Review Article

Endocrine Flawed In COVID-19 Era

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Abstract

The clinical practice and social relationships have been changed since the emergence of COVID-19. It is declared a global pandemic affecting millions of people across the world. SARS-CoV-2 virus while infecting human has been noted to affect several vital organs and biological systems. This can occur directly through virus-induced damage or indirectly due to the host response after virus entry, which produce a negative impact on body systems. Human endocrine system similar fatal effect. Thereafter, the knowledge and clinical expertise about the management of the endocrine pathological consequences of COVID-19 is essential in the current pandemic situation. The need of such clinical proficiency is increasing more demanding as SARS-CoV-2 pandemic is growing towards more devastating phase. The coronavirus enters the human body by using the angiotensin converting enzyme 2 (ACE-2). Other than the pneumocytes, ACE-2 is expressed by several endocrine glands like the pancreas, pituitary gland, adrenal glands, thyroid, ovary, and testes. Diabetes has a significant impact on covid 19. Diabetes Mellitus is one of the comorbidities most frequently linked to severity and mortality resulting from COVID-19 infection. Thus, careful management that includes modification of treatment may be needed to protect from the most dangerous outcomes of the virus infection or hospitalization with COVID-19, not only for patients with a known history of diabetes but also those suffering SARS-CoV-2 induced new-onset diabetes. Those suffering from obesity are more susceptible to SARS-CoV-2 as well as to adverse effects. In order to limit the susceptibility and severity of SARS-CoV-2 infection, there needs to be adequate management of nutrition of obese and undernourished patients. Hypothalamic-pituitary axis suppression, adrenal insufficiency, thyroid dysfunction, hypocalcemia, vitamin D lack, and vertebral fractures have also been reported as frequent findings in COVID-19 infected individuals who needed to be hospitalized and often associated with fatal clinical outcomes. Prompt glucocorticoid adjustment is also required in patients with COVID-19 having adrenal insufficiency. Addressing hormonal status may limit further treatment burden for a COVID-19 infected patient.

Keywords: Endocrine; SARS-COV; ACE-2; COVID-19; Pandemic; Diabetes Mellitus; Thyroid; Adrenal; Obesity; Pancreas

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Introduction

COVID-19 excessively distresses individuals with endocrine disabilities, accordingly stroking them at a higher risk for the severity of the disease and increased morbidity and mortality [1, 2]. In December 2019, there was an outbreak of meager cases of pneumonia of unrevealed basis of the disease from Wuhan, Hubei in China [3-6]. The spread of the COVID-19 rapidly occurred to the remaining parts of the globe. Over the months that have followed, millions have been affected globally with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection that is frequently known as COVID-19 [7, 8]. Internationally, "as of 6:30 pm CEST, 30 July 2021, there have

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been 196,553,009 confirmed cases of COVID-19, including 4,200,412 deaths, reported to World Health Organization (WHO). As of 29 July 2021, a total of 3,839,816,037 vaccine doses have been administered" [9]. Coronavirus 2019 (COVID-19) pandemic is an immense tragedy in the history of medical science in this century [10]. Although there are considerable differences in death rates were observed diverse around the globe, studies have consistently shown that comorbidities, primarily type 2 diabetes mellitus, suggestively increase fatal outcomes, including death among patients with SARS-CoV-2 [11, 12]. Hospital admission of diabetic patients is out of proportion compared to the general population, as evidenced by higher admissions rates to hospitals among diabetes patients [13-16]. A study in China revealed that patients admitted in ICU have much more comorbidities than non-ICU admitted patients [17]. Research based on autoptic evidence of COIVID-19 patients reveals that the pathology of SARS-CoV-2 involves multiple endocrine glands. The endocrine glands frequently affected are the thyroid, parathyroid, pituitary gland, pancreas, adrenals, testis and sometimes parathyroid glands. Multiple pathological processes of COVID-19 include inflammation, vascular derangement, and autoimmune reactions to ensure functional impairment, even on some occasions the irreversible loss of endocrine damage [18-22].

