REVIEW

Early and late endocrine complications of COVID-19

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Abstract

Endocrine system plays a vital role in controlling human homeostasis. Understanding the possible effects of COVID-19 on endocrine glands is crucial to prevent and manage endocrine disorders before and during hospitalization in COVID-19-infected patients as well as to follow them up properly upon recovery. Many endocrine glands such as pancreas, hypothalamus and pituitary, thyroid, adrenal glands, testes, and ovaries have been found to express angiotensin-converting enzyme 2 receptors, the main binding site of the virus. Since the pandemic outbreak, various publications focus on the aggravation of preexisting endocrine diseases by COVID-19 infection or the adverse prognosis of the disease in endocrine patients. However, data on endocrine disorders both during the phase of the infection (early complications) and upon recovery (late complications) are scarce. The aim of this review is to identify and discuss early and late endocrine complications of COVID-19. The majority of the available data refer to glucose dysregulation and its reciprocal effect on COVID-19 infection with the main interest focusing on the presentation of new onset of diabetes mellitus. Thyroid dysfunction with low triiodothyronine, low thyroid stimulating hormone, or subacute thyroiditis has been reported. Adrenal dysregulation and impaired spermatogenesis in affected men have been also reported. Complications of other endocrine glands are still not clear. Considering the recent onset of COVID-19 infection, the available follow-up data are limited, and therefore, long-term studies are required to evaluate certain effects of COVID-19 on the endocrine glands.

Key Words

- thyroid
- COVID-19
- testes
- ovary
- endocrine
- diabetes
- vitamin D

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Introduction

Most patients affected by the novel coronavirus disease 19 (COVID-19) are asymptomatic or present with mild flu-like symptoms. Around 14% of cases are severe and 5% are life-threatening (1). SARS-CoV-2 enters the lung, deposits in the lung parenchyma, and afterward enters into the host cells. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) on host cells act as receptors for the virus (2). Viral mRNA has been

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detected in blood, stool, and urine samples of patients with COVID-19 suggesting that SARS-CoV-2 can interact with ACE2 and TMPRSS2 expressed in other organs as well (3, 4). This interaction leads to multi-organ involvement, including cardiovascular, gastrointestinal, nervous, and endocrine system (4, 5).

Endocrine glands such as pancreas, hypothalamus, pituitary, thyroid, adrenal glands, testes, and ovaries have been found to express ACE2 and TMPRSS2, with the highest concentration in the testes, followed by thyroid, and the lowest in the hypothalamus (6, 7). Since the pandemic outbreak, the aggravation of original endocrine diseases caused by COVID-19 or the adverse prognosis of the disease in patients with endocrine history, such as those with obesity and diabetes mellitus (DM), is under investigation. However, data on new early and late onset manifestations are limited (8, 9, 10, 11).

The aim of this article is to review the early and late endocrine complications of COVID-19 and specifically for (1) glucose metabolism, (2) hypothalamus and pituitary, (3) thyroid gland, (4) adrenal glands, (5) reproductive system, and (6) calcium and vitamin D metabolism.

Methods

Authors collected, analyzed, and present information on early and late endocrine complications of COVID-19. English language literature was searched in PubMed until July 2021 using combinations of relevant terms, such as COVID-19, endocrine, hormones, thyroid, adrenals, reproductive, testes, ovaries, vitamin D, calcium, parathormone, diabetes, pancreas, and glucose. These words were used as MeSH terms, in order to cover other relevant possible words missing. Alike works found in the references of the studies identified were also reviewed.

The early and late endocrine complications of COVID-19 are summarized in Table 1.

Glucose metabolism

Diabetes mellitus (DM) has been in the highest rank of comorbidities in hospitalized patients with COVID-19 (1, 12). Available evidence indicates that older adults with DM are at greater risk to develop severe COVID-19 disease, subsequent complications, and have increased mortality (13, 14, 15). Diabetic microvascular and macrovascular complications may be responsible for these outcomes (16, 17, 18). Moreover, chronic inflammation and increased thromboembolic risk that exist mainly in diabetic people with obesity may negatively affect the immune response (19, 20, 21). Growing data indicate also that hyperglycaemia on admission and during hospitalization in people with or without diabetes is a predictor of worse prognosis, severity, and mortality of COVID-19 (22, 23, 24, 25, 26). On top of the above, early and late effects of COVID-19 on glucose metabolism are of great interest.

