Turk J Endocrinol Metab. 2020;24:335-42

Dealing with COVID-19: Through Endocrinologist's Eyes

Endokrinologların Gözüyle COVID-19 ile Mücadele

Cem SULU, Pınar KADIOĞLU

Department of Internal Medicine, Division of Endocrinology-Metabolism and Diabetes, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, TURKEY

Abstract

Less than a year ago, none of us had heard of novel coronavirus disease (COVID-19). Today, it has become the main topic of our daily conversations. This disastrous disease has united the medical professions belonging to various specialties to fight against the disease in collaboration. However, the exact role of endocrinologists still remains elusive. The coronavirus could potentially infect organs other than the lungs, such as the pancreas, thyroid, adrenal glands, and pituitary, as reflected by various endocrinological manifestations. The direct invasion of organ systems and indirect mechanisms such as induction of autoimmunity could be responsible for the endocrinological consequences. A large body of literature on its pathophysiology, management, and associated conditions is growing, and its association with endocrinological diseases is increasingly being recognized. However, data that would guide the proper management of these endocrinological disorders during this novel pandemic are still lacking. This review presented a brief overview of the association of COVID-19 with endocrinological diseases and methods to ease the management of some frequently encountered endocrinological problems.

Keywords: COVID-19; diabetes mellitus; pituitary; thyroid; adrenal insufficiency

Özet

Bir yıldan az bir süre önce hiçbirimiz yeni koronavirüs hastalığı (COVID-19) hakkında fikir sahibi değildik. Günümüzde ise bu hastalık hayatımızın merkezine yerleşmiş vaziyette. Virüsle mücadele için çeşitli uzmanlık branşlarından hekimler bir araya geldiler. Bu topkeyün savaşta endokrinologlara düşen spesifik görevler henüz net değildir. Koronavirüs akciğer dışında pankreas, tiroid, hipofiz bezi ve adrenal bezler gibi endokrin sisteme ait organlara da hasar vererek endokrinolojik semptom ve bulgulara yol açabilir. Endokrinolojik manifestasyonların altında yatan muhtemel mekanizma organ sistemlerinin virüs tarafından invazyonu ve otoimmünitenin tetiklenmesi ile açıklanabilir. COVID-19'un patofizyolojisi, tedavisi ve eşlik eden komorbititeler hakkında literatür günden güne zenginleşmekte, virüsün endokrinolojik hastalıklar ile olan ilişkilerine ait farkındalık artmaktadır. Buna karşın pandeminin seyrinde rastlanan endokrinolojik problemlerin akılcı yönetimi aydınlatılmaya muhtaçtır. Bu derleme COVID-19 ile endokrinolojik hastalıkların arasındaki ilişkiye ışık tutmak ve COVID-19 seyrinde sıkça rastlanılan endokrinolojik hastalıkların tedavisine yol göstermek amacıyla yazıldı.

Anahtar kelimeler: COVID-19; diabetes mellitus; hipofiz; tiroid; adrenal yetersizlik

Introduction

Less than a year ago, none of us had heard of the novel coronavirus disease (COVID-19) and very few people were aware of the existence of such virus called "coronavirus"; however, today, it stays to the core of our daily lives. The World Health Organization declared COVID-19 as pandemic on 11 March, and since then, this global health problem continues to spread worldwide despite vigorous efforts. Unexpectedly, this disastrous disease has united the medical professions belonging to various specialties to fight against the disease in collaboration.

Address for Correspondence: Pınar KADIOĞLU, Department of Internal Medicine, Division of Endocrinology-Metabolism and Diabetes, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, TURKEY
Phone: +90 212 414 30 00 **E-mail:** kadioglup@yahoo.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 27 Jul 2020 **Received in revised form:** 23 Oct 2020 **Accepted:** 10 Nov 2020 **Available online:** 10 Dec 2020

DOI: 10.25179/tjem.2020-78280

However, the particular role of endocrinologists is yet to be determined.