Objectives of the Study

This paper aims to point up so far published information on COVID-19 with endocrine comorbidities. Furthermore, reiterate already prevailing data from preceding coronavirus outbursts experience for effective risk categorization and developing treatment protocol for patients with SARS-CoV-2 disease. This manuscript primarily focused on the endocrinopathic engagement of SARS-CoV-2 infection, as alteration of this system can contribute more in COVID-19 related mortality and morbidity. Extensive research regarding COVID-19 is ongoing to better understand the impact of endocrine involvement; thereby, more evidence-based management guidelines are expected to emerge shortly. We focused on being too aware of the endocrine sequelae of COVID-19, which might be overlooked during its management, might bring a new disaster. This paper will address precautionary measures and overall treatment measures of endocrine disease settings in the background of worldwide lockdown, movement control order (MCO), restrictions, regulations being levied, and suggest real-world instructions for ongoing endocrine management. This paper possibly makes a platform for further research to explore many unknowns in the endocrine field by covid 19 and to understand the pathophysiology of new-onset endocrine diseases by SARS-COV-2.

Materials and Methods

Published papers writing about endocrine changes in SARS-CoV-2 and SARS-CoV patients were incorporated. We have made a wide-ranging literature hand search for articles in PubMed and Google Scholar databases till June 2021, with the following keywords: "COVID-19", "diabetes mellitus," "thyroid disorders," "adrenal insufficiency," "Cushing's syndrome," " hypothalamus-pituitary axis," "obesity" "management," "treatment" and "guidelines" with interposition of the Boolean operator "AND."

Covid 19 with Endocrine Pancreatic Changes and Diabetes Mellitus

Several viruses have been spotted as one of the perpetrators of developing diabetes mellitus in humans [23, 24]. Those viruses include Coxsackie B virus, enteroviruses, retroviruses, mumps, rubella, Epstein-Barr, cytomegalovirus, and varicella-zoster (Figure 1) [25, 26]. Research studies have also reported that coronavirus, including COVID-19, can cause diabetes mellitus in animals and humans [16, 27, 28]. Multiple research studies confirmed that the SARS-CoV-2 virus enters human lungs, pancreas, and other tissue cells through binding with the ACE-2 [29-35]. The expression of ACE-2 is much more robust in pancreatic endocrine tissue than exocrine tissue. The amount of cellular-level tissue destruction by SARS-CoV directly depends on the neck and neck of the countenance of tissue ACE-2. Thus, SARS-CoV viruses extensively whittle away pancreatic β-cells and cause of acute of diabetes mellitus, revealing a potential diabetogenic action of this virus (Figure 2) [21, 36-38].

Similarly, as pancreatic β-cells abundantly express ACE-2 receptors, the SARS-CoV-2 virus utilizes those receptors to enter β-cells and cause profound impairment of its physiology through damage, consequently worsening hyperglycemia in patients with among already diagnosed cases of diabetic

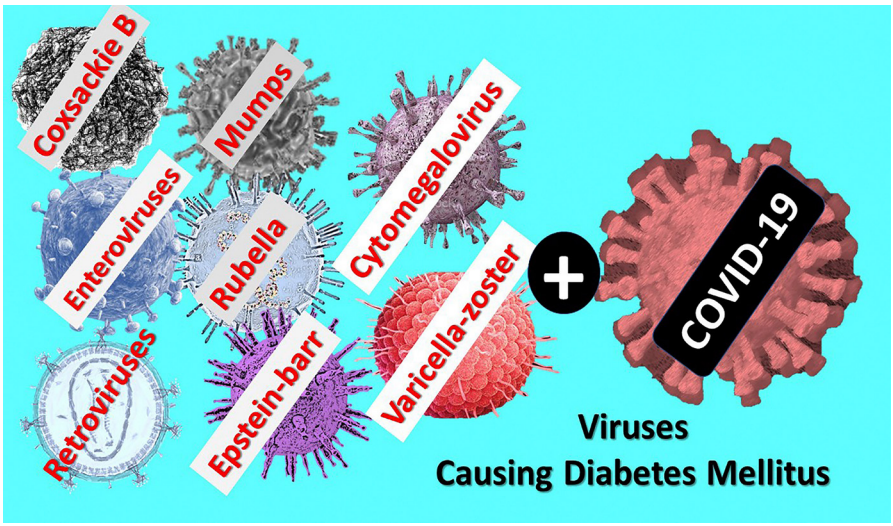

Figure 1 : Illustrating viruses causing diabetes mellitus.s

individual (Figure 2). These category patients frequently develop life-threatening outcome diabetes, for example, ketoacidosis or hyperosmolarity, and require high-dose insulin [39, 40]. Additionally, several patients develop diabetes mellitus due to complication COVID-19 hitherto nondiabetic has been steadily quantified [41, 42]. The temporary or insistent hyperglycemia among COVID-19 cases and the factual incidence and characterization of this afresh developed diabetes are to date under potential research issues. International registry hard work is continuing to assemble and evaluate those cases globally [27, 43, 44]. Since pancreatic β-cells richly contain ACE-2 receptors, they thereby are injured by SARS-CoV-2 with significant hyperglycemia worsening in patients diagnosed with diabetic individuals, frequently byzantine with acute life-threatening medical emergency of diabetes known as diabetic ketoacidosis (DKA) along with high-dose insulin requirement [45-47].

