# Metabolic and Endocrine Complications of Long-COVID-19: A Review

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**ABSTRACT**

Over the past two years, the outbreak of coronavirus disease of 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has centralized the interest of the health care systems and the scientific world. The majority of COVID-19-infected individuals recover fully. However, about 12–50 % of patients experience various mid- and long-term effects after recovering from the initial illness. These mid- and long-term effects are collectively known as post-COVID-19 condition or 'long-COVID'. In the coming months, the long-term consequences of COVID-19 on the metabolic and endocrine systems may expect to rise and pose a global healthcare challenge. This review article discusses the possible metabolic and endocrine complications of long-COVID and the relevant research findings.

## Introduction

In February 2020, the International Committee on Taxonomy of Viruses defined the current coronavirus disease of 2019 (COVID-19) global pandemic as a potentially severe respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Gradually it was proved to be a systemic disease with multiple extra-pulmonary manifestations that surge the lethality of COVID-19 infection. These extra-pulmonary involvements mainly include cardiac, kidney, vascular, gastrointestinal, and central nervous system complications [2]. According to the pathophysiology of COVID-19, the ubiquitous expression of angiotensin-converting enzyme 2 (ACE2), the receptor responsible for the entry of SARS-CoV-2 at the cellular level, widespread endothelial damage, and altered immune responses result in multiple organ involvement of the disease [3].

Many of the COVID-19-infected patients recover within about two 'weeks' time. However, some patients remain symptomatic. This can last for months after first being infected or may have new or recurring symptoms later [4]. Anyone infected with COVID-19 could be subjected to this condition, despite the mild initial presentation. Individuals with this condition are named as having post-COVID conditions, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), chronic COVID, post-COVID-19 syndrome or 'long-COVID' [5]. Long-COVID-19 is a novel condition that is still being studied.

As of August 2022, there have been 595,219,966 confirmed cases of COVID-19, including 6,453,458 deaths globally, as reported by the World Health Organization (WHO) [6]. As a result of the effective vaccines, advancements in testing, measures taken on transmission prevention/control, and relevant national and international legislation, the effect of COVID-19 virus infection has now become less fatal than it was in 2020 and has led to restrictions only limited to public behavior over the world. In many countries, COVID-19 has changed into an endemic condition, and it is likely to remain so through the coming years unless immunity-evading new variants emerge. Meantime, long-COVID or post-COVID-19

syndrome has emerged as a great challenge globally, and it is likely to continue to represent a significant health problem in the coming years [7]. This review article explores the possible metabolic and endocrine complications of long-COVID and summarizes the relevant research findings.

## Review methodology

We performed a narrative review of literature by searching Google Scholar, PubMed, and MEDLINE for original articles, review articles, systematic reviews, randomized control trials, and meta-analysis published in the English language from January 01, 2020, to August 15, 2022, using search string of medical subject headings (MeSH) including the terms long-'COVID,' 'long-haul 'COVID,' 'post-acute COVID-'19,' 'chronic 'COVID,' 'metabolic effects of COVID-'19,' and 'endocrine complications of COVID-'19'. The relevant articles were identified and manually reviewed for relevance with the context.

## What is 'long-COVID-19'?

The majority of the individuals who are infected with COVID-19 recover fully. However, it is recently noted that about 12–50 % of patients experience an array of mid- and long-term effects, such as fatigue, breathlessness, and cognitive dysfunction, after the recovery from the initial illness. These mid- and long-term effects are collectively known as post-COVID-19 condition or 'long-'COVID' [8]. According to WHO, the long-Covid-19 condition is defined as individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms lasting at least two months and cannot be explained by an alternative diagnosis. The common symptoms of long-COVID-19 include fatigue, shortness of breath or difficulty breathing, memory, concentration or sleep problems, persistent cough, chest pain, trouble speaking, muscle aches, loss of smell or taste, depression or anxiety, and fever. Long-COVID-19 may cause difficulties in day-to-day functioning, such as work or household chores [9]. Knowledge and understanding of long-COVID conditions continue to grow. However, so far, no relationship has been observed between the initial severity of COVID-19 infection and the chance of developing long-COVID.