Importantly, COVID-19 may worsen glucose homeostasis. COVID-19 infection is characterized by severe inflammation (27, 28, 29) that may aggravate insulin resistance and subsequent hyperglycaemia through the cytokine storm in conjunction with counterregulatory hormones' dysregulation (30). It has been already documented that viral respiratory infections, even in healthy individuals, can cause acute transient skeletal muscle insulin resistance by increasing interferon-γ production (31). Previous studies suggest that inflammatory cells in severe acute respiratory syndrome and Middle East respiratory syndrome apart from infiltrating the lungs and causing lung injury and acute respiratory distress syndrome (ARDS) can also affect skeletal muscle and liver functions (32). These two organs are responsible for insulin-mediated glucose uptake and gluconeogenesis, and their induced malfunction by inflammation probably results in hyperinsulinaemia and hyperglycaemia (33). Glycemic control seems to play a vital role in regulating the inflammatory response and preserving tissue integrity and physiological function during the critical stages of infection. Interestingly, drugs often used in the treatment of COVID-19, such as corticosteroids or antiviral agents, might further aggravate hyperglycaemia by inducing insulin resistance or even lipodystrophy (11, 34). Furthermore, decreased exercise capacity, cachexia, and muscle weakness in patients during severe infection and long-term hospitalization may diminish insulin sensitivity, especially in survivors of ARDS and sepsis (35, 36). Moreover, rhabdomyolysis has been reported during the infection, which might contribute further to glucose dysregulation (37).

COVID-19 infection may trigger the presentation of new DM cases. Indeed, recent clinical evidence has suggested such an effect of SARS-CoV-2 with presentation of diabetic ketoacidosis (DKA) and hyperosmolarity, usually requiring higher doses of insulin to be controlled (38, 39, 40, 41, 42). German and Italian studies have described higher frequency of DKA and severe DKA in children and youth with new-onset type 1 diabetes mellitus (T1DM) in COVID-19 time, while the incidence of new-onset T1DM in the general population has not changed

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Table 1 Early and late endocrine complications of COVID-19.

Endocrine gland	Early complications	Late complications	Possible pathophysiological mechanisms
Glucose metabolism	Hyperglycemia on admission/ during hospitalization (22, 23, 24, 25) New presentation of DM with DKA or hyperosmolarity (38, 39, 40, 41, 42) Insulin-dependent DM or precipitation of T1DM (47, 48) Aggravation of glycemic control in preexisting DM (26, 42)	Permanent dysregulation of glucose homeostasis (38) T1DM or T2DM (38, 47, 48) Alteration of pathophysiology of DM (38)	Pancreatic β-cell loss or malfunction: cytolytic effect of the virus on β-cells (48, 59) Morphological, transcriptional, and functional changes of β-cells by SARS-CoV-2 infection (60, 61, 62) Effect of the virus on exocrine pancreas (pancreatitis) (57, 58) Hyperinflammation/cytokine storm (28, 30) Hypokalemia through reduction of ACE2 expression may decrease insulin secretion (11, 69) Drugs (corticosteroids, antivirals) (11, 34) Cahexia, muscle weakness, rhabdomyolysis lead to decreased insulin sensitivity (35, 36, 37) DPP4 potential SARS-CoV-2 receptor (70, 71, 72, 73)
Hypothalamus and pituitary	Possible hyponatremia (75)	No data so far	Possible inappropriate antidiuretic hormone secretion syndrome (75)
Thyroid	Low T3 concentrations (77, 78, 79, 80) Thyrotoxicosis (78, 81) Subacute thyroiditis (78, 82, 83, 84, 85, 86)	Low T3 concentrations (77, 78, 79, 80) Low TSH concentrations (77, 78, 79, 80) Hypothyroidism (78)	Direct virus effect on follicular cells (89) Immune mechanisms (76) Euthyroid sick syndrome (76, 93) Hypothalamic-pituitary dysfunction due to edema and neuronal degeneration (76) Drugs (glucocorticoids, heparin) (76, 95, 97, 98)
Adrenals	Possible adrenal insufficiency (99, 100, 101, 102)	Possible adrenal insufficiency (99, 100, 101, 102)	Adrenal hemorrhage (99, 100) Adrenal micro-infarction (100) Ischemic necrosis (101) Adrenalitis (101)
Testes	Semen virus detection (115)	Impaired spermatogenesis (106)	Direct virus effect (89, 106) Seminiferous injuries (106) Reduction in Leydig cells number (106) Inflammation (106)
Ovaries	Vaginal fluid positive (118) Increased risk for premature delivery (107, 122) Vertical transmission not confirmed (107, 121)	Adverse pregnancy outcomes (107, 122) Adverse perinatal outcomes (107, 122)	Inflammation (107, 122)
Calcium and vitamin D	Complicated recovery in patients with vitamin D deficiency and hypocalcemia (124, 125, 126, 127, 128) Vertebral fractures (126)	Vitamin D deficiency (123) Increased PTH (123)	Home isolation and low sun exposure during lockdowns (123)

ACE, angiotensin-converting enzyme; DKA, diabetic ketoacidosis; DM, diabetes mellitus; DPP4, dipeptylpeptidase 4; PTH, parathormone; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSH, thyroid stimulating hormone; T3, triiodothyronine.