An earlier study reported that hospitalized patients with mild coronavirus infection (without corticosteroid drugs) had a high-level fasting plasma glucose (FPG) than those with non-corona pneumonia [36]. Additionally, among COVID-19 cases receiving no glucocorticoid medication, 51% of them develop diabetes mellitus with no diabetic evidence beforehand. After that, hyperglycemia remains a self-determining prognosticator for fatal-outcome including death and disease miseries among COvID-19 patients with and without a history of diabetes mellitus [36]. A broad spectrum of the prevalence rate has been reported regarding the association of COVID-19 and non-communicable diseases (NCDs) among research reports within the country and globally. Nevertheless, the three most common NCDs [diabetes mellitus, hypertension, and cardiovascular disease (CVDs)] are frequently correlated with COVID-19 [48-50].

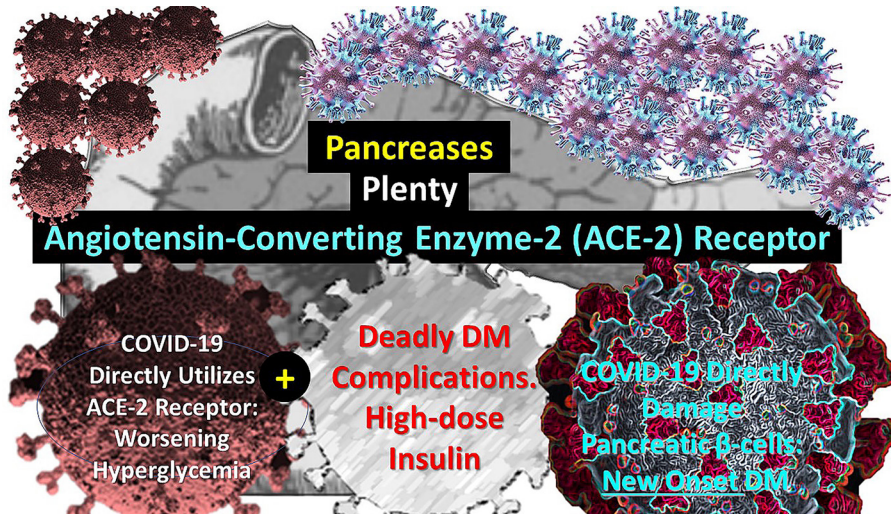

Figure 2 : Depicting the relation of ACE-2 receptor with COVID-19 and diabetes mellitus

It has been demanding to explore outstanding pathological aspects of diabetic COVID-19 infection because the number of cases is exploding [51]. Multiple studies reported that diabetes mellitus remains the top comorbidities of COVID-19, frequently speedily deteriorates towards grave prognosis, and a 7-30% prevalence rate was observed [52-54]. A self-determining correlation was observed between HbA_{1C} and COVID-19 mortality rates among the British in type 1 and 2 diabetic individuals [55, 56]. Another

comparative study between diabetic and non-diabetic individuals reported that diabetic COVID-19 cases with HbA_{1c} more than 7.5% (58 mmol/mol) had a higher possibility of hospitalization and mortality compared to HbA_{1c} below 7.5% (less than7.5% HR 1.50 [95% CI 1.40–1.60], below or equal to 7.5% HR 2.36 [2.18–2.56]) [56]. One more study observed that diabetic individuals with HbA1c more significant than 10% (86 mmol/mol) had a similarly high risk of mortality in-hospital than those COVID-19 cases with an HbA_{1c} of 6.5-7% (48–53 mmol/mol) [55]. There is a complex two-way bond between COVID-19 and diabetes [52, 57]. Firstly, diabetes is correlated with the higher possibility of developing severe COVID-19 [27]. Secondly, COVID-19 can give rise to the genesis of diabetes and worsen the glycemic control of the known diabetic individual (Figure 2). Thereby, the imperative need for pro-active management to minimize fatal diabetic complications [27].

