SYSTEMATIC REVIEW

Pediatric endocrinopathies related to COVID-19: an update

Elmira Haji Esmaeli Memar[1] · Reihaneh Mohsenipour[2] · Seyedeh Taravat Sadrosadat[3,4] · Parastoo Rostami[5]

Abstract

Background Coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh coronavirus to be linked to human disease. The SARS-CoV-2 virus may have several pathophysiologic interactions with endocrine systems, resulting in disruptions in glucose metabolism, hypothalamus and pituitary function, adrenal function, and mineral metabolism. An increasing amount of evidence demonstrates both the influence of underlying endocrine abnormalities on the outcome of COVID-19 and the effect of the SARS-CoV-2 virus on endocrine systems. However, a systematic examination of the link to pediatric endocrine diseases has been missing.

Data sources The purpose of this review is to discuss the impact of SARS-CoV-2 infection on endocrine systems and to summarize the available knowledge on COVID-19 consequences in children with underlying endocrine abnormalities. For this purpose, a literature search was conducted in EMBASE, and data that were discussed about the effects of COVID-19 on endocrine systems were used in the current study.

Results Treatment suggestions were provided for endocrinopathies associated with SARS-CoV-2 infection.

Conclusions With the global outbreak of COVID-19, it is critical for pediatric endocrinologists to understand how SARS-CoV-2 interacts with the endocrine system and the therapeutic concerns for children with underlying problems who develop COVID-19. While children and adults share certain risk factors for SARS-CoV-2 infection sequelae, it is becoming obvious that pediatric responses are different and that adult study results cannot be generalized. While pediatric research gives some insight, it also shows the need for more study in this area.

Keywords Coronavirus disease 2019 (COVID-19) · Endocrine · Infection · Pediatrics

Introduction

Coronavirus disease 19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh coronavirus to be linked to human disease. The major receptor for SARS-CoV-2 infection is believed to be angiotensin-converting enzyme 2 (ACE2) [1]. The binding of SARS-CoV-2 to ACE2 initiates a cascade that activates the nuclear factor-κB pathway, resulting in very high levels of proinflammatory cytokines and chemokines, which contribute to the development of acute respiratory distress syndrome (ARDS) in severe COVID-19 [2, 3]. The lethality of ARDS and non-pulmonary consequences in COVID-19 are considered to be caused by a cytokine storm, in which immune and non-immune cells produce massive quantities of proinflammatory cytokines, causing damage both inside and outside the respiratory system [4]. A limited but rising body of evidence suggests that underlying endocrine abnormalities may influence the outcome of COVID-19 and that the SARS-CoV-2 may have an effect on endocrine systems.

At first, it was assumed that infection with SARS-CoV-2 would cause similar but less severe symptoms and complications in children and adolescents [5]. Multisystem inflammatory syndrome in children (MIS-C) and atypical

✉ Parastoo Rostami
  Drp_rostami@yahoo.com

1 Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran

2 Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

3 Universal Scientific Education and Research Network (USERN), Tehran, Iran

4 Children's Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran

5 Growth and Development Research Center, Department of Endocrinology and Metabolism, Pediatric Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

endocrine responses have been observed in children infected with SARS-CoV-2 [6]. Recent understanding concerning the impact of SARS-CoV-2 infection on endocrine systems is summarized here, and current material on COVID-19 pandemic complications in endocrine diseases is reviewed. SARS-CoV-2 and endocrine disorders have been studied extensively in adults, but we have attempted to include all relevant pediatric data from PubMed as of March 2022. If available, we included data from adults, and we made a notation in the text when articles spoke of adult vs. pediatric research teams. SARS-CoV-2 infection in children has been shown to have a wide range of responses in the pediatric population [7]. Since children in the COVID-19 period need specific therapy, pediatric endocrinologists must comprehend the disease's symptoms and the limits of current knowledge.

For this purpose, a literature search was conducted in EMBASE, and data that were discussed about the effects of COVID-19 on endocrine systems were used in the current study (Supplementary Table 1). There are few data about the effects of COVID-19 on pediatric endocrine systems, so we tried to discuss related data in adults.

SARS-CoV-2 infection and subsequent endocrine dysfunction

The SARS-CoV-2 virus has several pathophysiologic linkages to the endocrine system and hence has the potential to disrupt pituitary, adrenal, and thyroid function, as well as glucose and mineral metabolism. Existing data are mostly favorable in terms of COVID-19-related endocrine problems in children (Table 1).

The similarities between COVID-19, SARS, and Middle Eastern respiratory syndrome show that the virus may enter the central nervous system through the olfactory bulb, including the hypothalamus [8]. Adult observational studies have indicated that COVID-19 disrupts posterior pituitary function and causes an immediate onset of syndrome of inappropriate antidiuretic hormone [9–11]. SARS survivors have been shown to have hypothalamic/pituitary dysfunction [12]. However, the only evidence of pituitary involvement in COVID-19 is a magnetic resonance imaging finding of pituitary stalk involvement in two adult patients; there have been no reports of pituitary hormone deficiency in adults or children with COVID-19 thus far [13].

There is evidence that people with COVID-19 may be at risk for adrenal and thyroid problems. In one study, it was shown that acutely unwell people with COVID-19 illness had greater cortisol levels than those without COVID-19, but there was a negative link between the degree of cortisol response and survival rate in those who were COVID-19 positive [14]. Computed tomography (acute adrenal infarction) and post-mortem investigations in individuals with severe COVID-19 and SARS-CoV-2 infection have also shown adrenal involvement [15, 16]. Adults with COVID-19 have been diagnosed with both thyrotoxicosis [as a result of elevated interleukin (IL)-6 levels] and hypothyroidism [17–19]. Although ACE2 is extensively expressed in the thyroid and to a lesser amount in adrenal tissue, and therefore

Table 1 The summary of the endocrinopathies in children and adults and their management

Diseases	Suggested mechanisms	Managements
Obesity	Low physical activity times Overfeeding	Provide age-appropriate nutrition; increase physical activity
Adrenal insufficiency	COVID-19 inhibits the adrenal stress response Presence of a hypercoagulable condition	Established recommendations for stress dosage of the corticosteroid
Diabetes mellitus	Insulin resistance due to high levels of cytokines during COVID-19	T1DM: parenteral insulin T2DM: (1) outpatients: glucagon-like peptide 1 analogs and dipeptidyl peptidase 4 inhibitors; (2) critical patients: insulin, metformin, TZD, SGLT2 inhibitors, and TZD, SGLT2 inhibitor
Thyroid diseases (subacute thyroiditis, hypothyroidism, hyperthyroidism)	Direct injury virus infection of the thyroidal cells and indirect destruction by cytokine storm	Nonsteroidal anti-inflammatory drugs, steroids, and nonspecific beta-blockers are suggested Levothyroxine Methimazole
Hypopituitarism	Hematogenous spread of the virus and infect the pituitary	Hydrocortisone Water and electrolyte
Metabolic bone disease	Vitamin D insufficiency may due to restrict outside time	Vitamin D supplementation Home delivery of burosumab injections for patients with hypophosphatemic rickets during the COVID-19 pandemic

COVID-19 coronavirus disease 2019, *TZD* thiazolidinedione, *SGLT2* sodium-glucose cotransporter receptor-2, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

children may potentially be at risk, thyroid and adrenal pathology in children with COVID-19 and MIS-C have not been documented [20].

