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Diabetes Mellitus and Covid-19: Arterial Hypertension Dyslipidaemia as Sequelae of Covid-19 Infection

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Abstract

As the population recovers from the coronavirus disease 2019 (COVID-19) pandemic, a subset of individuals is emerging as post-coronavirus disease (post-COVID) patients who experience multifactorial long-term symptoms several weeks after the initial recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. The aim of this systematic review is to present the latest scientific reports that evaluate changes in glucose levels, blood pressure readings and lipid profiles after recovery from COVID-19 to verify the hypothesis that new-onset diabetes mellitus, arterial hypertension and dyslipidaemia are a possible sequela of a COVID-19 infection. The open access databases PubMed and Google Scholar were searched. Articles investigating patients with residual clinical signs and biochemical alteration indicating diabetes, hypertension and dyslipidaemia at least a month after recovering from COVID-19 was included. It has been shown that a select number of patients were diagnosed with new-onset diabetes, arterial hypertension and dyslipidaemia after COVID-19 infection. Alterations in glucose levels, blood pressure and lipid profiles months after initial infection shows the importance of considering diabetes mellitus, arterial hypertension and dyslipidaemia as part of the multifactorial diagnostic criteria post-COVID to better provide evidence-based clinical care.

Introduction

COVID-19 causes in many patients, sequelae and complications that can last weeks, months and even generate permanent damage. The Long-COVID term, is currently used in the literature to describe the presence of persistent symptoms up to 12 weeks after the appearance of an acute COVID episode, which are not attributable to other causes; the term includes both type of patients; those who suffered from the disease and who never recovered, as well as those who did not have symptoms, but were left with sequelae [1].

SARS-CoV-2 belongs to the β-coronavirus family. The virus targets the Angiotensin-Converting Enzyme 2 (ACE2) as its main receptor as it is widely expressed in the vascular endothelium; respiratory epithelium; alveolar monocytes and macrophages [2]. Likewise, the pathophysiological process correlates with damage to a large number of organs, which conditions for a wide variety of symptoms and potential sequelae.

A meta-analysis of more than 120 thousand patients concluded that the persistence of signs or symptoms of COVID could be present in 56.9% of cases, up to a period of 6 months, from which general symptoms were the most common. Other authors have agreed that fatigue has persisted and headache after the end of the disease. According to the PHOSP-COVID collaborative group, the ten most frequent symptoms in a population of 2320 patients from the United Kingdom up to one year after hospital discharge, were: fatigue 60.1%, muscle pain 54.6%, physical slowness 52.9%, lack of sleep 52.3%, dyspnea 51.4%, joint problems 47.6%, bradypsychia 46.7%, short-term memory loss 44.6% and limb weakness 41.9% [3]. Another study with 100 patients who survived intensive care secondary to COVID-19 found that within two months of hospital discharge they continued to have asthenia, dyspnea and post-traumatic stress disorder. It has also been reported that survivors of severe conditions hospitalization have presented a higher rate of hypoxemia compared to those who did not require in-hospital treatment.

Other literature sequelae reported include: attention disorder, hair loss, dyspnea, ageusia, polypnea, anosmia, cough, arthralgia, diaphoresis, chest pain, nausea, memory loss, hearing loss, anxiety, depression, anxiety, skin disorders, digestive disorders, weight loss, myalgia, tachycardia, palpitations, red eyes, pulmonary fibrosis, diabetes mellitus, arterial hypertension, myocarditis, arrhythmias, among others [4].

The seriousness of the clinical picture in hospitalized COVID-19 patients requires greater professional attention by medical staff and the rest of the healthcare team. The number of symptoms and its variability clearly illustrates the multisystem nature of COVID-19 infections. It has also been shown and recorded that there is a positive relationship between the severity of hospitalization for this pathology and the severity with which long COVID occurs [5]. Due to the severity that all surviving patients in this sample presented, it is likely that the intensity and frequency of sequelae is greater than that reported in other similar studies.

