

## Review Article

### The covid-19 impact on the pituitary gland

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#### Abstract

The Coronavirus 2019 (Covid-19) disease pandemic continues to infect a great number of human population, causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Global healthcare system has been significantly burdened since the percentages of mortality and morbidity are highly rising. As time passes and more studies have been conducted, it is increasingly clear that Covid-19 does not only affect the respiratory system, but has also multiple effects on cardiovascular, endocrine and neurological systems.

Detailed research was performed via the PubMed database using the following keywords: covid-19, infection, impact, pituitary gland, vaccination. The research was made in the articles from 2019, when Covid-19 first emerged and subsequently.

Covid-19 virus has cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor. This process requires the transmembrane serine protease 2 (TMPRSS2) protein. Both ACE2 and TMPRSS2 are widely expressed in many endocrine glands.

This review analyzes the endocrine manifestations of Covid-19 on the pituitary glands. On this review we underline the most common pituitary diseases that Covid-19 is responsible for, which are the pituitary apoplexy, hypophysitis, hypopituitarism and adrenal cortex insufficiency.

*KeyWords: covid-19, infection, impact, pituitary gland, vaccination*

#### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first emerged in late 2019-early 2020 and was identified as the cause of universal spread of a fatal pulmonary virus. The subsequent pandemic Covid-19 is recognized as one of the most serious challenges that the worldwide healthcare system faces with. The impact that Covid-19 has on patients does not only regards the pulmonary system, but also the cardiovascular and the pituitary system (1-3).

Covid-19 was initially identified as a lethal respiratory virus that causes SARS-CoV-2. However, as the Covid-19 continues to exist on global health care systems, extrapulmonary manifestations have been found. Covid-19 has been proven to directly affect the cardiovascular, neurological and endocrine system. The extrapulmonary infection of Covid-19 is due to the expression of angiotensin-converting enzyme 2 receptor (ACE 2), which allows the virus to enter the cells, resulting in the

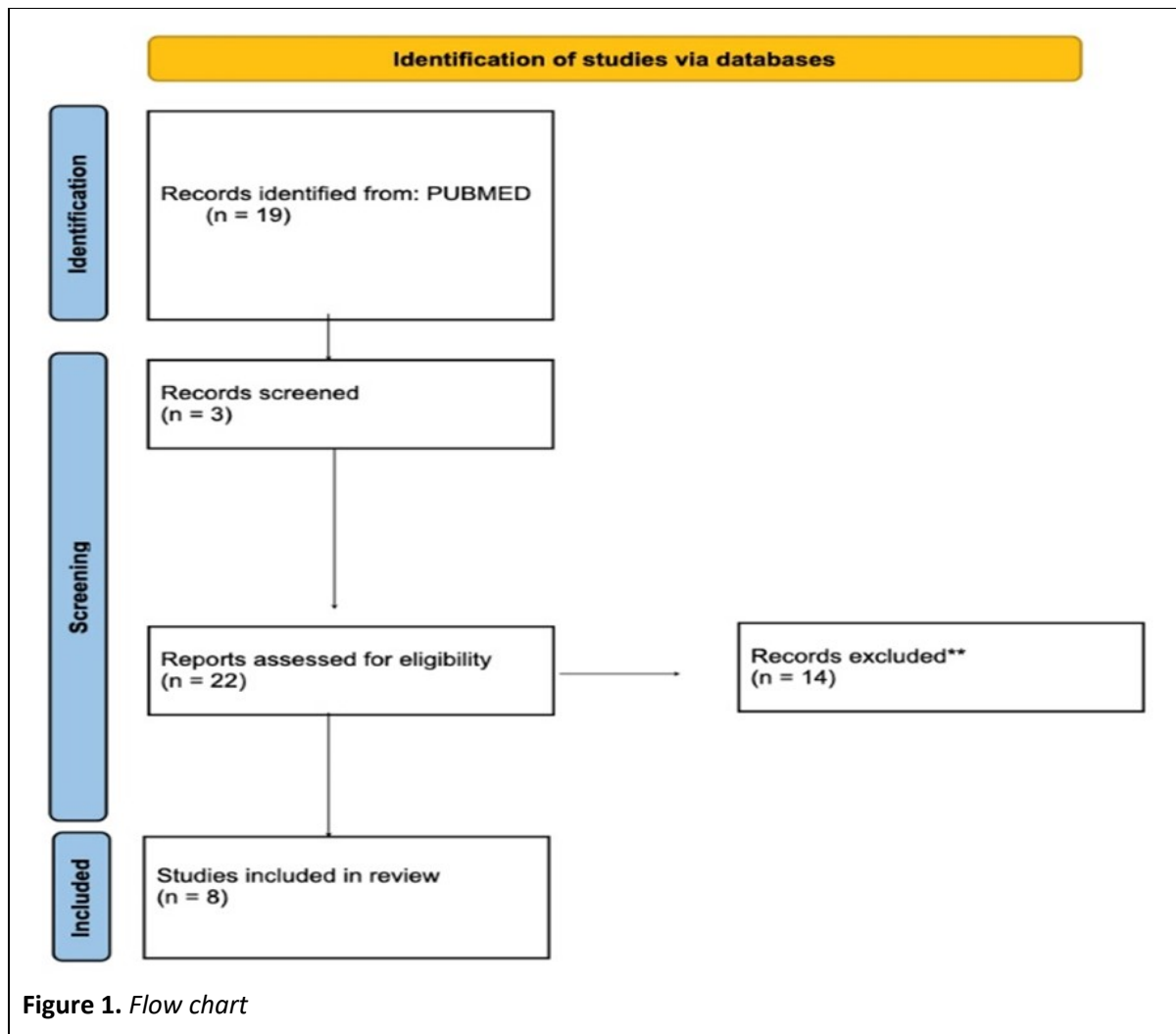
damage of multiple organs and tissues. This process requires the transmembrane serine protease 2 (TMPRSS2) protein, as both ACE2 and TMPRSS2 are widely expressed on many endocrine glands (4). In our study, we will analyze the effects that Covid-19 has on the endocrine system and specifically on the pituitary glands, reporting the “endocrine phenotype” of Covid-19 (1). Aim of this study is to shortly review the manifestations of Covid-19 on pituitary glands and its implications on pituitary diseases which can be at increased risk with respiratory complications.

