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Guest Editorial

The Potential Role of Photobiomodulation in Long COVID-19 Patients Rehabilitation

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COVID-19 generally presents as flu-like symptoms such as fever, cough, and asthenia. Patients of all ages can suffer from severe lung injuries, but in case of high-risk individuals such as elderly or those with underlying diseases, it can exacerbate to interstitial pneumonia, acute respiratory distress syndrome (ARDS), and subsequent multiorgan failure, which are the key elements of their severe acute respiratory failure and high death rates.

In 80–90% of patients, the infection is mild or asymptomatic. It becomes severe in ~10% of cases that is associated with dyspnea, hypoxemia, and extensive (>50%) radiological involvement of the lung parenchyma. More emergency conditions happen in ~5% of cases with respiratory failure, pneumonia, shock, multiorgan failure (such as acute kidney injury, coagulopathy, and gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain), and death. Death is almost always caused by ARDS and multiorgan failure as mentioned. One of the other main symptoms of COVID-19 patients is critical illness polyneuropathy (CIP), which may occur after COVID-19. A study showed that up to 46% of patients hospitalized in the intensive care unit suffering from ARDS presented with CIP. CIP causes generalized and symmetrical weakness (distal greater than proximal, but including diaphragmatic weakness), distal sensory loss, atrophy, and decreased or absent deep tendon reflexes, and leads to prolonged mechanical ventilation need. It is also associated with fatigue, pain, loss of range of motion, dysphagia, anxiety, depression, posttraumatic stress disorder (PTSD), and even cognitive loss.[1,2]

Current management of COVID-19 is supportive and all suggested drugs are mainly focused on antiviral therapy, oxygenation, and anti-inflammatory effects alongside with anticoagulation therapy. No definitive evidence exists that interventions other than remdesivir therapy result in important benefits and harms for any outcomes.[3]

As the time goes by, scientist's knowledge evolve around COVID-19 characteristics. The concept of chronic COVID-19 or so called long COVID-19 has been introduced since after COVID-19 treatment studies have shown that different symptoms persist. A study showed that a small percentage of patients (2.6%) were completely without any COVID-19–related symptom, while 32% had one or two symptoms and 55% had three or more. However, none of them suffered from signs or symptoms of acute illness such as fever. Quality-of-life decrease was reported in 44.1% of patients. Fatigue and dyspnea were reported among a high percentage (53.1% and 43.4%) of individuals, and chest pain and joint pain were seen in less frequently (27.3% and 21.7%). Therefore, almost always individuals need postdisease rehabilitation. After the acute phase, routine respiratory rehabilitation focuses on inspiratory muscle training if inspiratory muscles are weak, including slow and deep course of breathing, thoracic extension exercise with shoulder elevation, mobilization of respiratory muscles, airway clearance techniques (as needed), diaphragmatic breathing, and even positive expiratory pressure devices. In case of mobility and functional rehabilitation, physiotherapy should start sooner in the acute inpatient setting and continue after transfer to inpatient rehabilitation. Patients should be mobilized early with frequent posture changes, bed mobility, sit-to-stand, and easy bed exercises according to their respiratory and hemodynamic states. Muscle strengthening exercises should be progressive with active limb exercises.[4]

As mentioned earlier, long COVID-19 phenomenon is a new challenging subject that needs novel interventions more than before to maximize patients' course of health in the shortest time possible.

Some recent studies have discussed an application of photomedicine called photobiomodulation therapy for management and treatment of COVID-19 disease with other therapeutic modalities such as antiviral photodynamic therapy that may be beneficial in different stages of the disease such as stifling the cytokine storm, improving cellular regeneration of the lungs, damaged tissues' oxygenation, and

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also in viral load reduction in upper respiratory tract, blood, and even deep body tissues that are the accumulation places for viral agents (lungs etc.).[5–8]

With special attention to the photobiomodulation phenomenon, it seems that this modality might be helpful for decreasing the symptoms and time of long COVID-19 with its metabolic, immunological, anti-inflammatory, and pain killing effects.

AU5 ▶ In the respiratory system, the most important victim of the chronic symptoms, with suitable parameters of photobiomodulation in tissue regeneration field we may be able to help damaged cells both directly with direct light therapy and indirectly with systemic effects on cells and blood factors to improve conditions for cellular regeneration with AU4 ▶ better oxygenation and adequate ATP supplementation on chronic obstructive pulmonary disease which is a chronic lung disease that resembles the chronic damages of COVID-19 disease. This strongly approves the hypothesis that this method can be effective in long COVID-19. Also, with the discovery of positive effects of the combination of photobiomodulation and stem cells, we can use them on both resident stem cells and stem cells diffused in the blood stream (hematopoietic stem cells). These actions can be done with direct light emission to the lungs locally (transthoracic photobiomodulation) and to the blood directly (intravenously) or indirectly (subcutaneously). Hence, recent positive studies have shown that light emission to the blood cell production centers such as bone marrow may lead to better systemic effects.