Due to the high expression of ACE2 in pancreatic islet cells, SARS-CoV-2 infection may have a diabetogenic impact irrespective of the stress response associated with severe sickness [21]. Adults, but not children, with COVID-19 have been reported to develop diabetes mellitus for the first time [22, 23]. Contrary to expectations, the most critically ill individuals with COVID-19 have low lipid levels. These individuals had very low levels of total cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol, indicating a strong inflammatory (cytokine) impact. Lipid levels rise concurrently with a decrease in inflammatory markers in recovering intensive care unit (ICU) patients. While the long-term repercussions of this occurrence are unknown, decreased lipid levels in conjunction with higher inflammatory markers do seem to be associated with a poor result [24, 25].

COVID-19 does not seem to have a direct effect on the parathyroid glands or on mineral ion balance at the moment. However, research suggests that persons with severe COVID-19 may have a decrease in blood calcium levels [26, 27]. There are few occurrences of hypocalcemia in pediatric patients with MIS-C; however, there are no systemic findings in children at the moment, and probable reasons remain unknown [28, 29].

Complications and management of COVID-19 in children with pre-existing endocrine disorders

The complications of SARS-CoV-2 infection have been predominantly documented in adults with underlying endocrine problems. While adult results should not be generalized to children, the studies clearly indicate potential dangers for the pediatric group. The purpose of this section is to summarize what is currently known about COVID-19 in patients with underlying endocrine problems and how it may affect pediatric patients.

There is currently no evidence that central hormone deficiency increases the risk of contracting SARS-CoV-2. Children and adolescents with multiple pituitary hormone deficiency, on the other hand, have distinct treatment challenges due to the complexity of their medical condition. Infants and toddlers with diabetes insipidus who have respiratory issues as a result of COVID-19 exposure have a significantly increased risk of acquiring abnormal blood salt levels [30]. Due to variables including lower fluid intake, higher irreversible losses, and the difficulty for adipsic individuals with diabetes insipidus to tolerate oral desmopressin, patients with diabetes insipidus are at an increased risk of severe hypernatremia, which may be exacerbated by venous thrombosis in the acute illness [31–34]. Patients with adrenal insufficiency (including those on corticosteroid replacement therapy) are at greater risk of respiratory and adrenal issues if they get COVID-19, a virus that has not been extensively studied in adults or children.

Currently, there is no evidence that children and adolescents with underlying thyroid abnormalities are at a greater risk of contracting SARS-CoV-2 infection or that their clinical course is changed. It is necessary to bear in mind, however, that patients with Graves' disease who receive antithyroid drug (ATD) treatment are at an increased risk of agranulocytosis and secondary infections [35]. This is critical since one study found that more than half of COVID-19 non-survivors had a subsequent infection [36]. In adults with COVID-19, underlying thyroid illness, especially hypothyroidism, does seem to be a risk factor for a more severe disease course [37–39].

Adults with diabetes mellitus, obesity, or hypertension are at increased risk of COVID-19 infection and have a greater incidence of complications and mortality [39–43]. The T1D Exchange provided data on 64 persons with type 1 diabetes (T1D); 33 had COVID-19-positive symptoms but were not tested or had COVID-19-negative symptoms; 65.5% of participants were between the ages of 19 and 20 [44]. COVID-19-positive individuals had a higher mean glycosylated hemoglobin A1c (HbA1c) (8.5% vs. 8%), were more likely to present with diabetic ketoacidosis (DKA) (45.5% vs. 13.3%) and needed a greater level of care than COVID-like individuals. In England, a population-based study found that patients with an HbA1c of 86 mmol/mol (10.0%) or greater had an increased risk of COVID-19-related mortality [hazard ratio = 2.23, 95% confidence interval (CI) = 1.50–3.30; $P < 0.0001$ in T1D] [45].

Children with T1D and COVID-19 were shown to have higher HbA1c, higher hospitalization rates, non-Hispanic Black ethnicity, and public insurance, according to T1D Exchange data in the pediatric population (unpublished data). During the coronavirus pandemic, children newly diagnosed with T1D are more likely to develop DKA and have more severe DKA [46]. However, evidence suggests that children with T1D and COVID-19 have clinical outcomes that are equivalent to those of children who do not have diabetes [47]. Children with diabetes have encountered significant obstacles as a result of the COVID-19 epidemic, most notably due to extensive school and childcare facility closures. In a study from Greece, 34 children with T1D who used insulin pumps and continuous glucose monitoring had no significant increase in time in range during lockdown but did have increased blood glucose variability compared to the prelockdown period [48]. Additionally, the children in this research had significant alterations in their food routines during lockdown. Restrictions imposed in response to the

COVID-19 pandemic have led to reduced physical activity and dietary modifications, as well as changed diabetes management behaviors, all of which may raise the risk of poor nutrition, excessive weight gain, and increased diabetes management stress [47].

Numerous investigations have shown no difference in obesity rates between children with moderate COVID-19 and those with severe COVID-19 [49–51]. While obesity is not more prevalent in pediatric patients hospitalized for COVID-19 than in the general pediatric population, the severity of COVID-19 illness may be connected with obesity, as it is in adults. Obesity was found to be a risk factor for mechanical ventilation in one investigation of 50 pediatric patients hospitalized with COVID-19 [52]. Additionally, a recent multicenter investigation of COVID-19 infection in 281 hospitalized children under the age of 22 years showed obesity (odds ratio = 3.39, 95% CI = 1.26–9.10; P = 0.02) and hypoxia on admission as the only two underlying risk factors for severe respiratory illness [53]. In adults, obesity-related adverse outcomes may be mediated by pre-existing cardiovascular and renal illness, as well as hypertension [54].

Children who have metabolic bone disease or skeletal dysplasia that leads to respiratory insufficiency as a consequence of an irregular chest wall structure may be more susceptible to COVID-19 complications [55]. Immunity and autophagy are both influenced by vitamin D; however, it is not known whether vitamin D deficiency enhances the chance of COVID-19 infection or its repercussions. Data from the UK Biobank did not show a correlation between SARS-CoV-2 infection and decreased blood 25-OH-vitamin D concentrations after controlling for confounding factors, despite the findings of certain observational studies of adults [56].

