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Impact of exercise on COVID-19 severity in patients with obstructive sleep apnea

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Abstract

Since the discovery of the new coronavirus in December 2019, a pandemic has set in, impacting quality of life not only by vulnerability to the course of infection, but also in its lingering consequences after the viral picture, popularly known as long covid. Although the mechanism and all the factors involving long covid are still uncertain, many diseases have been greatly mentioned, being obstructive sleep apnea one of them, due to its strong correlation with obesity and the greater potential for pro-inflammatory signaling through deregulation of the sirtuin pathway. In this present study, we sought to evaluate the possible beneficial impact of physical activity as a remodeling factor of inflammatory signaling through the activation of the SIRT-1 pathway.

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Introduction

Obstructive sleep apnea (OSA) is characterized as an obstruction of the airway during sleep, which happens repeatedly during this period. [1] This interruption of breathing triggers a desaturation of oxygen in the blood, promoting a baroreflex sympathetic response, with an adrenergic discharge promoting tachycardia and hypertensive peak, as means of resolution to momentary hypoxia. [2]

In constancy, the body suffers a dysfunction of the baroreflex, correlating the presentation of the disease and accentuating its risk factors, which are obesity, heart disease, type 2 diabetes mellitus. The inflammatory environment caused by oxidative stress is exacerbated with each new airway obstruction, causing the patient to run into a continuous metabolic disorder.

Obesity, as a risk factor for the disease, already establishes an inflammatory environment in the patient, through excess adipose tissue and increased secretion of cytokines and pro-inflammatory factors, generating an inflammatory low-grade [3] With apnea, this inflammation receives even more stimulus, generating a chronic inflammatory plateau ready to trigger with any stimulus. With the spread of COVID-19, when infected by the virus, the patient receives the necessary stimulus to trigger even more exacerbated inflammation, which will be a pleasant environment for the virus, since hypoxia can lead to an attempt of regulation by the renin angiotensin aldosterone axis, generating an upregulation in the angiotensin-converting enzyme 2 (ACE-2), the gateway for the virus. Furthermore, the high release of cytokines and pro-inflammatory factors generates chemotaxis of defense cells, such as neutrophils, generating a non-localized immune response, further complicating the defense against the virus. [4]

During regular physical exercise, SIRT1 pathway signaling occurs, leading to the expression of neuroprotective agents and decreased oxidative stress. [5] With this, remodeling of inflammatory processes potentially deleterious to the body occurs. The aim of this study was to hypothesize the positive impact of regular physical activity as a protective factor against the systemic damage caused in the long covid after infection with SARS-CoV-2.

Methodology

This study was a review and did not require Ethics Committee approval as the authors only accessed published data. The search terms were "COVID-19" OR "SARS-CoV-2" AND "obstructive sleep apnea syndrome" in the following databases: PubMed, LILACS, and SciELO. The search was limited by date, selecting only papers published from 2019 onwards, since the discovery of the new coronavirus emerged in December 2019. Only articles that used the English language in the title, keywords, and abstract were included. Conference abstracts and journal editorials were not included in this review. The authors individually searched the articles following the established criteria for inclusion and exclusion and, after two meetings, decided which articles should be included. The results of this review are presented primarily descriptively, without meta-analysis or statistical evaluation of the results.

Results

The initial search yielded 139 papers. After reading the titles of these papers and their abstracts, 10 articles were selected for this review (Table 1). Three were excluded because they were letters to the authors. Four retrospective cohorts were found, including one multicenter cohort from France, New York, and Chicago; two prospective cohorts from India and Singapore; and one study of genetic analysis in addition to database analysis.

