Metabolic and endocrine complications of long COVID-19: A review

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Abstract

Over the past two years, the COVID-19 outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), centralized the interest of the health care systems and the scientific world. Majority of the COVID-19 infected individuals fully recover. However, about 12%-50% of patients experience a variety of 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 health care challenge. This review article aims to discuss the possible metabolic and endocrine complications of long-COVID and the relevant research findings.

Introduction

The present COVID-19 global pandemic is defined as a potentially severe respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by the International Committee on Taxonomy of Viruses in February 2020 [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 principally 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 who 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 (PCC), 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-19' [5]. Long COVID-19 is a novel condition which is still being studied.

As of August 2022, there have been 595,219,966 confirmed cases of COVID-19, including 6,453,458 deaths, reported to World Health Organization (WHO), globally [6]. As a result of the effective vaccines, advancements in testing, measures taken on transmission prevention/control and relevant national and international legislation, the COVID-19 virus has now become less fatal than it was in 2020 and has led to limited restrictions only in public behavior over the world. It can be argued that in many of the countries, at present COVID-19 has changed into an endemic condition and it is likely to remain endemic through the coming years unless and until immunity-evading new variants emerge. In the meantime, long-COVID or post-COVID-19 syndrome still 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 aims to explore the possible metabolic and endocrine complications of long-COVID and to summarize the relevant research findings on the same.

Review methodology

We performed a narrative review of literature searching Google Scholar, PubMed and MEDLINE for original articles, review articles, systematic reviews, randomized control trials (RCTs) and meta-analysis published in 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 fully recover. However, it is recently evident 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 the World Health Organization, 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 that last for 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 functioning in day to day life, such as work or household chores [9]. Knowledge and understanding of long COVID conditions are growing. However, there is no relationship to find so far 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). 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). Global prevalence for 30, 60, 90, and 120 days after infection have 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].

Tough the presence and reactivation of chronic viral infections [i.e. Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV)] have been sugested as probable contributors to Long COVID, well-characterized studies in post-acute cohorts of individuals with COVID-19 over a extended duration, consistent with current long COVID definitions are limited. In a cohort of 280 adults with prior SARSCoV-2 infection, Peluso et al., have observed that long COVID symptoms were independently associated 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 most strongly associated with fatigue (OR 2.12). Underlying HIV infection has 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). Findings of this recent study have suggested differential effects of chronic viral co-infections on the likelihood of developing long COVID and predicted discrete syndromic patterns [11].

Zubchenco et al have conducted a pilot observational study to describe clinical and laboratory features of post-COVID manifestations associated by reactivation of herpes virus infections (CMV, EBV, HHV6). Eighty eight patients have been recruited in this study, including individuals with reactivation of herpes viruses, 68 (72.3%) (main group) and 20 (27.7%) subjects without detectable DNA of herpesviruses (control group). Patients with post-COVID manifestations have presented with reactivation of EBV in 42.6%, HHV6 in 25.0%, and EBV plus HHV6 in 32.4%. Compared with controls, patients with herpes virus infections presented with more frequent slight fever temperature, headache, psycho-neurological disorders, pulmonary abnormalities and myalgia ($p < 0.01$), activation of liver enzymes, elevated 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 the post-COVID syndrome. [12].

Su et al have conducted a deep multi-omic, longitudinal study with 309 COVID-19 patients from initial diagnosis to convalescence (2–3 months later), integrating clinical data and patient-reported symptoms. Study has found four post-acute sequelae of COVID-19 (PASC) anticipating risk factors at the time of initial COVID-19 diagnosis namely, type 2 diabetes, SARS-CoV-2

RNAemia, Epstein-Barr virus viremia, and specific auto-antibodies. 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 have 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 patients is sparse [14]. The clinical spectrum of long COVID-19 is highly heterogeneous. It is likely that the organ dysfunction and damage upon the acute COVID-19 infection is possibly involved in 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 initial 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 not only cardiovascular homeostasis, but 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]. Other contributory factors which lead to long COVID include the persistent viremia and 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 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 (IL-7 and IFNγ) are causative for the 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 damage to the blood brain barrier. It is reported that the systemic hyper-inflammation is a leading cause of neurodegeneration and cognitive decline of long COVID. These proposals urge further studies to prevent a delayed pandemic of new neurodegenerative conditions [24-26]. Higher level of NLRP3 inflammasome activation together with IL-18 and IL-1β are found in COVID-19 patients 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 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, timing of illness, sex, duration, viral variant, and vaccination status. According to current estimates about 12%-50% of individuals who are 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 up to a great extent.

