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Basic mechanisms of SARS-CoV-2 infection. What endocrine systems could be implicated?

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Abstract
Although SARS-CoV-2 viral attacks starts by the interaction of spike protein (S Protein) to ACE2 receptor located at the cell surface of respiratory tract and digestive system cells, different endocrine targets, endocrine organs and metabolic conditions are of fundamental relevance for understanding disease progression and special outcomes, in particular those of fatal consequences for the patient. During pandemic, moreover, a specific phenotype of COVID-19 metabolic patient has been described, characterized by being at particular risk of worse outcomes. In the present paper we describe the mechanism of viral interaction with endocrine organs, emphasizing the specific endocrine molecules of particular relevance explaining COVID-19 disease evolution and outcomes.

Keywords SARS-CoV-2 · COVID-19 · Mechanisms · Endocrine systems · Diabetes mellitus · Pituitary · Thyroid · Calcium · Hypoadrenalism

1 Introduction

Endocrine targets are of particular relevance for either SARS-CoV-2 viral entrance to the cells as well as regarding modulation of disease expansion in a given host [1]. Lung cells are among others of the respiratory tract, those through which serious disease is initiated. Expression of different molecules in the respiratory tract cells surface is therefore crucial for SARS-CoV-2 viral attack. Besides this respiratory tropism, digestive epithelium is another entrance door for SARS-CoV-2 and part of the initial symptoms are clearly related to the viral invasion of the gut system. Once the disease has achieved this point, systemic involvement may happen and it is at this moment when endocrine organs involvement may take place, either as victims of the viral attack or as suicidal actors amplifying the viral damage, in particular cytokine storm expansion.

In this paper we aim to make an overview of these two pivotal positions of the endocrine organs and system in the COVID-19 sanitary earthquake.

2 COVID-19 and pathogenic mechanisms

COVID-19 can alter the function of different endocrine glands and metabolic processes and put patients at risk of acute or late-onset endocrine or metabolic dysfunction. In addition, preexisting endocrine disorders or metabolic processes can increase the predisposition to develop COVID-19 or a more severe clinical presentation and outcome (Fig. 1).

SARS-Cov-2 infection has a similar mechanism of action than SARS-Cov-1 and this is by via binding to ACE2 protein, which has an important expression in several endocrine tissues including testis, thyroid, adrenal, pituitary, hypothalamus and adipose tissue [2]. The SARS-Cov-2 virus binds to the ACE2 receptor and uses the cellular serine protease TMPRSS2 for S protein priming. Both ACE2 and TMPRSS2 mRNA have been reported in different endocrine tissues [2]. The possible mechanisms by which the SARS-CoV-2 virus, after entering an endocrine gland and

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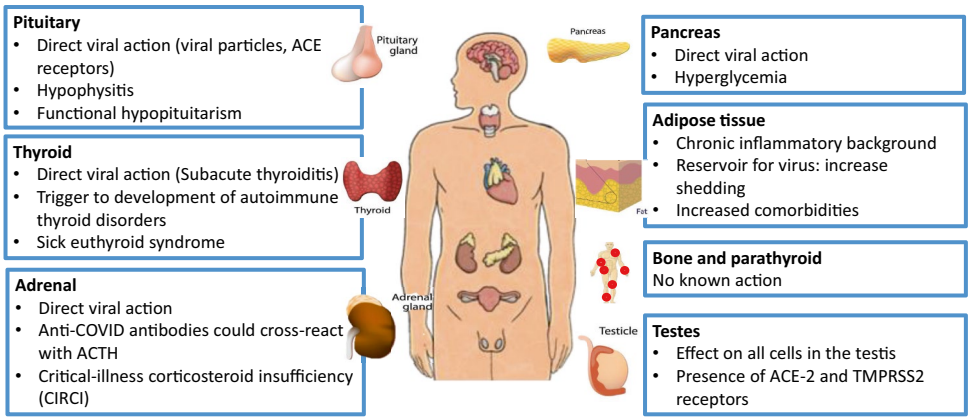


Fig. 1 Different pathogenic mechanisms including direct and indirect viral action could explain why different endocrine glands/organs that can be affected by COVID-19

binding the ACE2 receptor, can produce damage include characteristically thrombosis and hypoxia that are typical of highly vascularized organs, such as endocrine organs particularly the pituitary. In addition, other mechanisms that can play a role include immune response against the virus and cytokine storm [2].

2.1 Pathogenic mechanisms involved in COVID-19 infection targeting different endocrine organs

The hypothalamic-pituitary (HP) axis may also be a target of the SARS-CoV-2 [3]. Coronavirus infections can also affect the central nervous system, including the hypothalamus and pituitary. It is still not well known whether the entry is via bloodstream or direct though the cribriform plate. Direct deleterious effect on these organs is suggested by the fact that SARS-CoV-1 viral particles have been detected in autopsy studies involving neuronal degenerated tissue [4]. In this regard, ACE2 and cellular serine protease-TMPRSS2 receptors, that are entries of the SARS-CoV-2 virus, are present in the hypothalamic-pituitary region [5]. SARS-CoV-2 has been reported in the cerebrospinal fluid and also in autopsy studies of the hypothalamus in COVID-19 patients [6, 7]. Another possible mechanism of pituitary injury during COVID-19 is the generation of an immune-mediated hypophysitis, which has also been previously reported in SARS-CoV-1. Moreover, functional hypopituitarism probably related to the increase in circulating cytokines produced by the viral infection has been reported in both SARS-CoV-1 and SARS-CoV-2 infections. It is interesting that abnormalities related to hypopituitarism can persist long-term after SARS-CoV-1 infection, even months after the infection [1]. This could also be the case in SARS-CoV-2, in which follow-up studies of pituitary function are ongoing.