According to a recent meta-analysis and systematic review conducted using 50 studies [10], the estimated global pooled prevalence of long-COVID-19 conditions was 0.43 (95 % CI: 0.39, 0.46). In this study, regional prevalence estimates were Asia-0.51 (95 % CI: 0.37,0.65), Europe-0.44 (95 % CI: 0.32,0.56), and North America-0.31 (95 % CI: 0.21,0.43) and global prevalence for 30, 60, 90, and 120 days after infection were estimated to be 0.37 (95 % CI: 0.26,0.49), 0.25 (95 % CI: 0.15,0.38), 0.32 (95 % CI: 0.14,0.57), and 0.49 (95 % CI: 0.40,0.59), respectively [10].

Though the presence and reactivation of chronic viral infections (i.e., Epstein-Barr virus [EBV], cytomegalovirus [CMV], and human immunodeficiency virus [HIV]) have been suggested as probable contributors to long-COVID, well-characterized studies in post-acute cohorts of individuals with COVID-19 over an extended duration, consistent with current long-COVID definitions are limited. In a cohort of 280 adults with prior SARSCoV-2 infection, Peluso et al. [11] observed an independent association of long-COVID symptoms with serological evidence of recent EBV reactivation (early antigen-D [EA-D] IgG positivity) or high nuclear antigen IgG levels, but not with ongoing EBV viremia. Evidence of EBV reactivation (EA-D IgG) has been most strongly associated with fatigue (odds ratio [OR] 2.12). Underlying HIV infection is also independently associated with neurocognitive long-COVID (OR 2.5). Further, the patients who had serologic evidence of prior CMV infection were less likely to develop neurocognitive long-COVID (OR 0.52) and tended to have less severe ( > 5 symptoms reported) long-COVID (OR 0.44). The findings of this recent study suggested differential effects of chronic viral co-infections on the likelihood of developing long-COVID and predicted discrete syndromic patterns [11].

Zubchenco et al. [12] conducted a pilot observational study to describe clinical and laboratory features of post-COVID manifestations associated with the reactivation of herpes virus infections (CMV, EBV, and human herpesvirus-6 [HHV6]). Eighty-eight patients were recruited in this study, including 68 (72.3 %) individuals with the reactivation of herpes viruses (the main group) and 20 (27.7 %) subjects without detectable DNA of herpesviruses (the control group). Post-COVID manifestations presented with reactivation of EBV in 42.6 %, HHV6 in 25.0 %, and EBV plus HHV6 in 32.4 % of the patients. Compared with controls, patients with herpes virus infections presented with more frequent slight fever temperature, headache, psycho-neurological disorders, pulmonary abnormalities, myalgia ($p < 0.01$), activation of liver enzymes, elevated C-reactive protein (CRP) and D-dimer, and suppressed cellular immune response ($p \leq 0.05$). These results highlight the possible involvement of reactivated herpes virus infections, primarily EBV infections, in severe COVID-19 and the development of post-COVID syndrome [12].

Su et al. [13] conducted a deep multi-omic, longitudinal study with 309 COVID-19 patients from the initial diagnosis to convalescence (2–3 months later) and integrated clinical data and patient-reported symptoms. The study found four PASC anticipating risk factors at the time of initial COVID-19 diagnosis, namely, type 2 diabetes, SARS-CoV-2 RNAemia, EBV viremia, and specific autoantibodies. SARS-CoV-2-specific and CMV-specific CD8 + T cells exhibited unique dynamics during the recovery in the patients with gastrointestinal PASC. Further, the analysis of symptom-associated immunological signatures has shown coordinated immunity polarization into four endotypes, exhibiting divergent acute severity and PASC. The immunological associations between PASC factors have been diminished over time, leading to distinct convalescent immune states in these patients [13].

## Pathophysiology of long-COVID-19

The pathophysiology underlying long-covid remains unclear. Several studies have elaborated on putative mechanisms. However, evidence based on clinical trials among long-COVID-19 patients is sparse [14]. The clinical spectrum of long-COVID-19 is highly heterogeneous. It is likely that organ dysfunction and damage upon acute COVID-19 infection is the possible cause of persistent symptoms [15]. However, studies have shown that patients who experienced mild or moderate levels of COVID-19 disease can still present lingering symptoms that are not associated with organ dysfunctions [16, 17]. The quality of current research findings is inadequate due to heterogeneity in timings of inclusion during the course of COVID-19, lack of adjustments for the severity of the in-

itial disease and treatment, quality of healthcare, and a lack of appropriate comparator groups. Further, it has been shown that the pathophysiology of symptoms could overlap with other issues that are not specific to COVID-19. Therefore, the proposed mechanisms are hypothetical and subject to change.

