vitamin D and HMB (hydroxymethylbutyrate) in Long COVID; and aerosol-carried corticosteroids + hypertonic-chloride-sodium solution in lung fibrotic sequelae.

Keywords: SARS COV2; COVID; HMB (Hydroxymethylbutyrate); Vitamin D

Introduction

The current SARS COV2 pandemic has become the most formidable challenge modern Medicine has ever encountered [1-7]. Most newly released pharmacological compounds and sera have shown deceptive outcomes [8-10]. The rapid appearance of multiple variants has reduced the efficacy of vaccines, and many times it has created the “asymptomatic-carrier” condition [11-13]. Both original strain and subsequent variants may lead not only to death, but also to post-illness situations that are often confusing and misunderstood. Along these pages we will try to differentiate them and present the tools we already have to confront them.

Differences between long covid and covid sequelae conceptual differences

Long COVID, long haulers, etc., are denominations used to describe a situation that arises among COVID- convalescent patients, but not implying a constant condition [14-16]. The permanence of symptoms beyond expected time (four weeks) will be considered a “long COVID”, and the suffering subject will be referred to as “long hauler” (Figure 1).

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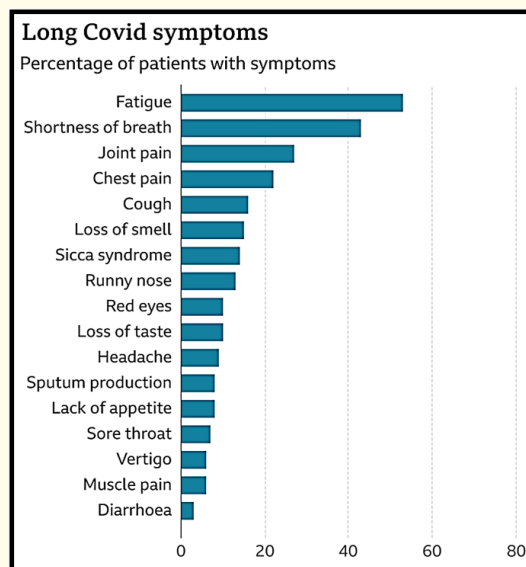


Figure 1: Long-covid symptoms according to frequency.

On the other hand, the illness itself may lead to sufficient damage in target organs as to create permanent post-COVID complications; these are the COVID sequelae, which can be improved spontaneously or with therapies, but will persist over time [17,18].

They have been compiled in an extensive work carried out in the Middle East [19,20] and can be summarized as follows:

A. Cardiorespiratory

- a. Cardiological: Increased incidence of coronary heart disease (myocarditis, arrhythmias, heart failure, etc).
- b. Respiratory
 - i. Permanent thickening of the intralobular and interlobular septum (fibrosis).
 - ii. FEV 25-75 impairment.
 - iii. Reduced diffusion capacity.

B. Glucometabolic

- a. Increased risk of dyslipidemia
- b. Increased risk of hyperglycemia
- c. Endocrinological complications.

Hypocortisolism.

Primary and central hypothyroidism.

C. Neuropsychiatric

- a. Neuromusculoskeletal
 - i. Persistent musculoskeletal aches and pains
 - ii. Femoral head necrosis
 - iii. Residual damage from stroke.
- b. Psychiatric complications
 - i. Depression
 - ii. Post traumatic stress disorder and panic disorder
 - iii. Somatoform pain disorder
 - iv. Chronic fatigue syndrome.