Thyroid dysfunction is a frequent finding in COVID-19 patients that can be mediated by direct or indirect viral effects. In SARS-CoV-1 infection, destruction of the follicular epithelium and the parafollicular cells were reported [8]. ACE2 expression has been found in thyroid follicular cells, and cases of atypical subacute thyroiditis with negative autoantibodies have been found associated with SARS-CoV-2 infection [9–12]. This type of thyroiditis has been traditionally associated to a viral origin. A recent report showed scintigraphy findings typical of subacute thyroiditis in one third of patients three months after COVID infection, pointing to a much more prevalent phenomenon than previously thought and it is now considered as a sequela associated with COVID-19 [10]. The COVID-19 cytokine storm may eventually precipitate the development of autoimmune thyroid disorders including Graves' disease, Graves' ophthalmopathy, and Hashimoto thyroiditis [13]. Nevertheless, the most common thyroid manifestation in COVID-19 patients, mostly in hospitalized patients, is a kind of euthyroid sick syndrome, including decrease in T3 and T4 in some occasions, which run in parallel with an increase in cytokines. These abnormalities could also be very persistent in time as it was also reported in SARS-CoV-1 [14]. Follow-up studies regarding these abnormalities are still awaiting.

A direct cytopathic effect on adrenal cortical cells with generation of diverse lesions, including necrosis of these cells, has been reported in autopsies from SARS-CoV-1 patients [4]. A similar effect could happen in SARS-CoV-2 virus, as ACE2 receptors are present in the adrenal gland. Another possible mechanism that has been described in SARS-CoV-1 is the homology between certain amino acid sequences of the virus and have with ACTH. In this regard, antibodies that are primarily produced against SARS-CoV-1 could also cross-react and destroy ACTH [15]. This mechanism could happen not only in SARS-CoV-1, as has been described, but also in SARS-CoV-2 as SARS-CoV-2 is structurally more than 95% homologous to SARS-CoV-1. However, this

mechanism of production of adrenal insufficiency has not been proved yet in SARS-Cov-2. Moreover, another possible mechanism that could provoke adrenal insuficciency in severe forms of COVID-19 is a critical illness related corticosteroid insufficiency (CIRCI). This condition is directly related to the severity of the stress situation generated during a critical illness. In this regard, severe forms of COVID-19 could produce CIRCI and cause inadequate stress corticosteroid mediated response [16].

There is no data on the potential direct effect of COVID-19 on the parathyroid glands or the bones. Nevertheless, hypocalcaemia is a frequent complication and is a predictor of more severe forms of COVID-19 and an unexpected high frequency of silent fractures has been described in these patients [17].

Severity and fatality related to COVID-19 have been observed more in males than in females [18]. Regarding the testis, ACE2 and TMPRSS2 are expressed both in spermatogonia and somatic (Leydig and Sertoli) cells. The testes are probably a high-risk organ for SARS-CoV-2 infection. Destruction of germ cells with reduced sperm cell count [19] and lymphocytic infiltrates in Sertoli and Leydig cells [19, 20] has been reported in the testis from autopsies of SARS-CoV-1 patients, pointing to an immune-mediated damage. SARS-CoV-2 viral particles have also been observed in testis autopsies of these patients [20]. Semen analyses of men with COVID-19 have shown the presence of SARS-CoV-2, but little is yet known about its potential relationship with infertility development [21]. In females ACE2 is also expressed in the ovary, but TMPRSS2 appears to be absent.

2.2 Pathogenic mechanisms, endogenous and exogenous molecules involved in COVID-19 infection in different metabolic and endocrine organs.

2.2.1 Diabetes

It is now accepted that diabetes is an important risk factor for COVID-19 infection and the severity of disease [22–24]. A significant part of this risk condition can be attributed solely to hyperglycemia. People with type 1 and type 2 diabetes have an increased risk of hospitalization, need of intensive care and mortality from COVID-19 due to bad glycemic control in a dose-dependent manner [25]. COVID mortality related to any type of diabetes has been associated with aging, mal gender, low socioeconomic conditions, non-white ethnicity, previous cardiovascular disorders, impaired renal function, poor glycemic control, as well as to obesity and underweight. According to this phenotype, a nationwide Swedish study [26], has found that type 2 diabetes people showed increased risk of hospitalization, admission to intensive care and death for COVID-19 in comparison to type 1 diabetes subjects. These later presented few admissions into intensive care and deaths compared to type 2. People with type 2 and type 1 diabetes have a higher risk of hospitalization, intensive care and mortality compared to control population. However, this excess of risk only remained significant in type 2 diabetes after adjustments for comorbidities and pharmacological treatment.