The COVID-19 virus is communicated via respiratory precipitations and aerosols from individual to individual, remaining close contact without any intermediate host [58]. ACE-2 has been recognized as a responsible receptor for SARS-CoV and is exceedingly found on the pulmonary epithelial tissues[59,60], cardiac myocytes, vascular endothelium, and various other cells type [61]. ACE-2 is also expressed in the pancreas and causes damage to the pancreas in a proportion of patients with SARS-CoV-2 infection[21]. However, dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Nevertheless, explanatory research does not propose a distinguished effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 vulnerability[28]. Poor glycemic control represents crucial risk factors for worse COVID-19 outcomes[53, 62].

Data suggest that the risk of being infected with COVID-19 is not increased for individuals with diabetes mellitus. However, the close relationship between the presence of diabetes and the poor outcome of the viral infection has been observed, particularly in subjects with poor glycemic control [63]. Quite a few pathogenic processes, together with the inflection of an immune response, proclivity to severe disease outcome, related morbidities, and everyday use of agents able to modify angiotensin-converting enzyme 2 (ACE-2) activity, make a diabetic person vulnerable to severe or critical outcomes [64].

It is estimated that there are about 463 million diabetic adult individuals worldwide [65]. Therefore, a notable proportion of the population is at a higher risk of suffering the adverse effects of COVID-19 infection. Although the pathophysiology for this higher risk has not been determined entirely, factors that may be responsible include predisposition to infection, increased inflammation, and deterioration of co-morbidities [66].

There can be an increase in the release of inflammatory mediators, including lipopolysaccharide, inflammatory cytokines, and chemokines like TNFα, IL-1β, IL-6, IL-8, IL-17, and toxic metabolites in the blood of those infected with SARS-CoV-2 virus[67-70]. Modulation of natural killer cell activity modulation and formation of IFNγ can lead to increased permeability of the vasculature and /or interstitium for inflammatory mediators [71]. There is also increased production of ROS (reactive oxygen species) in subjects infected with SARS-CoV-2 [72]. These events eventually result in fibrosis of the lung, acute lung damage, and acute respiratory distress syndrome (ARDS)[73,74]. ROS production and activation of the renin-angiotensin-aldosterone system (RAAS) by the virus via increased angiotensin II expression lead to insulin resistance, hyperglycemia, and damage of vascular endothelium[28]. These changes lead to cardiovascular events, thromboembolism, and disseminated intravascular coagulation [75,76]. An increase in clotting components like fibrinogen and D-dimer have also been observed in COVID-19 Infection, which eventually leads to a rise in blood viscosity and widespread damage of vascular endothelium and related cardiovascular events thromboembolism and DIC[77,78]. The outcome of all these mechanisms can lead to thrombosis, pulmonary embolism, and eventually death[79]. Biologically, individuals who have diabetes have instability in glycemic control, immune response impairment, and comorbidities like obesity also contribute to fatality due to the viral infection [80].

Meta-analysis has shown an 87% higher death risk in diabetic patients with COVID-19 than non-diabetic COVID-19 patients [81]. Pre-existence of diabetes was associated with a higher risk of about twofold of suffering severe or critical COVID-19 illness and ~threefold rise in the risk of in-hospital mortality [82].

Studies revealed that patients infected with COVID-19 who had no other comorbidities except diabetes (n = 24) had a higher risk of developing severe pneumonia. The levels of inflammation-related

biomarkers in the serum-like C-reactive protein, IL-6, serum ferritin, and D-dimer, coagulation index were noted to be significantly higher ($P < .01$) in infected subjects with diabetes in comparison to non-diabetic individuals, showing that diabetic patients are more prone to inflammatory storm eventually resulting in rapid deterioration of health condition when infected with COVID-19 [83].

The outbreak of SARS-CoV in 2003 suggests that covid 19 can worsen glycemic control in preexisting diabetes caused by the stress of a critical illness by increased secretion of counter-regulatory hormones like catecholamine, cortisol, Glucagon, and growth hormone[84]. Besides this, there is an expression of ACE-2 in acinar cells and within islet cells of Langerhans of the pancreas[35]. When SARS-CoV-2 binds with ACE-2 receptor on islet cells of the pancreas, temporary inflammation occurs in the organ, causing induction of transient hyperglycemia [2,85]. This transient insulin-dependent diabetes mellitus is resolved when the disease is resolved[36].

