Encountering COVID-19 as Endocrinologists

Eun-Jung Rhee[1], Jung Hee Kim[2], Sun Joon Moon[1], Won-Young Lee[1]

[1]Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine;
[2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

The world is entering an era of disaster and chaos due to coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2. Since its first emergence in December 2019 in Wuhan, China, COVID-19 has swept through Asia and propagated throughout the world to Europe and North America. As of April 13, 1,773,084 people were infected and 111,652 people had died from COVID-19 globally, and new record levels of infection are being reported every day. Based on the data that have been amassed so far, the primary risk factors for a severe disease course or even mortality from COVID-19 are underlying diseases such as diabetes and hypertension. As the global prevalence of diabetes continues to increase, patients with endocrine diseases such as diabetes mellitus and those who are on long-term corticosteroid therapy due to adrenal insufficiency or hypopituitarism are at risk for a poor prognosis of COVID-19. As endocrinologists, we would like to briefly review the current knowledge about the relationship between COVID-19 and endocrine diseases and to discuss what we can do for the safety and health of our patients with endocrine diseases in this globally threatening situation.

Keywords: COVID-19; Endocrinologists; Diabetes mellitus; Adrenal insufficiency; Severe acute respiratory syndrome coronavirus 2; Endocrine system diseases

INTRODUCTION

The entire world is encountering an unexpectedly disastrous situation due to coronavirus disease 2019 (COVID-19). In December 2019, the China National Health Commission reported that cases of pneumonia with an unknown cause had been detected in Wuhan in Hubei Province. The disease then rapidly spread from Wuhan to other areas of China and throughout the world. On January 3, 2020, a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV)—with phylogenetic similarity to the SARS coronavirus (SARS-CoV), the cause of the 2003 SARS outbreak, was isolated in samples of bronchoalveolar lavage fluid from patients in Wuhan and was confirmed as the cause of the novel atypical form of pneumonia [1]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern [2].

Although the first outbreak in China subsided due to the forceful closure of the city of Wuhan by the Chinese government, carriers of the virus in the incubation period had already dispersed throughout the world, and had started to spread the disease to other continents. As of April 13, 1,773,084 people were infected and 111,652 people had died from COVID-19 globally; remarkably, the disease spread to this extent within only 84 days since the first WHO situation report was released on January 21, at a time when there were only 282 confirmed

cases of COVID-19 worldwide [3]. In the Western Pacific region, China had the highest number of COVID-19-infected people (83,597 cases and 3,351 deaths), followed by Korea, with 10,537 confirmed cases and 217 deaths. In the European region, Spain had the highest number of confirmed cases (166,019, with 16,972 deaths), followed by Italy, with 156,363 confirmed cases and 19,901 total deaths. The United States of America (USA) had the highest number of confirmed cases in the world, with 524,514 cases and 20,444 deaths, mainly in the state and city of New York. All 50 USA states are under a disaster declaration for the first time in history, which means that federal funds are allowed to be used by state and local governments during the pandemic. This disastrous pandemic is threatening the health and economic well-being of the world, in both developed and developing countries.

In this review, we would like to present a brief overview of the current knowledge on COVID-19 and its relationship with endocrine diseases, and to suggest some recommendations as endocrinologists encountering this disease.

WHAT WE KNOW ABOUT COVID-19

According to phenome sequencing, SARS-CoV-2 is a betacoronavirus of the same subgenus as SARS-CoV, with which it shares a sequence identity of approximately 80% [4]. Based on RNA sequence similarity, it is likely that the primary source is bats; however, it is not certain whether SARS-CoV-2 is transmitted directly from bats [5]. It is known that SARS-CoV-2 enters the cell via the angiotensin-converting enzyme 2 (ACE2) receptor, similar to SARS-CoV [4]. Transmission between people is thought to occur mainly via respiratory droplets, which can travel less than roughly 2 m, and also by touching infected surfaces. A study showed that the virus could remain viable in aerosols for more than 3 hours, meaning that the possibility of aerosol transmission cannot be excluded [6]. The clinical course of the disease varies from mild to critical, and risk factors for severe illness are advanced age, living in a nursing home or long-term care facility, chronic lung disease, serious heart conditions, an immunocompromised condition, severe obesity, diabetes, chronic kidney disease treated with dialysis, and liver disease [7].