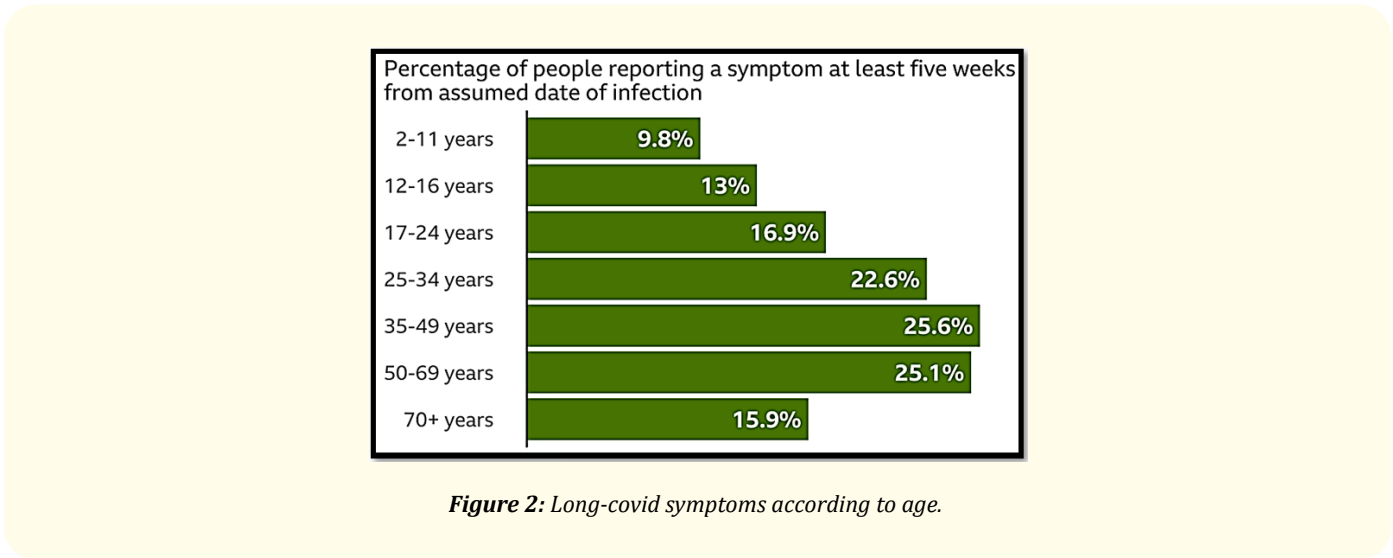
D. Others (will be described further on, in this article).

Pathophysiological differences

The possible causes of Long COVID are multiple, and still obscure. The permanence of virus in tissues, the impossibility of completely stopping the cytokine storm, the endotheliitis persistence etc. the mastocyte-cells endless reaction, are among the potential causes of this condition [21-23]. One unexplored, yet interesting possibility concerns the down regulation of the hypothalamic-pituitary-adrenal axis by the use of corticosteroids as part of the treatment, when many times they are withdrawn at hospital dismissal, without considered the gradual reduction which should be a dogma in these cases. As far as sequelae are referred, the previous damage provoked by both exaggerated inflammation and/or thrombi, thus avoiding correct blood-perfusion to tissues, is the origin of permanent physical handicap [24,25].

Clinical differences

Long Covid implies a constellation of symptoms and is not related to aging [26-28]. What is more, middle-aged patients are more likely to develop long COVID (Figure 2).



As far as sequelae are concerned, the stress has been put on initial ARDS [29] (Figure 3).

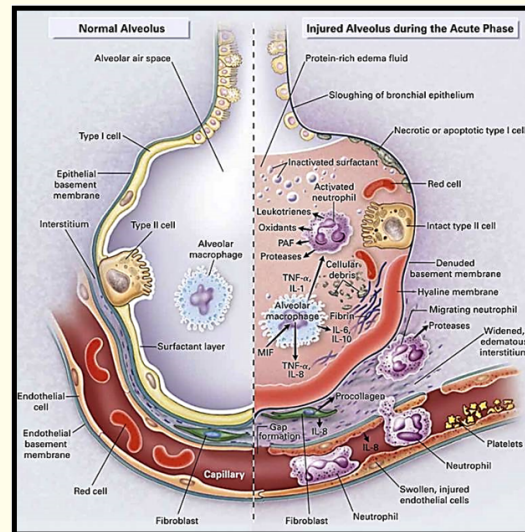


Figure 3: Development of ARDS.