As Angiotensin-Converting Enzyme 2 (ACE2) receptor is widely expressed in many tissues of the body (i.e., epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic β cells, and renal podocytes), SARS-CoV-2 invades many tissues and exerts multiorgan and multisystem impacts mainly via the renin-angiotensin system. This hormonal and enzymatic system regulates cardiovascular homeostasis and also pulmonary, renal, and innate immunological systems and the gut microbiome [18]. It has been suggested that the oxidative stress and inflammation caused by the virus result in weak immunologic responses and incomplete virus eradication. Further, residuals and antigen remnants produce the ongoing inflammatory response with a vicious cycle leading to the chronic phase of the disease known as long-COVID-19 [19]. Other contributory factors leading to long-COVID-19 include persistent viremia, inadequate antibody generation and psychological factors such as post-traumatic stress disorder (PTSD) [20, 21]. Genomic studies have suggested that some individuals are more prone to develop long-COVID-19 due to their genetic profile principally related to the immune system, such as human leukocyte antigen (HLA) [19]. Some studies have suggested that direct invasion of SARSCOV-2 is responsible for persistent neuropsychiatric outcomes [22]. Dysregulated immunologic response and virus-induced cytokine storm is another mechanism proposed for the persistent syndrome. Pro-inflammatory cytokines (interleukin 7 [IL-7] and interferon-gamma [IFNγ]) are causative for post-stroke depression [23].

RNA of SARS-COV-2 can remain in the central nervous system after the acute phase of the infection, resulting in neuronal loss. Systemic inflammation occurs in COVID-19, causes generalized endothelitis, and damages the blood-brain barrier. Systemic hyperinflammation is reported to be a leading cause of neurodegeneration and cognitive decline of long-COVID-19. These proposals urge further studies to prevent a delayed pandemic of new neurodegenerative conditions [24–26]. Higher levels of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and IL-18 and IL-1β, are observed in patients with COVID-19, which can produce adverse effects on cerebral function [27]. Further, NLRP3 inflammasome-mediated systemic inflammation leads to pathological accumulation of the peptides/proteins, i.e., fibrillar amyloid-β, resulting in the induction and aggravation of neurodegenerative illnesses such as Alzheimer's disease [28, 29].

## Metabolic and endocrine aspects of long-COVID-19: Potential mechanisms and related studies

The estimates on long-COVID-19 prevalence are diverged by ethnicity, racial composition, geographic location, the timing of illness, sex, duration, viral variant, and vaccination status. According to current estimates, about 12–50 % of individuals infected with SARS-CoV-2 will likely develop long-COVID 19 [30]. However, to date, the metabolic and endocrine aspects of long-COVID-19 have not been studied extensively.

### Overweight/obesity

Overweight/obesity is an established major risk factor in the development of severe infection or death from COVID-19 infection. It also appears to significantly increase the risk of developing long-term complications of the disease, the long-COVID. Though long-COVID-19 may be different in its pathogenesis from acute SARS-CoV-2 infection, it is relevant to consider the underlying metabolic factors that contribute to the severity of the initial infection as an underlying risk for long-COVID [30]. In 2020, Leong et al. [31] conducted mendelian randomization studies to analyze potential causal associations of 17 cardiometabolic risk factors (including body mass index (BMI) type 1 diabetes, type 2 diabetes, hemoglobin A1c, waist-hip ratio, CRP, etc.), with susceptibility to severe SARS-CoV-2 infection. This study provided genetic evidence to support higher BMI as a causal risk factor for COVID-19 susceptibility and severity. Further, they reported that obesity-related cardiometabolic diseases such as type 2 diabetes, chronic kidney disease, stroke, and coronary heart disease may mediate the relationship between BMI and higher risk of severity for COVID-19 [31]. The association between long-COVID and overweight/obesity was examined in a retrospective cohort study in Italy, with the participation of 5750 frontline healthcare workers who were tested for close contact with a confirmed case in the absence of personal protective equipment. During this study, each COVID-positive healthcare worker was investigated for cardiovascular risk factors or respiratory diseases. Among them, 352 (6.1 %) were infected by SARS-CoV-2, and 168 cases evolved to long-COVID. The patients who had COVID for more than 35 days had a significantly higher BMI than the patients who did not get long-COVID. Moreover, overweight healthcare workers also showed a significantly increased risk of developing long-COVID [32]. In 2021, the United Kingdom (UK) BioBank data analysis of mortality due to COVID-19 also showed that individuals with higher BMI had an increased risk of COVID-19-related mortality [33].