No agent has yet demonstrated efficacy as a specific treatment for COVID-19. Several therapies, such as remdesivir (an antiviral agent), hydroxychloroquine/chloroquine (an antimalarial agent), tocilizumab (an interleukin-6 receptor inhibitor), and convalescent plasma therapy are under investigation [8-11]. Al-

though many attempts are being made to develop vaccines against COVID-19, the WHO indicated in February 2020 that it expected a vaccine to become available in no earlier than 18 months [12]. As of April 8, 2020, among 115 vaccine candidates, the five most advanced candidates (mRNA-1273, Ad5-nCoV, INO-4800, LV-SMENP-DC, and pathogen-specific aAPC) were in phase 1 trials [13]. Regarding treatment, concerns have been raised regarding a possible increased risk for adverse outcomes in patients using ACE inhibitors or angiotensin receptor blockers, which can increase the expression level of ACE2 receptors [14]. However, it is not recommended to discontinue these agents due to a lack of sufficient evidence, and because doing so can also worsen cardiovascular or kidney disease [15,16].

PATIENTS WITH ADRENAL INSUFFICIENCY OR HYPOPITUITARISM OR WHO ARE ON LONG-TERM GLUCOCORTICOID TREATMENT

Currently, no evidence indicates that patients with adrenal insufficiency (AI) or hypopituitarism are at an especially high risk for COVID-19 infection. However, several studies, including data from Korea, have demonstrated that AI patients have a two-fold to eight-fold higher risk for infection, which inherently increases the risk of death from COVID-19 [17-22]. In AI patients, the innate immune response (e.g., natural killer cell cytotoxicity) is impaired, thereby potentially compromising antiviral immune defense mechanisms and increasing patients' susceptibility to respiratory viral infections [23,24]. Moreover, the lifelong requirement for nonphysiological glucocorticoid replacement using currently available preparations may place AI patients at an increased risk for infectious diseases.

Infection is a condition of acute stress that triggers a cytokine-mediated inflammatory response, which requires an increased dose of glucocorticoids. Since adrenal crises precipitated by infections are the major cause of death in AI patients [25,26], an immediate modification of the glucocorticoid regimen, as indicated in so-called "sick day rules," should be conducted at the beginning of an infection. Whenever any AI patient presents with a cough, sputum, or fever (≥37.5°C), which are symptoms suspicious for COVID-19, they need to immediately double or triple their daily oral glucocorticoid dose and continue the increased dose until the symptoms resolve. While doing so, patients need to consume more electrolyte-containing fluids as tolerated. If a patient's condition deteriorates, or a patient cannot

eat due to vomiting or diarrhea, he or she should go to the hospital and immediately receive an injection of 100 mg of hydrocortisone. Unfortunately, in Korea, hydrocortisone self-injection kits are not available. Therefore, patients should immediately present their steroid emergency card, which indicates that they are AI patients, and their leaflet with information on adrenal crisis to be shown to doctors [27], as these documents clearly describe the need to inject 100 mg of hydrocortisone immediately, followed by continuous infusion of 200 mg for 24 hours. Furthermore, patients are advised to obtain sufficient hydrocortisone and fludrocortisone supplementation to prepare for "sick day rules" and "social distancing" during the COVID-19 outbreak.

Chronic exogenous glucocorticoid administration, including through the topical, inhaled, oral, intra-articular, and parenteral routes, is widely used to treat various disorders. Excessive glucocorticoid use itself is associated with severe and intractable courses of viral infections due to the immunosuppressive actions of glucocorticoids [28-30]. The anti-inflammatory action of glucocorticoids may mask fever and indicators of active infection. Therefore, patients taking supraphysiological doses of glucocorticoids may be more susceptible to COVID-19, although there is still little concrete evidence regarding this issue. Furthermore, suppression of the hypothalamic-pituitary-adrenal (HPA) axis in long-term steroid users may cause symptoms of AI. The dose and duration of glucocorticoids that suppress the HPA axis have not been well established. However, patients currently receiving or with a history of prior exogenous glucocorticoid therapy exceeding 5 mg of prednisolone or equivalent for longer than 3 months should follow the above-mentioned "sick day rules" [31]. Therefore, those patients should be monitored to detect AI symptoms at an early phase and should be prompted to modify their glucocorticoid replacement dose in order to prevent adrenal crisis and mortality.