But even after surviving that dramatic situation, the pulmonary interstitial tissue will remain swollen and become stiff, thus leading to invalidating pulmonary fibrosis [30-34] (Figure 4).

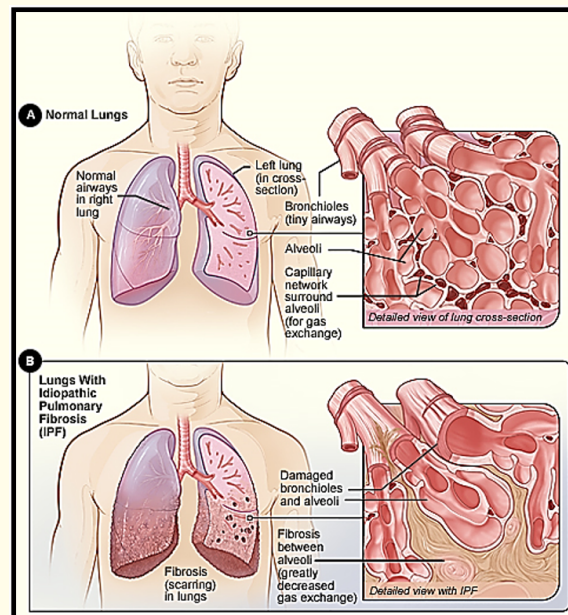


Figure 4: Development of fibrosis.

Yet, the sequelae are not limited to lungs, as we can encounter both permanent and even life-threatening conditions in most organs (Figure 5).

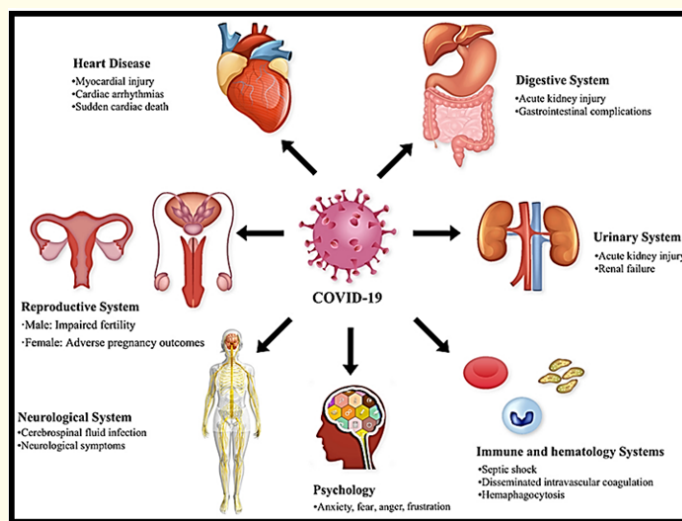


Figure 5: Covid extra pulmonary targets.

Statistical differences

Long COVID has been considered in some articles, but more intense survey is still lacking. We will refer to a recent, large survey conducted by UK Institute of Health (NICE) [30]: Over the four-week period, an estimated 1.1 million people in private households in the UK reported experiencing long COVID (symptoms persisting more than four weeks after the first COVID-19 episode that are not explained by something else).

Long COVID symptoms were adversely affecting the daily activities of 674,000 people, with 196,000 of these subjects reporting their ability to undertake day-to-day activities had been considerably limited.

Of these people, 697,000 had COVID-19 at least 12 weeks previously, and 70,000 had COVID-19 at least one year previously.

Prevalence rates of self-reported long COVID were greatest in people aged 35 to 69 years, females, those living in the most deprived areas, those working in health or social care and those with a pre-existing, activity-limiting health condition.

Symptom prevalence at 12 weeks post-infection was higher for female participants (14.7%) than male participants (12.7%) and was highest among those aged 25 to 34 years (18.2%).

Now referring to sequelae, we must divide it by affected area or organ. For doing that, we will mention a recent survey made by the Ontario (CA) Sanitary Authorities.