The pathogenesis of COVID-19 involves the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into host cells through angiotensin-converting enzyme 2 (ACE2). This enzyme acts as a receptor for SARS-CoV-2 and is found in various organs other than the lungs, such as the pancreas, thyroid, adrenal glands, and pituitary. The expression of ACE2 may explain endocrinological complications of the virus. According to some but not all published data until date, patients with diabetes are apparently more prone to COVID-19, and once they get infected, the prognosis is worse. This holds true for obese patients with COVID-19, as they need more intensive care and intubation more readily. Moreover, the virus may itself locate in the thyroid gland, as the gland is strictly contiguous to the structures of the superior airway. It can also cause subacute thyroiditis like any other viral infections. The consequent thyrotoxicosis may worsen cardiac instability, with increased morbidity. Serious systemic infections also entail the possibility of the sick euthyroid syndrome, further complicating the proper evaluation of thyroid function tests. For any acute illness, COVID-19 may cause acute adrenal insufficiency (AI), necessitating the implementation of glucocorticoids. In addition to these, the virus can trigger autoimmune processes that may have various endocrinological consequences. A wide spectrum of hormonal derangements caused by direct and indirect mechanisms may occur throughout the course of COVID-19 and warrants endocrinologists to take more responsibility on the frontline. A large body of literature on its pathophysiology, management, and associated conditions is growing; however, several unanswered questions remain concomitantly, rendering COVID-19 still a hot topic. This review aimed to present a brief overview of the association of COVID-19 with endocrinological diseases and to guide endocrinologists encountering this disease.

COVID-19 and Diabetes Mellitus

Patients with diabetes are more prone to infectious diseases because of multiple perturbations of both innate and humoral immunity (1). Previous viral pandemics have proven that diabetes has profound inhibitory effects on the immune system (2,3). During SARS-CoV-1 (2002) and influenza A (2009) pandemics, patients with diabetes more often suffered from complications requiring hospitalization, needed more intensive care, and had a higher rate of mortality than those without diabetes (4,5). This will probably hold true for COVID-19 as more than half of severe cases have diabetes (6). Numerous studies have reported a high prevalence of diabetes among patients with COVID-19, with some of them reaching up to 37% (7). Another study from Italy noted that diabetes was the second most common comorbidity associated with COVID-19 after hypertension (8). Several postulated mechanisms exist regarding this close relationship.

Chronic hyperglycemia and co-existent visceral obesity induce a pro-inflammatory milieu that exerts negative effects on leukocyte chemotaxis and phagocytosis. Moreover, diabetes impairs the secretion of inflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor. Immunoglobulins are glycosylated, a process that diminishes their biological functions (9). Another possible explanation unique to COVID-19 can be an increased expression of ACE2 because of treatment with ACE inhibitors (ACEI) and angiotensin receptor blockers or de novo upregulation of this enzyme in patients with diabetes (10).

The association of COVID-19 with diabetes would be more complex than expected. Exocrine pancreas injury during severe COVID-19 infection has been speculated in 17% of patients as manifested by increased serum amylase and/or lipase (11). Moreover, there are published data suggesting that SARS-CoV-induced pancreatic beta cell damage can be responsible for the development of acute diabetes in patients infected with SARS (12). Although coronaviruses are not typically deemed to play a role in the etiopathogenesis of type 1 diabetes mellitus, SARS-CoV and SARS-CoV-2 are potential environmental triggers for the development of type 1 diabetes mellitus. This fact is suggestive of a vicious cycle between COVID-19 and diabetes. Drugs used for treating COVID-19 (lopinavir and ritonavir) can increase insulin resistance and hence worsen glycemic control (13).