Obesity

Obesity is taken into consideration during the outbreak of COVID-19 for two reasons. First, according to reports from the World Health Organization, during an outbreak of COVID-19, the prevalence of childhood and adolescent obesity due to low physical activity times and overfeeding has increased [57]. A large pediatric primary care study showed a significant increase in obesity rates among children ages 2 through 17 since the onset of the COVID-19 pandemic [58], and obesity-related lifestyle behaviors have also changed [59]. Second, obesity as a comorbidity likely increases susceptibility and severe COVID-19 infection in pediatrics and adolescents [60]. During the COVID-19 outbreak in Canada, obesity was introduced as the third factor among children with severe infection after malignancies and immunosuppression [51]. Obesity may be a risk factor regardless of age,

gender, and higher body mass index (BMI) related to the risk of requiring invasive mechanical ventilation [61]. Furthermore, adult patients with obesity are more likely to have some symptoms, including fever, dyspnea, and caught [62]. Because of the lack of enough studies, the impact of obesity on COVID-19 in the pediatric population has not been well explained. Poor immune response, cardiopulmonary disease, and chronic inflammation that link obesity to COVID-19 and have been proven in adult patients have also been shown in children [63]. Obesity is associated with overexpression of angiotensin 2 [64]. Obesity limits respiratory muscle movement and worsens general conditions in pediatric patients [65]. Asthma and obstructive sleep apnea are linked to obesity, which is related to a higher risk of pulmonary infections [66]. Cardiac anatomy changes, higher blood pressure and medications [67], intima layer artery thickening [68], endothelial dysfunction, and damage to the endothelium due to leptin perivascular adipose tissue have been explained in obese children. In obese individuals, chronic inflammation impairs the regulation of anticoagulant factors that contribute to venous thromboembolism during COVID-19 [69]. Angiotensin converting enzyme converted angiotensin 2 to angiotensin type 1–7. Unlike angiotensin 2, which has inflammatory effects, angiotensin 1–7 acts as an anti-inflammatory [70]. Therefore, it is assumed that this imbalance may cause immune response dysregulation [71]. In patients with obesity, adipocytokines, such as leptin, may change the function and number of immune cells, leading to an increase in the number of activated macrophages (M1) and effector T helper 1 (Th1) and Th7 cytotoxic T cells and then a decrease in the number of regulatory T cells and M2 macrophages. Macrophages derived from visceral adipose tissue secrete large amounts of inflammatory cytokines, including nitric oxide IL-12, IL-1b, IL-6, and tumor necrosis factor-α (TNF-α) [72]. In individuals with obesity, SARS-CoV-2 enters fat cells by binding to ACE2, which could lead to increased viral load and prolonged viral spread due to their altered immune responses and cytokine response in adipose tissue [73]. There is evidence of endothelial dysfunction in obesity [74] and kidney disease [75]. Obesity is usually associated with comorbidities, such as hypertension, hyperinsulinism, type 2 diabetes (T2D), and thrombogenic events, which decrease the body's ability to overcome COVID-19 [76]. Fortunately, these comorbidities are not common in children. It seems that obese individuals spread more enormous amounts of the virus through inhalation and can infect other people [77]. Since the effectiveness of the influenza vaccine due to alterations in the immune system decreased in obese people, this phenomenon may also occur in the vaccination against SARS-CoV-2, which leads to decreased immunization against COVID-19 in obese people patients [78]. A large retrospective cohort study from the Society of Critical Care Medicine Viral Respiratory Illness Universal Study

registry assessed all children hospitalized with COVID-19 from March 2020 to January 2021; 31.5% of patients had obesity. In adult patients, obesity was associated with more severe COVID-19 diseases and more extended hospitalization, but unlike adults, the risk of mortality in obese children was not higher than that in non-obese patients. They found no relation between obesity and a higher risk of MIS-C because inflammatory and proinflammatory alterations due to obesity may have less impact on the immune dysregulation response in MIS-C. Furthermore, they have shown a negative correlation between age and high BMI with illness severity from COVID-19 in pediatric patients [60].

Management

Due to social isolation, lack of exercise, and food insecurity in socioeconomically challenged homes, the pandemic-related closure of schools, camps, and extracurricular sports and activities has dramatically affected children's and adolescents' health [79]. In one of our centers, we have seen a large rise in the number of children under 19 who arrive with new-onset diabetes. The majority of the increase is attributed to the rise in T2D. It is critical to promote good eating habits and provide age-appropriate nutrition and physical activity guidelines. During the COVID-19 pandemic, racial/ethnic and socioeconomic differences exacerbated health inequities, notably concerning weight control. Healthcare practitioners should continue to educate patients about the importance of eating healthily and exercising regularly. We advocate for the use of telemedicine treatments to supplement pediatric weight control.

The likelihood of developing premature atherosclerotic cardiovascular disease (ASCVD) in children who have undergone MIS-C is unknown; however, individuals with a history of Kawasaki disease and persistent aneurysmal dilatation are regarded to be at a high risk of developing ASCVD. Coronary artery aneurysms have been detected in 6%–24% of patients with MIS-C, and Kawasaki disease characteristics have been observed in up to 40% of patients [79–81]. Recent evidence suggests that pediatric children with MIS-C who receive intravenous immunoglobulin or an IL-6 antagonist, such as tocilizumab, recover without complications [82]. Given the uncertain risk of complications, children who have recovered from MIS-C should receive a longer-term cardiac follow-up.

Adrenal insufficiency

ACE2 is expressed in small amounts in adrenal tissue, but COVID-19 can inhibit the adrenal stress response through different mechanisms. It has been shown that the virus contains amino acids such as adrenocorticotropin hormone. Antibodies against these amino acids and adrenocorticotropin hormone function cause a limited adrenal stress response and adrenal insufficiency [83]. Another mechanism may be due to the hypercoagulable condition during the infection leading to acute adrenal infarction [84]. On the other hand, patients with previous adrenal insufficiency are at a higher risk of infection because of reduced cortisol secretion, especially during the acute phase of adrenal insufficiency. Adrenocortical necrosis and hemorrhage during severe COVID-19 infection may cause adrenal insufficiency. Medications may cause adrenal insufficiency during COVID-19 infection. Martino et al. [85] showed that the risk of developing COVID-19 in patients with adrenal insufficiency is lower than that in the normal population, which may be due to more attention and care. On the other hand, patients taking supraphysiological doses of glucocorticoids may be more prone to COVID-19 [86]. Although adrenal involvement has been shown in adults with COVID-19, significant adrenal disease in children with COVID-19 has not been reported [15]. There are limited data available in pediatric patients with adrenal insufficiency and COVID-19. Nevertheless, Raisingani [87] showed that the mortality rate and severe disease increased in children with adrenal insufficiency and COVID-19 compared with children with COVID-19 and no adrenal insufficiency.

