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Implicaciones de la infección por SARS-CoV-2 en el sistema endocrino

Implications of SARS-CoV-2 infection on the endocrine system

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Resumen

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SARS-CoV-2; COVID-19: Sistema Endocrino; Tiroides; Glándulas suprarrenales

Introducción: La infección por Coronavirus (COVID-19) ha sido un problema de salud pública desde su inicio en el año 2020 en Wuhan, China. Su principal vía de entrada celular es la enzima convertidora de angiotensina 2 (ACE2). A pesar de que el pulmón es el principal órgano perjudicado por su elevada concentración de ACE2, también existe dicha enzima en órganos endocrinos, provocando alteraciones en dicho sistema hormonal. **Objetivo**: Efectuar una revisión sistemática sobre las implicaciones de la infección por SARS CoV-2 en el sistema endocrino. **Metodología:** Estudio no experimental, descriptivo, se realizó una búsqueda sistemática sobre la influencia del SARS-CoV-2 en el sistema endocrino desde enero del año 2020 hasta agosto del año 2023. **Resultados**: Algunas estructuras del sistema endocrino son susceptibles a la infección por SARS-CoV-2 como la hipófisis anterior, debido a que se ubica fuera de la barrera hematoencefálica, otras zonas afectadas como la glándula tiroides presenta susceptibilidad por sus altas concentraciones de ACE 2 y también se ha observado mayor grado de severidad en pacientes sin timo porque aumenta la probabilidad de aparición de neumonía. **Conclusión**: Existe una relación entre la gravedad de dicha infección viral y la disminución de las concentraciones hormonales séricas de TSH, T3, T4. **Área de estudio general:** Medicina. **Área de estudio específica:** Medicina Interna. **Tipo de estudio:** Revisión Bibliográfica.

Keywords:
SARS-CoV-2; COVID-19: Endocrine System; Thyroid; Adrenal Glands

Abstract

Introduction: Coronavirus (COVID-19) infection has been a public health problem since its inception in 2020 in Wuhan, China. Its main route of cellular entry is angiotensin-converting enzyme 2 (ACE2). Although the lung is the main organ affected due to its high concentration of ACE2, this enzyme also exists in endocrine organs, causing alterations in the hormonal system. Objective: To conduct a systematic review on the implications of SARS-CoV-2 infection on the endocrine system. Methodology: Non-experimental, descriptive study, a systematic search was conducted on the influence of SARS-CoV-2 on the endocrine system from January 2020 to August 2023. Results: Some structures of the

endocrine system are susceptible to SARS-CoV-2 infection such as the anterior pituitary because it is located outside the blood-brain barrier, other affected areas such as the thyroid gland is susceptible because of its high concentrations of ACE 2 and has also been observed greater degree of severity in patients without thymus because it increases the likelihood of developing pneumonia. Conclusion: There is a relationship between the severity of this viral infection and the decrease in serum hormone concentrations of TSH, T3, T4.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) health pandemic has been a public health problem worldwide since its beginnings in 2020 in Wuhan, China, and despite attempts to reduce its spread, its adaptive capacity to become an agent capable of causing damage to any part of the human body is surprising.(1)Being a member of the coronavirus family, it is characterized by presenting a single RNA chain with four structural proteins within which they cover: the envelope, the membrane, the nucleocapsid and the spike protein.(2).

Inflammatory cytokines together with neutrophils and inflammatory cells lead to epithelial damage, in addition, oxidative stress towards type II pneumocytes prevents the production of antioxidants necessary for the formation of pulmonary surfactants, added to the use of oxygen in severe patients that induces an accumulation of cellular reactive oxygen species in mitochondria that allow cell apoptosis.(3). This is why the first organ affected is the lung, this is because SARS-CoV-2 has preference over pneumocytes due to their high concentrations of angiotensin converting enzyme 2 (ACE2), in addition, cellular damage leads to hypoxia and the respiratory center may be compromised, this added to the cytokine storm worsens the clinical picture, since it involves other adjacent structures.(4).

