

ACE-2 receptor-associated COVID-19 lesions and sequelae

Lesiones y secuelas por COVID-19 asociadas al receptor ACE-2

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Abstract:

The infection by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the greatest global public health problem since the emergence of this pathogen in 2019 in China; since that time the medical and scientific community has focused on describing the pathophysiological mechanisms of the infection to offer better treatment alternatives to patients and make prognoses of the infection, however, the anatomical regions where the virus infects must be considered. The objective of this review is to describe the sites of colonization of the virus, the underlying mechanisms of injury in organs and systems and the consequences caused by the infection. For this research a literature search was performed using PubMed and Google academic databases, using the following keywords: ACE-2 receptor, coronavirus, COVID-19, and coronavirus receptors, a total of 87 publications were selected and those that were not useful for our objectives were excluded, resulting in a total of 41, which were qualitatively analyzed to be included. The exact pathophysiological mechanisms of the lesions caused by SARS-CoV-2 in various organs remain to be understood, so research efforts should continue to clarify all the damage pathways and allow the development of better preventive and therapeutic tools.

Keywords:

SARS-CoV-2 receptor, ACE-2 expression, angiotensin receptor, COVID-19

Resumen:

La infección por el nuevo síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) se ha convertido en el mayor problema de salud pública mundial desde la aparición de este patógeno en el año 2019 en China; a partir de ese momento la comunidad médica y científica se ha enfocado en describir los mecanismos fisiopatológicos de la infección para ofrecer mejores alternativas de tratamiento a los pacientes y hacer pronósticos de la infección, sin embargo, hay que considerar las regiones anatómicas donde infecta el virus. El objetivo de esta revisión es describir los sitios de colonización del virus, los mecanismos de lesión subyacentes en órganos y sistemas y las consecuencias ocasionadas por la infección. Para esta investigación se realizó una búsqueda de la literatura utilizando las bases de datos de PubMed y Google académico, empleando las siguientes palabras claves: receptor ACE-2, coronavirus, COVID-19 y receptores de coronavirus, se seleccionaron un total de 87 publicaciones se excluyeron los que fueron útiles para nuestros objetivos, resultando un total de 41, los cuales se analizaron cualitativamente para poder ser incluidos. Aún falta comprender los mecanismos fisiopatológicos exactos de las lesiones causadas por el SARS-CoV-2 en varios órganos, por lo que se deben continuar los esfuerzos en investigación para clarificar todas las vías de daño y permitir el desarrollo de mejores herramientas de prevención y terapéuticas.

Palabras Clave:

Receptor SARS-CoV-2, expresión de ACE-2, receptor de angiotensina, COVID-19

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INTRODUCTION

COVID-19 (coronavirus 19 disease), was named by the World Health Organization (WHO) to encompass the broad spectrum of clinical manifestations of such pathology produced by a coronavirus, which was reported for the first time in late 2019.¹ In Wuhan city, within Hubei province, China, the first case of atypical pneumonia emerged in a group of patients caused by a new coronavirus, SARS-CoV-2.² Since then, the infection has spread throughout the world, causing the death of more than six million people and more than 600 million infected.³ It is currently known that infected people have not only presented respiratory symptoms, but also symptoms associated with other systems of our body, such as the gastrointestinal, cardiovascular, and neurological systems, among others. This suggests that the virus can be found in different regions of our body and that it requires the presence of receptors that allow entry into the cells; in this case, it is the angiotensin-converting enzyme receptor 2 (ACE-2). This review presents the organs and tissues that can be colonized by SARS-CoV-2 and thus be able to predict the risks and sequelae that the human being can have because of COVID-19 to know the care to be taken and how to approach patients considering that they can reach other symptomatology in the future.⁴⁻⁷

METHODOLOGY

A search for articles related to COVID-19 and ACE-2 receptor was performed using PubMed and Google academic databases, using the following keywords: ACE-2 receptor, coronavirus, COVID-19, and coronavirus receptors. The following inclusion criteria were used: No publication time restriction, Spanish, English, and Portuguese languages, systematic reviews, meta-analyses, and case reports, in addition to the reference lists of those articles; a total of 87 publications were selected that had our keywords in both the title and abstract; Subsequently, we excluded those that had the keywords, but were not related to our research or were not useful to meet the objective of this work, resulting in a total of 41 publications, which were finally analyzed qualitatively using the mixed methods assessment tool (MMAT) in order to be included in this review and the information was synthesized.⁸

