The Interplay Between COVID-19 and Pediatric Endocrine Disorders. What have we Learned After More than Three Years of the Pandemic?

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ABSTRACT

As an increased body of COVID-19 related research is now available, it becomes apparent that the effects of COVID-19 extend beyond that of the respiratory system. Among others, the endocrine system is particularly vulnerable to perturbation from the COVID-19 infection. The present scoping review summarizes the bidirectional relationship between COVID-19 and endocrine system in children and adolescents, by describing both the possible susceptibility of children and adolescents without endocrinopathies to endocrine disorders following COVID-19 infection, but also the potential susceptibility to COVID-19 infection and severe infection, or the aggravation of endocrine dysfunction in patients with pre-existing endocrine diseases. Data suggest increased obesity and diabetes rates, as well as increased severity and frequency of diabetic ketoacidosis following COVID-19 infection. Conversely, patients with diabetes and obesity may experience a more severe course of COVID-19 infection. However, in the majority of cases, children and adolescents with well-managed and regulated endocrine disorders do not appear to be at increased risk of infection or severe infection from COVID-19. Thus, adhering to the appropriate "sick day management rules", maintaining adequate supply of medications and supplies, keeping close contact with the therapeutic team and seeking medical help without delay when needed, are the main recommendations for a safe outcome. Additional lessons learnt during the pandemic include the risk for mental health diseases caused by children's disrupted routine due to COVID-19 related protective measures and the importance of adopting alternative communication options, such as telehealth visits, in order to ensure uninterrupted endocrine care.

Introduction

Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed a great impact on human lives and societies worldwide and has caused devastating morbidity and mortality since it first appeared in China in December 2019 [1]. The virus gains cellular access by binding of its spike glycoprotein on the angiotensin converting enzyme 2 (ACE2) receptor on the epithelial surface of human cells in a process requiring the transmembrane serine protease 2 (TMPRSS2). Subsequently it enters the nucleus via an endosomal pathway so that it can be replicated [1, 2]. ACE2 receptors and TMPRSS2 are not only expressed in pneumocytes, but also in other tissues, therefore, its effects extend beyond that of the respiratory system and many other organs and systems are also affected, such as the gastrointestinal, nervous, endocrine systems, the skin and the heart [3].

With regard to the endocrine system, ACE2 receptors and TMPRSS2 are expressed in different endocrine glands, including the pituitary, the thyroid gland, the adrenal glands, the pancreas, the testes, and the ovaries [4], which explains the endocrine vulnerability seen in subjects with COVID-19.

Whilst a potential clinical impact of COVID-19 on the endocrine system in the adult and pediatric populations was recognized from early studies, a significant and continuously accumulating body of data are now available regarding the effects of COVID-19 on endocrine function. Thus, the aim of this scoping review is to summarize the available evidence on the effects of COVID-19 on each of the endocrine axes in order to deepen our understanding on short- and long-term endocrine consequences, increase awareness in healthcare providers and institute appropriate investigations, and optimal management. Available data are presented from two different aspects: i) potential triggering of endocrine complications by COVID-19 in patients without pre-existing endocrine diseases, and ii) potential susceptibility to COVID-19 infection and severe infection, or aggravation of endocrine dysfunction in patients with pre-existing endocrine diseases.

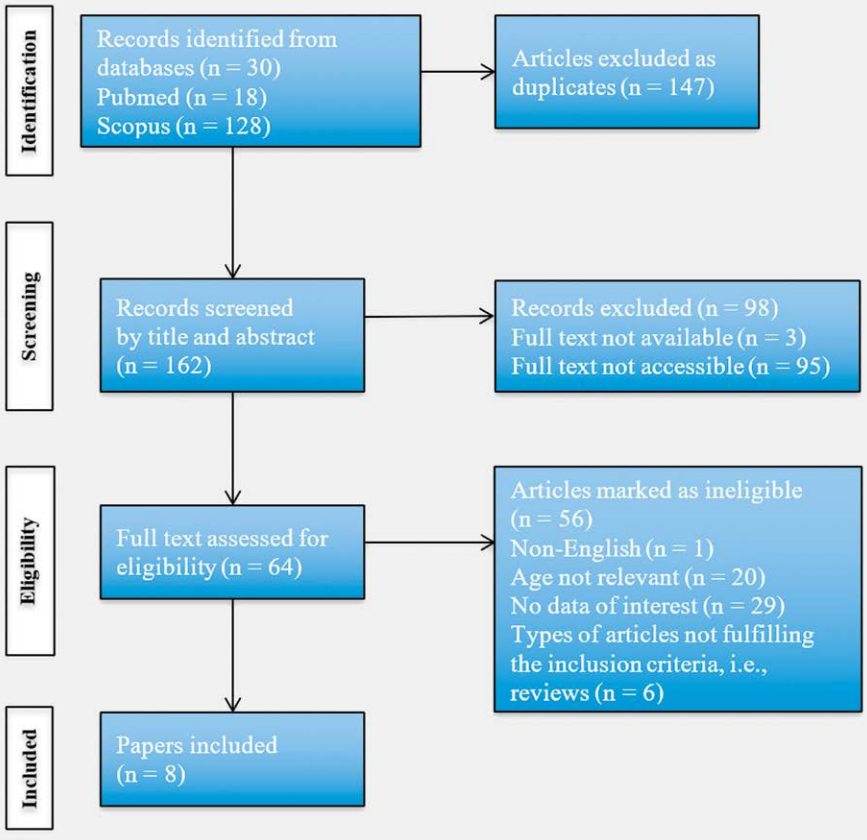
Materials and Methods

A comprehensive literature research was conducted from February 2020 up to June 2023. Data were extracted from two scientific databases, Medline (Pubmed) and Scopus. Search terms included "endocrine", "COVID-19", and "children". All articles that examined the association between COVID-19 and endocrine conditions in children and adolescents were considered eligible for this review. The design of this systematic review followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and checklist (▶ **Fig. 1**).

Inclusion criteria: children < 18 years old, endocrine disease, human studies, papers written in English language, types of sources: reports, original research articles. Exclusion criteria: non-human studies, absent or inadequate methodology, papers not relevant to the topic. All the articles that were identified from searches of the electronic databases were imported into the Mendeley software 2023, version 2.93.0, and duplicates were removed. The articles included are summarized in ▶ **Table 1**.

Results

The present review summarizes the available body of COVID-19 related literature that refers to the bidirectional relationship between COVID-19 and endocrine diseases in children and adolescents. Both the possible susceptibility of children and adolescents without previously known endocrinopathies to endocrine disorders following COVID-19 infection, but also the potential susceptibility to COVID-19 infection and severe infection, or the aggravation of endocrine dysfunction in patients with pre-existing endocrine diseases are described.



▶ **Fig. 1** PRISMA flow diagram describing the stages of the search strategy.

▶ **Table 1** Summary of included articles.