AU6 ▶ In subjects with fatigue, we might be able help the body with systemic effects such as better oxygenation and improvement in cellular function in different organs and the whole body. ATP, and intercellular signaling molecule able to modulate molecular and cellular cascades, can be effective in muscular performance that explains the role of phototherapy in muscular tissues. Also, we could help these tissues by increasing glycogen in muscle cells, increasing their regeneration, improving their function, and better the oxygenation. Of course, we can increase NO molecules, a highly potential vasodilator, with phototherapy that leads to increase of blood stream and oxygenation that can be profitable. In the photobiomodulation method for reaching better systemic and muscular effects, direct emission to blood cells (increase in cellular efficiency) may be effective. However, with the arrival of whole body photobiomodulation devices, we can target the entire body and its cells but, more companies should work on the development of these systems and make them more public.

AU7 ▶ Transcranial phototherapy that includes a new field of studies and its positive effects have been discovered in neurological and psychiatric disorders such as brain traumas, stroke, Alzheimer, depression, Parkinson, and PTSD may be able to help us with not only controlling and improving the central nervous system but also with decreasing the remaining headaches and management of depression that are symptoms of long COVID-19 with right parameters. Positive effects of neovascularization of transcranial photobiomodulation can play a major role in the healing of neural damages. For this method, we can use direct emission of light to the brain, and systemic effects of intravenous laser therapy might be beneficial as well. Maybe another proof for this hypothesis can be the discovery of positive effects of photobiomodulation on fibromyalgia, which is correlated with depression, anxiety, and PTSD besides frequent chronic pain.

Most scientists believe that central nervous system effects are responsible for loss of smell and taste. A study showed that scientists cured anosmia in Parkinson's disease patients with photo therapy.[7] Therefore, we may benefit from transcranial phototherapy besides direct laser therapy to these tissues (nose and tongue) that are perfectly in reach.

Photobiomodulation therapy can have positive effects on chronic damages of the cardiovascular system with more oxygenation, improvement of blood growth factors, and immunomodulation, too. Improvement in the function of blood cells such as platelets can be helpful and can prevent further clotting in the vessels. Of course, we can benefit from direct laser therapy in these organs, too. Phototherapy can have positive effects on angiogenesis with VEGF, type ◀ AU8
1 collagen, and hypoxia-inducible factor-1a increase and downregulation of tissue remodeling marker matrix metalloproteinase-2 and be beneficial in reconstruction of vascular damage and management of cardiovascular disorders. Also, in myocardial ischemia, we could give tissues more time to heal by improving oxygenation and better blood supplement.[8]

For musculoskeletal symptoms, we might be able to use systemic photobiomodulation beside physical interventions and exercises as already mentioned.

In conclusion, photobiomodulation could help damaged tissues to regenerate by enhancing cellular division, distinction, migration, and oxygenation. These effects can be used in combination with stem cell therapy to reduce chronic symptoms of this disease according to recent studies about the combination of photobiomodulation and stem cells. This ability of photobiomodulation can be justified by its proven effects on ROS increase, ATP and cAMP pro- ◀ AU9
duction, NF-κB activation, and decrease in apoptosis and modulation of intercellular Ca and NO.

Adhering to correct protocols based on scientific facts and ◀ AU10
using suitable physical parameters such as right dosage, right wavelengths, and reaching the appropriate dosage in tissues especially deep tissues such as lungs, heart, and brain are the key elements of this method's success. The beneficial wavelength range should be $\sim$660–1100 nm (optical window) and 400–600 for intravascular application based on documented articles that are easily accessible for all physicians. However, with minimal changes, special hand pieces can be designed for this disease and other respiratory diseases. Of course, we cannot deny the therapeutic effects of laser acupuncture, a combination of electromagnetic radiation and acupuncture science. In this field, special methods are being used for systemic treatment of these patients, and lately there have been many activists in this field and we should wait for their results. Here we should emphasize on the fact that using suitable protocols guarantees better results. Using optical and therapeutic windows is approved by physicians and researchers in this field absolutely.

Owing to the numerous unknowns of this widespread disease, with each day moving forward we gather more information and we can use them to optimize our management methods as time goes by. Naturally, the first priority is the treatment of this disease and then controlling its long-term symptoms that affect daily lives of especially elderly

patients because of their old immune system and poor mitochondrial function, which make them more prone to inflammation state. Also, these symptoms are more frequent in patients with underlying diseases such as diabetes, hypertension, thyroid disorders, and immune deficiency, so all modalities that help us with these diseases should be welcomed. Beside routine rehabilitation methods, photobiomodulation can be recommended as a cheap noninvasive less problematic adjuvant therapy. It seems like in the near future with this treatment modality's ability and meticulous and well-planned clinical trials on these patients and acquiring special and effective treatment protocols, we may be able to help patients.

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