Obesity is conversely related to the development of COVID-19 via various molecular mechanisms. Therefore, individuals with obesity are recommended to belong to the COVID-19-susceptible population and require more protective measures. Obesity-related decontrolled immune response, endothelium imbalance, metabolic dysfunction and its associated comorbidities, chronic inflammation, and dysfunctional mesenchymal stem cells/adipose-derived mesenchymal stem cells are found to play key roles in driving systemic inflammation resulting in cytokine storm and promoting pulmonary fibrosis triggering functional failure of the lungs, which are the main characteristics of severe COVID-19. Obesity may also compromise motile cilia on airway epithelial cells and impairs the functioning of mucociliary escalators. This reduces the clearance of SARS-CoV-2. Obese and diseased adipose tissues overexpress the receptors and proteases for the entry of SARS-CoV-2, implicating their possible roles as virus reservoirs and reinforce aggressive systemic inflammation and immune response [34].

### Diabetes and metabolic syndrome

Diabetes is associated with an increased risk of severe COVID-19 infection, which is associated with the new onset of diabetes and severe metabolic complications [35]. The link between COVID-19 and new diagnoses of diabetes has been studied in many different

ways; some studies have only examined children, adults, or hospitalized individuals. This makes it difficult to compare and draw conclusions. Studies from the UK, Germany, and the United States have confirmed a raised risk of developing diabetes following COVID-19 infection. Findings indicate that COVID-infected people are anywhere between 31 and 166 % more likely to later develop diabetes (both type I and type II) compared to uninfected people [36].

Patients with diabetes and metabolic syndrome are the main risk groups for developing life-threatening outcomes of COVID-19. A noteworthy number of patients who died from COVID-19 had been suffering from pre-existing diabetes with or without obesity and hypertension [37]. Recent research findings have indicated that the same group of patients are at an increased risk of long-COVID.

In 2021, Montefusco et al. [38] studied the cute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. They conducted a cohort study with 551 hospitalized COVID-19 patients in Italy and found that 46 % of patients were hyperglycemic, and 27 % were normoglycemic. Continuous glucose monitoring revealed altered glycometabolic control with insulin resistance and an abnormal cytokine profile, even in normo-glycemic patients. These glycemic abnormalities were detected for at least 2 months in the patients who recovered from COVID-19, suggesting the association between COVID-19 and aberrant glycometabolic control, which can persist even after recovery [38].

Changes in lipid profiles associated with COVID-19 infection have been reported in many studies. The main changes include decreased serum total cholesterol, HDL-cholesterol, LDL-cholesterol, Apo A1 levels, and elevated triglycerides. The suggested mechanisms include direct cellular infection and disruption of several fundamental lipid biosynthesis pathways by cytokine storm-mediated hyper-inflammatory conditions [39]. Most of these studies have been conducted during the acute phase of the infection. Follow-up studies on lipid metabolism in long-COVID patients are needed.

The association between COVID-19 and diabetes-related metabolic derangement is described as a mutually reinforcing vicious cycle, as on the one hand, the inflammation in acute COVID-19 infection leads to a persistent deterioration of the metabolic situation, on the other hand, diabetes is a state of chronic inflammation which changes the innate and adaptive immune systems that aggravate the symptoms of long-COVID [40].

