

Pediatric Endocrinology of Post-Pandemic Era

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The COVID-19 pandemic has brought about significant changes in the global health and medical environment. In order to prevent viral transmission, governments implemented strong social distancing, even lockdowns. The closure of schools has reduced physical activity among children and adolescents. Children, especially those with chronic diseases, are often reluctant to visit or even give up visiting hospitals, resulting in delayed diagnosis or missing the right timing for treatment. New guidelines are needed for the management of patients with endocrine diseases such as diabetes or thyroid disease, as well as children with chronic diseases who need regular clinical monitoring. Therefore, it is necessary to analyze the previous research on pediatric endocrinology reported during COVID-19, guide the direction for future research, and establish guidelines to care for pediatric patients with endocrine diseases in the post-pandemic era.

Key Words: COVID-19; Pediatrics; Endocrine System Diseases; Diabetes Mellitus; Obesity

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) as a pandemic.¹ The COVID-19 pandemic has made a major impact on the way of life of people worldwide. Above all, the medical system and disease proportions have changed greatly. On the discovery of the first case in Korea on January 20, 2020, the Korea Centers for Disease Control and Prevention (KDCC) raised the alert to level 3 on January 27 and implemented social distancing. Subsequently, the Ministry of Education postponed the opening of schools and strongly inhibited students' outdoor activities for nearly 3 months from May until the beginning of limited school opening.^{2,3} During this period, students who stayed at home and took online classes experienced serious increases in weight. Their regular lives were affected such that they had increased screen time and tended to eat more snacks instead of healthy food.^{4,5}

Research on COVID-19 has increased exponentially around the world. In the beginning of the pandemic, studies that were published focused mainly on evidence about the diagnosis, treatment, complications, and epidemiologic data of patients with COVID-19. Due to the prolonged pandemic, reports on the indirect effects of COVID-19 have also increased.^{6,7} Majority of these studies were about mental

and social problems caused by the lockdown or social distancing due to COVID-19. Furthermore, the number of studies on the progression and incidence of diseases since COVID-19 has been increasing, most of which focus mainly on chronic diseases in adults.⁸ The European Society for Endocrinology recently published a statement on COVID-19 and endocrine diseases.⁹

In children and adolescents, social distancing and wearing masks have sharply decreased the occurrence of respiratory diseases; however, there is a marked increase in obesity in children, and this in turn has increased the rates of endocrine diseases such as diabetes, thyroid disease, and precocious puberty.

DIABETES AMONG CHILDREN AND ADOLESCENTS DURING THE COVID-19 PANDEMIC

Many epidemiological studies and reviews reported that individuals with diabetes are more vulnerable to COVID-19.^{10,11} Patients with poorly controlled diabetes are vulnerable to various infectious diseases. Approximately 20-30% of patients hospitalized with COVID-19 were diabetic, and they had a mortality rate 2 to 3 times higher than that of patients without diabetes.^{12,13} Furthermore, diabetes has been reported to be one of the most common comorbidities among patients with COVID-19.^{14,15}

Unlike in adults, the majority of cases of childhood and adolescent diabetes with COVID-19 showed relatively only mild to moderate symptoms. Of the 15,500 total children who underwent COVID-19 testing, 11 had Type 1 diabetes, six of whom were COVID-19 positive and either showed no symptoms or had a mild course, and they had no increased risk of hospitalization.⁴ However, the occurrence of diabetic ketoacidosis (DKA) was around twice as high compared to the previous rate (aRR 1.8-2.7), and the occurrence of severe DKA with pH <7.1 has also increased (aRR 1.4-2.1). Patients in younger age groups (below six years old) exhibited a higher risk of DKA (RR 2.1-2.8).¹⁶ The analysis of related factors is still lacking. Although the causes of DKA are multifactorial, it has been speculated that reduced medical service, fear of approaching the health care system, and more complex psychosocial factors had an influence.^{17,18} On the contrary, some studies have reported that during the quarantine, there were fewer cases of DKA. However, these were more severe than the ones in previous years.¹⁹