Some studies have ranked hypertension and cardiovascular diseases as the top-tier risk factors for a dismal prognosis of COVID-19 (14). Obesity and cardiovascular diseases are well-known comorbidities in patients with diabetes (15). Therefore, diabetes and its associated conditions together make patients more susceptible to COVID-19 and worsen the outcome. Although there are hypothetical concerns regarding the effects of renin angiotensin blockers and some antidiabetic treatment on COVID-19, no concrete evidence exists that suggest drug modification (13,16). Metformin is protective against pneumonia through its immunomodulatory and antiproliferative effects in rat models (17). It also reduces the mortality rate from COVID-19 (18). Patients with diabetes are advised to continue metformin irrespective of their COVID-19 status.

ACE-2 has been believed to act as a receptor for the coronavirus (19). Pioglitazone increases the expression of ACE-2. Therefore, some clinicians avoid prescribing this drug in patients with diabetes infected with COVID-19 (19). In a study that compared sulfonylureas and thiazolidinediones, thiazolidinediones were found to be protective against pneumonia (20).

In addition to pioglitazone, sodium-glucose co-transporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1Ra), and insulin may increase the expression of ACE-2 (19). SGLT-2i and GLP-1Ra are shown to be beneficial in cardiovascular and renal complications of diabetes, which worsen the course of COVID-19 (21,22). The association between ACE-2 expression and antidiabetic drugs represents only a minority of complex interplay between diabetes treatment and COVID-19. Inflammation plays a major role during COVID-19. Dipeptidyl peptidase 4 (DPP4) is expressed in various tissues, including the immune system. It plays crucial functions in glucose and insulin homeostasis and in the propagation of inflammation (23). In addition, it was suspected to act as a receptor for another coronavirus MERS-CoV (24). High mortality in patients with diabetes infected with MERS-CoV has been associated with DPP4-related immune dysregulation. Previous studies have revealed their anti-inflammatory properties. However, the hypothesis regarding their preventive functions against viral contamination and attenuated complications remains to be established (23). The robust relations between respiratory tract infections and DPP4 inhibitors have not been completely conceptualized yet (25). All these findings indicate a reasonable but poorly established relationship between DPP4 inhibitors and COVID-19. The same is true for SGLT2 and pioglitazone (26,27). Therefore, the possible role of antidiabetics in COVID-19 pathophysiology, course, and complications has been suggested through various mechanisms. Some proposals are contradictory, as outlined above. To date, no concrete evidence exists to prefer one class of antidiabetics over another.

Another highly debated topic is the use of ACEIs and angiotensin II receptor blockers (ARB). Previous studies have indicated that the renin-angiotensin-aldosterone system (RAAS) inhibitors increase the expression of ACE2 , which acts as a receptor for coronavirus invasion (28). Hence, there have been concerns about the increased predisposition to develop infection and increase the severity of COVID-19. These drugs are essential in the treatment of chronic complications of diabetes. Several attempts have been made to elucidate the associations between RAAS inhibitors and COVID-19. Current data recommend not to discontinue ACEIs or ARBs in the COVID-19 pandemic (29). Further studies with a large number of patients are needed to draw definitive conclusions regarding COVID-19, treatment of diabetes, and its complications. Until then, patients with these conditions should be instructed to continue their usual care.

Optimal glycemic control is of great significance; all patients with COVID-19 should have a baseline evaluation of glycemic status. Among those with prior diabetes, strict blood glucose monitoring, and appropriate interventions are mandatory. The "sick-day rules" need to be followed to overcome imminent diabetes decompensation. If this does not prevent the glycemic status from getting worse, contacting healthcare providers through telephone, e-mail, or video conference is recommended. The same rules of social distancing and personal hygiene for the community also meticulously apply to patients with diabetes.