Hyperglycemia impairs immune responses and is associated with organ damage and systemic complications, thus increasing mortality. SARS-CoV exerts direct damage through cytokine storm to the pancreatic cells that express ACE2 at high levels, causing acute hyperglycemia. The presence of SARS-CoV in pancreatic tissues has been confirmed by immunohistochemistry and in-situ hybridization techniques [41, 42]. Based on these findings, it is hypothesized that COVID-19-positive patients could be subject to virus-mediated pancreatic damage, resulting in the development of diabetes. Obesity could worsen COVID-19 outcomes and mortality; COVID-19 patients with a BMI > 35 kg/m$^2$ have shown a sevenfold higher risk of receiving invasive mechanical ventilation than patients with a BMI < 25 kg/m$^2$. In other models of viral infection, obesity, and its associated inflammatory state have impaired the immune system and altered immune responses. Hence it is postulated that obesity-associated direct viral damage to the pancreatic ß-cells could lead to the development of type 2 diabetes in COVID-19 patients [43]. It is further evident that SARS-CoV-2 mediated reprograming of cholesterol metabolism upregulates the expression of several lipid synthesis modulators (such as sterol regulatory element–binding proteins 1/2, CD36, peroxisome proliferator-activated receptor γ or diacylglycerol O-acyltransferase-1) resulting in the production of cholesterol and lipid droplets [44].

## Endocrine glands

Numerous publications are available on the worsening of pre-existing endocrine disorders by COVID-19 infection or the adverse prognosis of the disease in endocrine patients. Data on endocrine disorders during the infection and upon recovery is scarce.

SARS-CoV-2 gets its cellular access with the help of the ACE2 receptor in a process that requires a transmembrane serine protease 2 (TMPRSS2) protein. ACE2 and TMPRSS2 are widely expressed in many endocrine glands, including the hypothalamus, pituitary, adrenal gland, thyroid, testes, and pancreatic islets [45]. After entering the cells, the virus induces cell damage by releasing proinflammatory cytokines, namely tumor necrosis factor-alpha, IFN-gamma, IL6, and acute phase reactants like ferritin, CRP, and D-dimer [46]. This impact on the endocrine system both during and after the recovery of the disease [44]. Several studies have confirmed thyroid and pituitary disruptions in COVID-19 patients, leading to a significant interest in the impact of COVID-19 on the endocrine system [46]. Therefore, endocrinological evaluations should be considered part of the armamentarium in the management of patients recovering from COVID-19 who continue to get affected by debilitating symptoms, with diligent cognizance about the involvement of the hypothalamo-pituitary-adrenal axis and adrenal and thyroid functions [45].

In 2020, Hanley et al. [47] published the findings of histopathological studies conducted in post-mortems of the severely-infected COVID-19 patients. Their study showed the evidence of four dominant interrelated pathological processes in severe COVID-19, diffuse alveolar damage, thrombosis, haemophagocytosis, and immune cell depletion. Hanley et al. also reported novel autopsy findings, including pancreatitis, pericarditis, adrenal micro-infarction, secondary disseminated mucormycosis, and brain microglial activation [47].

## Thyroid gland

In 2020, Lania et al. [48] conducted a single-center retrospective study on 287 hospitalized (non-intensive care unit) patients with COVID-19 and reported hypothyroidism in 5.2 % of these patients. The majority of them were sub-clinical [48].

In 2021, Khoo et al. [49] published the findings of a cohort observational study on 456 patients from the UK (334 had COVID-19 and 122 did not) that assessed the acute effects of COVID-19 on thyroid function and determined if these effects persisted on recovery from COVID-19. They found that the majority of patients with COVID-19 (86.6 %) were euthyroid, and had a lower admission TSH and FT4 compared to those without COVID-19. TSH levels of the patients were observed to recover to baseline on follow-up [49].

In 2021, Chen et al. [50] published the data of another retrospective Chinese study to evaluate thyroid function in 50 patients with COVID-19. About 56 % (28/50) of the patients with COVID-19 in this study showed lower TSH than the normal range. The TSH

and serum total triiodothyronine (TT3) levels of the patients with COVID-19 were significantly lower than those of the healthy control group and non-COVID-19 patients with pneumonia. The more severe the COVID-19 infection, the lower the TSH and TT3 levels were, with statistical significance ($p < 0.001$). The degree of the decrease in TSH and TT3 levels was positively correlated with the severity of the disease. After recovery, no significant differences in TSH, TT3, TT4, free triiodothyronine (fT3), and free thyroxine (fT4) levels were found between the COVID-19 and control groups [50].