Author(s)	Title	Year	Type	Country
Kiess W et al. [113]	Covid19 pandemic and pediatric endocrinology and metabolism-are we through with it?	2021	Editorial	Germany
Han JA et al. [15]	Impact of the COVID-19 pandemic on seasonal variations in childhood and adolescent growth: Experience of pediatric endocrine clinics	2021	Original research	Korea
Calcaterra V et al. [68]	Non-thyroidal illness syndrome and SARS-CoV-2-associated multisystem inflammatory syndrome in children	2022	Original research	Italy
Zachurzok A et al. [118]	An attempt to assess the impact of pandemic restrictions on the lifestyle, diet, and body mass index of children with endocrine diseases – preliminary results	2022	Original research	Poland
Tenenbaum A et al. [121]	Growth assessment of children during the COVID-19 pandemic—Can we rely on parental measurements?	2021	Original research	Israel
Alsulaimani SA et al. [86]	Effect of the COVID-19 Pandemic on Treatment Adherence Among Children with Congenital Adrenal Hyperplasia.	2022	Original research	SAU
Shafiee A et al. [50]	Comparison of COVID-19 outcomes in patients with Type 1 and Type 2 diabetes: A systematic review and meta-analysis	2022	Meta-analysis	Iran, USA
Peinkhofer M et al. [96]	Reduction in pediatric growth hormone deficiency and increase in central precocious puberty diagnoses during COVID 19 pandemics	2022	Original research	Italy

Endocrine Disease

Obesity

During the COVID-19 pandemic, the pediatric population was mildly affected by the virus itself, however, children's lives were profoundly disrupted. Children were subjected to home confinement and alterations in eating behaviors and lifestyle modifications. The implementation of measures, such as social distancing, closure of schools, nurseries and sports facilities, not only promoted an unprecedented psychological burden in children, including anxiety and loneliness [5], but also a change in weight dynamics. Worsened dietary habits associated with increased snacking, higher consumption of ultra-processed and preserved food due to fear of food shortage or financial difficulties [6] were documented.

In addition, physical activity was declined in favor of sedentary behavior due to prolonged school closure, attendance of school lessons remotely, and restriction of children's regular, physical, extracurricular and outdoor activity [7]. Excessive screen time also resulted in sedentary behavior and snacking, which caused further reduction in energy expenditure and an escalation of pediatric overweight and obesity [8]. "Covibesity" is a new term that has been introduced and reflects the aggravation in obesity rates during the pandemic [9].

During the pandemic, weight gain was reported in 25–41.7 % of adolescents from different countries [10, 11]. Several studies have reported an increase in food intake resulting in weight gain [10, 12]. A study from Palestine showed that 41.7 % of adolescents gained weight due to increased consumption of fried food, carbohydrate-rich food, and dairy products [11]. In a study from China, children and adolescents of all age groups exhibited weight gain [10]. Similar results were shown in a study from Poland, according to which reduced vegetable, fruit, and legume consumption during the pandemic was associated with an increase in BMI [13], as well as in a study from Italy [14]. A registry-based study of approximately 150 000 children in Germany exhibited an exceptional aggravation of BMI-SDS, which was increased by more than 30 times, after the COVID-19-induced measures, particularly in children already affected by overweight or obesity [8]. The seasonal variation in BMI z-score was also affected during the COVID-19 pandemic in a Korean population; as opposed to the previous years, BMI z-score was increased even in spring [15].

Weight gain during the summer holidays is well known and a proportionate increase in childhood obesity rates to the duration of school closure has been proposed. This has been attributed to obesogenic behaviors during less structured days [16]. An association between overweight/obesity rates and economic crises or natural disasters has also been established [17, 18]. Similarly to previous findings, it has been reported that during the COVID-19 pandemic limited purchasing access to nutrient-dense foods (e. g., fresh fruits and vegetables) has led families to buying high-calorie foods, such as sweets, desserts, sugary drinks, or canned food [12]. During the pandemic, in the US the percentage of families with difficulty accessing food increased by 20 % due to financial reasons, closed stores, or the fear of transmitting the virus [12].

The finding of increased obesity rates during the pandemic is of major importance knowing that childhood obesity, an epidemic on its own, is likely to persist into adulthood and that earlier onset is associated with more severe sequelae related to comorbidities including hypertension, impaired glucose metabolism, increased cardiovascular risk, depression or cancer [19]. Therefore, the importance of healthy nutritional behaviors during the COVID-19 pandemic has been underlined [20].

Pre-existing obesity

Obesity has been recognized as one of the most prominent risk factors for severe COVID-19, hospitalization and increased mortality in adults, but also in children [20]. According to the CDC, obesity was present in 48.3 % of all COVID-19 hospitalized adult patients and the Louisiana Department of Health reported a prevalence of 28 % in COVID-19 adult non-survivors [21, 22]. Based on the existing data, the US Centers for Disease Control and Prevention (CDC) listed obesity as a risk factor for severe outcomes of COVID-19, together with diabetes and hypertension [23].

In a retrospective cohort study including data from 795 patients from 45 sites in the United States, obesity was recognized as a risk factor for disease severity for pediatric patients hospitalized with COVID-19. Compared to hospitalized children without obesity, hospitalized children with obesity were more likely to be diagnosed with multisystem inflammatory syndrome in children (35.7 % vs. 28.1 %, $p = 0.04$) and had higher Intensive Care Unit admission rates (57 vs 44 %, $p < 0.01$) with more critical illness (30.3 vs. 18.3 %, $p < 0.01$). The adjusted length of stay was also longer in patients with obesity (2.4 vs. 1.5 %, $p = 0.38$) [24]. Another study by Ortiz-Pinto et al. also showed that the presence of obesity as comorbidity in pediatric patients is an independent risk factor for COVID-19 infection, but also that long-term obesity entails a higher risk of infection compared to obesity of shorter duration. This could be due to increased vulnerability to infection caused by altered immunological mechanisms in the case of persistent obesity [25].

Several pathophysiological mechanisms have been implicated in the interaction between obesity and COVID-19 infection or severity. First, it is well documented that obesity represents a state of chronic inflammation secondary to adipose tissue hypoxia, which is reflected by increased levels of IL-1, IL-6, and TNF-α, and may affect the host response to SARS-CoV-2 [26]. In addition, obesity is characterized by CRP elevation, which is triggered by adipocytic IL-6 and has been correlated with poor COVID-19 outcomes [27]. It is also hypothesized that T-cell insulin resistance and exhaustion results in immunological dysregulation in obesity [26]. The existing immune dysfunction may be exaggerated by attenuated Mas receptor signaling of angiotensin 1–7 [28]. Furthermore, increased levels of DPP-4 and the consequent hyperinsulinemia may exacerbate COVID-19 risks [29]. Finally, obesity-related complications, including obesity hypoventilation syndrome and obstructive sleep apnea, which compromise respiratory function, but also thrombosis risk, diabetes, and hypertension may also explain COVID-19 severity [30].

Diabetes

During the COVID-19 pandemic, increased number of newly diagnosed type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) cases has been reported in European pediatric populations [31], which are far beyond the previously expected trajectories [32]. This is consistent with findings in adult populations [33]. Strikingly, incident T2DM cases represented for the first time the majority (53 %) of all newly diagnosed pediatric diabetes cases in 2020 and severe DKA in T2DM cases at presentation were also more during the COVID-19 pandemic [32]. This is of particular concern, knowing that T2DM has a more aggressive course in adolescents than in adults and that progression to insulin dependence due to deterioration of β cell function is rapid [34]. The age at presentation of T1DM was younger compared to previous years in a study from Spain [35], whereas no statistical difference was found in the age at presentation in a study from Greece [36]. Increased severity and frequency of DKA at diagnosis has also been documented, hypothetically due to delayed care-seeking or, hypothetically, due to SARS-CoV-2 aggressiveness [36, 37]. Of interest, one case of multisystem inflammatory syndrome in children (MIS-C) has been reported in a child with diabetic ketoacidosis [38]. Newly diagnosed DKAs were increased in 44 % and new cases of DKA in established T1DM diagnoses were increased in 30 % of pediatric endocrine centers in a study from 51 countries worldwide [39].