CORONAVIRUS DISEASE

This new disease, caused by the SARS-CoV-2 coronavirus, is transmitted through the inhalation route and directly reaches cells whose surface has the ACE-2 receptor. Although many people can become infected and show no symptoms, most of the infected population presents fever, nasal congestion, fatigue, headache, and other signs or symptoms related to the upper respiratory tract that can quickly trigger severe acute respiratory

syndrome (SARS), which is characterized by the absence of upper respiratory tract signs or symptoms, dry cough, minimal findings on chest auscultation and the presence of consolidations on chest radiographs. Although SARS-CoV-2 in the lungs contributes to severe symptoms by itself, it has been observed that in some patients this symptomatology can be more complicated, exacerbated, or intensified, mainly in people with comorbidities such as heart disease, diabetes, obesity, and asthma, although the mechanisms by which these risks increase are not understood to date, possible explanations have been described based on clinical findings, such as a higher proportion of neutrophils and lymphocytes and increased values of D-dimer and C-reactive protein.⁹⁻¹¹

PATHOPHYSIOLOGY OF SARS-CoV-2 INFECTION

The new coronavirus, which causes severe acute respiratory syndrome, is a single-stranded positive-sense RNA virus belonging to the betacoronavirus genus and is composed of four structural proteins: nucleocapsid protein (N), membrane protein (M), envelope protein (E), and spike protein (S). It shares 79% of its nucleotide sequence with SARS-CoV, the virus that caused the SARS epidemic between 2002 and 2004, with which it also shares a similar route of entry, as well as with Middle East respiratory syndrome (MERS-CoV). In order to infect our cells it uses the "S" protein by binding to the ACE-2 receptor, which is a carboxypeptidase that is part of the renin-angiotensin-aldosterone system (RAAS), whose main function is to catalyze the conversion of angiotensin I (AG 1-7) to angiotensin II (AG-2), which is biologically active through its vasoconstrictor effect and by stimulating the production of aldosterone, a hormone that increases sodium reabsorption at the level of the distal tubule of the nephron and increases potassium excretion. For its activity, this enzyme must bind to a receptor, ACE-2. Since 2003, Wen hui Li and coworkers have identified ACE-2 as a functional receptor for SARS-CoV, which allows the virus to enter host cells and cause infection. SARS-CoV-2 has a 10- to 20-fold higher affinity for this receptor, in addition to showing stronger binding, which has generated a greater infectious capacity to acquire COVID-19. The spike (S) protein of coronaviruses binds to the ACE-2 receptor and thus facilitates fusion between the cell membranes of both the host and the virus, which leads to the destruction of our cells, causing the generation of inflammatory mechanisms whose final result causes symptomatology associated with infected organs and tissues.^{2,7,12-14}

TISSUES WHERE ACE-2 RECEPTOR IS EXPRESSED

Due to the fact that people with COVID-19 present a great variability of clinical manifestations, research has been carried out trying to explain this diversity of symptoms, finding that ACE-2 is expressed not only in the lungs, but in multiple organs, which are affected by SARS-CoV-2 infection. Table 1 shows the

data extracted from the literature showing the organs and tissues whose cells have the ACE-2 receptor on their surface and the damage and symptoms caused by the viral infection.^{2,5,13}

PROBABLE SEQUELAE OF THE INFECTION

Given that the main target organ for SARS-CoV-2 infection is the lung, it is inevitable that it will be the tissue with the greatest long-term effects, such as reduced lung capacity, dyspnea, pulmonary fibrosis, and chronic lung disease.¹⁵⁻¹⁹

At the renal level, glomerular dysfunction can trigger chronic kidney disease that may require lifelong renal function replacement therapy in patients.^{5,6,9}

In the gastrointestinal tract, the gut-lung axis has been described as responsible for damage to the intestinal mucosa, possibly conferring an increased risk of inflammatory bowel disease and chronic liver disease, as well as increased injury at the

pulmonary level due to modification of the immune response by producing an unhealthy gut microbiome.²⁰⁻²²