SARS-CoV-2 needs to interact with angiotensin-converting enzyme 2 to enter human cells, this allows the virus to influence the endocrine system, through the hypothalamic-pituitary axis, because its tissues express ACE2.Many investigations indicate that infection by this viral agent alters endocrine functions in several glands such as: pituitary, thyroid and adrenal glands.(5).

The pituitary gland is highly vascularized and its endothelium has a high concentration of ACE2, which allows it to be an important target during COVID-19 infection, therefore, there are cases of acute inflammation and persistent effects in this area.

However, despite the theory indicating a high risk of damage by this virus, there is still little clinical evidence of direct damage to this gland.(6). Similarly, there is a large number of ACE2 cell receptors in the thyroid parenchyma that can predispose to a COVID-19 infection, this allows for timely identification of patients vulnerable to the disease, thus implementing timely therapeutic intervention. The impact of the thyroid hormone on many organs such as the cardiovascular and respiratory organs is also known. And even, it is added, those thyroid alterations prior to the infection that can aggravate the SARS-CoV-2 infection.(7).

During critical illness, glucocorticoids are essential to protect the body from cardiac shock and to prevent overactivation of the immune system. In some patients, glucocorticoid metabolism is significantly reduced, and in many cases, corticosteroid insufficiency is associated with critical illness, thus developing adrenal insufficiency, a product of direct cytotoxic actions of pathogens.(8).

Symptoms and signs are becoming less severe, although the involvement of other organs far from the respiratory system is undeniable, since ACE2, being the gateway for SARS-CoV-2, can be found in other organs. This explains the appearance of symptoms and signs that are not specific, such as fever, cough, dyspnea, dizziness, vomiting, headache, asthenia, anorexia, myalgia, etc. This results in a clinical picture that can vary and can present asymptomatic patients to patients with high requirements for invasive supplemental oxygen.(9).

There are reports of patients who recovered from SARS-CoV-2 infection, many report the appearance of new symptoms that persist for weeks, making follow-up difficult, especially in developing countries such as Latin America, where the health system is fragile, making it very difficult to study and understand the infectious process caused by this viral agent in the long term.(10). Even to this day, it continues to have a great impact on hospitals, some authors mention that endocrine disorders can be treatable, so management offers a better quality of life.(6).

Currently, the contribution of endocrine dysfunction to the symptoms experienced by patients with COVID-19 has not been fully elucidated, some disorders are treatable and their diagnosis and treatment can offer significant improvements in quality of life.(6).Therefore, it is of utmost importance to understand the degree of affectation of the virus in the different endocrine structures and its short and long-term effects, sinceEach viral evolution brings with it new challenges in the pathophysiological and clinical understanding of the disease(11).

Goals

General

- To carry out a systematic review on the implications of SARS-CoV-2 infection in the Endocrine System through a search of transcendental bibliography for its pathophysiological and clinical understanding.

Specific

- Review the main endocrine organs affected by this viral infection.
- Explain the pathophysiological mechanisms of SARS-CoV-2 in the Endocrine System.
- Determine the main clinical manifestations of COVID-19 in relation to the Endocrine System.

Methodology

The study method is non-experimental, descriptive through a systematic review of the influence of SARS-CoV-2 on the endocrine system from January 2020 to August 2023, with emphasis on the pathophysiology, the main organs affected and its clinical repercussions.

A search for scientific articles from Internet portals was carried out, with the help of the free search engine PubMed, using the terms SARS-CoV-2, COVID-19, Endocrine System, thymus, Thyroid, Adrenal gland, and Boolean operator was also used.¨AND¨.Articles with an emphasis on other organs and systems that were not related to the central theme were then excluded (Figure 1).

Inclusion criteria:

1. Pathophysiology studies of SARS-CoV-2 within the endocrine system.
2. Scientific evidence describing endocrinological clinical manifestations in COVID-19.
3. Population over 18 years of age, regardless of gender, diagnosed with SARS-CoV-2 infection.
4. Scientific articles from January 2020 to August 2023, freely accessible in English or Spanish.