Different hypotheses have been formulated to causally explain such an association; one plausible explanation that the generalized multisystemic inflammation process observed in SARS-CoV-2 infection potentiates a hyperglycemic state and vice-versa, and this phenomenon possibly favors viral replication [27]. Additionally, abnormal acute glycosylation of the SARS-CoV-2 virus has been suggested as a potentiator of viral pathogenesis through modification of viral epitopes that otherwise would have been targeted by the immune system [28]. And also, glycosylated ACE2 on target cells enhances viral tropism and penetration, leading to a higher intensity of COVID-19 infection and severity in hyperglycemic people [28].

The virus infects peripheral monocytes in a more efficient way under hyperglycemic conditions and upregulates ACE2. After this happens, improved cytokine production by immunocompetent cells take place and can turn to an overexaggerated production of what has been denominate “cytokine storm”. Thus, an adequate insulin treatment is required to control the glucose availability for activated M1 macrophage and the glycolytic flux that feds the viral replication process. In this regard, the viral enhancement of hypoxia-inducible factor-1a (HIF-1a) is a critical regulator of glycolysis in this situation, in a way that a metabolic rewiring is produced at the monocyte levels which is beneficial for the viral replication and shedding.

In addition, it has been proposed that complementing the treatment with an eucaloric ketogenic diet could be a potential metabolic tool for reducing adenosine triphosphate production from aerobic glycolysis in the M1 macrophage phenotype [29]. This combined therapeutic option could theoretically reduce the overproduction of cytokines and, consequently, the accumulation of neutrophils, monocytes, and platelets from the blood. In addition, it could be advantageous for the metabolism of anti-inflammatory M2 macrophages because these cells predominantly express oxidative phosphorylation enzymes and are best fed by the oxidation of fatty acids in the mitochondria.

Finally, it has been demonstrated that human β-cells express viral entry proteins and SARS-CoV-2 indeed

infects and replicates in cultured human islets. Infection of endocrine pancreas leads to morphological and functional changes, including reduced numbers of insulin-secretory granules in β-cells and impaired glucose-stimulated insulin secretion [30].

2.2.2 Obesity

Obesity is an important risk factor for contracting COVID-19, as it is also for other infections either of viral or bacterial origin and also for developing more severe forms of the disease [31]. Obesity is usually causally associated with pulmonary dysfunction, thus facilitating viral and bacterial infections. Several mechanisms have been proposed to explain the higher risk of obesity to contracting COVID-19. One feasible option is related to the higher expression of ACE2 in adipocytes which may facilitate prolonged viral shedding [32, 33]. Another important mechanism involved in the increased severity in obese people is associated to the COVID-19 driven cytokine storm, which is characterized by an overproduction of pro-inflammatory cytokines and an increase in inflammatory cells with a decrease in anti-inflammatory cytokines and regulatory cells [34, 35]. The cytokine storm identified in multiple respiratory viral infections including COVID-19 exhibits an overproduction of interferon, tumor necrosis factor α, interleukins, and different chemokines. Considering that subjects with obesity have also a pre-set proinflammatory milieu, it is feasible that COVID-19 could further exacerbate this basal obesity-related inflammation, exposing them to an absolute higher level of circulating inflammatory molecules compared to lean human subjects. This seems a plausible mechanistic explanation of the increased risk of severe complications of COVID-19 in subjects with obesity [36].

Obese individuals may exhibit greater viral shedding suggesting potential for enhanced viral exposure, especially if several family members are overweight. This may be aggravated in overcrowded multigenerational households, which are more common in the socioeconomically deprived communities in which obesity is prevalent [37]. In addition, as it has been described for influenza infection, obesity not only increases the severity but also enhances viral diversity. The altered microenvironment associated with obesity supports the emergence of a more virulent influenza virus population capable of inducing greater disease severity. This could be related to an impaired interferon response in obese subjects, which has been demonstrated in experimental models, both in obese mice and obesity-derived human bronchial epithelial cells [38]. The same could happen in COVID-19 infection in humans.

3 General mechanisms involving endocrine molecules as SARS-CoV-2 viral targets

SARS-CoV-2 viral entry requires at least two host proteins [39]: the angiotensin converting enzyme-2 (ACE2) and the TMPRSS2 protease. Angiotensin-converting enzyme 2 (ACE2) is the only recognized human homologue of ACE, the key regulator of blood pressure, and has approximately 42% identical protein sequences. Since its discovery in 2000 [40, 41], ACE2 has been implicated in heart function, hypertension, and diabetes, with its effects being mediated, in part through its ability to convert angiotensin II to angiotensin. ACE2 biology and crucial contribution to SARS-CoV-2 viral disease development will be extensively covered in another chapter of the present issue. SARS-CoV-2 targets cells through the viral structural spike protein (S protein) that binds to the ACE2 receptor. ACE2 is expressed in human pancreas, and coronavirus could enter beta-cells binding to its receptor, causing acute beta-cell dysfunction, hyperglycemia and transient diabetes [42]. A chapter in this monograph focuses on the study of this mechanism and COVID-19 infection. The transmembrane serine protease type 2 (TMPRSS2) in the host cell activates viral S protein and cleaves ACE2 receptor, further promoting viral binding to host cell membrane [39].