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., have 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, C-reactive protein etc.], with susceptibility to severe SARS-CoV-2 infection. This study has provided genetic evidence to support higher BMI as a causal risk factor for COVID-19 susceptibility and severity. Further they have reported that the obesity-related cardiometabolic diseases such as type 2 diabetes, chronic kidney disease, stroke, and coronary heart disease may be mediators of the relationship between BMI and higher risk of severity for COVID-19 [31]. Association between long COVID and the overweight/obesity has been studied using 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 positive healthcare worker has been investigated for cardiovascular risk factors or respiratory diseases. Among them 352 (6.1%) have been infected by SARS-CoV-2, and 168 cases evolved to long COVID. The patients who were having COVID more than 35 days have shown a significantly higher BMI than the patients who did not get long COVID. Moreover, the healthcare workers who were overweight also have shown a significantly increased risk of developing long COVID [32]. In 2021, The United Kingdom (UK) BioBank data analysis of COVID-19 mortality has also shown that individuals with higher BMI, had an increased risk of COVID-19-related mortality [33].

It has been shown that Obesity is conversely related to the development of COVID-19 via various molecular mechanisms. Therefore, it is recommended that individuals with obesity 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, dysfunctional mesenchymal stem cells/adipose-derived mesenchymal stem cells are found to play key roles in driving systemic inflammation resulting the cytokine storm and promoting pulmonary fibrosis triggering lung functional failure which one of the main characteristics of severe COVID-19. Obesity may also compromise motile cilia on airway epithelial cells impairing the functioning of muco-ciliary 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 its possible roles as virus reservoir and accelerator reinforcing violent systemic inflammation and immune response [34].

Diabetes and metabolic syndrome

Diabetes is associated with an increased risk of severe Covid-19 and the COVID-19 infection 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 looked at children, some are only on adults, some only on hospitalized people. This makes it difficult to compare and draw conclusions. Studies from the United Kingdom, Germany and United States have confirmed a raised risk of developing diabetes following COVID-19 infection. Findings have indicated that the 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].

It has been proven that the patients with diabetes and metabolic syndrome are in the main risk groups for developing life-threatening outcomes of COVID-19. A noteworthy number of patients who died from COVID-19 were 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., studied the cute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. They have conducted a cohort study with 551 hospitalized COVID-19 patients in Italy. There results have shown that 46% of patients were hyperglycemic, and 27% were normoglycemic. On continuous glucose monitoring, they have reported altered glycometabolic control, with insulin resistance and an abnormal cytokine profile, even in normo-glycaemic patients. These glycaemic abnormalities have detected for at least 2 months in the patients who recovered from COVID-19 suggesting that COVID-19 is linked with aberrant glycometabolic control, which can persist even after recovery [38].

COVID-19 infection associated lipid profile changes have been reported in many studies. Main changes include decline in serum total cholesterol, HDL-cholesterol, LDL-cholesterol and Apo A1 levels and elevated triglycerides. Direct cellular infection and disruption of several fundamental lipid biosynthesis pathways by cytokine storm mediated hyper-inflammatory condition are the suggested mechanisms [39]. Most of these studies have been conducted at the acute phase of the infection. Follow up studies on the lipid metabolism on long COVID patients are needed to be conducted.

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

Hyperglycemia impairs the immune responses and associates with organ damage and systemic complications increasing mortality. SARS-CoV, exerts direct damage through cytokine storm to the pancreatic cells, that highly express ACE2 causing acute hyperglycemia. Presence of the 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. It has been proven that obesity worsened COVID-19 outcomes and mortality. COVID-19 patients with a body mass index (BMI) >35 kg/m^2 have shown a sevenfold higher risk to receive invasive mechanical ventilation than patients with BMI<25 kg/m^2. Obesity and its associated inflammatory state have impaired the immune system and altered immune responses in other models of viral infection. 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 upregulate the expression of several lipid synthesis modulators (such as SREBP1/2, CD36, PPARγ or DGAT-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 are scares.

SARS-CoV-2 gets its cellular access with the help of the angiotensin-converting enzyme 2 (ACE2) receptor in a process that require a transmembrane serine protease 2 (TMPRSS2) protein. ACE2 and TMPRSS2 are widely expressed in many endocrine glands, including hypothalamus, pituitary, adrenal gland, thyroid, testes, and pancreatic islets [45]. After getting into the cells, virus induce the cell damage by releasing proinflammatory cytokines namely TNF-alpha, IFN-gamma, IL6 and acute phase reactants like ferritin, CRP and D-dimer [46]. This leads to the impacts of the virus

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 growing a vast interest over COVID-19 impacts on the endocrine system [46]. Therefore, it has been suggected that endocrinological evaluations should be considered as 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, adrenal and thyroid functions [45].

In 2020, Hanley et al., published the findings of histopathological studies conducted in post-mortems of the severely infected COVID-19 patients. This study has shown the evidences for four dominant interrelated pathological processes in severe COVID-19; diffuse alveolar damage, thrombosis, haemophagocytosis, and immune cell depletion. They 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., conducted a single-centre retrospective study by recruiting 287 hospitalized (non-intensive care unit) COVID-19 patients and reported that among them hypothyroidism was present in 5.2%. The majority of them were sub-clinical [48].