PATIENTS WITH DIABETES MELLITUS

According to the Ninth Diabetes Atlas from the International Diabetes Federation, 463 million people in the world have diabetes [32]. The high global prevalence of diabetes makes it an especially concerning risk factor as the COVID-19 pandemic progresses. As we all know, patients with diabetes are more susceptible to infectious diseases, regardless of the source of pathogens. For example, patients with diabetes were more vulnerable to SARS and Middle East respiratory syndrome, the two previous worldwide fatal respiratory infections caused by coronaviruses in the last decades [33,34].

COVID-19 predominantly affects older men and those with comorbidities such as hypertension and diabetes [35]. In previous reports, the proportion of COVID-19 patients with diabetes ranged from 6% to 37%, and diabetes was the first or second most common comorbidity (Table 1) [36-55]. A study from China reported that 17% of critically ill patients with SARS-CoV-2 pneumonia at a single center in Wuhan had diabetes, and in another report analyzing 140 hospitalized COVID-19 patients, hypertension (30.0%) and diabetes (12.1%) were the most common comorbidities [38]. In a Korean report, among the 75 patients who died from COVID-19, 46.7% had endocrine and metabolic diseases, such as diabetes or hypothyroidism [48]. In an Italian report, diabetes was the second most common comorbidity associated with COVID-19 next to hypertension, similar to previous reports from other countries [53].

Diabetes is associated both with the risk of COVID-19 infection and the severity of COVID-19. In a nationwide report from China analyzing 1,099 selected COVID-19 patients, patients with severe disease were more likely to have diabetes than those with non-severe disease (16.2% vs. 5.7%) [37]. In another report of 191 Chinese inpatients with COVID-19, more non-survivors than survivors had diabetes (31% vs. 14%) and in a univariate analysis, diabetes was associated with a 2.9-fold increased risk for in-hospital death, although the significance disappeared in a multivariate analysis [43]. Lastly, in a meta-analysis analyzing eight studies with data on 46,248 patients, diabetes was the second most prevalent comorbidity after hypertension, although diabetes was not a significant determinant of disease severity [54].

The mechanism that increases susceptibility to COVID-19 in patients with diabetes has not been conclusively established, but several theories have been proposed. First, expression levels of ACE2, the cellular receptor of SARS-CoV-2, are known to be increased in the lung, kidney, heart, and pancreas in rodent models of diabetes [56,57]. In a genome-wide Mendelian randomization study, diabetes was causally associated with increased lung ACE2 expression [58]. These studies support the hypothesis that patients with diabetes are especially susceptible to SARS-CoV-2 infection. In addition, some researchers have suggested that using renin-angiotensin aldosterone system blockers such as ACE inhibitors and angiotensin receptor blockers might increase the expression of ACE2 receptors, thereby increasing patients' susceptibility to SARS-CoV-2 [59,60]. However, as the control of comorbidities such as hypertension in patients with COVID-19 and diabetes is important for survival, and given the absence of further evidence of risk or benefit,