(43, 44, 45). DKA diagnosis may be attributed to delayed hospital attendance and diagnosis of T1DM because of the overall public health impact (46). On the other hand, the postulation that COVID-19 could precipitate or accelerate T1DM onset is a possibility.

A potential link has been reported in a North West London Study where an apparent increase in DKA was noticed compared with usual admissions at two of the five units. Five out of 30 children with DKA had a positive COVID swab as evidence of SARS-CoV-2 infection or exposure. The authors raised awareness that there may be a link, but the increase in DKA may reflect pandemic-related delayed presentations of new cases of T1DM, resulting in an increased number of presentations with DKA (47). Furthermore, a recent case report presented a 19-year-old German male who was hospitalized with DKA and insulin-dependent DM with the absence of typical diabetic autoantibodies, 5–7 weeks after asymptomatic COVID-19 infection. Authors suggested that SARS-CoV-2 infection might damage β cells in pancreas through a direct cytolytic effect of the virus (48). Increased psychological stress during lockdown could also contribute especially in genetically susceptible individuals. Past coronavirus outbreak studies have also reported higher rates of hyperglycaemia on

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admission, irrespective of preexisting glycemic status, disease severity, or glucocorticoid use (49, 50).

Of note, several case series of euglycaemic DKA in patients with T2DM and COVID-19 while on sodium-glucose cotransporter-2 inhibitors (SGLT2is) have been reported (51, 52). SGLTis act on glucose and sodium excretion inducing osmotic diuresis and potential dehydration in critically ill patients, especially in a setting of anorexia and vomiting (53). The risk for euglycaemic DKA seems even more enhanced during COVID-19. Specific precipitating factors apart volume depletion by vomiting and anorexia may include a direct cytolytic effect of the virus on β-cells with consequent decreased endogenous insulin secretion and an increased inflammatory response with elevated interleukin-6 contributing to ketoacidosis (54). Furthermore, an international randomized control trial (dapagliflozin in respiratory failure in patients with COVID-19) is ongoing with dapagliflozin in patients with COVID-19 (55) in order to evaluate its safety and efficacy in conjunction with its implications in adults with cardiovascular, metabolic, or renal risk factors. However, early data from this phase 3 trial show that dapagliflozin failed to prevent organ dysfunction and all-cause mortality among hospitalized patients with COVID-19 at risk for developing serious complications, while its safety profile proved to be consistent.

There are several possible underlying pathophysiological mechanisms that would explain the damage of the pancreatic islets by SARS-CoV-2 and the subsequent loss of insulin secretory capacity. The immune response mediated by the virus with release of chemokines and cytokines might affect pancreatic cells and impair their ability to sense glucose concentrations and release appropriate amounts of insulin. Immune response may further impair the ability of liver, muscles, and other peripheral organs to uptake glucose (6, 38). Pancreatic islets express ACE2, facilitating damage during the infection, as indicated by elevated levels of circulating pancreatic enzymes (56, 57, 58). In a recent experimental study with derivatives from human pluripotent stem cells, it was demonstrated that the high expression of ACE2 in β cells and consequently the high β cells' permissiveness to SARS-CoV-2 can induce inflammatory cytokine release, β-cell apoptosis, and decreased insulin secretion (59). These findings were confirmed by a study that presented data from both human pancreatic islet cultures and COVID-19 full-body postmortem examinations. It was shown that SARS-CoV-2 infects and replicates in human islets, inducing morphological, transcriptional, and functional changes with subsequent reduction of insulin-secretory granules and impairment of glucose-dependent insulin secretion of β cells (60).