Management

Individuals who are steroid-dependent or fear that they may have adrenal suppression should exercise vigilance to prevent infection with SARS-CoV-2. Patients with symptomatic COVID-19 should be handled according to established recommendations for stress dosage [88, 89].

Diabetes mellitus and impaired glucose metabolism

Is diabetes mellitus a risk factor for increasing the severity of COVID-19?

Diabetes mellitus, prediabetes mellitus, and hyperglycemia are independent risk factors associated with moderate to severe COVID-19, increased morbidity and mortality, and a significant increase in inflammatory cytokines compared with non-diabetic patients [45, 90, 91], but diabetes is not related to an increased risk of SARS-CoV-2 [92]. Immunological dysregulation associated with hyperglycemia, endothelial damage, and increased levels of cytokines and oxidative stress related to coronavirus infection led to

multiple organ dysfunction and thromboembolic risk [93]. One cohort study revealed that patients with an HbA1c of 10.0% or higher had increased COVID-19-related mortality [45]. Furthermore, antiviral drugs and systemic corticosteroids used for COVID-19 may exacerbate hyperglycemia and the severity of the disease in diabetic patients [94]. In human studies, high glucose levels lead to increased SARS duplication, the production of mitochondrial reactive oxygen, and the activation of hepatocyte nuclear factor-1α, and glycolysis maintains this duplication [95].

In patients with T2D, neutrophil, and complement dysfunction, high proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, and decreased viral clearance can exacerbate the clinical course of COVID-19 [96]. During the COVID-19 outbreak, children with new-onset-dependent diabetes may develop DKA but have more severe clinical manifestations. Their prognosis has not been worse than that of patients without diabetes [46, 47]. On the other hand, one study among adult patients reported a mortality rate of approximately fifty percent among patients with DKA in COVID-19. Although DKA may occur in T2D, a combined DKA/hyperglycemic hyperosmolar state should be considered and has higher mortality than DKA alone [93, 97].

Is COVID-19 a risk factor for developing new-onset diabetes mellitus?

High levels of IL-6, IL-1β, TNF-α, monocyte chemoattractant protein-1, and inducible protein-10 during COVID-19 can cause insulin resistance. As mentioned above, obesity associated with T2D exacerbates the cytokine reaction that contributes to lowering insulin sensitivity and worsening hyperglycemia in patients with diabetes and prediabetes. COVID-19, as a viral infection, can trigger the presentation of diabetes in genetically predisposed individuals [98]. The expression of ACE2 in β-cells as a receptor for COVID-19 may cause pancreatic damage and result in pancreatic endocrine and exocrine dysfunction [99]. In one study, among the patients hospitalized for COVID-19, 2.8% had newly diagnosed diabetes, and a systematic review showed 10% newly diagnosed diabetes mellitus among the patients with COVID-19 [93, 100].

Management

During COVID-19 infection, regular consultation and monitoring of blood glucose levels (via finger sticks or continuous glucose monitors) are necessary. Insulin doses should be adjusted according to self-monitoring blood glucose. Furthermore, patients should check ketones in addition to blood glucose monitoring, and if ketones are present, increase correction doses of insulin. Adequate hydration of the patient

effectively controls blood glucose levels [101]. Regular physical activity and correcting eating habits are helpful.

In patients with T2D acute hyperglycemia due to exacerbation of inflammation, insulin resistance must be controlled rapidly and effectively. Some medications are used for glycemic control in patients with T2D, but the choice of medication during COVID-19 infection should be based on the patient's condition. Glucagon-like peptide 1 analogs and dipeptidyl peptidase 4 inhibitors in mild to moderate symptoms have glucose-lowering efficacy and inflammatory action in outpatient and hospitalized patients. Insulin infusion in critically ill diabetic patients has been suggested for adequate glycemic control and D-dimer and IL-6 levels [94]. Metformin, as a lowering glucose agent, had anti-inflammatory action related to significantly lower mortality compared to patients not receiving metformin [102]. During severe COVID-19 infection (ICU-admitted patients), metformin, thiazolidinedione (TZD), sodium-glucose cotransporter receptor-2 (SGLT2) inhibitors, and TZD, SGLT2 inhibitors were used in hospitalized patients, but moderate disease has not been recommended to use. [94].

Due to increased insulin resistance and ketone generation, viral infections might be more challenging to control in patients with diabetes [103, 104]. Given the positive correlation between a higher HbA1c level and the prevalence of DKA in children with T1D, a large proportion of the pediatric T1D population may be at increased risk of developing DKA in the presence of COVID-19 infection [105, 106]. To reduce the risk of DKA, practitioners should familiarize themselves with sick day guidelines and be available for guidance during times of illness. Patients should be advised to monitor their blood glucose levels more often during COVID-19 illness, either with continuous glucose monitors or with finger sticks [101]. Insulin doses may need to be adjusted more often, and additional fast-acting insulin correction boluses may be required to avoid severe hyperglycemia or ketoacidosis [107]. Patients should monitor ketones regardless of blood sugar levels and increase correction dosage and fluid intake if ketones are detected. Encouraging remote blood glucose monitoring with continuous glucose monitoring is a great tool that should be made available to all families.

Additional guidelines for children with T2D include those discussed in the obesity section below. All children must engage in regular physical exercise and practice good dietary practices during this epidemic. Telemedicine is a helpful method for maintaining regular contact with the diabetes team and counseling and managing patients with T1D and T2D during COVID-19 infection. However, there are limited data, and further research is needed. A review among patients with T2D and T1D showed that telemedicine could reduce HbA1c by approximately − 0.01% to − 1.13% and − 0.12% to − 0.86%, respectively [108].

Thyroid disease

Thyroid cells express transmembrane protease serine 2 and ACE2 as receptors for COVID-19 even more than the lungs, explaining distinct thyroid manifestations during infection [20]. Direct injury virus infection of the thyroidal cells and indirect destruction by cytokine storms during COVID-19 may lead to thyroid gland damage that presents to subacute thyroiditis with three-phase thyrotoxicosis, hypothyroidism, and finally euthyroidism [109]. Thyroid hormones act as modulators of the immune system [110]. Normal values of T4 and T3 can exacerbate the production and release of inflammatory and proinflammatory cytokines, which develop into a "cytokine storm". T4 activates human platelets, which can contribute to clotting as a complication of virus infections [111]. There is no evidence that thyroid disease predisposes individuals to COVID-19 infection, but uncontrolled hyperthyroidism is a risk factor for complications. Patients with thyroid disease should continue their medication as before [84]. Three thyroid disorders, hypothyroidism, subacute thyroiditis, thyrotoxicosis, and nonthyroidal illness, have been described during the COVID-19 pandemic. The severity of COVID-19 is an essential determinant of the type of thyroid disorder [112]. One study reported a prevalence of 5.2% hypothyroidism in hospitalized patients with COVID-19, predominantly subclinical hypothyroidism, and another showed 20.2% of patients with thyrotoxicosis [18]. Fibrillation in a patient without a history of previous cardiovascular disease may indicate a thyrotoxicosis state [113]. Furthermore, lower thyroid stimulating hormone (TSH) and free T3 values correlated with the severity of COVID-19 [114].