Direct damage of β-cell, insulin resistance induced by cytokine, hypokalemia, and drugs used to treat COVID-19 (corticosteroids, ritonavir, or lopinavir) can deteriorate the control of glucose in diabetic patients [2]. The two-way interaction between COVID-19 and diabetes mellitus sets up a vicious cycle. Thus, diabetes mellitus must take all necessary precautions and ensure reasonable glycemic control amid the ongoing pandemic [86].

"Sick day rules" need to be implemented to avoid possibly placing the health of diabetic individuals in jeopardy[87]. Type 1 diabetic patients with fever and hyperglycemia; these patients need to monitor blood glucose and ketone levels in urine more frequently and adjust basal insulin requirement or use indemnification bolus proactively to maintain euglycemia and adapt measures to maintain appropriate glycemic control[88]. In case of doses of an oral drug, metformin is to be stopped in all subjects who are hospitalized, and the drug can be recommenced following through clinical and laboratory appraisal of renal status, and blood lactate. A recent study suggest that progress to severe COVID-19 disease may be reduced in those taking metformin[89-91]. There is a potentially higher risk of developing ketoacidosis and dehydration in patients taking sodium-glucose cotransporter-2 inhibitors (SGLT-2i), and thus this treatment should be halted [92]. Since the protective effect of DPP4i and statins has been indicated in a recent study, it may be beneficial for the patients who are already consuming such a drug to continue taking it if no specific contraindications are present. Hyperglycemia can be controlled most effectively with insulin in hospitalized highly ill patients and is also the case for COVID-19 infection [16]. Subcutaneous Bolus basal regimen preferred for patients with persistently high blood glucose levels, and critical patient in ICU setting should be treated with intravenous insulin infusion [93]. Suppose infusion pumps for intravenous insulin are unavailable. In that case, alternative subcutaneous regimens need to be used to manage hyperglycemia, and mild diabetic ketoacidosis [94]. Insulins requirements are exceptionally high in individuals treated with dexamethasone and the use of insulin in the range of 1.2–1.5 units/kg [88].

Covid 19 and Diabetes Mellitus in Pregnancy

Gestational diabetes mellitus (GDM) is a frequent medical complication during pregnancy. Pregnant COVID-19 individuals might be at an augmented health threat in developing more serious disease processes when compared to non-pregnant individuals. Furthermore, there may be an amplified risk of adversative pregnancy consequences, for example, preterm birth and many more[95].

During an evolving pandemic with a highly infectious virus, screening oral glucose tolerance tests (OGTTs) involves high exposure risks and health service burden. These patients need to stay in hospitals and laboratories, susceptible to contracting and spreading the disease for a long time. Careful consideration needs to be given to the screening of GDM by routine use of OGTT in the context of the impact of the local pandemic, including community transmission rates. In the pandemic context with SARS-CoV-2 infection, the recently released new guidelines and recommendations by international authorities have considered some medical services to be unessential in antenatal care in an attempt to lower the risk of pregnant women contracting the virus. Some of the recommendations of the Royal College of Obstetricians and Gynecologists (RCOG) [96-98] Australia [98, 99], and Canada[100] refer to screening for gestational diabetes, illustrated in Table1.

Covid 19 and Obesity

Obese individuals infected with COVID-19 should be considered as a higher risk population [101]. Chronic diseases like obstructive sleep apnea, diabetes mellitus, and lung surfactant dysfunction are linked to obesity, thus intensifying the risk of COVID-19 correlated with worsening the disease process [102]. Management of subjects with severe obesity in intensive care is invariably challenging [103]. Obesity is likely an independent risk factor for severe SARS-CoV-2 illness and needs to be investigated further [104]. Association has been observed between obesity and pulmonary dysfunction, hypercoagulability, and raised risk of thrombosis, emerging as an essential factor resulting in a more severe clinical course in COVID-19 patients [105].

Various mechanisms have been suggested regarding the association between obesity and poor outcome of COVID-19 [106]. Higher ACE-2 expression in adipose tissue may lead to increased duration of viral exposure in obese subjects due to prolonged viral shedding, thus increasing SARS-CoV-2 infection susceptibility and disease aggravation risk [107]. Chronic inflammation driven by obesity, aberration of cytokine activation, lowered adiponectin and raised leptin secretions, and innate and adaptive immune dysfunction may contribute to worsening clinical outcomes in patients with COVID-19 [108].