Ketoacidosis results from insufficient insulin secretion to meet the glycemic needs due to autoimmune destruction of β cells in the case of T1DM. In some of the cases, new-onset insulin-requiring diabetes following COVID-19 was autoantibody negative, suggesting that COVID-19 may be associated with β cell destruction [40]. Indeed, it has been suggested that SARS-CoV-2 may be diabetogenic [41]. SARS-CoV-2 RNA has been detected in pancreatic β cells of patients with COVID-19 [42], however there is conflicting evidence regarding the presence of ACE2 receptors in β cells [43, 44].

Suggested pathophysiological mechanisms of COVID-19-triggered diabetes include: i) direct attack of pancreatic β cells by SARS-CoV-2, ii) stress response to severe COVID-19 infection due to increased cortisol and to the cytokine storm, resulting in hyperglycemia [45] and iii) the significant insulin resistance seen in patients with COVID-19 that results in β cell failure [46]. In some of the cases, the risk for diabetes following COVID-19 may be attributed to the COVID-19-related increase in body mass index [47].

Based on the above, awareness of healthcare providers should be raised so that in persons aged < 18 years diabetes is screened for in the presence of symptoms such as polyuria, polydipsia, increased hunger, weight loss, fatigue, abdominal pain, nausea and vomiting, following COVID-19 diagnosis.

An aspect that should not to be ignored is that the imposed anti-pandemic measures have also affected the inpatient care provided in newly diagnosed T1DM. Diabetes education requires long face-to-face meetings of the patient and the family with the healthcare team. Preventive measures during the pandemic did not allow increased exposure to and from the personnel, which usually comprises multiple members, including diabetes nurses, diabetes educators, doctors, dietitians, psychologists, social workers [48]. In addition, the COVID-19 protection measures resulted in restriction in the number of family members that received education to only one, making diabetes management at home more difficult. This necessitated the adoption of alternative educational options, such as virtual clinic training or setting up communication platforms, which require not previously existing infrastructure and additional time spent by the therapeutic team [49].

Pre-existing diabetes

Data regarding susceptibility of patients with diabetes to infection with COVID-19 are inconclusive. The majority of pediatric patients with pre-existing diabetes do not appear to be more susceptible to SARS-CoV-2 infection and patients below 25 years exhibit a mortality rate that approaches zero according to a study by Elbarbary et al. [39, 50]. However, children with T1DM that contracted SARS-

CoV-2 were more likely to develop DKA [51] and were more frequently symptomatic and with more severe symptoms compared to patients without endocrinopathies or with other endocrine conditions [39]. Furthermore, the proportion of patients with T1DM who required admission to Intensive Care Unit was higher (21.2 %) compared to patients diagnosed with other endocrine conditions. Similarly, patients with T1DM needed bronchodilators and glucocorticoids more frequently (24.8 %) than patients with other endocrine conditions who were tested positive for COVID-19 (e. g., type 2 diabetes: 13.5 %, obesity: 15.4 %). They also needed oxygen, non-invasive or invasive ventilation, antibiotics and antiviral agents more frequently [39].

COVID-19 severity has also been associated with uncontrolled diabetes in adults. However, contrary to the findings in children, a whole population study showed increased mortality risk after COVID-19 infection in patients with T1DM and T2DM [52].

Several pathophysiological mechanisms have been proposed to explain increased susceptibility of patients with diabetes to more severe COVID-19 infection, particularly in adults. First, diabetes causes a hyperinsulinemia-induced reduction in the activity of ADAMTS17, the protease that cleaves ACE2, leading to increased expression of ACE2 and, thus, facilitating the SARS-CoV-2 cell entry [53, 54]. Second, diabetes is associated with factors that exacerbate the immunodeficiency, such as complement defects, reduced antigen stimulated IL-6, IL-8, and TNF-α [55], impairment of T-regulator cells and antigen presenting cells [24]. A third mechanism involves medications frequently used to treat diabetes in adults, including ACE1 inhibitors, angiotensin receptor blockers and thiazolidenediones, which may upregulate ACE2 expression. Fourth, co-existing hypertension and obesity may contribute to the pre-existing chronic inflammation by acting via HIF-1α and toll-like receptors, leading to impaired immune-mediated clearance of SARS-CoV-2 [24, 56]. Lastly, dipeptidyl peptidase-4 (DPP-4), a surface glycoprotein which degrades glucagon like peptide (GLP-1) and also functions as a surface receptor for coronaviruses [57], is elevated in diabetes [58]. All the above mechanisms may predispose patients with diabetes, particularly adults, to cytokine storms resulting in end organ injury and mortality [59].

Particular reference should be made to the changes caused by COVID-19 in diabetes management, which is much more challenging and demanding compared to other endocrine disorders. In the same study by Elbarbary et al., it was found that insulin adjustments were needed in 56.6 % of pediatric endocrine centers for T1DM and in 26.9 % of centers for T2DM [39], whereas for other endocrine conditions adjustments to therapies were required in a lower proportion of the patients (obesity: 23.1 % of centers, adrenal disorders: 28.8 % of centers, pituitary disorders: 26.6 % [39]. Furthermore, more than 20 % of the centers worldwide reported shortages of diabetes supplies, such as glucose test stripes, blood glucose sensors and insulin due to the COVID-19 related restrictions.

Additional challenges regarding diabetes management due to COVID-19-related measures include accessibility to medical care. It has been reported that during the pandemic medical care was mostly delivered face-to-face using appropriate personal protective equipment and to a lesser extend using telephone and video consultations [39]. However, due to the parents' fear of exposing their children to SARS-CoV-2 and because priority was given to COVID-19 related health services, routine follow-up visits were limited [39]. This was mitigated to some extend by enhancement of remote healthcare for children with diabetes in some centers during the pandemic, including telehealth visits and remote transmission of data from insulin pumps, glucose meters or CGM devices via a cloud-based platform [60]. Nonetheless, the importance of physical examination including assessment for lipohypertrophy at insulin injection sites or assessment for neuropathy, pubertal examination, anthropometric measurements, blood pressure measurement, but also screening for comorbidities, such as retinopathy, nephropathy, celiac disease, thyroid disorders and dyslipidemia, cannot be ignored. Also, the increased burden on health care providers caused by telehealth visits and the cost related to communication platforms for patients and doctors represent additional barriers to telemedicine.

Despite the aforementioned treatment challenges during the pandemic, a study from India showed that glycemic control was adequately maintained in children with T1DM possibly due to a steady daily routine in the lockdown and when family support was strong [61].

Hypothalamic-pituitary-thyroid axis

ACE2 receptors are expressed in thyroid tissue and are key components of physiological processes. In fact, ACE2 receptors are more highly expressed in thyroid cells than in lung cells [62]. Although most patients with COVID-19 are euthyroid, according to studies in adults COVID-19 has been implicated in thyroid dysfunction through four different potential mechanisms: i) direct thyroid tissue damage [63], ii) immune-mediated thyroid damage through activation of inflammatory factors and cytokines, iii) non-thyroidal illness syndrome (NTIS) and iv) hypothalamic-pituitary injury that causes dysfunction of the hypothalamic-pituitary-thyroid action [64].