Management

All collected data about thyroid damage and COVID-19 have recommended regular monitoring of thyroid function during acute infection and treatment. There are no data on the treatment of thyrotoxicosis and sick euthyroid syndrome in hospitalized patients with COVID-19 [112]. Since the clinical course of thyroiditis is benign, a watch-and-wait approach is sufficient, but in severely symptomatic patients, non-steroidal anti-inflammatory drugs, steroids, and non-specific beta-blockers are suggested [115, 116]. If hypothyroidism and TSH are > 10 mIU/mL, levothyroxine therapy should be started [84]. Patients with primary hypothyroidism or hyperthyroidism should be treated as usual. ATDs such as methimazole should be warned about the risk of agranulocytosis and consequent bacterial infection. Because the symptoms of ATDs (fever, sore throat, and cough) are similar to COVID-19, a fast medical check is advised if symptoms emerge. Similar to other viruses, COVID-19 may cause thyroid storms in people with uncontrolled hyperthyroidism. Thyroid cancer patients who underwent surgery with replacement levothyroxine had no increased risk of infection. Immunosuppression may increase the infection risk in a portion of chemo patients. The American Thyroid Association and the American Association of Endocrine Surgeons say that due to the tumor's slow growth, most thyroid cancer operations may be safely deferred [117].

Hypopituitarism

ACE2, as a COVID-19 receptor on central nervous tissues, may play a role in COVID-19 neural invasion [118]. In addition, the hematogenous spread of the virus can infect the pituitary [119]. Children with hypopituitarism are not at increased risk for COVID-19, and they are not at increased risk of developing severe COVID-19 disease following infection.

Management

During the COVID-19 outbreak, regular monitoring is necessary for children with hypopituitarism to take their medication correctly. They have been taught that increased dose of hydrocortisone according to the severity of their disease. Some reports in adult patients with growth hormone deficiency suggest stopping growth hormone during hospitalization with COVID-19, but there are no data among pediatric patients [120, 121]. In diabetes insipidus, the water and electrolyte balance should be considered. Children with numerous pituitary hormone deficits may be at a greater risk of COVID-19 complications and death, especially if central adrenal insufficiency is not treated appropriately. In the absence of published data or standards, we propose that children's pituitary hormone deficits be managed according to known protocols. While current guidelines for adults with growth hormone insufficiency suggest discontinuing growth hormone therapy during hospitalization with COVID-19, there is a dearth of research on the impact of growth hormone treatment in children with COVID-19 [120].

Metabolic bone disease

Vitamin D supplementation has not been shown to protect against COVID-19 or its consequences. Randomized experiments are now being conducted to ascertain whether vitamin D supplementation may help prevent or lessen the severity of COVID-19. Prolonged home quarantine to prevent the spread of COVID-19 may restrict outside time, increasing the risk of vitamin D insufficiency and related

consequences such as rickets, osteomalacia, and symptomatic hypocalcemia [122, 123]. Clinicians should continue to adhere to existing vitamin D supplementation guidelines for individuals at risk of insufficiency. The Food and Drug Administration has authorized home delivery of burosumab injections for patients with hypophosphatemic rickets during the COVID-19 pandemic.

The American Society of Bone and Mineral Research, the American Association of Clinical Endocrinology, the Endocrine Society, the European Calcified Tissue Society, and the National Osteoporosis Foundation have issued a joint statement outlining guidelines for managing osteoporosis in adults during the COVID-19 pandemic, some of which may need to be modified for pediatric patients. Essential measures to preserve bone health should be advocated in children with poor bone density, including proper calcium and vitamin D consumption, as well as sex steroid replacement where necessary. Weight-bearing exercise is critical for bone health optimization and should not be overlooked; physical therapy services are readily accessible through telemedicine and can be used to lead treatment in the home when necessary. Advanced therapy should be maintained when practicable, especially in children at high risk of fragility fractures.

Due to the long-acting nature of intravenous bisphosphonates, it is typically regarded as safe to postpone therapy for at least 6–9 months in adults [124]. In youngsters, however, continued new bone formation and the emergence of stress risers during intermittent bisphosphonate medication may raise the risk of fracture if treatment is significantly delayed [125]. Consider switching patients from pamidronate to zoledronic acid, which is injected over a shorter time period and needs fewer infusions. Clinicians may elect to forego pre-treatment laboratory testing for repeat infusions if the patient has no history of hypocalcemia with previous infusions, is consuming an adequate amount of calcium and vitamin D through diet or supplementation, has no renal disease, and has a stable overall health status. In most patients, DXA scans and other imaging may be postponed if the findings of the dual-energy X-ray absorptiometry (DXA) scan do not need a change in care.

Precocious puberty

There are some reports that represent precocious puberty in girls during COVID-19 [126–128]. According to the first report, an increase in diagnoses and a quicker puberty progression were observed. It was hypothesized that these trends were related to an increase in electronic device use, an increase in BMI, and possibly an increase in eating. The second study confirmed the rise in precocious puberty diagnoses as well as the net prevalence of females.

In a study conducted by Turriziani Colonna et al., children who presented with suspected central precocious puberty (CCP) during the COVID-19 outbreak were assessed. It was observed that among all patients who were referred for CCP, 11 (39.3%) new CCP were diagnosed during COVID-19, and 22/45 (48.9%) of the patients showed an increased pubertal progression rate, with more children in the T3 and T4-5 phases [128]. In another study, it was mentioned that of 124 patients with idiopathic precocious puberty, 46.8% were diagnosed during one year of this pandemic, and the rest were diagnosed during three years before the COVID-19 pandemic [129]. Additionally, other studies confirmed that COVID-19 is related to precocious puberty in children [130–133].

Conclusions

SARS-CoV-2 has the capacity to affect the majority of endocrine systems mechanistically. While little is known regarding the association between COVID-19 and endocrine problems in children, published data in adults have indicated pathology associated with diabetes mellitus, obesity, pituitary, adrenal, and thyroid illness. The following aspects of COVID-19 and endocrine diseases in children and adolescents are highlighted by current data: (1) antithyroid medication and continuous corticosteroid therapy are likely to enhance the risk of SARS-CoV-2 infection; patients should be counseled about this risk and advised to take further measures to avoid infection; (2) MIS-C seems to increase the incidence of hypocalcemia in children, and those who develop coronary artery aneurysms may be at increased risk of developing ASCVD later in life; (3) children with T1D and a higher HbA1c are more likely than children with better diabetes management to be hospitalized with COVID-19. The COVID-19 pandemic has produced a variety of difficulties for pediatric diabetes treatment, including school closures, interrupted schedules, and stress associated with diabetes control during lockdown times; (4) obesity does not seem to enhance the incidence of infection with SARS-CoV-2 in children, but it may be a risk factor for COVID-19-related problems in this group; and (5) COVID-19 treatment in children with diabetes insipidus needs special attention to fluid and salt balance. It may necessitate a modification in the method of desmopressin administration if the intranasal version is used.