Other endocrine molecules have been described as virus targets, as neuropilin-1 (NRP1) or human dipeptidyl peptidase 4 (DPP-4) (Fig. 2). Table 1 summarizes the endocrine targets effects on COVID-19 of each molecule reported in this chapter.

3.1 TMPRSS2 protease

Transmembrane serine protease type 2 (TMPRSS2) is a cell surface protein primarily expressed across the respiratory and digestive tracts. SARS-CoV-2 requires TMPRSS2 as well as ACE2 receptor for entry into epithelial host cells. Both ACE2 and TMPRSS2 are present in nasal and bronchial epithelium and pneumocytes, described as SARS-CoV-2 primary target cells in the early infection phase. Furthermore, coronavirus replication in the lungs needs TMPRSS2. Experimental studies showed that TMPRSS2-/- knockout mice infected with coronavirus reduced the severity of the infectious disease with lower viral replication in lungs than wild-type mice [43], indicating the critical role of this pathway in coronavirus disease initiation.

Gastrointestinal symptoms, such as diarrhea and abdominal pain, are observed in COVID-19 patients, often preceding respiratory symptoms. TMPRSS2 is also expressed in intestinal epithelial cells across the gastrointestinal tract, which is the target for many enteric viruses. Some studies have shown that SARS-CoV-2 infects intestinal enteroids

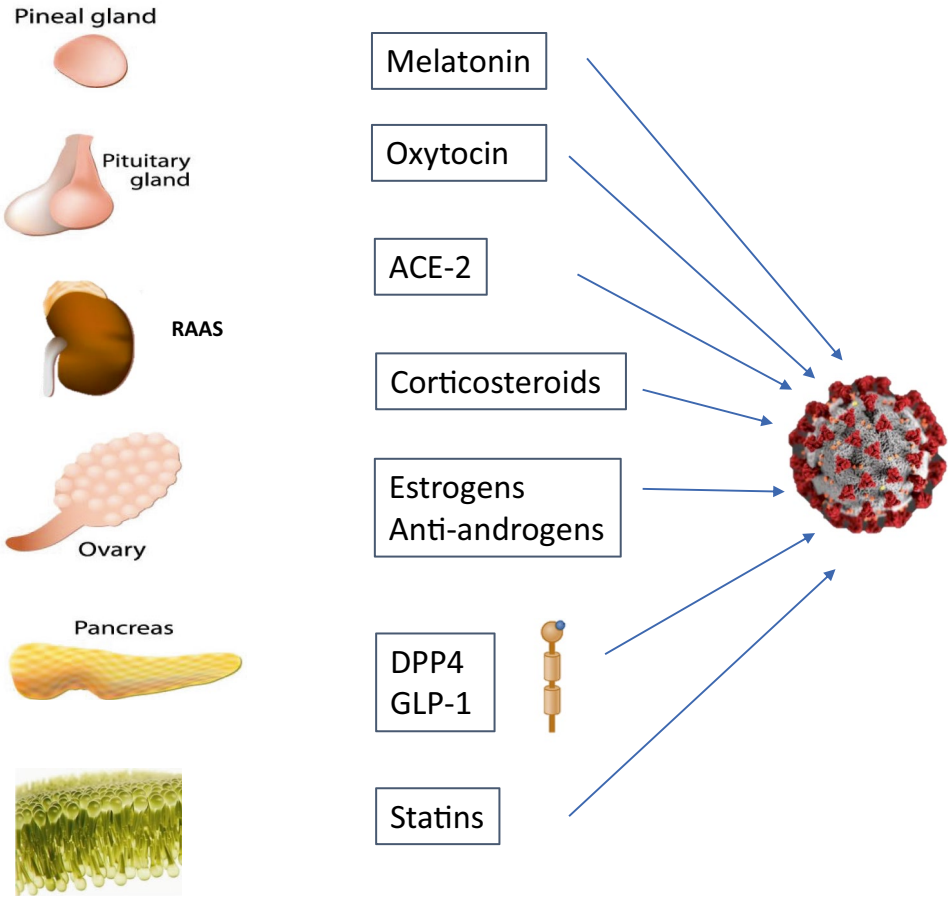


Fig. 2 Possible endocrine and metabolic targets that have been considered for COVID-19 therapy. Different hormones and drugs have been included as possible targets for COVID-19 including melatonin, oxytocin, DPP-4 (human dipeptidyl peptidase 4) inhibitors, GLP-1 (glucagon-like peptide-1) agonists, ACE-2 (angiotensin converting enzyme-2) inhibitors, corticosteroids, estrogens, anti-androgens and statins

cells and TMPRSS2 as well as TMPRSS4 promotes SARS-CoV-2 active infection in these cells [44]. Many endocrine tissues and organs, such as pancreas, thyroid, testis or pituitary, express TMPRSS2 and this could be related to endocrine manifestations of COVID-19 disease [45].

Androgens upregulate the transcriptional activity of the TMPRSS2 gene which could contribute to the male predominance observed in severe infections [46]. TMPRSS2 is also expressed in prostate epithelial cells and, different mutations in its gene, particularly its fusion, represents one of the most frequently biologic defects observed in primary prostate cancer. Confirming the hypothesis that androgenic upregulation may be of importance in disease severity, it has been described that patients with prostate cancer treated with androgen deprivation seem to be partially protected from SARS-CoV-2 infection [47]. In this sense, as TMPRSS2 inhibitors are currently available for treating prostate cancer, this could represent an appealing target for the prevention or treatment of COVID-19 disease [39, 46].