The most commonly reported persistent neuropsychiatric symptoms were fatigue (range: 30 - 78%) and headache (18 - 50%), followed by cognitive symptoms (e.g. attention disorder; memory loss, anxiety [11 - 55%]), sleep disorder (11 - 65%) and smell/taste dysfunction (10 - 43%).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated long-term neuropsychiatric symptoms may occur through direct viral neuroinvasion, or most frequently through inflammatory mediators.

In a systematic review of 35 articles and 123 patients, Parsons., *et al.* (2020) modelled and quantified the locations of neurological events using magnetic resonance imaging. 77.2% (95/123) of patients had white matter changes (i.e. corticospinal tract), 74.0% (91/123) had grey matter changes (i.e. bilateral superior temporal cortices, precentral cortices, pallidum) and 58.5% (72/123) had cerebral microbleeds.

In a systematic review of seven articles and 1,643 patients, Neishaboori., *et al.* (2020) investigated central nervous system (CNS) neurological complications. The incidence of any CNS complication was 6.3% (95% confidence interval [CI]: 3.32 - 9.98), with encephalopathy in 2.6% (95% CI: 1.31 - 4.25) of patients.

Other CNS findings (i.e. brain leptomeningeal enhancement, dysexecutive syndrome, brain perfusion abnormalities and ataxia) were found in 13.4% (95% CI: 0.90 - 35.5) of patients.

Depression (12%; 95% CI: 3 - 23) and sleep disorder (11%; 95% CI: 3 - 24) required a follow-up of patients ranged from a mean of 14 - 110 days post-viral infection.

Mood, anxiety or psychotic disorder was reported for the first time in 8.6% (95% CI: 8.3 - 9.0) of patients at Taquet., *et al.* (2021).

The most commonly reported persistent respiratory symptoms were cough (range: 20 - 27%) and shortness of breath (16 - 55%).

Post-mortem studies and reviews have noted diffuse alveolar damage, indicating that longer-term pulmonary sequelae are also possible from COVID-19; for example, interstitial pulmonary fibrosis and pulmonary hypertension.

In a systematic review and meta-analysis of 28 studies and 9,442 patients, Michelen., *et al.* (2020) described 46% of patients reported shortness of breath.

In a systematic review and meta-analysis of seven articles and 380 patients, Torres-Castro., *et al.* (2020) reported that the most common persistent respiratory findings (14 - 84 days after discharge, measured by spirometry) were altered diffusion capacity of the lungs for carbon monoxide (39%; 95% CI: 24 - 56) and restrictive pattern (15%; 95% CI: 9 - 22).

Trinkmann., *et al.* (2021) reported there was decreased lung function in approximately 50% of patients, as measured by spirometry.

The most commonly reported persistent cardiovascular and cerebrovascular symptoms were chest pain (range: 12 - 24%), tachycardia (11 - 34%), and palpitations (10 - 40%).

Thrombosis and acute ischemic stroke are recognized complications of COVID-19. In a systematic review and meta-analysis of seven studies and 970 patients, Vakhshoori., *et al.* (2020) reported that acute cardiac injury occurred in 15% (95% CI: 11-20) of patients. In autopsies of 41 patients that died from COVID-19, evidence of cardiac infection was found in 30 patients, resulting in cardiac inflammation and electrocardiographic changes.

Other organs damage has already been mentioned (see above).

The most common persistent symptom for other organ systems in another review was hair loss (25%; 95% CI: 17 - 43), followed by arthralgia (19%; 95% CI: 7 - 34), sweats (17%; 95% CI: 6 - 30), nausea/vomiting (16%; 95% CI: 10 - 23) and weight loss (12%; 95% CI: 7 - 18).

Moreno-Perez., *et al.* (2021) reported that 19.6% of patients experienced myalgia and or arthralgia, and 10.5% reported sporadic diarrhea.

Governments of countries around the globe should be dealing with the possibility of prolonged hospitalization of COVID-19 patients and its enormous strains on the healthcare system.