Table 1. Proportion of Patients with Diabetes among COVID-19 Infected Patients

Country/no. of patients analyzed	Proportion of patients with diabetes in the total population	Proportion of severe vs. non-severe patients with diabetes	Glycemic status or HbA1c levels	Reference
Wuhan, China /99 patients	12/99 (12.1%)	-	Mean glucose: 7.4 mmol/L 52% had hyperglycemia (>6.1 mmol/L)	[36]
Wuhan, Huanan seafood marker, China/41 patients	8/41 (20%)	8% vs. 25% ($P=0.16$)	-	[35]
Data from NHC, China/1,099 patients	81/1,099 (7.4%)	16.2% vs. 5.7% (severe vs. non-severe) 26.9% vs. 6.1% (primary composite end point[a] met vs. unmet)	-	[37]
Wuhan, China/52 critically ill patients	9/52 (17%)	22% vs. 10%	Hyperglycemia in 35%	[38]
Wuhan, China/140 patients	17/140 (12.1%)	13.8% vs. 11.0% ($P=0.615$)	-	[39]
Wuhan, China/138 patients	14/138 (10.1%)	22.2% vs. 5.9%	-	[40]
Shanghai, China/51 patients	3/51 (6%)	-	-	[41]
Wuhan, China/137 patients	14/137 (10.2%)	-	-	[42]
Wuhan, China/191 patients	36/191 (19%)	31% vs. 14% (non-survivors vs. survivors) Univariate OR for in-hospital death: 2.85 for diabetes, disappeared in multivariable analysis	-	[43]
Wuhan, China/201 patients	22/201 (10.9%)	19.0% vs. 5.1% (ARDS vs. no ARDS) 25.0 vs. 12.5% (non-survivors vs. survivors, $P=0.15$) HR for ARDS in bivariate Cox regression analysis: 2.34 for diabetes, 1.13 per 1 mmol/L increase in glucose levels	Median (interquartile range) of glucose (mmol/L): 6.0 (5.00–7.95) Median glucose (mmol/L): 7.4 vs. 5.4 (ARDS vs. no ARDS) Median glucose (mmol/L): 7.1 vs. 7.8 (non-survivors vs. survivors, $P=0.92$)	[44]
Wuhan, China/174 patients	37/174 (21.2%)	All parameters were significantly higher in patients with diabetes Mortality higher in patient with diabetic complications	-	[45]
Chinese CDC/72,314 cases (44,672 confirmed, 16,186 suspected, 10,567 clinically diagnosed, 889 asymptomatic)	-	Overall CFR: 2.3% CFR in diabetes: 7.3%	-	[46]
Wuhan, China/29 inpatients with diabetes	-	-	Among 881 capillary blood glucose tests, 56.6% showed abnormal results: 29.4% of preprandial blood glucose tests, and 69% of postprandial blood glucose tests showed abnormal results; 10.3% of the patients experienced at least one episode of hypoglycemia	[47]
Korea/75 mortality cases	35 had endocrine disease including diabetes, hypothyroidism, etc. out of 75 (46.7%)	-	-	[48]

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Table 1. Continued

Country/no. of patients analyzed	Proportion of patients with diabetes in the total population	Proportion of severe vs. non-severe patients with diabetes	Glycemic status or HbA1c levels	Reference
Korea CDC-operated NNDSS, Korea/66 fatal cases	23/66 (36.5%)	-	-	[49]
Korea CDC, Korea/54 mortality cases	16/54 (29.6%)	-	-	[50]
KNCCMC, Korea/28 patients	2/28 (7.1%)	-	-	[51]
CDC COVID-19 Response Team, USA/74,439 patients	784 (10.9%)	32%, 24%, and 6% in ICU-admitted, hospitalized (non-ICU), and non-hospitalized patients	-	[52]
Italy/patient number not given	33.9%	-	-	[53]
Meta-analysis/46,248 patients	9%	OR (95% CI) for severe vs. non-severe status: 2.07 (0.89–4.82)	-	[54]
Meta-analysis in China/1,527 patients	9.7%	RR (95% CI) for ICU vs. non-ICU: 2.21 (0.88–5.57)	-	[55]

COVID-19, coronavirus 2019; HbA1c, hemoglobin A1c; NHC, National Health Commission; OR, odds ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome; HR, hazard ratio; CDC, Centers for Disease Control and Prevention; CFR, case-fatality rate; NNDSS, National Notifiable Disease Surveillance System; KNCCMC, Korea National Committee for Clinical Management of COVID-19; ICU, intensive care unit; RR, risk ratio.
[a]The primary composite end point was admission to ICU, the use of mechanical ventilation, or death.

the European Society of Cardiology and the American College of Cardiology/American Heart Association have recommended that these patients should continue treatment with their usual antihypertensive therapy [16,61].

Poor glycemic control should also be considered as a potential risk factor affecting the prognosis of COVID-19, although it has not yet been established whether poor glycemic control in uninfected patients with diabetes could increase their susceptibility to COVID-19. Furthermore, there are limited data on the association between good glucose control and a favorable prognosis. Surprisingly, none of the studies presenting information on COVID-19 patients with diabetes reported patients' mean hemoglobin A1c (HbA1c) levels, and few studies reported their mean glucose levels, which means that glycemic control has not been considered as a determinant of patients' prognosis (Table 1).