The COVID-19 pandemic will aggravate obesity, metabolic syndrome, and its related comorbidities if enforced shelter-in-home laws and physical distance limitations are not taken into account, which we believe is very important. There is a direct link between sedentary activity and increased risks of developing T2D and precocious puberty over time [126–136]. We must continue to give the necessary

assistance to our patients to mitigate the pandemic's health repercussions for the future generation.

Declarations

Ethical approval This research was done under permission of Ethics Committee of Tehran University of Medical Sciences.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55:2000607.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
3. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.
4. Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity. 2020;52:731–3.
5. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. Pediatr Infect Dis J. 2020;39:469–77.
6. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2. J Clin Invest. 2020;130:5967–75.
7. Naja M, Wedderburn L, Ciurtin C. COVID-19 infection in children and adolescents. Br J Hosp Med (Lond). 2020;81:1–10.
8. Steardo L, Steardo L Jr, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol (Oxf). 2020;229:e13473.
9. Ata F, Almasri H, Sajid J, Yousaf Z. COVID-19 presenting with diarrhoea and hyponatraemia. BMJ Case Rep. 2020;13:e235456.
10. Habib MB, Sardar S, Sajid J. Acute symptomatic hyponatremia in setting of SIADH as an isolated presentation of COVID-19. IDCases. 2020;21:e00859.
11. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18–22.
12. Leow MKS, Kwek DSK, Ng AWK, Ong KC, Kaw GJL, Lee LSU. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol (Oxf). 2005;63:197–202.
13. Pascual-Goñi E, Fortea J, Martínez-Domeño A, Rabella N, Tecame M, Gómez-Oliva C, et al. COVID-19-associated ophthalmoparesis and hypothalamic involvement. Neurol Neuroimmunol Neuroinflamm. 2020;7:e823.
14. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol. 2020;8:659–60.
15. Leyendecker P, Ritter S, Riou M, Wackenthaler A, Meziani F, Roy C, et al. Acute adrenal infarction as an incidental CT finding and a potential prognosis factor in severe SARS-CoV-2 infection: a retrospective cohort analysis on 219 patients. Eur Radiol. 2021;31:895–900.
16. Santana MF, Borba MGS, Baía-da-Silva DC, Val F, Alexandre MAA, Brito-Sousa JD, et al. Case report: adrenal pathology findings in severe COVID-19: an autopsy study. Am J Trop Med Hyg. 2020;103:1604–7.
17. Ippolito S, Dentali F, Tanda M. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. J Endocrinol Invest. 2020;43:1171–2.
18. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol. 2020;183:381–7.
19. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol. 2020;8:739–41.
20. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene *ACE2* in a wide variety of human tissues. Infect Dis Poverty. 2020;9:45.
21. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7.
22. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Res Clin Pract. 2020;164:108166.
23. Hollstein T, Schulte DM, Schulz J, Glück A, Ziegler AG, Bonifacio E, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab. 2020;2:1021–4.
24. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol. 2020;14:297–304.
25. Wang G, Zhang Q, Zhao X, Dong H, Wu C, Wu F, et al. Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study. Lipids Health Dis. 2020;19:204.
26. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020;57:262–5.
27. Qian GQ, Yang NB, Ding F, Ma AHY, Wang ZY, Shen YF, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. QJM. 2020;113:474–81.
28. Almoosa ZA, Al Ameer HH, AlKadhem SM, Busaleh F, AlMuhanna FA, Kattih O. Multisystem inflammatory syndrome in children, the real disease of COVID-19 in pediatrics-a multicenter case series from Al-Ahsa. Saudi Arabia Cureus. 2020;12:e11064.
29. Samuel S, Friedman RA, Sharma C, Ganigara M, Mitchell E, Schleien C, et al. Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR-positive SARS-CoV-2 infection,

including drug-induced changes in the corrected QT interval. Heart Rhythm. 2020;17:1960–6.

30. Christ-Crain M, Hoorn EJ, Sherlock M, Thompson CJ, Wass JAH. Endocrinology in the time of COVID-19: management of diabetes insipidus and hyponatraemia. Eur J Endocrinol. 2020;183:G9-15.

31. Behan L, Sherlock M, Moyles P, Renshaw O, Thompson C, Orr C, et al. Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study. Eur J Endocrinol. 2015;172:243–50.

32. Crowley RK, Sherlock M, Agha A, Smith D, Thompson CJ. Clinical insights into adipsic diabetes insipidus: a large case series. Clin Endocrinol (Oxf). 2007;66:475–82.

33. Cuesta M, Hannon MJ, Thompson CJ. Adipsic diabetes insipidus in adult patients. Pituitary. 2017;20:372–80.

34. Darmon M, Timsit JF, Francais A, Nguile-Makao M, Adrie C, Cohen Y, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrol Dial Transplant. 2010;25:2510–5.

35. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–421.

36. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.

37. Boelaert K, Visser WE, Taylor PN, Moran C, Léger J, Persani L. Endocrinology in the time of COVID-19: management of hyperthyroidism and hypothyroidism. Eur J Endocrinol. 2020;183:G33–9.

38. Dworakowska D, Grossman AB. Thyroid disease in the time of COVID-19. Endocrine. 2020;68:471–4.

39. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730–41.

40. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.

41. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775–6.

42. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.

43. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17:259–60.

44. Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the US. Diabetes Care. 2020;43:e83–5.

45. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8:823–33.

46. Ho J, Rosolowsky E, Pacaud D, Huang C, Lemay JA, Brockman N, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatr Diabetes. 2021;22:552–7.

47. DiMeglio LA, Albanese-O'Neill A, Muñoz CE, Maahs DM. COVID-19 and children with diabetes—updates, unknowns, and next steps: first, do no extrapolation. Diabetes Care. 2020;43:2631–4.

48. Christoforidis A, Kavoura E, Nemtsa A, Pappa K, Dimitriadou M. Coronavirus lockdown effect on type 1 diabetes management on children wearing insulin pump equipped with continuous glucose monitoring system. Diabetes Res Clin Pract. 2020;166:108307.

49. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429–36.

50. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, metropolitan region. J Pediatr. 2020;223:199–203.e1.

51. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020;174:868–73.

52. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City. New York JAMA Pediatr. 2020;174:e202430.

53. Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr. 2021;230:23–31.e10.

54. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

55. Brizola E, Adami G, Baroncelli GI, Bedeschi MF, Berardi P, Boero S, et al. Providing high-quality care remotely to patients with rare bone diseases during COVID-19 pandemic. Orphanet J Rare Dis. 2020;15:228.