The probable destruction of the β-cells of the islets of Langerhans in the pancreas may trigger insulin-dependent diabetes mellitus and further increase morbidity and mortality in patients.^{6,23,24}

In the central nervous system, systemic inflammation and entry of the virus through ACE-2 receptors expressed in the brain are probably responsible for a decrease in cognitive capacity, memory loss, fatigue, and neurogenic hypertension.^{6,25-27}

In the cardiovascular system, endothelial dysfunction caused by vasoconstriction due to decreased ACE-2 levels is an important risk factor for the development of acute coronary syndrome and cerebral vascular disease, so having COVID-19 would further increase the predisposition to one of these pathologies, which are among the main causes of mortality in adults and morbidity in young patients.²⁸⁻³⁰

Table 1. Tissues where ACE-2 receptor is expressed and the pathophysiological mechanisms of SARS-CoV-2.

Organs with ACE-2 receptor on their surface	Specific location	Results reported as a consequence of infection by the presence of the ACE-2 receptor.
Lungs	-Mature epithelial cells. -Type II pneumocytes. -Alveolar macrophages.	ACE-2 expression has been detected in secretory cells of the bronchial branches and on the apical surface, mainly in mature epithelial cells, i.e., in well-differentiated hair cells and type II alveolar cells. The lung tissue of coronavirus-infected patients shows distinct patterns of damage, such as diffuse alveolar damage, fibrin and collagen deposits in the alveolar space, epithelial cell desquamation, and mononuclear leukocyte infiltrates in the alveolar interstitium. Inflammation in the alveoli causes surfactant fluid to be ineffective and alveolar fluid to accumulate, which causes collapse and inefficient filling, resulting in an imbalance between ventilation and perfusion (tissue hypoxia), manifesting as dyspnea and respiratory distress in patients. ¹⁵⁻¹⁹
Kidneys	Kidneys-Apical surface of proximal tubules. -Podocytes. -Glomerulus	Angiotensin-2 exerts different functions in the body depending on the receptor to which it binds. Binding to the type 1 receptor (AT1) produces increased sympathetic nervous system activity, electrolyte reabsorption (mainly sodium), aldosterone secretion, increased water retention, and inflammation; on the other hand, binding to the type 2 receptor (AT2) generates completely opposite effects. The ACE-2 receptor is highly expressed in the apical surface area of the proximal tubules and is also localized in the glomerulus; if the number of ACE-2 is lost due to its internalization by binding to SARS-CoV-2 when it infects the cell it causes an increase in angiotensin II because it no longer binds to its unregulated ACE-2 receptor, thus leading to increased sodium reabsorption producing an increase in blood volume and consequently an increase in blood pressure figures and renal damage. Furthermore, since SARS-CoV-2 has been found in nephrin-positive cells from the kidneys of patients with COVID-19, it is hypothesized that podocytes could be direct targets for SARS-CoV-2 infection. ^{5,6,9}
Gastro intestinal tract	-Esophagus and stomach. -Liver. -Brush border of mature enterocytes.	Dan Harmer et al. demonstrated in 2002 that ACE-2 is highly expressed in the intestine, particularly in the ileum, duodenum, jejunum, cecum, and colon. Further RNA sequencing studies found that the site of highest expression is the brush border of mature enterocytes. When SARS-CoV-2 binds to the ACE-2 receptor, the host cell internalizes it causing a decrease in the expression of the latter, this leads to a decrease in the expression of the amino acid transporter B0AT1 that is present in enterocytes, which causes a decrease in the intestinal microbiota because