COVID-19 and Obesity

The prevalence of obesity among patients hospitalized with COVID-19 was 61.3%; however, it may differ among different populations (30). Hence, the effects of obesity on patients with COVID-19 remain to be elucidated. A meta-analysis confirmed that obesity might increase the risk for hospitalization, the need of invasive mechanical ventilation, intensive care unit admission, and mortality in patients with COVID-19 (31). The exact mechanisms through which obesity worsens COVID-19 remain to be established. Moreover, severe obesity is associated with sleep apnea syndrome and surfactant dysfunction that may complicate the disease course (15). Despite unproven, chronic low-grade inflammation of abdominal obesity may disturb immune responses through adipokines and cytokines such as tumor necrosis factor-alpha (32). It can also have deleterious effects on the lung parenchyma and bronchi, aggravating respiratory failure (32). Several comorbidities such as diabetes mellitus, cardiovascular diseases, and malignancy exist with obesity, which may increase COVID-19 severity (33). These findings highlight the need for meticulous preventive measures against COVID-19 in obese people and increased awareness of the risks that could worsen the prognosis.

COVID-19 and Thyroid Disease

Autoimmune thyroid disease is a common condition. Patients with both hyperactive and hypoactive thyroid seek medical guidance irrespective of whether they belong to a high-risk group. In these patients, blood monitoring to adjust thyroid medications or ensure euthyroidism overcomes the risk of COVID-19 exposure.

Fortunately, no firm evidence exists indicating that patients with existing autoimmune thyroid disease are more prone to COVID-19 or thyroid disease itself worsens the outcome. The use of antithyroid drugs (ATD) during COVID-19 pandemic presents a clinical challenge. A precautionary approach should be followed while awaiting further information. The use of these medications causes the risk of agranulocytosis, a rare but fatal complication with an incidence rate of 2.4-15.4 cases per million population/year (34). Patients with agranulocytosis experience severe neutropenia, which may, in turn, ease the progression of COVID-19 (35). The symptoms of agranulocytosis, such as fever, sore throat, and mouth ulceration, may overlap with that of COVID-19, hindering the differential diagnoses between the two diseases. Patients on ATDs who experienced symptoms suggestive of neutropenia should discontinue the drug and approach healthcare services for an urgent blood count (35). In these patients, testing for COVID-19 should also be considered depending on the presentation. Thrombocytopenia and lymphocytopenia are hematologic alterations observed throughout the COVID-19 course and do not warrant treatment cessation (36). If a full blood count cannot be performed instantly at the onset of symptoms suggestive of neutropenia, withdrawing ATD and restarting after one week is recommended if the symptoms have disappeared (35). If symptoms reoccur, patients are strongly advised to seek for urgent medical attention for considering alternative treatments.

Patients previously diagnosed with hypothyroidism do not need any particular precaution regarding COVID-19. Thyroid replacement therapy should be continued as usual. If a patient's condition worsen or there is significant weight change, thyroid function testing is recommended for dose modification.

Similar to other systemic diseases, severe COVID-19 is expected to cause low T3 syndrome, particularly if the infection involves the lower respiratory tract (35,37). This syndrome may be an adaptive response to acute illnesses and current data are not in favor of specific intervention (38).

Subacute thyroiditis (SAT) is a self-limited thyroid disease, which is typically preceded by the upper respiratory tract infection (39). It is characterized by neck pain, general symptoms, and thyroid dysfunction. SAT treatment includes beta blockers, steroids, or nonsteroidal anti-inflammatory drugs, depending on the clinical presentation. Interim guidance from the World Health Organization on the treatment of COVID-19 recommends against the use of steroids if not indicated for another reason (40). However, it is possible that thyrotoxicosis may negatively affect COVID-19. In a case series, no patients who experienced severe discomfort and were treated with steroids developed

signs or symptoms suggestive of COVID-19 relapse during follow-up (41). Therefore, it can be concluded that selected SAT patients may benefit from a low-dose regimen of steroid treatment. This may overcome negative outcomes associated with thyrotoxicosis in patients with COVID-19.