Therapeutic options

According to the evolution of the pandemic, widespread therapeutic alternatives have proved no benefit [31-34]. On the other hand, most promising outcomes have been obtained by repurposed drugs which -absurd as it may sound- have been disregarded so far. Comings and goings shown by vaccine manufacturers together with their fight not to prove own efficacy but to expose other's toxicity, has kept most of the independent, scientific community wondering. Never before -in modern Medicine- collateral situations such as isolation, depression, poverty, etc. have been so underrated [35-38]. Nutritional status, and consequently cachexia, increases the risk of mortality and needs to be treated with attention as other complications. Ensuring adequate nutrition in patients with COVID-19 who presented cachexia or associated symptoms has proven to be challenging due to intestinal alterations and inflammatory profile which complicate nutritional management. There is, however, little solid evidence of nutritional health approaches in assisting COVID-19 treatment or its management.

Long COVID

Long haulers can undoubtedly benefit from the use of Ivermectin (IVM) -as was proved in our previous post-COVID trial- in combination magnesium, vitamin D, and HMB (hydroxymethylbutyrate). This last one is a compound derived from leucine with ample evidence in promoting muscle recovery and bone health. HMB is responsible for some of the beneficial effects of protein and leucine in the diet.

It may be especially important for reducing the breakdown of muscle proteins.

While HMB is produced naturally by your body, taking it as a supplement allows for higher levels and may benefit muscle-recovery. Measures regarding maintenance of nutritional status and prevention of cachexia in hospitalised patients should be better explored for effective nutritional interventions in the future. The COVID-19 pandemic is an extraordinary global emergency that has led to the implementation of unprecedented measures in order to stem the spread of the infection. Internationally, governments are enforcing measures such as travel bans, quarantine, isolation, and social distancing leading to an extended period of time at home. This has resulted in reductions in physical activity and changes in dietary intakes that have the potential to accelerate transient sarcopenia, a deterioration of muscle mass and function (more likely in older populations), as well as increases in body fat. These changes are associated with a number of chronic, lifestyle diseases including cardiovascular disease (CVD), diabetes, osteoporosis, cognitive decline, and depression. CVD, diabetes and elevated body fat are associated with greater risk of COVID-19 infection and more severe symptomology, underscoring the importance of avoiding the development of such morbidities. Clinicians should consider the risks of acute sarcopenia when weighing up the risks and benefits of treatment (e.g. dexamethasone), and instigate multidisciplinary treatment including dietetics input.

We conducted a follow-up of 856 long-COVID patients discharged from hospitalization at a Public Hospital in Buenos Aires (Argentina), from July 2020 till December 2020.

All the patients included had not received IVM either before or during hospitalization. Instead, they had been treated with corticosteroids, antibiotics, blood-thinners, convalescent's plasma, etc. All of the above-mentioned patients received IVM, ranging from 12 up to 18 mg per os, on a weekly basis, until the symptoms disappeared, but no longer than 8 weeks (what happened first).

The average time needed to get rid of those disturbing symptoms were 36 days, ranging from 21 to 69 days.

The side effects reported by the IVM-treated patients were:

- 1) Diarrheic episodes in 5 patients.
- 2) Abdominal pain in 2 patients.

No cases of allergy were reported; neither were pregnant or lactating women among those treated, thus IVM contraindications could be disregarded. In fact, we support the combination of IVM, HMB and vitamins in post COVID subjects.

Post covid sequelae

Lung

The thickening of interalveolar tissue pathological is the substrate of Pulmonary Fibrosis (PF) and of Interstitial Pulmonary Diseases.

Pulmonary fibrosis is histologically characterized by inflammation and fibrosis, which affects predominantly alveolar walls and perialveolar structures with remodeling of the lung tissue [39-42].

Inflammation is the result of damage to the capillary-alveolar unit, which can recover completely or partially or progress to fibrosis.

This can vary in extent and speed of progression. The list of causes is very extensive and now, we will have to add COVID 19.