Two further studies also confirmed infection of β-cells in autopsy samples from people who died of COVID-19 and showed that COVID-19 infection leads to reduced production and release of insulin from pancreatic islet tissue. In particular, they showed that SARS-CoV-2 infection leads to the death of some of those all-important β-cells and causes transdifferentiation of the surviving cells (61, 62). In addition, several studies in mice support the hypothesis that ACE2 is important in β cell homeostasis. High fat diet may lead to reduction of ACE2, while deletion of ACE2 in diabetic mice induces hyperglycaemia, increases β cell oxidative stress, and decreases insulin secretion (63, 64, 65, 66).

In turn, acute hyperglycaemia seems to upregulate ACE2 expression and increase urinary ACE2 activity, which may consequently lead to increase of viral load. It has been shown that urinary ACE2 activity is elevated in patients with T1DM and T2DM, while urinary ACE2/creatinine is positively correlated with fasting blood glucose levels and glycated hemoglobin (HbA1C) (67, 68). In patients with DM, SARS-CoV-2, through reduction of ACE2 expression, results in decreased degradation of angiotensin II, increased secretion of aldosterone, and renal potassium loss. Hypokalemia can lead to further decrease of insulin secretion (69). Dipeptylpeptidase 4 (DPP4) is another possible coronavirus receptor that it is well known to have an important role in glucose homeostasis. Although it is not yet confirmed, DPP4 could also bind to SARS-CoV-2, affecting glucose homeostasis (70, 71, 72, 73).

Given the recent onset of COVID-19 pandemic, it is unclear whether the dysregulation of glucose metabolism induced by this type of coronavirus is permanent and can contribute to the development of overt DM in survivors. Moreover, whether SARS-CoV-2 can induce T1DM or T2DM or a new form of DM is a matter of scientific discussion. Long-term studies are required to evaluate whether the virus has a diabetogenic impact on individuals with higher risk for DM or whether it can totally change the picture of DM pathophysiology.

Hypothalamus and pituitary

There are no sound data indicating specific early or late hypothalamic or pituitary complications from COVID-19. Hypothalamic and pituitary tissues express ACE2 and could be potential SARS-CoV-2 targets either directly or via an immune-mediated process, as already demonstrated

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with other coronaviruses (2, 8, 9, 11, 74). Survivors of the SARS outbreak after recovery presented mild secondary hypocortisolism (40%) or central hypothyroidism (5%). The potential underlying mechanisms may include edema and neuronal degeneration (74). Hyponatremia is prevalent in around 20–50% of hospitalized patients with COVID-19, associated often with negative outcomes. It has been hypothesized that it could be related to inappropriate antidiuretic hormone secretion syndrome potentially caused by excess levels of interleukins that can induce the non-osmotic release of vasopressin (75). Therefore, even in lack of sound evidence, targeted endocrine work-up especially in patients with unexplained fatigue and mental impairment post COVID-19 should be considered (9).

Thyroid gland

Interesting data have been published recently on the possible thyroid complications of COVID-19 (76). When thyroid function was investigated in 50 patients with COVID-19 for a follow-up period of 3 months post diagnosis, 64% was found to have abnormal thyroid function. Of those, 56% presented lower thyroid stimulating hormone (TSH) levels, while many of them had also decreased triiodothyronine (T3) concentrations compared with a healthy control group. No significant differences in thyroxine (T4) levels were found. Additionally, the degree of the decrease in TSH and T3 was positively correlated with the severity of the disease, as reported in other studies, the more severe the infection, the lower the TSH and T3 levels (77, 78, 79). When the clinical characteristics of deceased and recovered patients with COVID-19 were retrospectively compared, it was found that TSH and free T3 concentrations were significantly lower in the deceased ones (80). Muller *et al.* (78) found a higher prevalence of thyrotoxicosis (15.3%) in COVID-19 patients compared with only 1.3% in the control group that returned to normal after pneumonia recovery. It should be noted that the definition of thyrotoxicosis is not strict in this study (78). A retrospective study investigated thyroid function in 287 non-critical patients hospitalized for COVID-19 (81), 20.2% of whom had thyrotoxicosis and 5.2% presented with hypothyroidism. Interestingly, it was found that the presence of thyrotoxicosis was significantly associated with increased IL-6 levels (81).