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

In 2021, Chen et al., 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 have shown TSH lower than the normal range. The levels of TSH and serum total triiodothyronine (TT3) of the patients with COVID-19 were significantly lower than those of the healthy control group and non-COVID-19 pneumonia patients. 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

decreases 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 have been found between the COVID-19 and control groups [50].

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

Pituitary gland

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

According to the review published by Mung and Jude 2021, there are three cases reported in the literature of pituitary apoplexy in the presence of macroadenoma and COVID-19. Of which one patient had low morning serum cortisol. Further there was one case study of a pregnant female presenting with pituitary apoplexy and asymptomatic SARS-CoV-2 infection [50]. Several case reports have suggested that there is an increased risk of pituitary apoplexy in patients with pituitary tumors with COVID-19 infection.

Adrenal glands

In 2021, Leyendecker et al., have 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 an acute biological adrenal gland insufficiency (8%). Univariate analysis in AAI+ patients have demonstrated a higher rate of ICU stay (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 have suggested AAI as a factor for poor prognosis.

Acute adrenal insufficiency has been reported in COVID-19 patients who are treated extensively with steroids once the drug is discontinued. Steroid-related metabolic adverse effects have commonly reported in COVID-19 patients. SARS-CoV-2 has been detected in adrenal gland cells of patients who died due to COVID-19 and the virus has been able to infect adrenal cells in-vitro. These findings suggest that the adrenal glands could be damaged due to COVID-19 [54]. The mechanism has reported to be the result of 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 through upregulating cytokines secreted by T helper 2 (TH2) cells which produce antibodies against pathogens [50].

Occurrence of hyponatremia has been reported nearly in one third of patients with COVID-19, with multifactorial origins. Proinflammatory cytokines like IL6 stimulate the release of antidiuretic hormones causing 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 the critically ill COVID-19 patients. Lower testosterone levels have been found in ICU patients with COVID-19 compared to those on a general medical ward in a series of 31 patients affected by SARS-CoV-2, 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 the lower testosterone levels but also impaired sperm quality and quantity have found in moderately affected individuals with COVID-19 [58].

Mannur et al have reported a case study on post-COVID-19-associated decline in long-term malefertility during assisted reproductive technology (ART). According to their report a couple

with female factor infertility has planned for *in-vitro* fertilization. After embryo freezing, the man became positive for COVID-19. He had experienced mild symptoms and on antipyretics, multivitamins and antioxidants. After two weeks he had tested negative for COVID-19 and his semen analysis revealed no evidence of virus in the semen. Then the *in-vitro* fertilization procedure restarted. The next semen analysis of the man has taken place 43 days after his recovery and showed severe 'oligo-astheno-teratozoospermia', with severe sperm DNA damage. There were no acrosomes with dummy and fragmented heads [59]. His pre-covid sperm concentration was 40.4 million/mL and it was reduced to 10 million/mL and to 22 million/mL at 1 month and 4 months post-covid, respectively. Progressive motility of the sperm was 51% pre-covid and 22% at post-covid (after 1 month). He had 12% of normal form sperms and 76% live sperms in semen before covid and these parameters have become less than 1% and 22% respectively after COVID-19 infection.This case report has concluded COVID-19 virus can impair male fertility with alterations in 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 have an impact on fertility during the illness.

Testes are vulnerable to SARS-CoV-2 viraemia. Virus has identified in the semen of acutely infected patients and during convalescence. ACE2 receptors have been demonstrated in testicular germ cells, Leydig cells, and Sertoli cells by single-cell RNA sequencing recently [54]. Autopsy findings have shown the presence of coronavirus-like particles in the interstitial compartment of the testes of COVID-19 patients providing evidence of direct testicular damage by SARS-CoV-2. Histological studies have demonstrated significant germ cell loss in the testes of Covid-19 patients at postmortem, with a near-complete absence of GC 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), up to date there are no evidence demonstrating COVID-19 effects on the female reproductive system [60,61]. Some reports on the menstrual irregularity have raised the likelihood of altered function of the female reproductive system in relation to Covid-19. In a recent survey conducted with 1031 women has reported that 46% of

them had experienced changes in their menstrual cycles since the jerk of the pandemic, including new-onset menorrhagia, dysmenorrhea, or increased variability of cycle length. These changes could be attributed to the alterations of psychological and physical health as a result of the pandemic [62]. However, the doubt if 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 has been published by Li et al., on impact of COVID-19 on female fertility [63]. The findings of this study answers many questions in this regard.

Conclusion

Currently, the numbers of COVID-19 infected patients are tailing off in almost all countries. However, the long COVID-19 or post COVID-19 syndrome could represent the next major health care 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 is basically comprised of observational cohort studies, case reports and autopsy studies. Present guidelines for patient management and pathophysiological mechanisms of metabolic and endocrine effects of COVID-19 are drawn on this available literature. Most of the 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 effect 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 with appropriate comparative groups. It is important to have data on metabolic and endocrine functions before and after the COVIS-19 infection.

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