3.2 Neuropilin-1

Neuropilin-1 (NRP1) is a pleiotropic type 1 transmembrane protein cell surface receptor involved in angiogenesis, tumorigenesis, viral entry, axonal guidance and immune function [48] and has been considered as a potential therapeutic target in differents pathologies as cancer or autoimmune diseases. NRP1 has been recently described in experimental studies to be a complimentary entry mediador factor of SARS-CoV-2 into host cells, in addition to ACE2 and TMPRSS2, thus acting as a potentiator of SARS-CoV-2 infectivity [49, 50]. SARS-CoV-2 S protein, which is instrumental for the binding and fusion with host cell membrane, is to get bound to NRP1 after its cleavage [49].

NRP1 is also used as a surface receptor by different proteins, as the vascular endothelial growth factor (VEGF) or semaphorin 3 family [51]. NRP1 is expressed in vascular endothelial cells and may contribute to the organ tropism of COVID-19 disease beside the respiratory tract [49, 50]. Severe and later stages of the disease are related to vascular dysfunction as arterial injury, increased coagulation or sepsis and could be possibly due to NRP1 [52, 53].

NPR1 has been found also to show different degrees of expression in parathyroid, adrenal and testis and a lower expression in thyroid gland compared to the former endocrine organs. Indeed, it is possible that NRP1 could participate in SARS-CoV-2 attack to the pituitary gland as VEGF receptors are also present in the pituitary [54].

Table 1 Endocrine targets with potential usefulness for SARS-CoV-2 treatment

	Possible action against SARS-CoV-2	Recommendation
TMPRSS2	• Viral alternative receptor	• No recommendation so far
NRP1	• Viral alternative receptor	• No recommendation so far
Melatonin	• Anti-inflammatory and antioxidant effects could be useful in the cytokine storm • Improves circadian rhythm, better sleep and shorter ICU stay	• Potentially useful in sleep regulation and neurocognitive protector as adjuvant therapy
Oxytocin	• Immunomodulatory and anti-inflammatory properties could reduce cytokine storm • Enhances endothelial integrity and could have cardio-protective properties and reduce thromboembolisms	• No recommendation till clinical trials are conducted
Corticosteroids	• Anti-inflammatory action	• Highly recommended in severe hospitalized patients
Antiandrogens	• Decrease TMPRSS2 expression	• Antiandrogens should be continued in patients previously treated No recommendation till clinical trials are conducted as primary indication
Estrogens	• Protective action in endothelial function • Stimulate humoral immune response • Modulate inflammatory response	• Menopausal hormonal therapy should be continued • Hormonal contraception treatment should be discontinued or switched to progesterone only contraceptives in hospitalized women • No recommendation till clinical trials are conducted
DPP-4	• Potential alternative viral target • Anti-inflammatory properties • Immunomodulator Facilitates glycaemic control	• DPP-4 inhibitors should be continued if previously indicated
Statins	• Promote plaque stabilization • Immune and anti-inflammatory effects helpful in the containment of the cytokine storm	• Statins should be continued if previously indicated

Hyperglycemia, ketosis and diabetic ketoacidosis have been observed in non-previously diabetic patients with COVID-19 [55]. An abnormal allele of NRP1 has been described in pancreatic beta cells [56] that could modify the binding of the S protein of SARS-CoV-2 to NRP1 in the islets and could potentially cripple the insulin secretory pathway causing hyperglycemia or even diabetic ketoacidosis. The upregulation of NRP1 in diabetic kidney cells suggests the importance of this protein in SARS-CoV-2 cell entry as a contributing factor and explains the increased risk of this infection in patients with diabetes [50].

As previously mentioned, a direct effect of SARS-CoV-2 virus on adipose tissue is plausible but not well known. *In vitro* studies have described NRP1 [57], ACE2 protein [58] and TMPRSS2 expression [45] in adipocytes and adipose tissues. Indeed, human adipose tissues present the highest level of NPR1 expression among all human tissues examined and high levels of ACE2 protein and TMPRSS2 expression [59], suggesting a possible direct role of SARS-CoV2 in adipose tissue that might explain the severity of the infection in obese patients.

A recent study has observed a reduction of the entry and infectivity of SARS-CoV-2 in the cell by inhibiting the interaction between virus S1 protein and NRP1 [49] suggesting a new therapeutic target pathway.

3.3 Pineal gland

Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, can protect against acute respiratory distress syndrome caused by viral and other pathogens through their known enhancement of increased inflammatory cytokines and reactive oxygen species generation. There are several mechanisms by which melatonin could have potential benefits in COVID-19 infection. In the first place, it could have antiviral activity. In studies performed through pharmacology-based platforms, melatonin has been found to be a potential drug with anti-CoV viruses' activity [60]. Moreover, melatonin can inhibit angiotensin II activation and facilitate angiotensin 1–7 action [61]. Melatonin has also very potent anti-inflammatory and antioxidant effects that could reduce and/or counteract proinflammatory cytokines during the cytokine storm observed in severe COVID-19 cases [62]. Notably, there is a well-known decrease of melatonin synthesis and secretion with aging condition, thus favoring a much severe COVID-19 clinical form, as the endogenous antioxidant and antiviral action of melatonin is naturally impaired. Moreover, long standing diabetes can be associated with autonomic neuropathy which impairs profoundly melatonin secretion [63]. Thus, melatonin impairment related to aging and/or diabetes may be an important risk factor

contributing to suffer COVID-19 infection and to develop a more severe outcome.