In this regard, international associations related to diabetes are suggesting strategies for strict glycemic control as a form of self-defense against COVID-19. The American Diabetes Association is providing a platform for health professionals to share and discuss their experiences with COVID-19 and diabetes and to share relevant sources [62]. The Korean Diabetes Association (KDA) released a proposal for the government on prioritizing COVID-19 screening in patients with diabetes who are 70 years or older based on recent data demonstrating that a high propor-

tion of COVID-19 patients in Korea have diabetes [63]. In addition, the KDA proposed recommendations for patients with diabetes regarding general hygiene, self-protection against the virus, and self-management rules for glycemic control in the COVID-19 emergency situation. The US Centers for Disease Control and Prevention also included patients with diabetes among the groups at a higher risk for severe illness after COVID-19 infection and requested that special attention be paid to these patients [7].

It is now obvious that diabetes is a clear risk factor for a poor prognosis in COVID-19 patients, and that patients with diabetes are more susceptible to COVID-19 than individuals without diabetes. As strict glycemic control is vitally important for improving the prognosis of patients with diabetes who contract any kind of infectious disease, it is mandatory to check glucose and HbA1c levels in COVID-19 patients with diabetes. In addition, we should instruct patients with diabetes to continue their usual care, both for diabetes and for any comorbidities such as hypertension and cardiovascular disease in order to reduce their cardiovascular risk, as cardiovascular disease was ranked as the top-tier risk factor for a poor prognosis of COVID-19 in some reports [54]. Patients should be encouraged to measure their blood glucose levels more frequently than usual in this situation, and to control their diet and continue physical activity as usual while

maintaining social distancing (e.g., through home training).

Hospitals and governments should prioritize COVID-19 testing in patients with diabetes ahead of other people without underlying diseases. If they are confirmed to have COVID-19, blood glucose monitoring should be more strictly performed, both in the hospital setting and in self-quarantine. In addition, physicians should check their patients' HbA1c levels once they are admitted to the hospital and look for ways to optimize their glycemic control as a way to improve their prognosis. Insulin therapy should be actively considered in COVID-19-infected patients, since infection is a known stressor, and the increased release of counter-regulatory hormones could increase blood glucose levels even in patients who have good glycemic control at other times.

CONCLUSIONS

Not many reports have yet investigated the relationships between endocrine diseases and COVID-19. We assume that the health professionals who are involved in treating and caring for patients with COVID-19 are so busy that they have not had enough time to analyze their patients' data, a situation exacerbated by their risk of contracting COVID-19. We appreciate and admire all the efforts of medical doctors, nurses, researchers, laboratory technologists, public officials, and police officers to care for COVID-19 patients, to conduct research to learn more about COVID-19, and to prevent the virus from being further propagated across nations and communities.

Although the whole world is striving to stop this pandemic, this global disaster will continue for a substantial period, since we still have not identified the exact characteristics of the virus. It will take some time to clearly understand the immune reaction to SARS-CoV-2, antibody formation, and the rate of mutation of SARS-CoV-2. It seems that 1 to 2 years will be needed to manufacture and distribute vaccines and antiviral agents targeting SARS-CoV-2. As a consequence, until then, we must remain keen to take good care of our patients with endocrine diseases, such as AI, hypopituitarism, diabetes, and others.

What more can we do in this situation besides providing routine medical care? As we have suggested above, we should be especially cautious when caring for patients who are vulnerable to this viral disease. For that matter, sharing our knowledge with and educating our patients in advance would be a wise strategy to fight this crisis together with our patients. Therefore, via telemedicine, digital health, or in outpatient clinics, we should try to share our knowledge with and inform our patients of what we

do and do not know about the disease, and encourage them to take prudent steps to protect themselves from the disease through strict self-hygiene, as well as self-management and lifestyle modifications in patients with diabetes. In addition, patients who are on corticosteroid treatment for diseases such as AI and hypopituitarism should have easy access to endocrinologists whenever they have questions and need help. This is how we, as endocrinologists, can protect both our patients and ourselves safely and wisely. We eagerly hope that in the very near future, we will defeat COVID-19 and return to our ordinary lives with our healthy patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Eun-Jung Rhee *https://orcid.org/0000-0002-6108-7758*
Won-Young Lee *https://orcid.org/0000-0002-1082-7592*

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