The alterations of FEV 25/75 by forced spirometry is the most useful and most commonly used diagnostic method. The mechanics of forced expiration is active, and dependent on the force produced by the thoracic wall. The expiratory abdominal and intercostal muscles compress the thorax, and the thorax is compressed by the alveoli, giving rise to an alveolar pressure + that pushes air out.

That amount of air exhaled, and the speed at which it moves, determines multiple spirometric values, among which we recommend:

- Expiratory flow 25 - 75%, FEF25 - 75%.
- It provides information on how much of the total exhaled air makes it between 25 and 75% of the expiration time.
- It is a flow and can be expressed as ml/s or as a percentage against its theoretical figures.
- Its normal value is greater than 60%.

Since for its calculation it eliminates the initial and final part of the flow-volume curve (which are more effort-dependent, and therefore less objective), it is considered an early marker of damage of the small airways, so that it can be altered much earlier than the other spirometric data. The carbon monoxide diffusion test (DLCO) provides comprehensive information on the entire diffusion process, which includes the passage through the capillary-alveolar barrier and its union with the haemoglobin (Hb).

In short, it represents the contact of the ventilated alveoli with the capillary bed.

It follows from this that a reduction in the gas exchange surface or an increase in the thickness of the alveolar-capillary membrane reduces the diffusion of CO.

Likewise, the decrease in blood flow or Hb concentration also decreases it.

In the pulmonary function laboratory, DLCO is measured, taking advantage of the high affinity of CO by Hb. Furthermore, the peculiarity that the partial pressure of CO in the plasma is practically zero, is advantageous for measuring lung diffusion capacity, since for this reason, the CO transfer depends only on its diffusion.

However, it is important to consider that it has important differences with the diffusion of the oxygen (O₂), so it corresponds to an approximation.

This test measures the amount of CO transferred from the alveolus to the blood per unit of time, and partial pressure difference of CO on each side of the capillary-alveolar membrane.

CO crosses the capillary-alveolar barrier in a similar way to O₂, but given its high affinity for Hb, (210 times that of O₂), CO quickly binds to it, so its pressure partial in blood is close to zero, throughout the entire route through the pulmonary capillary.

This makes it possible to estimate the diffusion gradient just by measuring the pressure of the alveolar CO.

In a 2015 trial, and to establish the effects of a pulmonary rehabilitation program in patients with ILD, a quasi-experimental study was developed in patients with intervention of continuous exercise in endless band, muscular strengthening of upper limbs, techniques of chest breathing and mobility and educational activities for 8 weeks; they were evaluated at start and end of the intervention the variables body mass index (BMI), dyspnea Medical Research Council, 6-minute walk test (6MWT), anxiety, depression and quality of life health related; paired t was used to analyze the means. Among the results, it should be noted that all patients completed the program of pulmonary rehabilitation.

The mean age \pm SD was 60.6 ± 13.9 years.

The forced vital capacity had a mean of $61.7 \pm 19.5\%$ of that predicted.

At the end of the program, a significant increase was found in the distance travelled in the 6MWT, mean difference of 615 ± 68.6 m ($p = 0.001$); anxiety had a decrease in the difference, mean 1.8 ± 2.1 ($p = 0.002$); Health-Related Quality of Life, St. George Respiratory Questionnaire, had a decrease in the total score, mean difference 14.2 ± 19.9 ($p = 0.008$); the CRQ-SAS questionnaire showed an increase in the total score, mean difference 0.7 ± 0.8 ($p = 0.003$).

Thus, it was concluded that pulmonary rehabilitation is a safe treatment, with good adherence and recommended for patients with ILD; the distance in the 6MWT showed that it must be always evaluated in a pulmonary rehabilitation program. The main event in the development of IPF is currently considered to be the injury of the cell of the alveolar epithelium, which stimulates the development of fibrosis, and that inflammation represents a secondary process.

An essential feature of IPF is fibroblast proliferation and abnormal accumulation of extracellular matrix molecules, especially collagen fibers.