Materials and Methods

Eligibility criteria

Included articles were original English language articles published from 1 December 2019 to 30 January 2022 investigating patients with residual clinical signs and biochemical alterations at least a month after recovering from COVID-19; specifically, articles investigated fasting glucose and C-peptide levels, blood pressure and lipid profiles. The eligible articles focused on patients over eighteen years of age. Confirmed infections were defined as positive real-time reverse-

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transcriptase polymerase chain reaction (RT-PCR) results from a nasopharyngeal and/or throat swab. Only studies reaching the statistical significance have been incorporated [6].

Selection process

The screening was mechanically performed by checking the publication date, record of patients testing positive for COVID-19 from a nasopharyngeal swab using the RT-PCR test during acute phase, persistent clinical alteration at least a month after recovery and biochemical investigations comparing baseline status to follow-up.

Data collection process

This review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Evaluation of the quality of the included studies was based on selecting only published peer-reviewed studies, excluding preprint manuscripts and case reports [7].

Outcome measures

The outcome measure was the alteration from baseline and prevalence of diabetes, arterial hypertension, or dyslipidaemia several months after infection with COVID-19.

Discussion

This systematic review compared studies that evaluated changes in glucose levels, blood pressure readings and lipid profiles after recovery from COVID-19 to verify the hypothesis that new-onset diabetes mellitus, arterial hypertension and dyslipidaemia are a possible sequela of a COVID-19 infection. Compiled studies investigating glucometabolic abnormalities showed that a select number of recovered COVID-19 patients were diagnosed with diabetes and had continuous hyperglycaemia several months after infection. Similarly, a recent systematic meta-analysis that pooled analysis from four observational studies showed a 59% higher risk of developing incident diabetes in the post-COVID phase [8]. Selected studies evaluating new-onset hypertension in COVID-19 survivors demonstrated elevation in systolic blood pressure and minimal diastolic blood pressure changes one to three months after recovery. Studies included in this review investigating lipid profiles revealed significant increases in triglycerides, LDL-C and total cholesterol levels in patients three to six months after being discharged from the hospital due to COVID-19 compared with those who did not require hospitalisation or had a milder initial infection. Since the selected studies provided evidence of long-lasting physiological changes several months after COVID-19, it is paramount to further discuss the possible pathophysiology of SARS-CoV-2 infection for the effective clinical management of post-COVID patients.

Multiple hypotheses have been proposed to explain the association between new-onset diabetes and COVID-19 infection. A possible mechanism for altered glucometabolic control is SARS-CoV-2 damaging the pancreas. The angiotensin-converting enzyme 2 (ACE2) plays a crucial role in glucose homeostasis and insulin secretion by regulating beta-cell physiology. Within the pancreas, ACE2 is expressed within the pancreas' endocrine islet cells, including beta cells. ACE2 primary protein facilitating SARS-CoV-2 attachment and entry into the host cells. Given the ability of SARS-CoV-2 to infect human-pluripotent-stem-cell-derived pancreatic cells in vitro and the presence of SARS-CoV-2 in pancreatic samples from COVID-19 patients, there is a strong suggestion that SARS-CoV-2 can invade the pancreas and directly cause pancreatic injury and diabetes by reprogramming cells to produce glucagon rather than insulin. Secondly, SARS-CoV-2 triggers macrophage-mediated cytokine storm in which elevated levels of circulating cytokines and immune cell hyperactivation leads to excess inflammation facilitating insulin resistance and beta cell hyperstimulation. SARS-CoV-2 induces a decrease in the enzyme SETDB2 within macrophages, causing increased transcription of inflammatory cytokines leading to damage to the pancreas. Autopsy tissue from patients who died of COVID-19 shown local inflammation caused by infections is associated with necroptotic cell death in islets causing islet damage [9]. Thirdly, alterations in post-translational protein modifications enables the breaking of central tolerance through the generation of neoepitopes that provide novel determinants that can activate T-cells that trigger autoimmune conditions like type 1 diabetes mellitus. Alternatively, steroids are used as an anti-inflammatory treatment in patients with COVID-19. A recent Cochrane study showed that systemic corticosteroids probably reduce all-cause mortality in people hospitalized due to systematic COVID-19. Glucocorticoids worsen insulin resistance, sustain gluconeogenesis, worsen glycaemic control and cause marked hyperglycaemia. In turn, this hyperglycaemia leads to reduced insulin sensitivity and increasing insulin secretion, interfering with glucagon-like peptide 1 (GLP-1) and enhances the production of glucagon. Unfortunately, the use of irrationally high doses of steroids in managing COVID-19 patients can lead to in-hospital glucocorticoid-induced hyperglycaemia (GIH). GIH is usually a temporary problem that resolves after discontinuing glucocorticoids, but data currently show that diabetes can persist and even unmask a pre-existing glucose metabolism disorder.