Exclusion criteria:

1. Scientific information obtained from pediatric patients and pregnant women

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2. Studies focused on the treatment of viral infection in patients with underlying diseases.
3. Reports that do not clarify the mechanism of SARS-CoV-2 pathogenesis.

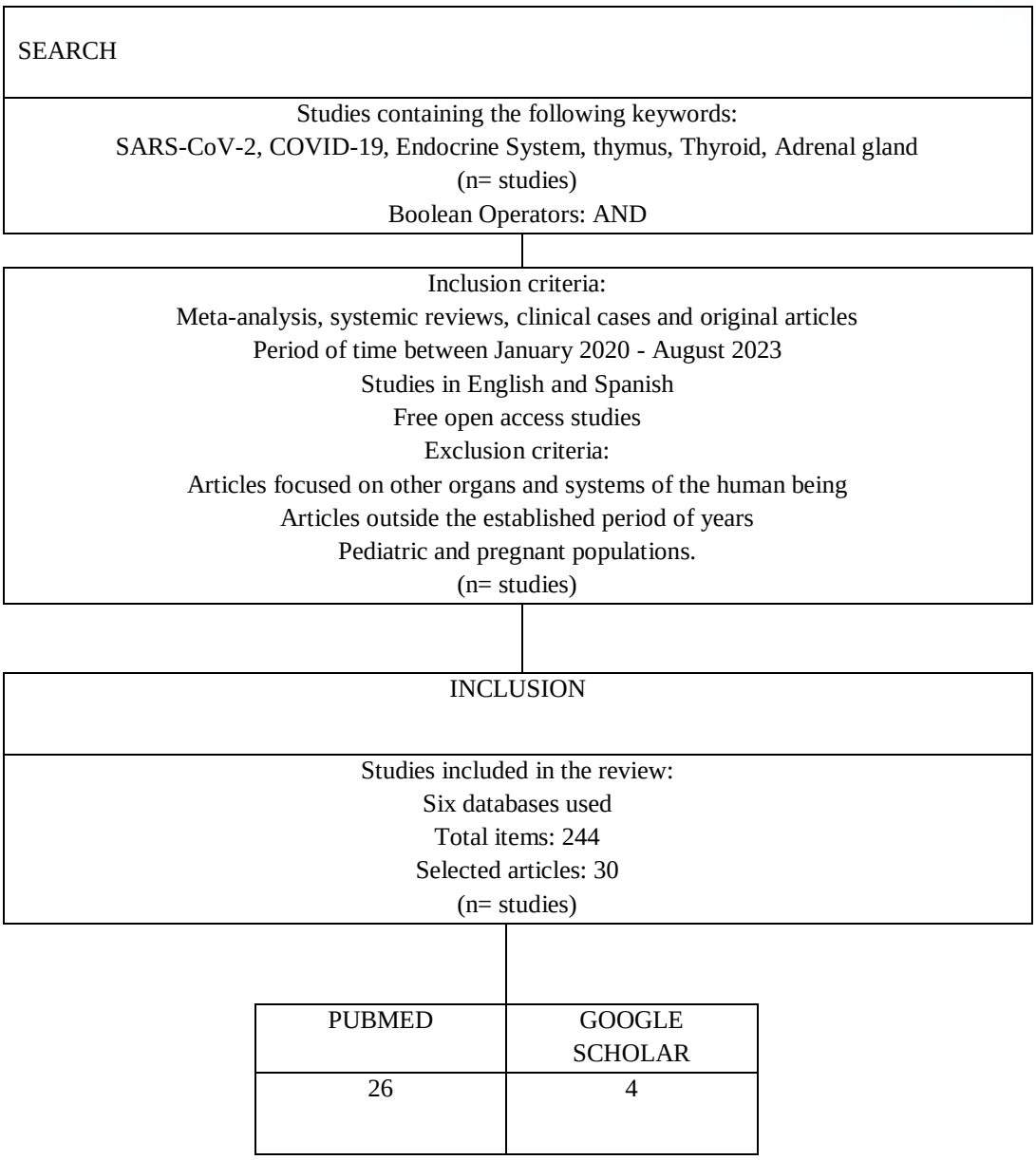

Figure 1.*Selection of the study sample*

Results and discussion

Pathogenesis

Coronaviruses are a family of RNA viruses that have an ovoid shape and belong to the order Nidoviral and are classified as "α", "β", and "γ". Their main characteristic is the high rate of mutation and recombination, that is, they can evolve rapidly and form new