56. Hernández JL, Nan D, Fernandez-Ayala M, García-Unzueta M, Hernández-Hernández MA, López-Hoyos M, et al. Vitamin D status in hospitalized patients with SARS-CoV-2 infection. J Clin Endocrinol Metab. 2021;106:e1343–53.

57. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19, 11 March, 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Accessed 11 Mar 2020.

58. Jenssen BP, Kelly MK, Powell M, Bouchelle Z, Mayne SL, Fiks AG. COVID-19 and changes in child obesity. Pediatrics. 2021;147:e2021050123.

59. Yang D, Luo C, Feng X, Qi W, Qu S, Zhou Y, et al. Changes in obesity and lifestyle behaviours during the COVID-19 pandemic in Chinese adolescents: a longitudinal analysis from 2019 to 2020. Pediatr Obes. 2022;17:e12874.

60. Tripathi S, Christison AL, Levy E, McGravery J, Tekin A, Bolliger D, et al. The impact of obesity on disease severity and outcomes among hospitalized children with COVID-19. Hosp Pediatr. 2021;11:e297–316.

61. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring). 2020;28:1195–9.

62. Hajifathalian K, Kumar S, Newberry C, Shah S, Fortune B, Krisko T, et al. Obesity is associated with worse outcomes in COVID-19: analysis of early data from New York City. Obesity (Silver Spring). 2020;28:1606–12.

63. Nogueira-de-Almeida CA. We need to look at the comorbidities of obesity during childhood and adolescence. Future. 2017;30:431–7.

64. Saiki A, Ohira M, Endo K, Koide N, Oyama T, Murano T, et al. Circulating angiotensin II is associated with body fat accumulation and insulin resistance in obese subjects with type 2 diabetes mellitus. Metabolism. 2009;58:708–13.

65. Rychter AM, Zawada A, Ratajczak AE, Dobrowolska A, Krela-Kaźmierczak I. Should patients with obesity be more afraid of COVID-19? Obes Rev. 2020;21:e13083.

66. Samuels JD. Obesity phenotype is a predictor of COVID-19 disease susceptibility. Obesity (Silver Spring). 2020. https://doi.org/10.1002/oby.22866.

67. Caixe SH, Benedeti ACGS, Garcia J, de Paula MW, Mauad Filho F, Del Ciampo LA, et al. Evaluation of echocardiography as a marker of cardiovascular risk in obese children and adolescents. Int J Clin Pediatr. 2014;3:72–8.

68. Garcia J, Benedeti ACGS, Caixe SH, Mauad F, Nogueira-de-Almeida CA. Ultrasonographic evaluation of the common carotid intima-media complex in healthy and overweight/obese children. J Vasc Bras. 2019;18:e20190003.

69. Korakas E, Ikonomidis I, Kousathana F, Balampanis K, Kountouri A, Raptis A, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab. 2020;319:E105–9.

70. Souza LL, Costa-Neto CM. Angiotensin-(1–7) decreases LPS-induced inflammatory response in macrophages. J Cell Physiol. 2012;227:2117–22.

71. Radzikowska U, Ding M, Tan G, Zhakparov D, Peng Y, Wawrzyniak P, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy. 2020;75:2829–45.

72. Magrone T, Jirillo E. Childhood obesity: immune response and nutritional approaches. Front Immunol. 2015;6:76.

73. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation, and cytokine amplification in coronavirus disease 2019? Obesity (Silver Spring). 2020;28:1191–4.

74. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis. 2018;61:142–50.

75. Lakkis JI, Weir MR. Obesity and kidney disease. Prog Cardiovasc Dis. 2018;61:157–67.

76. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation. 2020;142:4–6.

77. Yan J, Grantham M, Pantelic J, De Mesquita PJB, Albert B, Liu F, et al. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. Proc Natl Acad Sci U S A. 2018;115:1081–6.

78. Karlsson EA, Hertz T, Johnson C, Mehle A, Krammer F, Schultz-Cherry S. Obesity outweighs protection conferred by adjuvanted influenza vaccination. MBio. 2016;7:e01144–216.

79. Kinsey EW, Hammer J, Dupuis R, Feuerstein-Simon R, Cannuscio CC. Planning for food access during emergencies: missed meals in Philadelphia. Am J Public Health. 2019;109:781–3.

80. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334–46.

81. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307–22.

82. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183:982–95.e14.

83. Wheatland R. Molecular mimicry of ACTH in SARS–implications for corticosteroid treatment and prophylaxis. Med Hypotheses. 2004;63:855–62.

84. Mung SM, Jude EB. Interplay between endocrinology, metabolism and COVID-19 infection. Clin Med (Lond). 2021;21:e499–504.

85. Martino M, Aboud N, Cola MF, Giancola G, Ciarloni A, Salvio G, et al. Impact of COVID-19 pandemic on psychophysical stress in patients with adrenal insufficiency: the CORTI-COVID study. J Endocrinol Invest. 2021;44:1075–84.

86. Kaiser UB, Mirmira RG, Stewart PM. Our response to COVID-19 as endocrinologists and diabetologists. J Clin Endocrinol Metab. 2020. https://doi.org/10.1210/clinem/dgaa148.

87. Raisingani MG. Risk of complications in children with adrenal insufficiency and Covid-19. J Endocr Soc. 2021;5(Suppl 1):A721.

88. American Association of Clinical Endocrinologists. AACE position statement: coronavirus (COVID-19) and people with thyroid disease. 2020. https://www.aace.com/recent-news-and-updates/aace-position-statement-coronavirus-covid-19-and-people-thyroid-updated. Accessed 20 Mar 2020.

89. Arlt W, Baldeweg SE, Pearce SH, Simpson HL. Endocrinology in the time of COVID-19: management of adrenal insufficiency. Eur J Endocrinol. 2020;183:G25-32.

90. Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. J Med Virol. 2021;93:409–15.

91. Wang X, Liu Z, Li J, Zhang J, Tian S, Lu S, et al. Impacts of type 2 diabetes on disease severity, therapeutic effect, and mortality of patients with COVID-19. J Clin Endocrinol Metab. 2020. https://doi.org/10.1210/clinem/dgaa535.

92. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020;43:867–9.

93. Pal R, Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: a systematic review of literature. Diabetes Metab Syndr. 2020;14:1563–9.

94. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021;17:11–30.

95. Codo AC, Davanzo GG, de Brito ML, de Souza GF, Muraro SP, Virgilio-da-Silva JV, et al. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. Cell Metab. 2020;32:437–46.e5.

96. Chatterjee S, Ghosh R, Biswas P, Dubey S, Guria RT, Sharma CB, et al. COVID-19: the endocrine opportunity in a pandemic. Minerva Endocrinol. 2020;45:204–27.