Table 1. Summary of Studies

Author/Year	Study Design	Participants	Outcome	Conclusion
Beltramo,2021 [6]	Retrospective cohort	89.530	An increased risk for developing severe COVID-19 and increased mortality rates among patients with chronic respiratory disease have been elucidated.	Patients with COVID-19 and chronic respiratory diseases, such as sleep apnea, had more complications than patients with COVID-19 without previous respiratory diseases.
Chung,2020 [7]	Cross-Sectional	26,539 with COVID-19	High Risk of OSA and comorbities and risk of COVID-19	The study presents a relationship between the risk of OSA and contamination by Sars-Cov-2 and had a higher risk of hospitalization.
Goyal,2021 [8]	Longitudinal Study	67 with severe COVID-19	OSA developed after severe COVID-19	The study characterizes a high prevalence (73% of the analyzed patients) of OSA in patients after presenting several COVID and needing an intensive care unit.
Kar,2021 [9]	Prospective Observational Study	213 hospitalized patients with COVID-19	Estimate the prevalence of OSA in patients with COVID-19	The study concludes that OSA may be a risk factor associated with a worse prognosis for COVID-19.
Kravitz,2021 [10]	Retrospective Cohort Study	312 patients with OSA and COVID-19	Evidence relationship between OSA and COVID-19 severity/ hospitalization	The severity of obstructive sleep apnea was related to a possible risk factor for COVID-19 hospitalization, but no relationship was seen with the need for mechanical ventilation and death.
Maas,2020 [11]	Retrospective Cohort	9405 with COVID-19	OSA and Risk of COVID 19	Patients with OSA have 8-fold greater risk for COVID-19 and elevated risk for hospitalization
Strausz,2020 [12]	FinnGen Study (genome information with digital health care data)	445 with COVID-19 and 38 with OSA	OSA and Risk of COVID 19	Patients with OSA had the same risk of contracting COVID-19 compared to non-OSA patients, however they were at a higher risk of hospitalization and severe illness, regardless of other associated risk factors such as diabetes and BMI.

Discussion

By connecting with SARS-Cov-2 infection, the patient with sleep apnea, adheres to an environment of complication, not

only for the ongoing viral infection, but also for the risk factors correlated with OSA, such as obesity. The inflammation generated by hypoxia in OSA favors viral establishment, as the immune and inflammatory response is exacerbated and generalized, making specific mimicry difficult. Most studies have linked greater severity of viral infection in these patients, due to pre-infection oxidative and inflammatory stress, and may increase the risk of severe complications and hospitalization from COVID-19. An important theory that may hypothesize the greater pro-inflammatory potential would be due to a down-regulation of the sirtuins pathway. Sirtuins are a class of histone deacetylases that are dependent on nicotinamide adenine dinucleotide (NAD+). They are divided into seven types of sirtuins, being SIRT1 the most widely studied due to its potential role in modulating fundamental physiological processes for epigenetic modulation, involved in many physiological activities, such as apoptosis, cell division control, inflammatory response, stress metabolism. [13] Some recent studies, have related the action of sirtuins with neuroinflammation.[14] Faced with a pro-inflammatory status in the central nervous system (CNS), recruitment of the innate immune system occurs in which astrocytes, microglia, macrophages, NK cells, are present, producing pro-inflammatory factors to act against the causer of the local inflammatory process. [15] SIRT1 acts in an anti-inflammatory way by decreasing the secretion of cytokines, such as TNF-α and IL-6 produced by the cells of the innate system. [16] This pro inflammatory status in the CNS occurs as a result of several pathologies, one of them being obstructive sleep apnea syndrome (OSAS), which is characterized by a sleep disorder due to repetition apnea, chronic hypoxia, oxygen desaturation and hypercapnia. [17]

Situations of hypoxemia, sleep deprivation and snoring induce the chronic activation of proinflammatory cytokines [18] requiring a greater oxygen consumption by the brain, which is more sensitive to hypoxemic conditions. Thus, with the decrease of blood supply to the CNS, neuronal supplementation is compromised, causing apoptosis and local necrosis, which increases the chemotaxis of proinflammatory agents. [19] In a study performed by Hui Xie et al[20] it was observed that with intermittent hypoxemia, there was a reduction of brain-derived neurotrophic factor (BDNF) in mice, implying negatively in neuroplasticity, since BDNF is largely responsible for most neuroprotective factors such as neurogenesis, mitochondrial biogenesis and reduction of oxidative stress [21]. Paradoxically, BDNF activation can be stimulated during regular physical activity [22] since its activation can occur through the lactate-SIRT1- Fndc-5 axis during anaerobic activities. This is because, during physical activity, muscles release lactate, and when it crosses the blood-brain barrier, it stimulates the lactate-SIRT1- Fndc-5 axis, favoring BDNF release. [23] Faced with an active inflammatory process, there is increased signaling of oxidative stress, mediated mainly by NFκB and FOXO3 pathways. In this same context, SIRT1 presents an important role in deacetylating these transcription factors, positively impacting cell survival. [23]

Conclusion

The patient with OSA and COVID-19, in the presence of deregulated sirtuins pathway, introduces an exacerbated inflammatory process that is difficult to control by immune cells, complicating the prognosis and evolution of the disease. Thus, the practice of physical activity can be considered an important protective factor against the deregulation of sirtuins pathways and the exacerbation of pro-inflammatory factors that ensure a worse prognosis of the disease.

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