Non-thyroidal illness syndrome (NTIS) and thyroiditis have been reported in 3.6 % of adult patients with COVID-19, particularly in patients with an increased viral load of inflammatory markers [65]. In a study by Muller et al., adult patients with COVID-19 requiring high intensity care presented with thyrotoxicosis and suppressed TSH levels, either with or without increased free thyroxine levels, following subacute thyroiditis [66]. Interestingly though, TSH concentrations were not as suppressed, and free thyroxine concentrations were not as elevated as in the classic subacute thyroiditis. In addition, affected patients did not complain of neck pain, nor did they exhibit leukocytosis. In contrast, they exhibited lymphopenia, which is well described in COVID-19 [67]. NTIS has also been recognized in children with MIS-C and is considered as an energy-preserving adaptive mechanism during severe illness and hypercatabolic state [68]. Therefore, in patients with severe COVID-19 routine assessment of thyroid status is recommended.

NTIS is caused by physiological stress and is characterized initially by a reduction in total T3 and free T3 without a concomitant rise in TSH. Persistent illness results in reductions in TSH, free T4 and free T3 due to a reduction in hypothalamic thyrotropin-releasing hormone [69].

Interestingly, the available data suggest that after acutely altered thyroid function during COVID-19, thyroid function tests

return to baseline after recovery and by 3 to 6 months after the infection [70].

Pre-existing thyroid disorders

Regarding patients with pre-existing thyroid dysfunction, the majority of data comes from adult studies. Thus far, there is no evidence to support that patients with thyroid nodules, autoimmune thyroid disease or cancer are more susceptible to contracting COVID-19. In addition, hypothyroidism does not appear to increase the risk for more severe disease in adults with COVID-19 [71]. Among pediatric patients, it remains unclear whether pre-existing thyroid disease increases susceptibility to COVID-19 infection, however, data from a retrospective cohort study from the United States in children suggest that hypothyroidism is an independent risk factor for disease severity [72].

Patients with hyperthyroidism are also not at increased risk of COVID-19 infection. Only some subsets of hyperthyroid patients, such as patients with thyroid ophthalmopathy treated with glucocorticoids and immunosuppressive therapy are at increased risk for more severe disease once infected [73]. Also, COVID-19 may affect patients with hyperthyroidism in two additional situations; First, it may precipitate a thyroid storm particularly in poorly controlled patients with hyperthyroidism through activation of an excessive immune response. Therefore, it is recommended that patients with hyperthyroidism continue to receive their medications to avoid complications [74]. Second, patients with Graves disease treated with antithyroid medications are at increased risk of neutropenia/agranulocytosis and secondary infections [75]. Knowing that almost half of COVID-19 non-survivors had a secondary infection [76], this is of clinical relevance. Furthermore, symptoms of agranulocytosis, flu-like symptoms, may be difficult to differentiate from those caused by COVID-19. Therefore, it is recommended that in such cases antithyroid drugs are immediately discontinued and a full blood count is obtained to exclude neutropenia [71].

Hypothalamic-pituitary-adrenal axis

Glucocorticoids are known to stimulate the immune response against foreign antigens during the initial phase of a viral infection, whereas during the advanced phase of viral infection, glucocorticoids may attenuate the hypothalamic-pituitary-adrenal axis, thus cause glucocorticoid insufficiency [77].

Also, critical illness in general is known to cause corticosteroid insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis secondary to physiological stress [78]. In a study by Gonen et al., 8.2 % of adult patients with COVID-19 developed secondary adrenal insufficiency, which in some of the cases was transient and had resolved six months after the COVID-19 onset [79]. However, although there are some indications of adrenal insufficiency caused by COVID-19, this has not been confirmed and the majority of patients with COVID-19 seem to preserve their adrenal function during the first 48 hours after hospital admission. On the contrary, according to a study by Clarke et al., increased serum cortisol concentrations have been observed during the first 2 days of hospital admission in adult patients with COVID-19 [80], which suggests activation of the cortisol axis in acute illness and has been associated with increased mortality [81].

Interestingly, although symptoms reported by patients with long COVID are similar to those caused by adrenal insufficiency, for example, fatigue, postural hypotension and cognitive impairment, there is no evidence to support an association between the two [82].

Pre-existing adrenal disorders

Patients with existing primary adrenal insufficiency, including congenital adrenal hyperplasia, are slightly more susceptible to infections, as primary adrenal insufficiency is associated with diminished natural immunity function through defects in the neutrophil and natural killer action [83]. However, there is insufficient data to support increased COVID-19 specific infection risk. On the other hand, it is well established that increased susceptibility to infections can be due to insufficient increase in the hydrocortisone dose at the beginning of an infection and that adrenal insufficiency is potentially associated with increased mortality due to adrenal crisis [84]. Therefore, recommendations suggest that asymptomatic children should remain on their regular doses, but symptomatic children should immediately increase the hydrocortisone doses and add an extra doubled dose [39]. Also, adhering to protective measures and sick-day rules is highly recommended [85, 86].

Similarly, in the case of Cushing syndrome, the importance of adhering to protective measures, reinforcement of sick-day rules, treatment of comorbidities and titration of pharmacotherapy doses based on clinical characteristics, is emphasized [87].

Hypothalamic-pituitary-gonadal axis

Various studies in adult male patients with COVID-19 have shown a reduction in total or calculated free testosterone levels [88]. The majority of men with low calculated free testosterone levels also had low or normal serum LH values, suggesting hypogonadism due to hypothalamic-pituitary dysfunction, which is known for physiological stressors [89]. Interestingly, lower median testosterone levels were observed in men with severe COVID-19 and testosterone levels were inversely related to cytokines, that is, IL-6, and C-reactive protein (CRP), which points towards immune-mediated hypogonadism [90]. The documented reduction in testosterone levels during the acute phase of the COVID-19 infection resolves spontaneously in the majority of the cases after recovery from COVID-19 [91].

Regarding the effects of COVID-19 on ovarian function or the hypothalamic-pituitary-gonadal axis in females, data are scant and inconclusive. Changes to women's menstrual cycle, including irregular periods, heavy periods and postmenopausal bleeding, have been reported [92], but it is not clear whether these changes are related specifically to COVID-19 or to psychological stress and weight gain. Precocious puberty, rapidly progressing puberty and precocious menarche have also been observed in pediatric endocrinology centers [93–96]. A direct effect of SARS-Cov-2 on the central nervous system could be hypothesized, through transportation through the blood-brain barrier and neural pathway activation, or an indirect effect through the release of pro-inflammatory cytokines [94]. Further research is warranted in order to confirm these observations for the adult population, but also for adolescents.

Anterior pituitary disorders

No pituitary disorders have been reported so far following COVID-19 infection in children, however, one case of pituitary apoplexy has been reported in a previously healthy 35-year old male secondary to COVID-19 infection [97]. This care report raises concerns for potentially missed diagnoses of CNS COVID-19 involvement. However, this potentially lethal complication is more likely an uncommon presentation of COVID-19.

Pre-existing pituitary disorders

Children with hypopituitarism are not at increased risk for COVID-19 infection. Those with secondary adrenal insufficiency are slightly more susceptible to infections, as in primary adrenal insufficiency, and the same recommendations apply [98].