strains. The main route of transmission for SARS-CoV-2 infection is through small droplets of saliva that are expelled when breathing or sneezing, which, when inhaled, reach the respiratory system.(9), where they need (ACE2) as a receptor to invade cells(1). Therefore, the virus has the viral glycoprotein S, which binds to the ACE2 cellular receptor with an affinity 20 times greater than SARS-COV-1.(6) (4), under the support of transmembrane serine protease 2 (TMPRSS2), the same one that is regulated by androgens(6).

The spike protein of the virus when it binds to the ACE2 receptor, causes the protein to be divided into S1/S2 and S2(4). The first case helps the recognition of the S protein by ACE2(12)and in the case of the S2 protein, it allows the membranes of the host and the host cell to be joined together(4).

It has been shown in vitro that furin effectively cleaves the S1/S2 site in SARS-CoV-2, unlike in SARS-CoV-1, which lacks association with this type of molecule.(12). In addition, TMPRSS2 does not cleave these S1/S2 peptides and in the event that the infection process is carried out in cells that lack this anchoring site, furin can promote cell fusion.(12).

When the virus enters the host, it encounters dendritic cells, which in turn phagocytose it. They then present it to T cells, which in turn release cytokines and induce apoptosis. However, this defensive mechanism is exacerbated to the point that there is an imbalance between the production and maturation of T cells.(13).

In the end, a cytokine storm is evident with the ability to break the endothelial cell membrane, allowing the virus to enter multiple organs.(4)This opens the way to the joint manifestation of an increase in interleukin 1β, interferon gamma, monocyte chemoattractant protein 1 and a decrease in albumin, neutrophils, CD8+ T cells and interleukin 10, the latter with antiviral function.(13).

ACE2 concentration levels determine greater or lesser susceptibility to infection in different organs, and are found in medium concentrations at the level of the lungs and the adrenal gland, compared to the small intestine, testicles, kidneys, heart, pancreas, thyroid and adipose tissue, which present higher concentrations of this enzyme, which does not allow us to understand why the lung is the main affected organ, since according to this author, it presents lower concentrations of ACE2, therefore, theoretically it should be the least affected organ in this comparative study.(1).

There is also a tumor necrosis factor alpha converting enzyme, which can cleave ACE2 to generate an active and soluble ectodomain, thereby increasing viremia and the spread of infection to other organs, in a theory called "double hit."(14).

Similarly, the body's response to interferon by the immune system was adequate at the level of the skin, pancreas, brain and blood vessels, which, despite having high concentrations of ACE2, the result was the same in both males and females. On the contrary, in women a negative correlation was determined between the levels of ACE2 and the response to interferon in the thyroid and lungs.(1).

When SARS-CoV-2 comes into contact with the lung, it releases metalloproteinases in the inflammatory phase of the acute inflammatory syndrome, causing epithelial and endothelial damage, promoting uncontrolled fibrosis. When there is epithelial deterioration, an exposed space remains, this produces activation of alveolar epithelial cells type 2 (AEC2), which cover the exposed alveolar space, however, when there is an extensive injury the cells cannot recover the epithelium and there is inadequate tissue repair accompanied by an overpopulation of fibroblasts.(3)The virus takes advantage of this vulnerability and can spread effectively in a weakened immune system, producing even more lung tissue damage, allowing the activation of macrophages and granulocytes, which pave the way for a massive release of cytokines with damage to multiple organs.(15).