#### Materials and methods

The PubMed database was searched extensively using specific keywords such as covid-19, infection, impact, pituitary gland, vaccination for relevant published sources. To ensure accuracy and adequacy, information was gathered through a common data extraction form designed for the aforementioned keywords. The research study

adhered to the guidelines of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), a comprehensive approach for conducting scoping reviews. By following PRISMA guidelines, a total of 19 records were initially identified through the PubMed search, and an additional 3 records were obtained through a thorough review of references.

After removing duplicates, the final number of screened records was 22. A total of 8 full-text articles were assessed for eligibility, resulting in the exclusion of 14 articles, titles, and abstracts that were not relevant. Hence, the specific article is based on the information retrieved from 8 reliable references (Table 1).



### Discussion

**Pathophysiology.** As we mentioned above, SARS-CoV-2 infects host cells by binding the ACE2 receptor. The mRNA of this protein is expressed in many tissues and therefore the virus has the possibility to widely spread to many organs causing infection outside the respiratory system (5).

Specifically, ACE2 is expressed in hypothalamus, pituitary, pancreas, thyroid and gonads, which are possible targets for the virus. Therefore, these organs are vulnerable to Covid-19 infections. The virus enters the brain either via the general circulation, passing through the blood brain barrier (BBB) or via the nasopharyngeal epithelial through

the olfactory bulb (6). Pituitary gland has rich vascularity and therefore can be damaged during Covid-19 infection. Moreover, pituitary can be damaged by conditions that alter the platelets' function and coagulation. Patients after the inflammatory state of SARS-CoV-2, have increased hypercoagulability with thrombocytopenia and high levels of fibrinogen and D-dimers. Thus, these patients are in high risk of pituitary damage and dysfunction of the endocrine system (4).