Diabetes insipidus

Management of diabetes insipidus during the pandemic posed a challenge due to the fear of overtreatment that can lead to retention of excess free water and, consequently, hyponatremia. In the scenario of reduced availability of electrolyte testing due to the pandemic-related restrictions, daily bodyweight measurements, drinking to thirst and never ignoring clinical symptoms of hyponatremia, were recommended as a means of mitigating the risk. In the case of severe COVID-19 pneumonia, hyponatremia may develop in the context of inappropriate antidiuretic hormone secretion, particularly in adipsic patients [99]. Systematic biochemical assessment of sodium levels and appropriate fluid administration are of vital importance during inpatient care, optimally guided by an Endocrinologist [100].

Parathyroid disorders

Viral infections are known to precipitate hypocalcemia [101]. The association between hypocalcemia and COVID-19 infection has also been reported [102], and it seems that hypocalcemia is a risk factor for severe disease and admission to the Intensive Care Unit [103, 104]. Suggested mechanisms of COVID-19 induced hypocalcemia include increased levels of unbound and unsaturated fatty acids [105] in patients with severe COVID-19 infection, which can trigger a cytokine storm [106], but also bind calcium [107]. However, it is not clear if this is an association only or there is a causal relationship between the two. Patients with severe infection are more likely to present with electrolyte derangement, including hypocalcemia, and have poorer outcomes.

With regard to the potential link between COVID-19 and hypoparathyroidism, evidence is lacking. There are only few case reports of hypoparathyroidism secondary to COVID-19 infection in adult patients [108, 109].

Patients with pre-existing parathyroid disorders

For children with pre-existing hypoparathyroidism, it is recommended that they comply with vitamin D and calcium supplementation and that they maintain serum calcium levels in the low normal range. It is also important that patients are frequently re-educated so that symptoms of hypocalcemia are recognized, and that emergency preparedness is ensured.

Primary hyperparathyroidism is rare in children. Recommendations include education on the symptoms of hypercalcemia and the importance of adequate hydration.

Metabolic bone disease

In a study by Alshukairi et al., children with osteogenesis imperfecta and COVID-19 exhibited a mild course of the disease and recovered without complications [110]. Children with metabolic bone disease or a skeletal dysplasia that affect chest wall structure and respiratory sufficiency may be at increased risk of COVID-19 complications [111]. In addition, transient benign hyperphosphatasemia (THI) has been reported in a 16-month-old patient in association with COVID-19 [112]. Therefore, THI should be considered as a possible diagnosis if alkaline phosphatase (ALP) is elevated in the absence of bone, liver or kidney disease [113].

Hyperinsulinemic hypoglycemia

The side effects of the medications used to treat hyperinsulinemic hypoglycemia should be taken into consideration during contamination with COVID-19. Specifically, diazoxide is known to cause water retention and pulmonary hypertension, and somatostatin analogues cause cardiac arrhythmias and cardiac conduction disorders, which may affect the course of the illness with COVID-19 [39]. Also, close monitoring of glucose concentrations and adequate hydration are essential.

Endocrine conditions and mental health during the COVID-19 pandemic

Mental health issues have been exacerbated during the pandemic throughout society and in patients with endocrine conditions [114]. Due to children's not completed development of the central nervous system, including the hypothalamus-pituitary-adrenal axis, children exhibit increased susceptibility. Anxiety, depression, sleep disorders, eating disorders and suicidal attempts were commonly reported problems among children and adolescents with endocrine problems and COVID-19 infection. [39]. Based on the above, routine medical care provided should be focused on providing psychosocial support to children and their families, particularly those suffering from chronic endocrine disorders.

Discussion

The impact of COVID-19 beyond the respiratory system has become apparent as our knowledge on this novel disease is increasing. Among others, the endocrine system is particularly vulnerable to perturbation from the COVID-19 infection and children are not exempt. However, in the majority of cases, pediatric endocrine disorders are not considered a poor prognostic factor for COVID-19 infection and most children and adolescents with well-managed and regulated endocrine disorders do not appear to be at increased risk of infection or severe infection from COVID-19 [39]. Importantly, obesity increases the vulnerability of the pediatric population to COVID-19 and severe COVID-19 and pediatric patients with T1DM or T2DM are also more likely to suffer from COVID-19 and to experience moderate to severe symptoms, particularly in the presence of comorbidities [115, 116]. Long-term studies are, however,

needed to further ascertain the potential association between COVID-19 and increased diabetes risk in children and adolescents.

Of note, children and adolescents with endocrine conditions who were admitted to the Intensive Care Unit often had comorbidities [117]. Comorbidities are less frequently seen in children and adolescents compared to adults, which probably accounts for the reduced vulnerability of children and adolescents to COVID-19. Taking, though, into consideration the rise in obesity and T2DM rates in children and adolescents, an increasing number of children and adolescents at risk could become apparent in the future.

One of the most important key messages of this literature review is the disruption of children's everyday routine during the COVID-19 pandemic that has resulted in a significant psychological burden, but also in a tremendous aggravation of childhood obesity, due to the unhealthy dietary choices that have prevailed and the COVID-19-induced lifestyle modifications [118]. The importance of the implementation of preventive or counterregulatory measures from policy makers and healthcare providers, including healthy nutritional behaviors, is highlighted.

Another important lesson from the existing literature is that the fear of becoming infected may have hindered families from seeking medical help. This appears to have resulted in delayed new diagnoses of many pediatric diseases [119], including endocrine disorders, and, particularly, DKA cases [36, 37]. Thus, a secure non-COVID-19 path through pediatric emergency department is essential so that delayed seeking of medical care and the associated complications are avoided. Also, although face-to-face visits are the commonest method of consultation, provision of efficient telemedicine methods (video calls, emails, text messaging) and remote consultations is also of significance. The experience so far shows that telemedicine will probably be integrated into clinical practice after the COVID-19 pandemic, as it was proven an essential tool for delivering care during the pandemic, despite the compromises involved [120, 121].

Importantly, it should be emphasized that due to redistribution of health care resources and due to health system capacities being directed to COVID-19 patients, patients with chronic afflictions, including endocrinopathies, were the most likely to lack specialized care. This is particularly true for patients with diabetes, since diabetes is more complex to treat than other endocrine conditions in children and is associated with increased risk of morbidity and metabolic complications, such as DKA.

In addition, in some parts of the world, access to endocrine and diabetes care medications and supplies was also restricted during the pandemic. Therefore, the American Diabetes Association (ADA) recommends adequate stores of simple carbohydrates, insulin, glucagon kits, ketone strips [122]. Healthy dietary behaviors and 150 minutes of weekly exercise are also encouraged.

Furthermore, the majority of children with endocrine disorders are not at increased risk for contamination or severe presentation of COVID-19, therefore adhering to the appropriate "sick day management rules", maintaining adequate supply of medications and supplies, being in close contact with the therapeutic team and seeking medical help without delay when needed, are the cornerstone of a safe and optimal approach [123]. Regarding healthcare providers, remaining up to date with emerging knowledge and literature, re-educating patients on all routine clinical visits with emphasis on emergency precautions, and highlighting potential risks taking into consideration mental and physical health parameters, is important to ensure quality of care. When face-to-face contact is not feasible, alternative communication methods, such as telemedicine care, should be adopted, as well as mailing of prescriptions instead of in person pickup, so that endocrine care remains uninterrupted. Also, although no deaths were observed for any endocrine condition during the pandemic, the potentially negative effects of the interaction between COVID-19 and endocrine conditions underscore the importance of adopting protective measures, including vaccination for eligible children and adolescents, against COVID-19 infection.