Clusters of this disease were reported during outbreaks of the viral infection (42); therefore, SAT cases may be increasingly reported in the near future. Thyrotoxicosis may cause tachycardia and impair cardiovascular functions. A prompt evaluation of thyroid function tests may allow early recognition and proper treatment. SAT can present a few weeks after the respiratory tract infection as a late complication. Thus, monitoring thyroid function tests during COVID-19 follow-up is reasonable. As a general approach, patients with either hypo- and hyperthyroidism should take their medications as usual. These recommendations are based on expert opinions and not on meta-analyses or systematic reviews. Further studies are needed for more specific instructions about the approach to thyroid disease in patients with COVID-19.

COVID-19 and Adrenal Insufficiency

Although several studies have reported that AI itself may increase the risk of infection up to eight folds (43), the current evidence does not specifically support the fact that patients with AI are particularly prone to COVID-19. However, several plausible mechanisms are available, which may render patients with AI susceptible to COVID-19. AI impairs firstly natural killer cell cytotoxicity; thus, compromising antiviral immune defense (44). An increase in stress-induced glucocorticoid plays a crucial role in the induction of the immune system, and the lack of this stimulant weakens the priming of the immune response (45). In contrast, replacement with supraphysiologic doses of glucocorticoids leads to immunosuppression. Excess glucocorticoids may hinder the identification of symptoms and signs of active infections, preventing the recognition of COVID-19. Apparently, the causal relationship between AI and COVID-19 is not unidirectional but rather bidirectional. Viral sepsis may cause hemorrhage and thrombosis of adrenal vein and precipitate acute AI, which is a crucial cause of mortality. Another remarkable hypothesis has been proposed about the molecular mimicry between certain amino acid sequences by the SARS-CoV and the host adrenocorticotropic hormone (ACTH). According to this hypothesis, antibodies produced against the viral particles will inadvertently destroy the circulating ACTH, thereby restricting the stress-induced cortisol rise (46). All these factors inherently render patients with AI susceptible to COVID-19 and in turn patients with COVID-19 to AI.

Infections precipitate adrenal crisis and are a major cause of death in patients with AI (47). Adrenal crisis is described as a shock state and an inability of an organism to cope with acute stress resulting from inadequate glucocorticoid response. Thus, all patients with AI should be educated appropriately to prevent such hazardous events. "Sick day rules" are a group of precautions that should be strictly followed during intercurrent acute illnesses. These include at least doubling the usual oral dose of glucocorticoids if a patient experiences symptoms suggestive of COVID-19, such as cough, sputum, and fever. The doubled (or tripled) doses of glucocorticoids should be continued until all these symptoms resolve. In addition, one needs to be adequately hydrated, preferably with electrolyte-containing fluids. These interventions are likely to prevent adrenal crisis and associated mortality. If the clinical condition worsens despite these measures or if the oral route is compromised because of vomiting or diarrhea, patients should immediately reach the emergency healthcare settings for parenteral glucocorticoid replacement and hydration. All patients with AI must ensure that they have enough supply of oral glucocorticoids, enabling them to adjust the dosage properly in suspicion of COVID-19.

COVID-19 and Pituitary Diseases

COVID-19 has deeply affected the evaluation and treatment of pituitary disorders. Pituitary surgery, the treatment of choice for the majority of pituitary diseases, is particularly affected because of diversion of healthcare resources from elective to urgent services. The patients requiring pituitary surgery are likely to be vulnerable to COVID-19. One possible explanation for this assumption could be that Cushing's disease causes immune suppression and diabetes. In addition,