Covid 19 and Adrenal Insufficiency

There has been the identification of SARS-CoV genome sequences in the cytoplasm of neurons in the hypothalamus and cerebral cortex [109]. It possibly causes induction of hypophysitis or affects the hypothalamus, directly resulting in impaired hypothalamic-pituitary axis (HPA) function. Leow *et al.* revealed that in patients who improved from SARS-CoV, there was an occurrence of hypocortisolism. The study included SARS-CoV infected patients who had well-functionating hypothalamic–pituitary–adrenal (HPA) axis. After recovery, these patients complained of malaise, fatigue, weakness, orthostatic dizziness, lassitude, apathy, anorexia, anxiety, and depression. Three months following recovery, it was noted that 39·3% of patients developed hypocortisolism, 83·3% of which had central hypocortisolism as shown by low adrenocorticotropic hormone (ACTH) levels[110].

Interestingly, most of these individuals did not receive any systemic glucocorticoids during treatment for SARS; thus, the possibility of HPA axis suppression by exogenous corticosteroid use was ruled out. The hypocortisolism was resolved in 62·5% of patients within a year with an average duration of 5·9±3·1 month since the condition developed was transient. Also, resolution of symptoms which include orthostatic hypotension, compared to the beginning of the study, was reported by these subjects [110].

Regarding cortisol dynamics, autopsy studies on patients who died from SARS-CoV-1 have found the adrenal cortical cells with degeneration and necrosis, suggesting a direct cytopathic effect. ACE receptors present in the adrenal cortical cells, cortisol dynamics are likely to be altered in patients with SARS-CoV-2 [110,111].

Previously, data published so far have not considered the possibility of direct viral aggression towards the adrenal gland in healthy subjects, also has not been considered in the data published to date [112]. Viral, bacterial, and fungal sepsis may cause adrenal hemorrhage, necrosis, or thrombosis with resultant acute hypoadrenalism. The possibility of venous thrombo-embolism occurring in COVID-19 infected patients and its favorable treatment by heparin in some of them have been suggested in recent findings [113]. Thus, a thrombotic event at the adrenal level in COVID-19 patients has to be considered as a reason for acute adrenal insufficiency. The resulting acute adrenal insufficiency with hormone production impairment can eventually lead to shock and worsening of the possibility of reacting to severe respiratory distress. Screening for pituitary-adrenal axis function and identifying this condition in due time could allow appropriate replacement therapy to avoid severe shock [111].

Individuals having adrenal insufficiency or uncontrolled Cushing's syndrome are at greater risk for death from a respiratory-related infection, like COVID-19, and in order to avoid complications, several vital recommendations need to be followed to avoid complications [18]. Subjects with adrenal insufficiency also have a higher risk of infection, which may be complicated due to the development of an adrenal crisis; however, no evidence is currently present to suggest that these patients are more prone to develop a severe disease course[114]. We emphasize the requirement for education (stringent social distancing rules, sick day rules), equipment (steroid emergency self-injection kit, sufficient glucocorticoid supplies),

and empowerment (COVID-19 guidelines, steroid emergency card) for adrenal crisis prevention [115].

When patients suffering from primary adrenal insufficiency develop an acute COVID-19 infection, a stress dose of glucocorticoid with oral administration of 20 mg hydrocortisone every six hours can be considered. This may prevent the appearance of an adrenal crisis[115]. There is a need to administer parenteral glucocorticoids in subjects with a worsening health condition in COVID-19. A proposed protocol includes intramuscular administration of 100 mg hydrocortisone, followed by 200 mg hydrocortisone per 24 hours through continuous intravenous infusion [116]. However, until this can be established, 50 mg hydrocortisone boluses should be administered every 6 hours [117]. If on fludrocortisone, the usual dose of (0.05-0.1mg/day) is continued[118].Serum potassium should be monitored strictly as hypokalemia has been reported in patients with COVID-19. [119].

COVID-19 and Gonads

In the testes, there is ACE-2 expression at a high level; as a matter of fact, the mRNA and protein for ACE-2 expression are almost highest in the testis of the human body [120] .ACE-2 is expressed by spermatogonia, Sertoli cells, and the Leydig cells[121]. There needs to be a cautious interpretation of the serum testosterone levels in COVID-19 infected patients since hypothalamic-pituitary-testicular axis suppression may occur in any acute illness that is critical in nature [122,123]. The biochemical manifestation of low follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone [2]. However, a study recently carried out with 81 COVID-19 infected men showed that serum testosterone was lower (not statistically significant), whereas there was a significantly higher level of serum LH than that of 100 age-matched healthy men. A significantly lower Serum Testosterone: LH ratio in COVID-19 patients with a negative association with disease severity was observed [124]. A raised level of serum LH in men with COVID-19 annul the possibility of suppressing the hypothalamic–pituitary–testicular axis and suggests primary Leydig cell damage [125,126]. COVID-19 effect on female gonads yet not much data avaiable.