Subacute thyroiditis has been reported in COVID-19 patients and typically involves an initial thyrotoxic hyperthyroid phase followed by a hypothyroid phase and then a euthyroid state or that of hypothyroidism. The exaggerated immune response to the virus and direct viral infection of the thyroid gland is known to be the main mechanism [51].

## Pituitary gland

Direct viral invasion of the olfactory nerve and the presence of the virus in cerebrospinal fluid are confirmed in many patients with COVID-19 who have complete or partial anosmia. ACE2 receptors are located in the pituitary gland, and hematogenous spread and direct viral invasion of the olfactory nerve are reported as the main mechanism for pituitary gland involvement in COVID-19 [52]. The pituitary gland has a rich vascular supply. Vascular endothelium has a high expression of ACE2 receptors; therefore, the pituitary gland is vulnerable to damage during COVID-19 infection [45].

In the review published in 2021 by Mung and Jude [50], three cases were reported of pituitary apoplexy in the presence of macroadenoma and COVID-19. Among them, one patient had low morning serum cortisol. Furthermore, in one case study, a pregnant female presented with pituitary apoplexy and asymptomatic SARS-CoV-2 infection [50]. Several case reports have suggested an increased risk of pituitary apoplexy in patients with pituitary tumors with COVID-19 infection.

## Adrenal glands

In 2021, Leyendecker et al. [53] published the findings of their study conducted to investigate the incidence of acute adrenal infarction (AAI) in 219 patients who underwent chest CT for severe SARS-CoV-2 infection and to correlate findings with prognosis. Of the patients with critical (n = 52) and severe lung (n = 167) parenchyma lesions, 51 (23 %) had CT scan signs of AAI, which was bilateral in 45 patients (88 %). Four patients had acute biological adrenal gland insufficiency (8 %). Univariate analysis in AAI + patients demonstrated a higher rate of stay at the intensive care unit (ICU) (67 vs. 45 %, $p < 0.05$) and a longer stay (more than 15 days for 31 % for AAI + vs. 19 %, $p < 0.05$) compared with AAI − patients [53]. They suggested AAI as a factor for poor prognosis.

Acute adrenal insufficiency has been reported in patients with COVID-19 treated extensively with steroids once the drug is discontinued. Steroid-related metabolic adverse effects have been commonly reported in patients with COVID-19. SARS-CoV-2 was detected in the adrenal gland cells of patients who died due to COVID-19, and the virus was able to infect adrenal cells in-vitro. These findings suggest that the adrenal glands could be damaged due to COVID-19 [54]. The mechanism results from the hypercoagulable state of the infection, which causes acute adrenal infarction. Adrenal insufficiency and COVID-19 show a bidirectional outcome on each other. Patients with adrenal insufficiency are at a higher risk of infection due to reduced adrenocorticotropic hormone secretion. Reports have indicated that hypocortisolism (defined as either 8 AM serum cortisol ≤ 138 nmol/L or stimulated cortisol ≤ 550 nmol/L following 250 mcg tetracosactide) affected 39.4 % of patients at ≥ 3 months following the acute infection [45]. Cortisol modulates the immune system by upregulating cytokines secreted by T helper 2 cells which produce antibodies against pathogens [50].

The occurrence of hyponatremia has been reported in nearly one-third of patients with COVID-19, with multifactorial origins. Proinflammatory cytokines like IL6 stimulate the release of antidiuretic hormones causing the syndrome of inappropriate antidiuretic hormone secretion. Another mechanism is hypovolemic hyponatremia due to vomiting, diarrhea, and inadequate oral intake [55].

## Reproductive tissues

Gonadal failure has been manifested, especially in critically ill patients with COVID-19. In a cohort of 31 patients affected by SARS-CoV-2, lower testosterone levels have been found in ICU patients with COVID-19 compared to those on a general medical ward, suggesting that the low testosterone levels may be secondary to hypogonadotropic hypogonadism driven as a result of critical illness [56, 57]. In a cohort study of 34 men, not only lower testosterone levels but also impaired sperm quality and quantity have been found in moderately affected individuals with COVID-19 [58].