Conclusions

The present review represents a comprehensive overview of the current knowledge on the interplay between COVID-19 and pediatric endocrine conditions based on the large body of research that has become available more than three years after the onset of the COVID-19 pandemic. It is also the first to focus on the bidirectional relationship between COVID-19 and pediatric endocrine conditions, offering a holistic approach of this issue. Both aspects of this two-way relationship have been highlighted; the potential susceptibility of children and adolescents without known endocrinopathies to endocrine disorders following COVID-19 infection, as well as the potential susceptibility to COVID-19 infection or the aggravation of endocrine dysfunction in patients with pre-existing endocrine diseases. Thus far, existing data suggest that there is a two-way relationship between endocrine disorders and COVID-19, however in the majority of cases this relationship is neither too strong nor permanent.

It should be kept in mind, though, that COVID-19 is a relatively new disease and despite the extensive relative literature, studies investigating the relationship between COVID-19 and endocrine disorders in children and adolescents are in some cases insufficient or based on very recent studies [72], and some conclusions are extrapolated by adult studies [124]. Therefore, the interplay between COVID-19 and pediatric endocrine conditions remains a key area for future research and long-term studies so that the initial observations are confirmed and under-researched fields are elucidated.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Wan Y, Shang J, Graham R et al. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94: 00127–20

[2] Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 8

[3] Roberts CM, Levi M, McKee M et al. COVID-19: a complex multisystem disorder. Br J Anaesth 2020; 125: 238–242

[4] Liu F, Long X, Zhang B et al. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol 2020; 18: 2128–2130.e2

[5] Loades ME, Chatburn E, Higson-Sweeney N et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. J Am Acad Child Adolesc Psychiatry 2020; 59: 1218–1239

[6] Ruíz-Roso MB, de Carvalho Padilha P, Matilla-Escalante DC et al. Changes of physical activity and ultra-processed food consumption in adolescents from different countries during Covid-19 pandemic: an observational study. Nutrients 2020; 12: 2289

[7] Mattioli AV, Pinti M, Farinetti A et al. Obesity risk during collective quarantine for the COVID-19 epidemic. Obes Med 2020; 20: 100263

[8] Vogel M, Geserick M, Gausche R et al. Age- and weight group-specific weight gain patterns in children and adolescents during the 15 years before and during the COVID-19 pandemic. Int J Obes 2022; 46: 144–152

[9] Huizar MI, Arena R, Laddu DR. "Covibesity," a new pandemic. Obes Med 2020; 19: 100282

[10] Yang S, Guo B, Ao L et al. Obesity and activity patterns before and during COVID-19 lockdown among youths in China. Clin Obes 2020; 10: 12416

[11] Allabadi H, Dabis J, Aghabekian V et al. Impact of COVID-19 lockdown on dietary and lifestyle behaviours among adolescents in Palestine. Dynam Hum Health 2020; 7: 2170

[12] Adams EL, Caccavale LJ, Smith D et al. Food Insecurity, the Home Food Environment, and Parent Feeding Practices in the Era of COVID-19. Obesity 2020; 28: 2056–2063

[13] Sidor A, Rzymski P. Dietary Choices and Habits during COVID-19 Lockdown: Experience from Poland. Nutrients 2020; 12: 1657

[14] Di Renzo L, Gualtieri P, Pivari F et al. Eating habits and lifestyle changes during COVID-19 lockdown: An Italian survey. J Transl Med 2020; 18: 229

[15] Han J, Chung Y, Chung I et al. Impact of the COVID-19 pandemic on seasonal variations in childhood and adolescent growth: experience of pediatric endocrine clinics. Children 2021; 8: 404

[16] Brazendale K, Beets MW, Weaver RG et al. Understanding differences between summer vs. school obesogenic behaviors of children: the structured days hypothesis. Int J Behav Nutr Phys Act 2017; 14: 100

[17] Rajmil L, Medina-Bustos A, Fernández de Sanmamed MJ et al. Impact of the economic crisis on children's health in Catalonia: a before-after approach. BMJ Open 2013; 3: e003286

[18] Zheng W, Yokomichi H, Matsubara H et al. Longitudinal changes in body mass index of children affected by the Great East Japan Earthquake. Int J Obes (Lond) 2017; 41: 606–612

[19] Malhotra S, Sivasubramanian R, Singhal V. Adult obesity and its complications: a pediatric disease? Curr Opin Endocrinol Diabetes Obes 2021; 28: 46–54

[20] Ribeiro KD, Garcia LR, Dametto JF et al. COVID-19 and nutrition: the need for initiatives to promote healthy eating and prevent obesity in childhood. Child Obes 2020; 16: 235–237

[21] Garg S, Kim L, Whitaker M et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 States, March 1–30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 458–464

[22] HealthLDo. Louisiana Department of Health Updates for 3/27/2020 Online: ldh.la.gov; 2020 cited Louisiana Department of Health. Available from http://ldh.la.gov/index.cfm/newsroom/detail/5517

[23] Prevention CfDCa. People who are at higher risk for severe illness. Online; 2020 March 26, 2020

[24] Tripathi S, Christison AL, Levy E et al. Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group. The impact of obesity on disease severity and outcomes among hospitalized children with COVID-19. Hosp Pediatr 2021; 11: 297–316

[25] Ortiz-Pinto MA, de Miguel-Garcia S, Ortiz-Marron H et al. Childhood obesity and risk of SARS-CoV-2 infection. Int J Obes 2022; 46: 1155–1159

[26] Daryabor G, Kabelitz D, Kalantar K. An update on immune dysregulation in obesity-related insulin resistance. Scand J Immunol 2019; 89: e12747

[27] Luo X, Zhou W, Yan X et al. Prognostic value of C-reactive protein in patients with COVID-19. MedRxiv 2020. DOI: 10.1101/2020.03.21.20040360

[28] Trim W, Turner JE, Thompson D. Parallels in immunometabolic adipose tissue dysfunction with ageing and obesity. Front Immunol 2018; 9: 169

[29] Stengel A, Goebel-Stengel M, Teuffel P et al. Obese patients have higher circulating protein levels of dipeptidyl peptidase IV. Peptides 2014; 61: 75–82

[30] Stein PD, Beemath A, Olson RE. Obesity as a risk factor invenous thromboembolism. Am J Med 2005; 118: 978–980

[31] Unsworth R, Wallace S, Oliver NS et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020; 43: 170–171

[32] Modarelli R, Sarah S, Ramaker ME et al. Pediatric diabetes on the rise: Trends in incident diabetes during the COVID-19 pandemic. J Endocr Soc 2022; 6: bvac024

[33] Ayoubkhani D, Khunti K, Nafilyan V et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ 2021; 372: n693

[34] Petitti DB, Klingensmith GJ, Bell RA et al. SEARCH for diabetes in youth study group. glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. J Pediatr 2009; 155: 668–672.e1

[35] Güemes M, Storch-de-Gracia P, Vinagre Enriquez S et al. Severity in pediatric type 1 diabetes mellitus debut during the COVID-19 pandemic. J Pediatr Endocrinol Metab 2020; 33: 1601–1603

[36] Kostopoulou E, Eliopoulou MI, Rojas Gil AP et al. Impact of COVID-19 on new-onset type 1 diabetes mellitus – a one-year prospective study. Eur Rev Med Pharmacol Sci 2021; 25: 5928–5935