Covid 19 and Thyroid Dysfunction

Information about the relationship between susceptibility to COVID-19 and thyroid conditions is inadequate, but individuals suffering from thyroid disease are neither at a higher risk of contracting the SARS-CoV-2 virus nor experiencing its complications [127,128]. However, if the prescribed thyroid medications are not instructed, uncontrolled thyroid disease may increase the risk of getting infected with the virus and developing complications [129]. A person's risk for infections and complications increases when receiving high-dose steroids, immunosuppressive drugs, and specific treatments [130]. Such individuals need to maintain caution. An increased risk of COVID-19 infection has not been observed in subjects having Graves' or other autoimmune thyroid diseases [131-133].

Prescribed medications both for hypothyroidism and hyperthyroidism must be continued as instructed. The majority of thyroid cancer patients are not likely to be more prone to SARS-CoV-2 infection. However, there may be an increased risk of infection with the virus or its complications for subjects with metastatic thyroid cancer (papillary or medullary) who have lung metastases or undergo certain kinds of cancer treatment [134]. Antithyroid drugs (ATDs) are not known to raise the risk of infection unless they cause neutropenia**.** Antithyroid drugs are not considered drugs that increase susceptibility to the virus or cause the development of more severe diseases [135]. Although rare, side effects similar to symptoms of COVID-19 infection like sore throat, fever, and pain in muscle may occur in subjects with Graves' disease receiving anti-thyroid medications, which may be due to a decrease in blood leukocyte count [136]. A patient with COVID-19 infection can continue consuming Antithyroid drugs unless neutropenia (neutrophil count of $< 1.0\times10^9$/L) develops [135]. Lymphopenia seems to appear in COVID-19 infection commonly and is not considered an indication for halting Antithyroid drug treatment [137].

An overlap of the symptoms due to neutropenia (sore throat, fever, flu-like illness, mouth ulceration) may occur due to infection with COVID-19 (new continuous cough, fever, flu-like illness). Clinically distinguishing between these two diagnoses would be difficult for both physicians and patients [135]. Infected individuals with thyroid eye disease are incredibly vulnerable and at very high risk of severe illness from COVID-19 on therapy with steroid at the dosage that is immunosuppressive or other immunosuppressive agents like mycophenolate and

Table 1 : Proposed new strategies of screening and postpartum follow-up during the COVID-19 pandemic.

	RCOG	Canada	Australia
Early	HbA1c or RPG	HbA1c or RPG	HbA1c and RPG
Pregnancy	HbA1c 5.9-6.4% or RPG 9–11 mmol/L	GDM if HbA1c ≥ 5.7% (39 mmol/mol) and/or RPG≥11.1 mmol/L	HbA1C ≥5.9%# Initial FPG FPG<4.7mmol/L is normal FPG 4.7 – 5.0 mmol/L→ OGTT, GDM criteria as noted FPG≥5.1mmol/L → GDM
Screening			GDM Diagnosis: HbA1c first trimester ≥ 5.9%) OGTT one or more •Fasting ≥ 5.1 mmol/L • 1 hour ≥ 10 mmol/L • 2 hour ≥ 8.5 mmol/L
24 to 28 weeks screening	HbA1c and either FPG or RPG. HbA1c ≥ 5.7% (39 mmol/mol) or FPG≥95mg/dL (5.6 mmol/L) or RPG ≥ 162 mg/dL (9 mmol/L) Furthermore, at any occasion of in pregnancy, women with high-level glycosuria (2+ or above), increases the possibility of diabetes (symptoms – nocturia, thirst, polydipsia), or large for gestational age (LGA) / polyhydramnios on ultrasound should be apprised for GDM.	HbA1c and RPG	FPG OGTT if FPG 4.7-5.0 mmol/L
Post-Partum Follow up	HbA1c screening at 3–6 months	OGTT delayed until safe	OGTT delayed 6 months postpartum or HbA1c 3–6 month

RCOG: Royal College Obstetrics and Gynecology

self-isolation/shield for at least 12 weeks as per govt rule should be advised[135,138]. All non-urgent surgery needs to be deferred [139]. Additionally, radioiodine administration for hyperthyroidism will have to be postponed; planned, elective radioiodine treatments have already been canceled by most Trusts. Such a decision is based on the prioritization of emergency care delivery and anticipated difficulties in adhering to radiation protection guidelines during this pandemic [140].