In addition, melatonin regulates the circadian rhythm. During the lockdown periods, disruption of the circadian rhythmicity has been very frequently described, especially in aged individuals. Chrono-disruption is also very common in hospitalized and critically ill patients. In this regard, treatment with melatonin in intensive care units has been found to improve sleep and shorten ICU stay [64]. In a recent retrospective study melatonin exposure after intubation was significantly associated with a positive outcome in COVID-19 and non-COVID-19 patients requiring mechanical ventilation [65].

Furthermore, melatonin can have neuroprotective properties. Cognitive deficits have been reported during COVID-19 infection [66]. Confusion, forgetfulness, fatigue and low mental energy may be some of the sequela of COVID-19 infection. Melatonin could have potential benefits in these patients as it can improve the quality of sleep and cognitive performance, mostly if they have required ICU support [67–69].

In summary, melatonin could have potential benefits in relation to its anti-inflammatory and anti-oxidative properties; it could also ameliorate chrono-disruption and have neuroprotective properties that could improve outcomes in COVID-19 patients. Notably, melatonin has a high safety profile, however the specific doses by which melatonin may reduce the severity of COVID-19 are not defined to date and further placebo-controlled randomized clinical trials are needed.

3.4 Oxytocin

There is probably a dysfunction on the oxytocin (OXT) secreting system related to SARS-CoV-2 infection. In this regard, situations that are known to increase the risk of developing COVID-19 and also of developing more severe forms, such as age and menopause, are associated with a decline in OXT [70]. In addition, evidence of an involvement of the hypothalamic-pituitary region characterized by an abnormal hyperintensity signal in mammillary bodies and hypothalamus has been reported in T-2 magnetic resonances of 2 COVID-19 patients [71]. Since the mammillary bodies are the center of OXT production, infection of these areas could probably lead to changes in OXT activity and secretion in COVID-19 patients.

OXT exerts different roles in the immune system. First, OXT can decrease different cytokines including IL-1 and IL-6 in the early phases of infectious diseases [72]. Thus, this could ameliorate COVID-19-related cytokine storm [70]. In addition, OXT could also prevent SARS-CoV-2infection itself, inducing γ-interferon production [73] and reversing lymphocytopenia, as it can promote differentiation of T-lymphocytes in the thymus [74]. Therefore, both mechanisms, if sufficiently activated, can be very beneficial, ameliorating and protecting from COVID-19 infection.

In addition to its effects on the immune system, OXT can enhance endothelial integrity [75] and has cardio-protective properties that could reduce inflammation and promote angiogenesis. These actions are probably very important in COVID-19 patients as OXT could thus reduce thromboembolisms and protect the cardiovascular system, which is a major target of this virus [76]. Of particular interest, it is the possible modulation of nitric oxide production by OXT, which is a key signaling molecule acting as a host response modulator in viral infections.

OXT could also have a role in some of the comorbidities that have been associated with a higher risk of more severe forms of COVID-19. OXT could reduce hyperlipemia and could also prevent weight gain and attenuate hypertension [70]. In addition, OXT has also been involved in the regulation of glucose metabolism and the development of diabetes mellitus [77]. In summary, if OXT could ameliorate these comorbidities, it could improve COVID-19 morbidity and mortality burden. As there are currently no specifically effective treatments for COVID-19, OXT could be a safe and cheap option and a clinical trial is warranted in these patients.

3.5 Corticosteroids

Corticosteroids have been used as an anti-inflammatory and immunosuppressive treatment for different diseases of different nature. Severe COVID-19 disease is characterized by an inflammatory organ injury and a high production of inflammatory endogenous molecules known as cytokine storm, which may progress to an Acute Respiratory Distress Syndrome (ARDS) as well as to other different organs damage, as i.e. vasculitis, kidney damage and myocarditis among other. Under the basis of its previous utilization in a variety of diseases, in which a high degree of endogenous inflammation concurs, corticosteroids were postulate as potentially useful and in fact they have demonstrated to contribute to reduce or attenuate the overactivation of the immune system in COVID-19 patients [78, 79].

Data reported regarding the effectiveness of glucocorticoids for COVID-19 treatment are somehow contradictory [80, 81], probably due to the heterogeneous characteristics of the patients and different classes of glucocorticoids used among the studies. However, the Recovery study, published in July 2020, showed that glucocorticoids, particularly daily 6 mg of dexamethasone treatment up to 10 days, reduced mortality in severe inpatients with COVID-19 receiving invasive mechanical ventilation or oxygen therapy [79]. These promising data led to the modification of the standard of care guidance for COVID-19, as shown in the last

recommendations of the World Health Organization (WHO) [82] that introduced systemic glucocorticoids in the treatment of severe and critical COVID-19 patients but not in patients with mild symptoms. Nowadays, many clinical studies are ongoing to check the effectiveness of glucocorticoids treatment in severe COVID-19 patients.