Pediatric patients with type 1, type 2, and monogenic diabetes do not have a higher risk of morbidity and mortality due to COVID-19. However, there is an increased risk for glycemic imbalance, therefore it is recommended they tighten their glycemic control.²⁰ Furthermore, the Italian Society for Pediatric Endocrinology and Diabetology (ISPED) published a statement regarding caring for children and adolescents with type 1 DM during the COVID-19 pandemic and suggested that telemedicine would be an effective new tool for patient care.²¹ In the UK, guidelines for remote glycemic control using Time In Range (TIR)% of continuous blood glucose monitoring system (CGMS) instead of HbA1c were announced.²² Recently, CGMS has been used more frequently in Korea; thus, it would be helpful to refer to these guidelines in providing care for patients with type 1 diabetes.

Angiotensin converting enzyme-2 (ACE-2) receptors, which are known receptors for SARS-CoV-2, are also expressed in the pancreas.²³ One study conducted a meta-analysis regarding SARS-CoV-2 and how it can cause type 1 diabetes, similar to the mumps virus or coxsackievirus B. The study found that COVID-19 can trigger severe DKA, but there is currently no evidence that SARS-CoV-2 can cause new onset Type 1 diabetes.²⁴ However, the data is constantly increasing and additional research is needed. Furthermore, though there are studies correlating adult type 2 diabetes and COVID-19, there is still not much data in children and adolescents, and this requires further research.

THYROID DISEASE DURING COVID-19

Thyroid disease is a relatively common endocrine disease. However, there is not much available data on how COVID-19 affected the incidence or clinical progress of thyroid disease. There was no mention of thyroid disease in *The statement of Endocrine, 2020*.⁹

With social lockdowns and distancing put in place due to COVID-19, it is likely that the patients with pre-existing thyroid problems could not undergo blood tests or comply with their medication, and patients exhibiting mild symptoms of thyroid dysfunction would be reluctant to visit the hospital, making it difficult to collect and analyze data.²⁵

Studies have reported on the relationship between thyroid disease and COVID-19 in adults. Several studies on cases of COVID-19 related thyroid disease and reviews have reported that there was an increased prevalence of thyrotoxicosis and inflammatory thyroiditis among patients with severe forms of COVID-19.²⁶⁻²⁸ In a cohort of 191 mild-to-moderate confirmed COVID-19 cases, 15% of these patients were observed to have thyroid dysfunction.²⁹ One retrospective study analyzed 50 patients with laboratory-confirmed COVID-19 and found that the TSH and serum total triiodothyronine (TT3) levels among patients with COVID-19 were significantly lower than those of the healthy control. However, none of the patients required medication and all of these values normalized after recovery.³⁰

One hypothesis that explains the increase in thyroid abnormalities among patients with COVID-19 is that the ACE2 receptors needed for SARS-CoV-2 to penetrate into cells are found in high concentrations in thyroid follicular cells. In addition, COVID-19 can cause direct or immune mediated injury through integrin $\alpha v \beta 3$.³¹

At present, there are no reports regarding COVID-19 and thyroid abnormalities in children. Therefore, research should also be conducted in children and adolescents with reference to adult studies.

OBESITY IN CHILDREN AND ADOLESCENTS DURING COVID-19

Obesity is a risk factor for increasing the severity and morbidity of COVID-19. The risk for obesity has increased due to social distancing and the reduction in physical activity from restrictions set in place to combat the COVID-19 pandemic.³²

Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) declared obesity as one of the risk factors that increases the severity of COVID-19.³³ An analysis of 50 child and adolescent patients hospitalized with COVID-19 showed that obesity (11 [22%]) was the most prevalent comorbidity.³⁴ In one study on the risk of obesity and COVID-19 in adults, mechanical ventilation was applied at a rate of 85.7% for patients with a body mass index (BMI) >35 kg/m², and this rate was 7.36 times higher than that of patients with BMI <25 kg/m².³⁵ The intensive care unit (ICU) hospitalization rate was higher for obese patients regardless of age or gender, and the presence of symptoms such as fever, cough, difficulty breathing, and death rate were higher.³⁶⁻³⁸