Fibroblast foci, widely distributed in the lung parenchyma, behave as small areas of acute lung lesions, where fibroblasts migrate, proliferate and they contribute to the accumulation of extracellular matrix molecules that damage the alveoli.

Thus, as a consequence of the interstitial and intraluminal deposits of connective tissue, produces a “remodeling” of the architecture of the lung.

On the other hand, fibroblasts are not a homogeneous population.

In the last decade, the concept of “phenotypic diversity” has emerged when observing, for example, that fibroblasts in IPF show a profibrotic secretory phenotype, with a lower rate of increase.

Myofibroblasts are the only population of fibroblasts that express characteristics of smooth muscle differentiation.

Fibroblasts positive for α -smooth muscle actin are increased in lung tissue of the patients with IPF and constitute the main component of fibroblastic foci.

In addition, these cells acquire an “aggressive” phenotype and seem to be the main responsible for the accumulation of collagen.

Likewise, the remodeling that is observed in the abnormal extracellular matrix of the lungs of patients with IPF is, at least in part, due to an imbalance between some components of the family of matrix metalloproteinases, such as collagenase 1 (metalloproteinase 1) or the gelatinases A and B (metalloproteinases 2 and 9, respectively), and tissue inhibitors of metalloproteinases. Lung scarring that occurs in interstitial lung disease cannot be reversed, and treatment is not always effective in stopping the final evolution of the disease. Some treatments can, nevertheless, improve symptoms or slow the progression of the disease.

Others can improve the quality of life.

Intensive research is underway to identify treatment options for specific types of interstitial lung disease.

However, based on currently available scientific evidence, the physician may recommend corticosteroids. Many people who are diagnosed with interstitial lung disease are treated with corticosteroids (prednisone), sometimes combined with other medicines that suppress the immune system.

Depending on the cause of the interstitial lung disease, this combination may delay or even stabilize the progression of the disease. In order to achieve greater bioavailability in the lung, and -at the same time- reduce the secondary impact on the body, this modality can be used inhalation, through:

- Budesonide aerosol, alone or in combination (Budesonide + formoterol)
- Fluticasone aerosol, alone or in combination (Fluticasone + salmeterol)

Beclomethasone aerosol, alone or in combination (Beclomethasone + salbutamol). Fluidifiers of the mucus at the ciliary level such as n-acetyl cysteine and hypertonic chloride sodium solution to nebulize, have been used as mucolytic agents, with very good results.

Their low cost, the lack of undesirable side effects, and the possibility of combining them with aerosolized corticosteroids and/or bronchodilators are a very remarkable option.

Oxygen can't stop lung damage, but it can: Facilitate breathing and physical activity.

Avoid or lessen the complications of low blood oxygen levels.

Reduce blood pressure on the right side of the heart.

Improve sleep and sense of well-being.

Patients are more likely to be given oxygen while you sleep or exercise, although some people may need it all the time.

The goal of pulmonary rehabilitation is not only to improve daily functioning, but also help people with interstitial lung disease to live fully and satisfactorily.

To achieve this, the pulmonary rehabilitation program focuses on:

- Physical exercises to improve endurance
- Breathing techniques that can improve lung effectiveness Psychological support
- Nutritional counselling.

Other sequelae

Neurological, psychiatric, renal, liver sequelae (and all others) shall be referred to the correct Specialty Facilities; but we must recognize the patient as a whole, so multi-disciplinary access is mandatory.

Conclusion

Both conditions (long COVID and COVID sequelae) mean a stressing and even life-threatening issue for most patients, a handicap they will carry for a long time (even forever) and also a giant burden for health systems worldwide [43-47]. In the above description, we have made a not-always-attainable differentiation between those conditions. The use of Ivermectin plus a combination of magnesium, vitamin D, and HMB (hydroxymethylbutyrate), arises as an effective, affordable way to reduce the long-haulers suffering [48,49]. And corticosteroid (mainly by aerosols) plus hypertonic-chloride-sodium solution will benefit those patients with lung sequelae.

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