In obese and diabetic patients, there are abundant adipocytes and their similar pulmonary lipofibroblasts of the alveolar interstitium with the capacity to differentiate into myofibroblasts and trigger pulmonary fibrosis that can be stabilized with thiazolidinediones.(16).

Hypothalamic and pituitary axis

Pathophysiology

The hypothalamus is part of the central nervous system, which is responsible for controlling the activity of the pituitary gland to a large extent. However, it can produce hormones such as vasopressin at the level of the supraoptic and paraventricular nuclei, releasing it into the bloodstream through the posterior lobe of the hypophysis. This hormone needs stimuli for its release such as: hypoxia, hypotension, hypoglycemia and hyperosmolality. Consequently, there is a powerful neurohormonal effect that regulates urine concentration, blood pressure, the release of glucocorticoids and catecholamines.(17).

The anterior pituitary gland, being outside the blood-brain barrier, is prone to being infected by SARS-CoV-2.(18)However, the spike protein of the SARS-CoV-1 virus in an experimental environment can cross this barrier(8).

Regarding immunoglobulins, in one study it was believed that the presence of antihypothalamic proteins would show some functional impairment, however, in patients with antibodies against prolactin cells, there was no apparent consequence.(5).

Neuropilin is another receptor used in viral infection. There are two types, both of which interact with their respective vascular endothelial growth factor ligands.(19)Neuropilin type 1 is expressed in the olfactory epithelium and in excitatory neurons(4), also facilitates angiogenesis. Neuropilin type 2 is involved in lymphangiogenesis. One characteristic is the increased expression of NRP-1 in infected patients, explaining the invasion of cells carrying this receptor.(19).

Binding of the virus's S1 peptide to the patient's neuropilin 1 aids cell invasion, and binding of vascular endothelial growth factor type A (VEGF-A) to the host's cellular receptor is associated with nociception. However, the S protein interferes with VEGF-A coupling, preventing its competitive binding.(19).

Another receptor called CD147 has a higher expression in brain tissue compared to lung tissue, consequently, the neuron and microglia have a higher probability of becoming infected.(20)Concerned about this finding, a study determined that the antibody against the CD147 receptor (anti-CD 147) blocked viral entry in its variants: alpha, beta, gamma and delta, giving an inhibition percentage greater than 50%.(21).

An inverse relationship has been observed between serum concentrations of interleukin and sodium, therefore, in one study, the IL-6 receptor antibody allowed to decrease the levels of this interleukin, and increased the serum sodium values and thus, corrected hyponatremia. Although, it is important to mention that an insufficient correction of the volemia leads to dehydration and hypernatremia.(18).

Clinical manifestations

Pituitary disorders include pituitary apoplexy, which is related to impaired coagulation.(18), which has a low incidence of 0.17/100,000 years, and involves a sudden hemorrhage together with a blood infarction within a macroadenoma, this ultimately leads to the appearance of headache, alteration of the visual field and ocular paralysis.(22).

Similarly, cases of pituitary apoplexy can be associated as a direct complication of viral infection or a coincidence.(2).

Hypophysitis is a difficult disorder to establish in the context of COVID-19, because many patients receive glucocorticoids as initial management and this allows for underdiagnosis.(18).

Thyroid

Pathophysiology

Angiotensin converting enzyme 2 is found in elevated levels in this endocrine gland, specifically in the thyroid follicular cells.(23).

A contributing factor to the cytokine storm is the increase in T-helper 17 cells, related to the increase in interleukin 6. Consequently, thyroid autoimmune diseases are associated with a worse clinical course, due to the basal increase in IL-6 and TNF alpha.(23).

The hormone triiodothyronine (T3) stands out for its regulatory role in the hyperactivation of the immune system, decreasing the response by macrophages to IL-6.(23). Its hormonal receptors are located in type II alveolar cells, in this area T3 has effects of hypertrophy, hyperplasia, greater release of surfactant and better absorption of fluid belonging to alveolar edema.(7).

Clinical manifestations

It has been observed that the more severe the clinical presentation of SARS-CoV-2, the greater the likelihood of a decrease in serum levels of T3, free thyroxine (T4) and thyroid-stimulating hormone (TSH).(24).