The preferred choice is a compound with a high glucocorticoid effect and no mineralocorticoid action, such as dexamethasone. Dexamethasone has a potent anti-inflammatory action, but also a very well-known hyperglycaemic effect. As mineralocorticoid action could be harmful due to the enhancement of RAAS, it may potentially stimulate the viral spread through ACE2 and also has detrimental effects on hypertension and cardiac and pulmonary function, therefore dexamethasone is a convenient option [83, 84].

The use of high doses of glucocorticoids may cause hyperglycemia in a high percentage of patients by increasing hepatic gluconeogenesis [85] and decreasing peripheral glucose use [86]. Indeed, high doses of glucocorticoids exacerbate hyperglycemia in patients with diabetes, previously diagnosed or undiagnosed, and may precipitate hyperglycemia and steroid-induced diabetes in those patients at risk [87]. Glycemic control in severe COVID-19 in patients treated with glucocorticoids is a challenge, especially in patients with previous diabetes treated with insulin due to the aforementioned effects upon glucose metabolism as well as the impact of high circulating concentrations of cytokines present in severe COVID-19 cases. Diabetes UK has published a clinical guideline for the hyperglycemia management in COVID-19patients treated with dexamethasone [87], recommending glucose monitoring to all patients and an initial insulin dose of 0.3 ui/kg/day, which should be quickly adjusted according to daily glucose levels. In our personal experience, these patients need high insulin doses of about 1–1.3 ui/kg/day on average, and active daily medical supervision to achieve glycemic goals between 7.7–10 mmol/l.

3.6 Antiandrogens and estrogens

Gender is one of the determinants for the evolution of severe forms of SARS-CoV-2 infection [88]. Men are more severely affected by COVID-19 than women, even after adjustments for age, BMI and comorbidities [89, 90]. A possible explanation of the worse prognosis in men could be the androgenic-enhanced expression of TMPRSS2 that facilitate SARS-CoV-2 cell entry. However, young men have better outcomes than older men despite having higher levels of testosterone. Among young men, those with androgenic alopecia present a higher risk of severe COVID-19 forms and worse outcomes [91], presumably due to increased intracellular conversion from testosterone to 5-alpha dihydrotestosterone, thus facilitating SARS-CoV-2 to increase infectivity.

Last but not least, low testosterone levels have also been associated to a poor prognosis and mortality in severe SARS-CoV-2 men cases [92]. A recent report indicates that in a cohort in which the mean age of men was 63 years, circulating testosterone was consistently low in those developing a more severe form of the disease [93]. On the other hand, a polymorphism of the androgen receptor gene has been described predisposing some men to develop more severe COVID-19 forms. These patients showed high circulating testosterone levels indicating receptor resistance [94]. Finally, low testosterone could also be related to hypothalamic hypogonadism, as observed in other metabolic, inflammatory diseases and severe COVID-19 forms. Therefore, the information published so far indicates that different factors interplay in the severity of COVID-19 disease in men, either in association with high or low circulating androgens.

Antiandrogenic treatment, particularly androgen receptor inhibitors as cyproterone, spironolactone, eplerenone or flutamide and 5-alpha-reductase inhibitors, as well as finasteride and dutasteride, seem to protect from COVID-19 in men. However, this question remains very controversial at the moment [95]. Spironolactone and eplerenone have both an antiandrogenic and an antagonistic mineralocorticoid effect, contributing to cardiovascular protection on these patients, as aldosterone represents the bioactive RASS end-product [96]. Dutasteride and finasteride are 5-alpha-reductase inhibitors that block the conversion of testosterone to 5-alpha DHT and mitigate TMPRSS2 expression in prostate cancer [97]. For these effects, they have been proposed as an adjuvant treatment for SARS-CoV-2 infection, particularly in men with androgenic alopecia. Different clinical trials using antiandrogen, aldosterone antagonist or TMPRSS2 inhibitors treatments trials are underway [92]. But, at the moment, results are not yet available. Male patients on previous antiandrogenic therapy for prostate cancer should continue the therapy with a careful evaluation and follow-up.

Concerning women, the increased risk of developing severe forms and complications of COVID-19 infections is mostly related to menopause age [98]. Indeed, estrogens may have a favorable effect against viral infections due to their protective action on endothelial function, the stimulation of the humoral immune response and the modulation of the inflammatory response [99–102]. Furthermore, the RASS is favorably modulated by estrogens in women [103, 104], while TMPRSS2 expression has a dual correlation with estrogens [105, 106]. In conclusion, estrogens, particularly estradiol, could be eventually protective against COVID-19 and may prevent severe complications. There are ongoing clinical trials using estrogens, progesterone and anti-androgens compounds, but no final data are currently available [92]. However, it is also crucial to remind that COVID-19 is associated to the development of micro and/or macro thrombotic events [107, 108], and this could represent a limitation for estrogens

utilization in this disease. Regarding women under menopausal hormone replacement therapy (MHT), it has been recommended to continue treatment, although adding low molecular weight heparin treatment in hospitalized cases [109]. However, the general advice on hormonal contraception treatment is to discontinue the therapy or switch to progesterone-only contraceptives in hospitalized women.