[37] Kamrath C, Mönkemöller K, Biester T et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. JAMA 2020; 324: 801–804

[38] Naguib MN, Raymond JK, Vidmar AP. New onset diabetes with diabetic ketoacidosis in a child with multisystem inflammatory syndrome due to COVID-19. J Pediatr Endocrinol Metab 2021; 34: 147–150

[39] Elbarbary NC, dos Santos TJ, de Beaufort C et al. The challenges of managing pediatric diabetes and other endocrine disorders during the COVID-19 pandemic: results from an international cross-sectional electronic survey. Front Endocrinol 2021. DOI: 10/3389/fen-do.2021.735554

[40] Hollstein T, Schulte DM, Schultz J et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab 2020; 2: 1021–1024

[41] Rubino F, Amiel SA, Zimmet P et al. New-onset diabetes in Covid-19. N Engl J Med 2020; 383: 789–790

[42] Steenblock C, Richter S, Berger I et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun 2021; 12: 3534

[43] Coate KC, Cha J, Shrestha S et al. HPAP Consortium. SARS- CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. Cell Metab 2020; 32: 1028–1040.e4

[44] Fignani D, Licata G, Brusco N et al. SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β-cells and in the human pancreas microvasculature. Front Endocrinol (Lausanne) 2020; 11: 596898

[45] Bronson SC. Practical scenarios and day-to-day challenges in the management of diabetes in COVID-19 – dealing with the 'double trouble'. Prim Care Diabetes 2021; 15: 737–739

[46] Armeni E, Aziz U, Qamar S et al. Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series. Lancet Diabetes Endocrinol 2020; 8: 660–663

[47] https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a3.htm?s_cid=mm7037a3_w)

[48] Regelmann MO, Conroy R, Gourgari E et al. on behalf of the PES Drug and Therapeutics Committee and Practice Management Committee. Pediatric endocrinology in the time of COVID-19: considerations for the rapid implementation of telemedicine and management of pediatric endocrine conditions. Horm Res Paediatr 2020; 93: 343–350

[49] Jones MS, Goley AL, Alexander BE et al. Inpatient transition to virtual care during COVID19 pandemic. Diabetes Technol Ther 2020; 22: 444–448

[50] Shafiee A, Teymouri Athar MM, Nassar M et al. Comparison of COVID-19 outcomes in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab Syndr 2022; 16: 102512

[51] Alfayez OM, Aldmasi KS, Alruwais NH et al. Incidence of diabetic ketoacidosis among pediatrics with type 1 diabetes prior to and during COVID-19 pandemic: A meta-Analysis of observational studies. Front Endocrinol 2022. DOI: 10.3389/fendo.2022.856958

[52] Barron E, Bakhai C, Kar P et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020; 8: 813–822

[53] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020; 318: 736–741

[54] Roca-Ho H, Riera M, Palau V et al. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci 2017; 18: 563

[55] Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus [DM]. FEMS Immunol Med Microbiol 1999; 26: 259–265

[56] Varin EM, Mulvihill EE, Beaudry JL et al. Circulating levels of soluble dipeptidyl peptidase-4 are dissociated from inflammation and induced by enzymatic DPP4 inhibition. Cell Metab 2019; 29: 5

[57] Raj VS, Mou H, Smits SL et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495: 251–254

[58] Ryskjaer J, Deacon CF, Carr RD et al. Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbAlc levels, but is not acutely affected by food intake. Eur J Endocrinol 2006; 155: 485–493

[59] Mehta P, Mc Auley DF, Brown M et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033–1034

[60] De Guzman KR, Snoswell CL, Taylor ML et al. A systematic review of pediatric telediabetes service models. Diabetes Technol Ther 2020; 22: 623–638

[61] Shah N, Karguppikar M, Bhor S et al. Impact of lockdown for COVID-19 pandemic in Indian children and youth with type 1 diabetes from different socio-economic classes. J Pediatr Endocrinol Metab 2021; 34: 217–223

[62] Li MY, Li L, Zhang Y et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020; 9: 45

[63] Yao XH, Li TY, HeZ C et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi 2020; 49: 009

[64] Chen W, Tian Y, Li Z et al. Potential interaction between SARS-CoV-2 and thyroid: A review. Endocrinology 2021; 162: bqab004

[65] Lui DTW, Ho C, Wing L et al. Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-moderate severity. Clin Endocrinol (Oxf) 2021; 95: 469–477

[66] Muller I, Cannavaro D, Dazzi D et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 2020; 8: 739–741

[67] Guan WJ, Ni ZY, Hu Y et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708–1720

[68] Calcaterra V, Biganzoli G, Dilillo D et al. Non-thyroidal illness syndrome and SARS-CoV-2-associated multisystem inflammatory syndrome in children. J Endocrinol Invest 2022; 45: 199–208

[69] Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 2014; 24: 1456–1465

[70] Khoo B, Tan T, Clarke SA et al. Thyroid function before, during, and after COVID-19. J Clin Endocrinol Metab 2021; 106: 803–811

[71] Boelaert K, Visser WE, Taylor PN et al. Endocrinology in the time of Covid-19: management of hyperthyroidism and hypothyroidism. Eur J Endocrinol 2020; 183: 33–39

[72] Banull NR, Reich PJ, Anka C et al. Association between endocrine edisorders and severe COVID-19 disease in pediatric patients. Horm Res Paediatr 2022. DOI: 10.1159/000524595

[73] Taylor PN, Zhang L, Lee RWJ et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. Nat Rev Endocrinol 2020; 16: 104–116

[74] Chen W, Tian Y, Li Z et al. Potential interaction between SARS-CoV-2 and thyroid: a review. Endocrinology 2021; 162: bqab004

[75] Ross DS, Burch HB, Cooper DS et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016; 26: 1343–1421

[76] Zhou F, Yu T, Du R 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: 1054–1062

[77] Isidori AM, Pofi R, Hasenmajer V et al. Use of glucocorticoids in patients with adrenal insufficiency and COVID-19 infection. Lancet Diabetes Endocrinol 2020. DOI: 10.1016/S2213-8587(20)30149-2

[78] Annane D, Pastores SM, Rochwerg B et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med 2017; 45: 2078–2088

[79] Gonen MS, De Bellis A, Durcan E et al. Assessment of neuroendocrine changes and hypothalamo-pituitary autoimmunity in patients with COVID-19. Horm Metab Res 2022; 54: 153–161

[80] Clarke SA, Abbara A, Dhillo WS. Impact of COVID-19 on the endocrine system: a mini review. Endocrinology 2022; 163: 1–20

[81] Tan T, Khoo B, Mills EG et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 2020; 8: 659–660

[82] ARC Study GroupMandal S, Barnett J, Brill SE et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021; 76: 396–398

[83] Bancos I, Hazeldine J, Chortis V et al. Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality. Eur J Endocrinol 2017; 176: 471–480

[84] Endocrinology Sf. (webpage). Online 2020 (updated March 11, 2020; cited 2020 March 15). Advice Statement. Available from https://www.endocrinology.org/news/item/14050/Coronavirus-advice-statement-for-patients-with-adrenal %2fpituitary-insufficiency

[85] Wiebke A, Stephanie EB, Simon HSP et al. Endocrinology in the time of COVID-19: management of adrenal insufficiency. Eur J Endocrinol 2020. DOI: 10.1530/EJE-20-0361