*Pituitary Apoplexy.* Covid-19 can cause thrombopenia, coagulopathy and dysfunction of platelets, and therefore it may have direct vascular damage to pituitary gland with ischemic and hemorrhagic signs of necrosis, due to ACE2 expression on cerebral vascular epithelium. Therefore, multiple studies have proven that Covid-19 could cause pituitary apoplexy. In particular, pituitary apoplexy is an acute clinical and surgical syndrome of sudden hemorrhage of pituitary gland, in which there is usually a pituitary microadenoma. Sudden onset of acute headache, visual disturbances and palsy of the ocular nerve are the main symptoms that patients report and they are due to a necrotic mass that compress the surround pituitary structures. As many studies report pituitary apoplexy is a rare event that presents to 2-12% of patients with microadenomas, but Covid-19 infection has highly increase the percentage of patients with pituitary apoplexy (1,5,7).

*Hypophysitis.* Hypophysitis is common adverse-effect of the anticancer immunotherapy with immune checkpoint inhibitors (ICPs) such as the monoclonal antibodies anti-CTLA4, anti-PD-1 and anti-PD-L1. These monoclonal antibodies express immune system against tumor cells causing severe endocrine diseases.

There are not yet enough studies that relate hypophysitis with Covid-19 infection. However, it is considered that patients with Covid-19 that receive a specific treatment, present reduced or at least a non-increased incidence of hypophysitis. That can be explained since Covid-19 treatment is based on the administration of glucocorticoid, which are also used for the resolution of hypophysitis.

*Hypopituitarism and adrenal insufficiency.*

ACE2 receptor has been identified to be present in the adrenal cortex and specifically, in the zona fasciculata and reticularis (glucocorticoid and androgen production), but not in the zona glomerulosa (mineralocorticoid production). In addition, TMPRSS2 is present in all 3 zones of adrenal cortex (4).

Adrenal function remains stable during Covid-19 infection in most cases. However, a great number of studies have reported that Covid-19 infection affects the hypothalamic-pituitary-adrenal (HPA) axis. In particular, there are some case reports following Covid-19 that have been reviewed with adrenal insufficiency secondary to acute adrenal infarction and adrenal hemorrhage (7).

Specifically, it is indicated that Covid-19 patients have highly increased levels of cortisol and adrenocorticotropic hormone (ACTH) and in patients with severe COVID-19 in comparison with those with mild-to-moderate disease forms, these hormones are significantly higher. However, cortisol levels are significantly lower in fatal cases of Covid-19 (4).

In summary, adrenal function has been retained in most patients with Covid-19. The high levels of cortisol are due to the treatment of Covid-19 infection with glucocorticoid, whereas the significantly low levels may be due to the damage of adrenal function, suppressing the hypothalamic-pituitary-adrenal axis (1,4,6,8).

*Covid-19 vaccination and pituitary diseases.* Published data and previous studies have reported some particular cases of adverse effects or some contradictions in relation to pituitary diseases as regards the vaccines, causing endocrine dysfunction. Specifically, hypophysitis has been reported not only after Covid-19 infection, but also after vaccination. ACTH deficiency of pituitary atrophy has also been described one day after mRNA Covid-19 vaccination. These vaccines have also been accused for apoplexy of pituitary glands. Vaccine efficacy can be reduced in patients who are immune suppressed or receive glucocorticoid treatment. In a survey of Pituitary Society Members most clinical doctors reported that they maintain the replacement dose of glucocorticoid

during vaccination and they increase it only in cases of adverse effects, as fever (1,6).

### Conclusion

Covid-19 pandemic has disrupted every aspect of our life and consist a high challenge for doctors, healthcare system and patients. In this review, we underline the involvement of coronavirus in the endocrine system and in particular, in the pituitary glands, as coronavirus enters endocrine cells via ACE2 and TMPRSS2 expressed on these tissues. Moreover, our review analyzes the pituitary apoplexy, hypophysitis, hypopituitarism and adrenal cortex insufficiency, as the most common pituitary diseases that Covid-19 is responsible for. Finally, risk factors and some adverse-effects have been reported on Covid-19 vaccination, which points out that more research and development need to be conducted for minimizing Covid-19 impact on human life and any adverse-effect of Covid-19 vaccination.

### Abbreviations

ACE2: angiotensin-converting enzyme 2 receptor  
 TMPRSS2: transmembrane serine protease 2 protein  
 SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

HPA: hypothalamic-pituitary-adrenal

ACTH: adrenocorticotrophic hormone

ICPs: immune checkpoint inhibitors

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

### Availability of Data and Materials

The data were collected via PubMed database. The information of this systematic review is available and accessible in the database mentioned using the keywords that have been mentioned above.

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