Up to date, eight studies have reported subacute thyroiditis associated with COVID-19 (78, 82, 83, 84, 85, 86, 87, 88). Patients included had an age range from 18 to 68 years, most of them were women of Italian origin. These patients had no serious COVID-19 infection symptoms but only mild fever and mild upper respiratory symptoms, and no one needed treatment in ICU. The symptoms of subacute thyroiditis were the expected and included fever, anterior neck pain, fatigue, tremors, sweating, and palpitations, while the time from COVID-19 diagnosis to typical thyroiditis symptoms ranged from 5 to 42 days. Many of these patients with classic subacute thyroiditis presented specific classic ultrasound patterns (82, 83, 84, 85, 86, 87, 88). Interestingly, diffuse mild hypoechoic or focal markedly hypoechoic areas at thyroid ultrasound or reduced radioisotope thyroid uptake have been also described for atypical thyroiditis (78). Most of these patients received corticosteroids, and the symptoms improved within few days (78, 82, 83, 84, 85, 86, 87, 88). Subacute thyroiditis is thought to follow a viral infection or a post-viral inflammatory response, especially in genetically predisposed individuals (9, 76).

The pathogenesis of thyroid dysfunction post COVID-19 is not completely understood. One hypothesis is the direct influence of SARS-CoV-2 on thyroid gland. In a recently published autopsy study, the SARS-CoV-2 genome was detected in 9 of 25 (36%) thyroid samples. Moreover, strong cytoplasmic staining for SARS-CoV-2 nucleocapsid antigen in thyroid follicular cells was observed (89). Ultrasound findings of thyroid inflammation have been observed in patients with classic subacute or atypical thyroiditis after COVID-19 (76, 78). Of course, there are other recent postmortem reports that did not detect SARS-CoV-2 in thyroid tissues either by immunohistochemistry or PCR analysis (90, 91, 92). Taken all these together and as ACE2 is highly expressed in thyroid tissue, a role of a direct damage by SARS-CoV2 on the thyroid gland is possible. Eventually, the thyroid damage can also be indirect, caused by immune mechanisms, such as the cytokines' storm (76, 89).

Another potential explanation could be an underlying non-thyroidal illness syndrome or euthyroid sick syndrome, which is often caused by critical illness (93). This is characterized by normal or low serum TSH and T3 levels, with normal or low T4 concentrations. This is a homeostatic mechanism to recover from severe illness (76, 93). An observational study from UK included 334 patients with confirmed COVID-19 without history of thyroid disease. Most of them presented with euthyroidism and mild reductions in TSH and free T4 (FT4) compatible with a non-thyroidal illness syndrome (94). The dysfunction of the hypothalamic-pituitary-thyroid axis might be an additive cause leading to decrease in TSH levels (76). Finally, indirect effects on thyroid

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or pituitary cells due to systemic immune-mediated post-viral inflammatory response could affect thyroid function (88, 95).

Additionally, drugs used for the management of COVID-19 can potentially affect thyroid function (76). Glucocorticoids could affect serum TSH levels, mainly by inhibiting thyrotropin-releasing hormone secretion in the hypothalamus or by suppressing TSH release in pituitary thyrotroph cells (96, 97). Heparin is indicated for hospitalized COVID-19 patients for thromboembolic event prevention, and it is known that it interferes with the measurement of serum free thyroid hormone due to significant increase of serum non-esterified fatty acid. Heparin causes a displacement of total T4 (TT4) from thyroid binding globulin (TBG), thus resulting in a measurement error increase of FT4. Therefore, in patients treated with heparin, measurement of total thyroid hormone levels, TSH, and TBG could help confirm patient's thyroid status (76, 98).

Overall, thyroid dysfunction is common in patients with COVID-19 infection. Physicians should be alert and screen COVID-19 patients for early and late thyroid disfunction (8, 9, 10, 11, 76).

Adrenal glands

Adrenal glands play a crucial role in the immune response, as they secrete cortisol and catecholamines. Patients with known adrenal insufficiency and Cushing's syndrome present higher susceptibility to infections, and special attention is required during the pandemic (8, 9, 10).

Few clinical cases of adrenal hemorrhage as a complication of confirmed COVID-19 infection have been described so far (99, 100). The first one is a 53-year-old Caucasian man from UK who had bilateral pulmonary emboli and a unilateral adrenal haemorrhage during the course of COVID-19 infection. He was treated with intravenous heparin for 5 days and was then converted to oral anticoagulation. He had no clinical or biochemical evidence of adrenal insufficiency (99). Another case is a 66-year-old woman from Israel who presented with acute COVID-19 infection. The patient was already known to have antiphospholipid syndrome and presented with primary adrenal insufficiency due to bilateral adrenal hemorrhage (100).