3.7 DPP-4

Human dipeptidyl peptidase 4 (DPP-4)/CD26 has also been identified as a functional receptor of the S protein of MERS-Co-V [110]. MERS-CoV binds to the DPP-4 receptor-binding domain and interacts with T cells and nuclear factors, such as NF-kB, which is critical in the pathogenesis of inflammatory disorders. DPP-4 is a known regulator of the immune system by activating T cells and enhancing the NF-kB pathway [111]. Transgenic mouse models expressing human DPP-4 exposed to MERS-CoV had an impaired monocyte/macrophage phenotype, CD4 + T cells, and lower TNF alpha, IL-6 and Arg1 [112]. The human DPP-4/CD26 may also interact with the S1 domain of the viral spike glycoprotein of SARS-CoV-2, thus allowing an additional way for virus entry into the cell [113].

Therefore, the question is whether DPP-4 inhibitors used currently for type 2 diabetes treatment may not just improve metabolic control in these patients but also contribute to modify COVID-19 attack, either inducing protection or progression of infection. It is tempting to postulate that inhibition of DPP-4 with the current antidiabetic drugs targeting this molecule may impair the virus/DPP-4 interaction, thereby enhancing the cell's self-defense from virus entrance. However, the binding of SARS-CoV-2 compared to MERS-CoV occurs at residues not located near the DPP-4 binding pocket of current gliptin drugs; thus, more studies are required to clarify this question [114].

It is also known that DDP-4 inhibition modulates inflammation and has anti-fibrotic effects. Depending on the potency of these properties, DPP-4 inhibitors may eventually have some protective effects in case of severe COVID-19 infection. The potential decrease of the magnitude COVID-19 cytokines storm under DPP-4 inhibitor treatment action sounds attractive but, so far, no data are available to provide a consistent answer.

3.8 Statins

A systematic review and meta-analysis found that the use of statins was associated with improved clinical outcomes in patients with COVID-19 [115]. The results to date have been controversial, as some studies but not all have found a reduced risk of severe COVID-19 presentation [116–119]. In those positive studies, although patients had multiple comorbid conditions mainly associated with an increased cardiovascular risk, statins were associated to a reduction of poor outcomes of COVID-19 disease [8, 9]. Mechanistically, there is evidence that cholesterol present in the cell membrane and the viral envelope could enhance SARS-CoV-2 cell entry as it does for other coronaviruses [120–122].

The known statins cardioprotective effects may have probably been implicated in the protection of COVID-19 cardiac injury, as recently reported in a series in which cardiac complications, including myocardial injury was only observed in 7% in those treated and 30% in non-statin treated patients [123]. Possible mechanisms implicated a greater plaque instability related to the COVID-19 inflammation milieu, especially when cytokine storm is present [120], thus treatment with statins in these patients could promote additional plaque stability. Moreover, statins have also immune and anti-inflammatory effects that could contribute to mitigate the cytokine storm. As a consequence of these reports, the recommendation for patients on statins, is to keep on the statins treatment in case of getting infected with COVID-19. In patients who haven't received this therapy previously, results of ongoing clinical trials are needed to make a firm recommendation on the initiation of statins. Nevertheless, their possible actions in cardiac protection, plaque stabilization, anti-inflammatory and immunomodulatory properties make them good candidates for high-risk COVID-19 patients [120].

4 Conclusions

COVID-19 pandemic has dramatically impacted the whole society worldwide and almost broken the health care system of some countries. Since the beginning of the pandemic, a metabolic and endocrine phenotype of patient has emerged and required quick adaptation and protection of these patients trough specific medical treatment of endocrine nature. With accumulating evidence generated in the last 18 months we now know that virtually all endocrine organs and systems may be affected by the SARS-cov-2 virus. As a consequence, the knowledge of the main features of endocrine nature that can be present in everyday patient is crucial for an adequate and successful therapeutic approach. From ACE2, TMPRSS2 to NRP1, many endocrine targets and molecules of endocrine nature are at the entrance of the viral attack and can contribute to its expansion and magnification of systemic lesions through amplification of cytokine storm. In this regard, optimization of glycaemic control and diminution of glycaemic excursions contribute to better outcomes in these patients. In addition, other relevant hormonal products, such as thyroid hormones, melatonin, oxytocin, sex hormones and corticosteroids have been either been

impacted by their organ lesion or as potential or demonstrated beneficial therapeutic agent.

Endocrinology of COVID-19 has revealed the existence of a specific phenotype including a high frequency of obese type 2 diabetic aged males, with all the concurrent metabolic components, but also with a high prevalence of hypovitaminosis D and hypocalcemia, hypogonadal function and multiple endocrine organs damage, including the hypothalamus. Thus, endocrinologists and physicians taking care of COVID-19 patients require to evaluate these conditions and implement the most appropriate support to achieve survival and prevent excessive mortality.

Author's contributions all authors reviewed current scientific publication regarding COVID-19 and endocrine systems, wrote differents parts of the paper and reviewed the whole manuscript.

Declarations

Conflict of interest The authors have declared that no competing financial interests exist.

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