both acromegaly and Cushing's disease cause cardiovascular comorbidity, which are evident risk factors for more severe infection. The decision, timing, and postoperative follow-up of patients with pituitary diseases pose a significant clinical challenge to clinicians even in the routine practice. Pituitary centers should continuously update their protocols according to the rapidly evolving course of COVID-19. As a general approach, the risks must be carefully balanced against the natural history of a pituitary disease. Considering irreversible morbidity such as vision loss in a patient with pituitary apoplexy can overcome undue delays. In contrast, a more flexible approach to asymptomatic patients with prolactinoma could protect the patients from excessive exposure to COVID-19. Similar to the Pituitary Society, we are in favor of stratifying cases as emergent, urgent, and elective. Decisions should be made on a case basis. Pituitary apoplexy and acute severe significant mass effect such as vision loss or suspicion of malignant pathology are clear indications for emergent intervention. Urgent surgery can benefit selected patients who have slow-progressive visual compromise, functioning tumors with aggressive clinical features, and unclear diagnosis. Patients with incidental and asymptomatic tumors, nonfunctioning adenomas, and functioning tumors adequately controlled with medical therapy do not need urgent treatment. These patients can be scheduled for a later time.

For patients whose surgery is deferred to a later time and decided to be followed up with medical treatment, the choice of medical treatment may have some implications regarding the COVID-19. Pasireotide, for example, may act synergistically with drugs used in COVID-19 treatment (azithromycin and hydroxychloroquine) and could prolong the corrected QT interval. Moreover, this drug may cause hyperglycemia and thus require close monitoring at the beginning of treatment. This may expose the patient to COVID-19. Hence, the decision to initiate pasireotide should be reconsidered carefully during this novel pandemic and should be reserved for highly resistant cases. Other somatostatin receptor ligands, requiring healthcare staff support for administration, may be allowed to be scheduled more frequently for avoiding further exposure, depending on the clinical context.

The approach to the medical treatment of various pituitary diseases should be addressed separately. For example, patients with prolactinoma can be initiated and continued safely with dopamine agonists until they do not have complaints necessitating emergent intervention. The medical management of Cushing's disease is not as easy as a prolactinoma. These patients have inherent risk factors for COVID-19 and the medical treatment used temporarily may precipitate AI in excessive doses. Thus, initial doses should be the lowest as possible and titrated according to the clinical response with more attention on imminent AI in case of over treatment. It should be kept in mind that mild hypercortisolemia may be better than the adrenal crisis in the short term (48). Patients should be informed about withdrawing the treatment for some time if they experience fever. In addition, they should be educated about the timing and dosing of glucocorticoid administration when there are symptoms suggestive of COVID-19.

Hypopituitarism is also a crucial issue. Principles of glucocorticoid and thyroid hormone replacement are depicted in respective sections above. Testosterone and estrogen administration and growth hormone replacements can be delayed; however, adequate testosterone levels should be ensured in men and insulin-like growth factor 1 should be maintained within normal limits whenever biochemical testing is feasible (49).

Conclusion

Several reports are being published about COVID-19 and its associations; however, data regarding COVID-19 and endocrine diseases are relatively scarce. In addition to encouraging patients to adhere to basic rules for protecting themselves from the disease through social distancing and self-hygiene, endocrinologists have additional tasks. Avoiding unnecessary routine appointments and reinforcing online consultations are cornerstones of a preventive strategy. The close monitoring of patients with AI or diabetes is crucial as COVID-19 may deeply affect glycemic control and increase the risk of adrenal crisis. Parenteral glucocorticoid re-

placement in patients with AI should not be delayed if a patient's clinical condition deteriorates. Education on "sick day rules" can prevent disastrous consequences. Patients with thyroid disease should continue their routine medications. The risk-benefit ratio should be carefully considered in patients with pituitary disorders, and interventions should be determined on a case basis depending on the severity of clinical features. Future studies on more specific aspects of the association between COVID-19 and endocrinological diseases are warranted.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