Although it is difficult to analyze the effects of obesity on COVID-19 in children due to lack of studies and relatively less severe cases as compared to adults, it has been reported that risk factors in adults also appear in children.³⁹ One

meta-analysis of 42 studies regarding severe COVID-19 infection and comorbidities showed obese children had a relative risk ratio of 2.87 (95% CI 1.16-7.07; $I^2=36\%$).⁴⁰

The effects of obesity on the severity of COVID-19 were studied extensively especially during the early days of the pandemic. Recently, however, there has been an increasing number of reports of obesity following the beginning of the COVID-19 pandemic. In a study which included 41 children and adolescents, the intake of potato chips, red meat, and sugary drinks increased significantly during the lockdown period. Furthermore, the study reported reduced sport activity and increased sleep and screen time.⁴¹ Another study was conducted on the increase in anxiety and depression following the stay-at-home order due to COVID-19.⁴² An online survey on lifestyle changes during the pandemic showed that more than 43% of respondents reported reduced physical activity, and more than 49% reported increased screen time and eating fast food, promoting an obesogenic environment.⁵

Concerns about obesity are also being raised in Korea.⁴³ During the period of school closure, there was a reported increase in the BMI of children and adolescents and a decrease in the levels of vitamin D.⁴

This pandemic is surely an unprecedented setback in the war on childhood obesity, and families, schools, and governments should make all possible efforts to minimize the occurrence of childhood obesity.⁴⁴

OTHER ENDOCRINE DISEASES DURING COVID-19

1. Adrenal insufficiency

Patients with adrenal insufficiency (AI) undergoing glucocorticoid replacement therapy are very susceptible to viral diseases causing fever, but there are no studies associating this disease with COVID-19. The recommended glucocorticoid dose to prevent adrenal crisis is generally similar to the one recommended for critically ill patients. If there are warning symptoms, an intravenous injection bolus of 100 mg hydrocortisone administered, followed by hydrocortisone (50 mg) intravenously every six hours, or 200 mg/day by continuous intravenous infusion.⁴⁵⁻⁴⁷

2. Pituitary disorders

Children diagnosed with hypopituitarism are not at an increased risk for COVID-19.⁴⁸ However, the risk may be increased due to the underlying causes of the pituitary disorder. Among patients with Cushing disease, craniopharyngioma, or growth hormone deficiency, many have central obesity and cardiovascular complications, which are associated with severe morbidity and mortality when infected with COVID-19. Cases of treatment-induced adrenal suppression should be treated with the recommended glucocorticoid dose of AI as mentioned above. Comorbidities and mortalities among COVID-19 patients with acromegaly may increase depending on whether or not they have abnormalities of the airway or chest wall anatomy.⁴⁹ If a patient has diabetes insipidus and/or hypoglycemia (hyper-

insulinemic, ketotic, or both) gets COVID-19, sufficient hydration and clinical monitoring are important and a more vigilant assessment should be provided.⁴⁸

CONCLUSIONS

The occurrences of acute respiratory diseases among children and adolescents during the COVID-19 pandemic have decreased dramatically due to government quarantine and personal hygiene measures such as distancing, wearing of face masks, and hand sanitation. However, it is clear that these measures cause difficulties in the treatment of chronic diseases. Among children and adolescents, the majority of chronic patients are pediatric endocrine patients with diabetes, thyroid disease, and obesity. However, the lack of sufficient and reliable data on the impact of COVID-19 on patients with endocrine disorders is becoming a barrier for research and patient care. More research is needed on children with endocrine diseases and their association with COVID-19. Based on the findings of this study, it is clear that we need to prepare for changes in the post-pandemic era.

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CONFLICT OF INTEREST STATEMENT

None declared.

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