There are also interesting data from autopsy studies regarding the effect of COVID-19 on adrenal glands (101, 102). In case series of nine full postmortem examinations of patients who died from confirmed COVID-19 in UK between March 1 and April 30, 2020, adrenal micro-infarction was found in three of them (33%) (102). Another autopsy study was performed on 28 deceased patients with confirmed SARS-CoV-2 infection in Western Brazilian Amazon. Adrenal lesions were found in 12 of 28 (42.9%) patients. Ischemic necrosis, cortical lipid degeneration, hemorrhage, or unspecific focal adrenalitis were idenitified, possibly directly linked to the viral infection (101).

To conclude, autopsy and limited clinical data indicate that the adrenal glands may be affected by COVID-19. Hypoadrenalism is life-threatening and therefore adrenal axis testing for COVID-19 patients with clinical suspicion of adrenal insufficiency may be considered.

Testes and ovaries

ACE2 receptors are highly expressed in testes and specifically on the seminiferous duct cells, spermatogonia, Leydig cells, and Sertoli cells (103, 104, 105). In a study with 12 deceased patients, SARS-CoV-2 was detected by PCR in the testes of one patient. However, the testes of most patients displayed seminiferous injuries, reduction in Leydig cells number, and mild inflammation, implying not only direct but also indirect effects due to immune mechanisms (106). In a recently published autopsy study, the SARS-CoV-2 genome was detected in six of nine (67%) of testes (89). Spermatogenesis is impaired in infected men, and delay in sperm maturation might be present. It is well known that spermatogenesis is a temperature-sensitive process; therefore, it may be also affected by high temperature. This can occur even in mild infections (107, 108). In most studies published so far, SARS-CoV- 2 was not detected in the semen of males recovered from COVID-19 (109, 110, 111, 112, 113, 114). There is only one study that reports virus detection within the semen of 6 of 38 patients (115). Most available data do not support a direct effect of SARS-CoV-2 on the testicular tissue or semen. However, the high expression of ACE2 receptors in testes and some recent – autopsy mainly – data maintain such a hypothesis as possible (89, 107, 108).

ACE2 receptors have been detected in the ovaries of both reproductive and postmenopausal women, including oocytes (116, 117). Data on possible effects of SARS-CoV-2 on ovaries are currently lacking, and the exact effect on female fertility still remains unknown. Positive vaginal fluid after infection has been reported in few cases only (118), while other ones failed to detect the virus in the vaginal fluid (119, 120). Larger studies indicate that intrapartum vaginal or orofecal SARS-CoV-2 transmission

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seems to be unlikely (107, 121). Regarding COVID-19 complications on pregnancy, there is confirmed increased risk for adverse pregnancy and perinatal outcomes, especially among women with certain demographic and health profiles (107, 122).

Calcium and vitamin D metabolism

Vitamin D receptor is expressed in most human tissues, and vitamin D has been implicated in both innate and adaptive immune response (9, 10, 11). Home isolation and low sun exposure during lockdowns might decrease vitamin D levels and impair immunity indirectly. Pizzini *et al.* reported data on post COVID-19 patients with low vitamin D and increased parathormone levels 8 weeks post symptom onset (123). According to large series of patients with COVID-19, hypocalcemia is highly prevalent and is associated with worse clinical outcomes and the need of hospitalization (124, 125). Various studies from different countries have reported poor vitamin D status, which is associated with disease severity, mortality risk, as well as the development of other endocrine complications of COVID-19 (126, 127, 128). In a Spanish pilot clinical trial, 537 hospitalized patients with COVID-19 pneumonia were randomized to calcifediol or not. Treatment with calcifediol was significantly associated with lower in-hospital mortality during the first 30 days (129). Considering the strong association of vitamin D with immune regulation as well as the above data, supplementation with cholecalciferol could be of some importance according to current recommendations (8, 9).

Recently, a cross-sectional study including patients from a single center reported high prevalence (36%) of morphometric vertebral fractures on lateral chest X-rays of patients with COVID-10 that could negatively influence respiratory function too (126). Physicians may offer therapeutic alternatives in patients with osteoporosis to avoid long-term complications during this era. Subcutaneous use of denosumab could be of some benefit to avoid intravenous administration of bisphosphonates (8, 9, 10).

Conclusions

Data so far have provided evidence for dysregulation of glucose metabolism in patients with or without previous DM. Thyroid dysfunction has been also reported with low T3, low TSH concentrations, or cases of subacute thyroiditis. There are also indications of possible adrenal complications and impaired spermatogenesis in affected men, while early or late complications of other endocrine glands are not clear. Given the very short history of COVID-19 infection, sound conclusions cannot be drawn. Long-term studies are required to evaluate certain effects of COVID-19 on the endocrine glands.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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