References

1. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14:303-310. [Crossref] [PubMed] [PMC]
2. Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology. 2003;8:S9-S14. [Crossref] [PubMed] [PMC]
3. Morra ME, Van Thanh L, Kamel MG, Ghazy AA, Altibi AMA, Dat LM, Thy TNX, Vuong NL, Mostafa MR, Ahmed SI, Elabd SS, Fathima S, Le Huy Vu T, Omrani AS, Memish ZA, Hirayama K, Huy NT. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. Rev Med Virol. 2018;28:e1977. [Crossref] [PubMed] [PMC]
4. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006;23:623-628. [Crossref] [PubMed]
5. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care. 2010;33:1491-1493. [Crossref] [PubMed] [PMC]
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720. [Crossref] [PubMed] [PMC]
7. Rhee EJ, Kim JH, Moon SJ, Lee WY. Encountering COVID-19 as endocrinologists. Endocrinol Metab (Seoul). 2020;35:197-205. [Crossref] [PubMed] [PMC]
8. Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used). Diabetes Res Clin Pract. 2020;162:108137. [Crossref] [PubMed] [PMC]
9. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020;162:108125. [Crossref] [PubMed] [PMC]
10. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21. [Crossref] [PubMed] [PMC]
11. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol. 2020;18:2128-2130. [Crossref] [PubMed] [PMC]
12. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47:193-199. [Crossref] [PubMed] [PMC]
13. Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. J Endocrinol Invest. 2020;43:1027-1031. [Crossref] [PubMed] [PMC]
14. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95. [Crossref] [PubMed] [PMC]
15. Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine. 2020;68:2-5. [Crossref] [PubMed] [PMC]
16. Bassendine MF, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: a role for dipeptidyl peptidase 4 (DPP4) in disease severity? J Diabetes. 2020;12:649-658. [Crossref] [PubMed]
17. Kajiwara C, Kusaka Y, Kimura S, Yamaguchi T, Nanjo Y, Ishii Y, Udono H, Standiford TJ, Tateda K. Metformin mediates protection against Legionella pneumonia through activation of AMPK and mitochondrial reactive oxygen species. J Immunol. 2018;200:623-631. [Crossref] [PubMed]
18. Hariyanto TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. Obes Med. 2020;19:100290. [Crossref] [PubMed] [PMC]
19. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract. 2020;162:108132. [Crossref] [PubMed] [PMC]
20. Gorricho J, Garjón J, Alonso A, Celaya MC, Saiz LC, Erviti J, López A. Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case-control study. Br J Clin Pharmacol. 2017;83:2034-2044. [Crossref] [PubMed] [PMC]