[86] Alsulaimani SA, Mazi A, Bawazier M et al. Effect of the COVID-19 pandemic on treatment adherence among children with congenital adrenal hyperplasia. Cureus 2022; 14: 27762

[87] John NP, Lynnette N, Martin R et al. Endocrinology in the time of COVID-19: Management of Cushing's syndrome. Eur J Endocrinol 2020. DOI: 10.1530/EJE-20-0352

[88] Temiz MZ, Dincer MM, Hacibey I et al. Investigation of SARS-CoV-2 in semen samples and the effects of COVID-19 on male sexual health by using semen analysis and serum male hormone profile: a cross-sectional, pilot study. Andrologia 2021; 53: e13912

[89] Woolf PD, Hamill RW, McDonald JV et al. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; 60: 444–450

[90] Dhindsa S, Zhang N, McPhaul MJ et al. Association of circulating sex hormones with inflammation and disease severity in patients with COVID-19. JAMA Netw Open 2021; 1–15

[91] Mehta OP, Bhandari P, Raut A et al. Coronavirus disease (COVID-19): comprehensive review of clinical presentation. Front Public Health 2021; 8: 582932

[92] Davis HE, Assaf GS, McCorkell L et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalmedicine 2021; 38: 101019

[93] Street ME, Ponzi D, Renati R et al. Precocious puberty under stressful conditions: new understanding and isnights from the lessons learnt from international adoptions and the COVID-19 pandemic. Front Endocrinol 2023; 14: 1149417

[94] Street ME, Sartori C, Catellani C et al. Precocious puberty and Covid-19 into perspective: potential increased frequency, possible causes, and a potential emergency to be addressed. Front Pediatr 2021; 9: 734899

[95] Baby M, Ilkowitz J, Cheema Brar P. Impacts of the COVID-19 pandemic on the diagnosis of idiopathic central precocious puberty in pediatric females in New York City. J Pediatr Endocrinol Metab 2023; 36: 517–522

[96] Peinkhofer M, Bossini B, Penco A et al. Reduction in pediatric growth hormone deficiency and increase in central precocious puberty diagnoses during COVID 19 pandemics. Ital J Pediatr 2022; 48: 49

[97] LaRoy M, McGuire M. Pituitary apoplexy in the setting of COVID-19 infection. Am J Emerg Med 2021; 47: 329.e1–329.e2

[98] European Society for Paediatric Endocrinology (ESPE). Coronavirus disease (COVID-19) information for children and adolescents living with endocrine conditions, including type 1 diabetes mellitus. Internet, Cited 23 Mar 2020. Available at: https://www.eurospe.org/news/item/14064/COVID-19-information-for-children-and-adolescents-living-with-endocrine-conditions-including-type-1-diabetes-mellitus)

[99] Liamis G, Milionis HJ, Elisaf M. Hyponatremia in patients with infectious diseases. J Infect 2011; 63: 327–335

[100] Christ-Crain M, Hoorn EJ, Sherlock M et al. Endocrinology in the time of COVID-19: management of diabetes insipidus and hyponatraemia. Eur J Endocrinol 2020; EJE-20–0338

[101] Booth CM, Matukas LM, Tomlinson GA et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003; 289: 2801–2809

[102] Di Filippo L, Formenti AM, Rovere-Querini P et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. Endocrine 2020; 68: 475–478

[103] Liu J, Han P, Wu J et al. Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. J Infect Public Health 2020; 13: 1224–1228

[104] Sun JK, Zhang WH, Zou L et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. Aging (Albany N. Y.) 2020; 12: 11287–11295

[105] El-Kurdi B, Khatua B, Rood C et al. Liptoxicity in COVID-19 study group. mortality from Coronavirus disease 2019 increases with unsaturated fat and may be reduced by early calcium and albumin supplementation. Gastroenterology 2020; 159: 1015–1018.e4

[106] De Oliveira C, Khatua B, Noel P et al. Pancreatic triglyceride lipase mediates lipotoxic systemic inflammation. J Clin Investig 2020; 130: 1931–1947

[107] Khatua B, Yaron JR, El-Kurdi B et al. Ringer's lactate prevents early organ failure by providing extracellular calcium. J Clin Med 2020; 9: 263

[108] Elkattawy S, Alyacoub R, Ayad S et al. A novel case of hypoparathyroidism secondary to SARS-CoV-2 infection. Cureus 2020; 12: e10097

[109] Georgakopoulou VE, Avramopoulos P, Papalexis P et al. COVID-19 induced hypoparathyroidism: a case report. Exp Ther Med 2022; 23: 346

[110] Alshukairi AN, Doar H, Al-Sagheir A et al. Outcome of COVID-19 in patients with osteogenesis imperfect: a retrospective multicenter study in Saudi Arabia. Front Endocrinol 2022; 12: 800376

[111] Brizola E, Adami G, Baroncelli GI et al. Providing high-quality care remotely to patients with rare bone diseases during COVID-19 pandemic. Orphanet J Rare Dis 2020; 15: 228

[112] Erat T, Atar M, Kontbay T. Transient benign hyperphosphatasemia due to COVID-19: the first case report. J Pediatr Endocrinol Metab 2021; 34: 385–387

[113] Kiess W, Tanja P, Anne J et al. Covid19 pandemic and pediatric endocrinology and metabolism – are we through with it? J Pediatr Endocrinol Metab 2021; 34: 535–537

[114] Duffus SH, Cooper KL, Agans RP et al. Mental health and behavioral screening in pediatric type 1 diabetes. Diabetes Spectr 2019; 32: 171–175

[115] Ho C, Ng NBH, Lee YS. Caring for pediatric patients with diabetes amidst the Coronavirus disease 2019 storm. J Pediatr 2020; 223: 186–187

[116] Dayal D. We urgently need guidelines for managing COVID-19 in children with comorbidities. Acta Paediatr 2020; 109: 1497–1498

[117] Zachariah P, Johnson CL, Halabi KC 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: 202430

[118] Zachurzok A, Wojcik M, Gawlik A et al. An attempt to assess the impact of pandemic restrictions on the lifestyle, diet, and body mass index of children with endocrine diseases – preliminary results. Nutrients 2021; 14: 156

[119] Kostopoulou E, Gkentzi D, Papasotiriou M et al. The impact of COVID-19 on paediatric emergency department visits. A one-year retrospective study. Pediatr Res 2022; 91: 1257–1262

[120] Cabana MD, Menard Livingston L. Will telemedicine be the blockbuster or Netflix of healthcare? Medpage Today 2020 Available from: https://www.medpagetoday.com/practicemanagement/telehealth/87662

[121] Tenenbaum A, Shefer-Averbuch N, Lazar L et al. Growth assessment of children during the COVID-19 pandemic-Can we rely on parental measurements? Acta Paediatr 2021; 110: 3040–3045

[122] Association AD COVID-19 from the American Diabetes Association (Online). ADA; 2020 March 2020:Webpage9. Available from https://www.diabetes.org/diabetes/treatment-care/planning-sick-days/coronavirus

[123] Kostopoulou E, Güemes M, Shah P. COVID-19 in children and adolescents with endocrine conditions. Horm Metab Res 2020; 52: 769–774

[124] Miller R, Ashraf AP, Gourgari E et al. SARS-CoV-2 infection and paediatric endocrine disorders: Risks and management considerations. Endocrinol. Diabetes Metab 2021; 4: 00262