Hypertension is a major risk factor for stroke, coronary artery disease (CAD), renal disease, heart failure and peripheral vascular disease; therefore, early diagnosis and timely intervention are crucial in preventing these complications. Possible mechanisms explaining the development of new-onset hypertension due to SARS-CoV-2 infection include renin-angiotensin-aldosterone system (RAAS) dysregulation. It is hypothesised that SARS-CoV-2 binds to the ACE2 receptor via its spike protein provoking transient ACE2 down-regulation consequently deregulating RAAS signalling. ACE2 facilitates the cleaving of angiotensin II and counter-regulates the RAAS, resulting in a local accumulation of angiotensin II. Angiotensin II leads to unfavourable effects, including vasoconstriction and hypertension, cellular differentiation and growth and inflammation. Angiotensin II regulates NADPH oxidase activity, leading to the increased production of reactive oxygen species (ROS), further damaging the endothelium and ultimately leading to organ damage. In addition, the imbalance leads to downregulation of the cardio protective factors angiotensin RAAS. In summary, SARS-CoV-2 dysregulates RAAS raising angiotensin II levels and causing vasoconstriction, resulting in hypertension.

The measurement of plasma lipids and lipoproteins is critical in cardiovascular disease (CVD) risk management. Multiple possible mechanisms may explain why patients experience new-onset dyslipidaemia after COVID-19 infection. For one, SARS-CoV-2 is an enveloped virus meaning a lipid bilayer surrounds it; therefore, lipid metabolism plays a crucial role in the viral life cycle [10]. The virus utilises its lipid envelope for invasion and targets lipid synthesis and signal modification of host cells to generate lipids for its envelope. Previous studies show that altered lipid metabolism occurs following infection with similarly structured viruses, indicating a biological relationship. Secondly, lipids play a crucial role in modulating the immune system. SARS-CoV-2 induces a so-called "cytokine storm" due to the excessive activation of immune cells causing immune-mediated inflammatory dyslipoproteinaemia and causing immune cells to

trigger a dysregulation of lipid production. Low HDL levels prevent its ability to bind and neutralise pathogen-associated lipids that mediate the excessive immune activation leading to chronic inflammation. Persistent pathophysiological and clinical alterations following COVID-19 infection call attention to the importance of mitigation strategies in COVID-19 prevention. A longitudinal observational study amongst vaccinated and unvaccinated SARS-CoV-2 infected healthcare workers not requiring hospitalization in Italy showed lower prevalence of long-COVID amongst vaccinated. Though association between vaccination against SARS-CoV-2 and long-COVID is important to consider in reducing the severity of COVID-19 and long-term effects.

Conclusions

It can be concluded from this review that people older than eighteen years of age are at an increased risk of developing new-onset incidents of diabetes, hypertension, or dyslipidaemia several months after COVID-19 infection. In addition to other post-COVID symptoms, patients presented with altered glucose levels, blood pressure and lipid profiles several months after recovery from COVID-19 infection. Therefore, it is imperative that hyperglycaemia and insulin resistance, increased systolic blood pressure and altered lipid profiles be considered a part of the multifaceted post-COVID. Evidence-based clinical guidelines for the diagnosis and management of post-COVID syndrome that consider alteration in glucose levels, blood pressure and lipid profiles need to be established to provide patients with integrated clinical care, follow-up and monitoring after COVID-19 recovery. Further investigation of the multifactorial long term medical consequences after recovery from COVID-19 need to be conducted.

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