97. Armeni E, Aziz U, Qamar S, Nasir S, Nethaji C, Negus R, et al. Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series. Lancet Diabetes Endocrinol. 2020;8:660–3.

98. Lönnrot M, Lynch KF, Elding Larsson H, Lernmark Å, Rewers MJ, Törn C, et al. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. Diabetologia. 2017;60:1931–40.

99. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol. 2020;18:2128–30.e2.

100. Cariou B, Pichelin M, Goronflot T, Gonfroy C, Marre M, Raffaitin-Cardin C, et al. Phenotypic characteristics and prognosis of newly diagnosed diabetes in hospitalized patients with COVID-19: results from the CORONADO study. Diabetes Res Clin Pract. 2021;175:108695.

101. Hill MA, Mantzoros C, Sowers JR. Commentary: COVID-19 in patients with diabetes. Metabolism. 2020;107:154217.

102. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, et al. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. Am J Trop Med Hyg. 2020;103:69–72.

103. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. J Med Virol. 2020;92:747–54.

104. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702.

105. Cengiz E, Xing D, Wong JC, Wolfsdorf JI, Haymond MW, Rewers A, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013;14:447–54.

106. Kahkoska AR, Shay CM, Crandell J, Dabelea D, Imperatore G, Lawrence JM, et al. Association of race and ethnicity with glycemic control and hemoglobin A1c levels in youth with type 1 diabetes. JAMA Netw Open. 2018;1:e181851.

107. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes Metab Syndr. 2020;14:211–2.

108. Ghosh A, Gupta R, Misra A. Telemedicine for diabetes care in India during COVID19 pandemic and national lockdown period: guidelines for physicians. Diabetes Metab Syndr. 2020;14:273–6.

109. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab. 2021;106:e926–35.

110. De Vito P, Incerpi S, Pedersen JZ, Luly P, Davis FB, Davis PJ. Thyroid hormones as modulators of immune activities at the cellular level. Thyroid. 2011;21:879–90.

111. Davis PJ, Glinsky GV, Lin HY, Mousa SA. Actions of thyroid hormone analogues on chemokines. J Immunol Res. 2016;2016:3147671.

112. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021;22:803–15.

113. Dhakal BP, Sweitzer NK, Indik JH, Acharya D, William P. SARS-CoV-2 infection and cardiovascular disease: COVID-19 heart. Heart Lung Circ. 2020;29:973–87.

114. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid. 2021;31:8–11.

115. Chakraborty U, Ghosh S, Chandra A, Ray AK. Subacute thyroiditis as a presenting manifestation of COVID-19: a report of an exceedingly rare clinical entity. BMJ Case Rep. 2020;13:e239953.

116. Brancatella A, Ricci D, Viola N, Sgrò D, Santini F, Latrofa F. Subacute thyroiditis after Sars-COV-2 infection. J Clin Endocrinol Metab. 2020. https://doi.org/10.1210/clinem/dgaa276.

117. Surgical Affairs Committee. Comment on thyroid surgery during the Covid-19 pandemic. Updated 7/13/2020. https://www.thyroid.org/covid-19/comment-on-thyroid-surgery-during-pandemic/. Accessed 13 July 2020.

118. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683–90.

119. Mussa BM, Srivastava A, Verberne AJM. COVID-19 and neurological impairment: hypothalamic circuits and beyond. Viruses. 2021;13:498.

120. Society for Endocrinology. COVID-19 resources for managing endocrine conditions. https://www.endocrinology.org/clinical-practice/covid-19-resources-for-managing-endocrine-conditions/. Accessed 30 Aug 2020.

121. European Centre for Disease Prevention and Control. COVID-19 in children and the role of school settings in COVID-19 transmission. https://www.ecdc.europa.eu/en/publicationsdata/children-and-school-settings-covid-19-transmission. Accessed 31 Aug 2020.

122. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nat Rev Dis Primers. 2017;3:17101.

123. Absoud M, Cummins C, Lim MJ, Wassmer E, Shaw N. Prevalence and predictors of vitamin D insufficiency in children: a Great Britain population based study. PLoS One. 2011;6:e22179.

124. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S, et al. Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med. 2018;379:2407–16.

125. Biggin A, Briody JN, Ormshaw E, Wong KKY, Bennetts BH, Munns CF. Fracture during intravenous bisphosphonate treatment in a child with osteogenesis imperfecta: an argument for a more frequent, low-dose treatment regimen. Horm Res Paediatr. 2014;81:204–10.

126. Stagi S, De Masi S, Bencini E, Losi S, Paci S, Parpagnoli M, et al. Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. Ital J Pediatr. 2020;46:165–75.

127. Verzani M, Bizzarri C, Chioma L, Bottaro G, Pedicelli S, Cappa M. Impact of COVID-19 pandemic lockdown on puberty: experience of an Italian tertiary center. Ital J Pediatr. 2021;47:52.

128. Turriziani Colonna A, Curatola A, Sodero G, Lazzareschi I, Cammisa I, Cipolla C. Central precocious puberty in children after COVID-19 outbreak: a single-center retrospective study. Minerva Pediatr (Torino). 2022. https://doi.org/10.23736/S2724-5276.22.06827-6.

129. Acar S, Özkan B. Increased frequency of idiopathic central precocious puberty in girls during the COVID-19 pandemic: preliminary results of a tertiary center study. J Pediatr Endocrinol Metab. 2021;35:249–51.

130. Mondkar SA, Oza C, Khadilkar V, Shah N, Gondhalekar K, Kajale N, et al. Impact of COVID-19 lockdown on idiopathic central precocious puberty–experience from an Indian centre. J Pediatr Endocrinol Metab. 2022;35:895–900.

131. Oliveira Neto CP, Azulay RSS, Almeida AGFP, Tavares MDGR, Vaz LHG, Leal IRL, et al. Differences in puberty of girls before and during the COVID-19 Pandemic. Int J Environ Res Public Health. 2022;19:4733.

132. Chioma L, Bizzarri C, Verzani M, Fava D, Salerno M, Capalbo D, et al. Sedentary lifestyle and precocious puberty in girls during the COVID-19 pandemic: an Italian experience. Endocr Connect. 2022;11:e210650.

133. Umano GR, Maddaluno I, Riccio S, Lanzaro F, Antignani R, Giuliano M, et al. Central precocious puberty during COVID-19 pandemic and sleep disturbance: an exploratory study. Ital J Pediatr. 2022;48:60.

134. Hamburg NM, McMackin CJ, Huang AL, Shenouda SM, Widlansky ME, Schulz E, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Arterioscler Thromb Vasc Biol. 2007;27:2650–6.

135. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. Am J Prev Med. 2011;40:174–82.

136. Tsai AC, Lee SH. Determinants of new-onset diabetes in older adults–results of a national cohort study. Clin Nutr. 2015;34:937–42.