21. Prattichizzo F, La Sala L, Rydén L, Marx N, Ferrini M, Valensi P, Ceriello A. Glucose-lowering therapies in patients with type 2 diabetes and cardiovascular diseases. Eur J Prev Cardiol. 2019;26:73-80. [Crossref] [PubMed]
22. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. 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. [Crossref] [PubMed] [PMC]
23. Valencia I, Peiró C, Lorenzo Ó, Sánchez-Ferrer CF, Eckel J, Romacho T. DPP4 and ACE2 in diabetes and COVID-19: therapeutic targets for cardiovascular complications? Frontiers in Pharmacology. 2020;11:1161. [Crossref] [PubMed] [PMC]
24. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495:251-254. [Crossref] [PubMed] [PMC]
25. Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2016;32:391-404. [Crossref] [PubMed]
26. Amin EF, Rifaai RA, Abdel-Latif RG. Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative-inflammatory-apoptotic pathway. Fundam Clin Pharmacol. 2020;34:548-558. [Crossref] [PubMed]
27. Ceriello A. Thiazolidinediones as anti-inflammatory and anti-atherogenic agents. Diabetes Metab Res Rev. 2008;24:14-26. [Crossref] [PubMed]
28. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med. 2020;27:taaa041. [Crossref] [PubMed] [PMC]
29. Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, Carmona-Rubio AE, Jacob M, Procop GW, Harrington S, Milinovich A, Svensson LG, Jehi L, Young JB, Chung MK. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1020-1026. [Crossref] [PubMed] [PMC]
30. Pettit NN, MacKenzie EL, Ridgway JP, Pursell K, Ash D, Patel B, Pho MT. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity (Silver Spring). 2020;28:1806-1810. [Crossref] [PubMed] [PMC]
31. Huang Y, Lu Y, Huang YM, Wang M, Ling W, Sui Y, Zhao HL. Obesity in patients with COVID-19: a systematic review and meta-analysis. Metabolism. 2020;113:154378. [Crossref] [PubMed] [PMC]
32. Zhang X, Zheng J, Zhang L, Liu Y, Chen GP, Zhang HP, Wang L, Kang Y, Wood LG, Wang G. Systemic inflammation mediates the detrimental effects of obesity on asthma control. Allergy Asthma Proc. 2018;39:43-50. [Crossref] [PubMed]
33. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Commentary: obesity: the "Achilles heel" for COVID-19? Metabolism. 2020;108:154251. [Crossref] [PubMed] [PMC]
34. Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. Hematology Am Soc Hematol Educ Program. 2017;2017:187-193. [Crossref] [PubMed] [PMC]
35. Boelaert K, Visser WE, Taylor PN, Moran C, Léger J, Persani L. Endocrinology in the time of COVID-19: management of hyperthyroidism and hypothyroidism. Eur J Endocrinol. 2020;183:G33-G39. [Crossref] [PubMed]
36. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95:834-847. [Crossref] [PubMed] [PMC]
37. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3:816-825. [Crossref] [PubMed] [PMC]
38. Dworakowska D, Grossman AB. Thyroid disease in the time of COVID-19. Endocrine. 2020;68:471-474. [Crossref] [PubMed] [PMC]
39. Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, Ito M, Kubota S, Fukata S, Miyauchi A. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. Intern Med. 2008;47:725-729. [Crossref] [PubMed]
40. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization; 2020. [Link]
41. Brancatella A, Ricci D, Cappellani D, Viola N, Sgrò D, Santini F, Latrofa F. Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? Insights from a case series. J Clin Endocrinol Metab. 2020;105:dgaa537. [Crossref] [PubMed] [PMC]
42. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;6:5. [Crossref] [PubMed] [PMC]
43. Tresoldi AS, Sumilo D, Perrins M, Toulis KA, Prete A, Reddy N, Wass JAH, Arlt W, Nirantharakumar K. Increased infection risk in Addison's disease and congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2020;105:418-429. [Crossref] [PubMed] [PMC]
44. Edvardsen K, Bjånesøy T, Hellesen A, Breivik L, Bakke M, Husebye ES, Bratland E. Peripheral blood cells from patients with autoimmune Addison's disease poorly respond to interferons in vitro, despite elevated serum levels of interferon-inducible chemokines. J Interferon Cytokine Res. 2015;35:759-770. [Crossref] [PubMed] [PMC]
45. Isidori AM, Arnaldi G, Boscaro M, Falorni A, Giordano C, Giordano R, Pivonello R, Pofi R, Hasenmajer V, Venneri MA, Sbardella E, Simeoli C, Scaroni C, Lenzi A. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency. J Endocrinol Invest. 2020;43: 1141-1147. [Crossref] [PubMed] [PMC]
46. Wheatland R. Molecular mimicry of ACTH in SARS - implications for corticosteroid treatment and prophylaxis. Med Hypotheses. 2004;63:855-862. [Crossref] [PubMed] [PMC]
47. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Ventz M, Quinkler M, Allolio B. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010;162:597-602. [Crossref] [PubMed]
48. Fleseriu M, Buchfelder M, Cetas JS, Fazeli PK, Mallea-Gil SM, Gurnell M, McCormack A, Pineyro MM, Syro LV, Tritos NA, Marcus HJ. Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic-an international perspective. Pituitary. 2020;23:327-337. [Crossref] [PubMed] [PMC]
49. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888-3921. [Crossref] [PubMed]