Mannur et al. [59] reported a case study on the post-COVID-19-associated decline in long-term male fertility during assisted reproductive technology (ART). According to their report, a couple with female factor infertility had planned for *in-vitro* fertilization. After embryo freezing, the man became positive for COVID-19. He had experienced mild symptoms and was on antipyretics, multivitamins, and antioxidants. After two weeks, he tested negative for COVID-19 and analysis revealed no evidence of the virus in the semen. Then the *in-vitro* fertilization procedure was restarted. The next analysis of the man's semen was 43 days after his recovery, and severe 'oligo-astheno-teratozoospermia' was observed, with severe sperm DNA damage. There were no acrosomes with dummy and fragmented heads [59]. His pre-COVID sperm count was 40.4 million/mL, and it reduced to 10 million/mL and 22 million/mL at 1 and 4 months post-covid, respectively. Progressive motility of the sperm was 51 % pre-COVID and 22 % post-COVID (after 1 month). He had 12 % of normal form sperms and 76 % live sperms in semen before the COVID-19 infection, and these parameters were less than 1 % and 22 %, respectively, after the infection. This case report concluded that the COVID-19 virus can impair male fertility and altered sperm morphology and DNA integrity could be a major post-COVID-19 complication in men and recommended that men for ART should be tested for COVID-19 before the procedure. These findings collectively conclude that SARS-CoV-2 may impact fertility during the illness.

Testes are vulnerable to SARS-CoV-2 viremia. The virus was detected in the semen of acutely infected patients and during convalescence. Recently, single-cell RNA sequencing demonstrated ACE2 receptors in testicular germ cells, Leydig cells, and Sertoli cells [54].

Autopsy findings showed the presence of coronavirus-like particles in the interstitial compartment of the testes of patients with COVID-19, providing evidence of direct testicular damage by SARS-CoV-2. Histological studies have demonstrated significant germ cell loss in the testes of patients with COVID-19 at post-mortem, with a near-complete absence of germ cells in the seminiferous tubules [45]. These evidences collectively suggest that testes are susceptible to damage by SARS-CoV-2, and the virus could cause morphological changes that impair germ cell functions. However, the long-term effects are yet to be elucidated.

Though ACE2 is also expressed in the ovaries and endometrium (though to a lesser degree compared to the male reproductive system), until now, there is no evidence demonstrating the effects of COVID-19 on the female reproductive system [60, 61]. Some reports on menstrual irregularity have raised the likelihood of altered function of the female reproductive system in relation to COVID-19. A recent survey conducted on 1031 women reported that 46 % of the participants experienced changes in their menstrual cycles since the pandemic, including new-onset menorrhagia, dysmenorrhea, or increased variability of cycle length. These changes could be attributed to the alterations in psychological and physical health as a result of the pandemic [62]. However, whether SARS-CoV-2 could deteriorate ovarian function remains unsolved. The effects of COVID-19 on the female reproductive system are yet to be studied in clinical trials. In 2021, a protocol paper on the impact of COVID-19 on female fertility was published by Li et al. [63], and the findings of this study answered many questions in this regard.

## Conclusion

Currently, the number of COVID-19-infected patients is tailing off in almost all countries. However, the long-COVID-19 or post-COVID-19 syndrome could represent the next major healthcare challenge of the world in the coming years. There is ample evidence in the literature to suggest the metabolic and endocrine derangement pertaining to COVID-19 infection. The current literature comprises of observational cohort studies, case reports, and autopsy studies. The current guidelines for patient management and pathophysiological mechanisms of metabolic and endocrine effects of COVID-19 are drawn in this available literature. Most available data on long-COVID-19 are on its prevalence, risk factors, and symptoms. More prospective cohort and population-based studies are required to evaluate the metabolic and endocrine effects of long-COVID-19. These studies should be planned considering the homogeneity of timings of inclusion of patients during and after the course of COVID-19, proper adjustments for the severity of the disease and treatments, and appropriate comparative groups. It is important to have data on metabolic and endocrine functions before and after the COVID-19 infection.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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