Hormone levels can be normal and still present alterations such as euthyroid patient syndrome, in which case low T3, normal or low T4 and TSH are observed.(25)It is very common for patients infected by SARS-CoV-2 to present a euthyroid state, accompanied by a certain degree of decrease in serum concentrations of TSH and T4, which after infection recovered their baseline in follow-up thyroid tests.(26).

The most common presentation of hyperthyroidism is Graves' disease and does not represent an increased susceptibility to infection.(7)Interestingly, an overexpression of ACE2 was found precisely in this type of pathology.(27).

Timo

Pneumonia was 3.8 times more frequent in patients who did not have this organ along with a greater number of infected lung segments.(28)A study in mice showed that the alpha variant of SARS-CoV-2 causes thymic atrophy and was correlated with the severity of the infection.(29).

Although, a case of thymic hyperplasia has also been reported after vaccination against COVID-19 in a patient with lymphoma, that is, the histological examination showed thymic hyperplasia due to a presumed immunological reaction to the underlying viral infection.(30).

Adrenal glands

Pathophysiology

There is a theory that mentions the molecular similarity between SARS-CoV-2 proteins and Adrenocorticotropic Hormone (ACTH) and high concentrations of anti-ACTH antibodies in patients with a prolonged COVID-19 infection.(18).

The main entry route is the ACE2 receptor, which is present in the adrenal cortex with high concentration in the fascicular and reticular zones, which are responsible for producing glucocorticoids and androgens.(6)There are other proteins that facilitate the cellular absorption of the Coronavirus such as: furins, neuropilin-1, type C lectins and the scavenger receptor B type 1, another alternative is the endosomal route, which requires cathepsin L and a low pH that allows the release of endosomes.(8).

Clinical manifestations

At first, elevated serum cortisol levels can be seen in patients infected with COVID-19, subsequently, adrenocorticotropic hormone increases significantly in these patients.(18). Three months after infection, hypocortisolism (<138 nmol/L at 8am) may occur in 39.4% of patients. Many infected patients may present fatigue, postural hypotension, and cognitive impairment. However, the fatigue experienced by patients cannot be explained by insufficient adrenal function.(6).

In severe cases of this infection there is a high concentration of cortisol, however, in fatal clinical evolutions the serum levels of this hormone are low compared to survivors.(18).

Conclusions

- SARS-CoV-2 uses the angiotensin-converting enzyme 2 to enter the human cell. This enzyme is usually found in high concentrations in the lung organ, however, it can also be found in endocrine organs and therefore cause alterations in this area.
- Since the cytokine storm accompanies the clinical picture, it causes a multitude of damages in the organism, for example, some hormones such as vasopressin are released in response to certain stimuli such as hypoxia, other structures such as the anterior pituitary gland, being located outside the blood-brain barrier, are prone to infection, and in the clinical manifestations there are coagulation disorders that affect the hypothalamic-pituitary axis leading to the appearance of headaches.
- The thyroid gland has high concentrations of ACE2, whose area, in case of an increase in interleukin 6, is very vulnerable to the harmful effects of the cytokine

storm and the more severe the clinical presentation, the greater the decrease in T3, T4 and TSH.

- Pneumonia is more frequent in patients who do not have a thymus, and a greater number of infected lung segments is also evident, therefore, this favors worsening the SARS-CoV-2 infection, because the thymus tries to protect the body by producing a greater number of T lymphocytes.
- There is a molecular similarity between ACTH and COVID-19 proteins, this may influence serum ACTH concentrations during infection, many patients present postural hypotension and fatigue that cannot be explained by insufficient adrenal function.

Conflict of interest

- The authors declare that there was no conflict of interest in relation to the submitted article, since the information obtained was from freely accessible scientific evidence.

Authors' contribution statement

- Erick Zabala contributed to the critical writing of the manuscript. Dr. Andrea López reviewed the text and made necessary corrections for the publication of this research work. The authors have read and accepted the published version of this research work.

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