In the thyroid gland, levels of expression of ACE-2 are high, which is more than in the lungs. Thyroid disorders related to COVID-19 include thyrotoxicosis, hypothyroidism, Subacute thyroiditis, and nonthyroidal illness syndrome. Moreover, a considerable change in thyroid cancer treatment plans is taking place with more teleconsultations and fewer diagnostic and therapeutical procedures [141].

Word Health Organization has not recommended thyroid function assessment for COVID-19 in their clinical management guidelines [142]. Nevertheless, alterations in thyroid function were already noted in some studies through the earlier coronavirus outbreak with SARS-CoV-2. In particular, serum levels of TSH, T3, and T4 in patients with SARS-CoV were reported to be significantly lower than in the control group in a study carried out by Wang et al. Positive correlation was observed between the severity of SARS and levels of T3, suggesting that more severe the disease, the lower was the level of T3 [143]. COVID-19-related thyroid disorders observed from the analysis of the current literature are hypothyroidism, hyperthyroidism, subacute thyroiditis, sick euthyroid syndrome. THYROCOV study provides the first evidence that COVID-19 may be associated with a high risk of thyrotoxicosis related to systemic immune activation induced by the SARS-CoV-2 infection [144].

In the acute phase of SARS COV 2, increased interleukins concentrations, particularly interleukin 6, lead to thyrotoxicosis, and Its prevalence correlates with the raised interleukin-6[144,145]. There are desiodases, thyroid hormone transport proteins disruption, and pituitary cell TSH secretion impairment resulting in abnormal thyroid functional parameters. There is a decrease in Free T3 concentration, which correlates with an increase in interleukin-6 and free T4 average or moderately decrease, and TSH normal or decrease [133,146]. Such

anomalies are known as “low T3 syndrome” or “euthyroid sick syndrome” (abnormal thyroid function parameters in non-thyroidal illness). Such anomalies in thyroid function tests are transient in general and require no specific treatment [133,143,147].

Conclusion

The involvement of the endocrine system with COVID-19 remains largely unexplored in the ongoing fight with the pandemic. This manuscript reviews what is known about the impact of COVID-19 on the pathophysiology and management of diabetes as well as other endocrine glands, like pituitary, adrenal, thyroid, and gonadal function. The available data regarding the relationship between the endocrine system and COVID-19 are primarily factual and conjectural. These findings must be validated through large scale clinical studies. However, for future research, there is plenty of scopes provided by the current data. An area of active research that can be explored for future research is the short-term and long-term systemic effects of COVID-19 infection. Although it may sound premature, awareness about these possibilities needs to develop among the endocrinologists in clinical practice, mainly when dealing with survivors of COVID-19 infection.

Recommendation

There need to be large-scale studies regarding the interaction between the endocrine system and COVID-19 infection. There should also be more studies to explore the effects of COVID-19 on the different endocrine glands such as the thyroid, parathyroid, adrenal, pituitary gland, and glands. Post COVID-19 endocrine complications should be kept in mind. A clear guideline can be developed for the proper management of COVID-19 patients who suffer from endocrine disorders. Subjects with adrenal disorder receiving steroid therapy should be carefully monitored. We recommend that individuals with endocrine disorders continue to be monitored through telemedicine service and create awareness among patients to report if they develop COVID-19 symptoms. All diabetic individuals should strict control of blood glucose and blood pressure. These patients must always stick to the treatment regime and remain close supervision of their physicians. We also recommend that subjects with diabetes and obesity must follow the preventive and protective measures and be timely referred when COVID-19 infection suspects for proper management. Also, the blood glucose level of a non-diabetic individual admitted to the hospital with COVID-19 must be monitored. Care should be taken for giving proper nutrition to obese as well as undernourished individuals for maintaining optimum energy. The endocrinologists should develop awareness to manage COVID-19 complications in patients with endocrine disorders and/or endocrine disorders resulting as complications after COVID-19 infection.

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Consent for Publication

All authors reviewed and approved the final version and have agreed to be accountable for all aspects of the work, including any issues related to the accuracy or integrity of Financial Support and Sponsorship

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