		the latter needs tryptophan to be able to develop; The absence of this amino acid decreases the expression of antimicrobial peptides that defend us from the colonization of pathogenic microorganisms, triggering an immune response through the release of cytokines and recruitment of neutrophils that can damage the intestinal mucosa. Experimental studies have shown that the absence of a healthy intestinal microbiome generates consequences in the preservation of the immune system, avoiding exaggerated or deficient responses to pathogens that can be harmful to other organs such as the lungs (gut-lung axis). ²⁰⁻²²
Páncreas	-Islets of Langerhans.	ACE-2 expression has been shown to be higher in islets of Langerhans (site of insulin production) and lower in exocrine cells. Daniel Batlle et al. suggested the possibility that SARS-CoV-2 could generate insulin-dependent diabetes mellitus through pancreatic β -cell depletion, there is currently insufficient evidence to determine whether COVID-19 can trigger that disease in patients. ^{6,23,24}
Brain	-Glial cells. -Neurons. -Cerebrospinal fluid.	It has been found that ACE-2 has a wide distribution at the encephalic level, specifically in glial cells, neurons, and cerebrospinal fluid. The coronavirus enters the central nervous system through the general circulation and neurons of the olfactory bulb, spreading rapidly throughout the brain and being the cause of anosmia; derived from this infection, decreased ACE-2 levels are associated with reduced baroreflex sensitivity. The RAA system plays a major role in blood pressure regulation, angiotensin-2 binding to its type 1 receptor (AT1) increases sympathetic tone, salt appetite, fluid intake, and vasopressin release; when hyperactivity is shown in this system (RAA), neurogenic arterial hypertension is triggered; when overexpression is present, all these effects are counteracted and there is even an improvement in baroreflex sensitivity; on the other hand, when ACE-2 receptor expression is decreased, these hypertensive effects are triggered. Neurological symptoms are usually very common in prolonged COVID, with fatigue and cognitive impairment being the most frequent up to 12 weeks post-infection, the possible mechanisms for this symptomatology being neuroinflammation and damage to blood vessels by coagulopathy and endothelial dysfunction leading to neuronal injury. ^{6,25-27}
Heart	-Cardiomyocytes. -Pericytes. -Fibroblasts. -Endothelial cells. -Leukocytes.	ACE-2 receptors are found in large numbers in cardiac muscle; SARS-CoV-2 infection causes injury to this organ, according to high levels of the enzymes troponin T and NT-proBNP found in patients with COVID-19; Luka Nicin et al. performed RNA sequencing in five patients with aortic stenosis, two with heart failure with reduced ejection fraction and one person with a healthy heart, finding that the ACE-2 receptor is expressed in five types of cardiac cells; in greater proportion in cardiomyocytes and pericytes and in smaller proportion in fibroblasts, endothelial cells, and leukocytes. In addition, they demonstrated that the expression of these receptors is more increased in patients with heart disease than in healthy hearts, which predisposes to endothelial damage in capillaries through entry into pericytes, triggering microcirculatory disorders. Therefore, patients with some prior cardiac disease often develop more severe coronavirus infection. ^{28,29}
Blood vessels	-Endothelial cells.	In blood vessel endothelial cells, when AG-2 is converted to AGE-1 by ACE-2, this process promotes activation of the enzyme nitric oxide synthase, producing nitric oxide and consequently dilating blood vessels; vasodilation protects endothelial function and decreases damage from inflammation. When ACE-2 levels are decreased by COVID-19, the benefits of GA-1 are lost, maintaining blood vessels with continued vasoconstriction culminating in endothelial dysfunction and inflammation. ^{6,30}
Oral cavity	-Mucosa. -Tongue epithelial cells. -Salivary glands.	ACE-2 expression has been found in some regions of the oral cavity and nasopharynx, although the mechanism of injury is unknown at this time, some clinical manifestations have been described such as non-bleeding but painful ulcers and white plaques that do not respond to antifungals on the dorsum of the tongue, in addition to symptoms similar to Kawasaki disease (erythema, dryness and bleeding of the mucosa). ^{5,6,31-33}
Bladder	-Urothelial cells of the bladder.	ACE-2 expression has been identified in urothelial cells of the bladder; in addition, some studies report lower urinary tract symptoms in patients with COVID-19: increased urinary frequency, nocturia, urgency, and urinary incontinence, which could suggest a direct lesion of the virus to this organ; however, to date this remains unknown. ^{5,18,34}
Female reproductive system	-Epithelial cells of the uterus, breast and ovary.	Angiotensin-2 is essential to maintain an adequate ovulatory cycle in women; an alteration in the distribution and levels of ACE-2 could generate abnormal uterine bleeding and endometrial hyperplasia; it is currently unknown how this pathological process would take place. ^{5,35}
Testicles	-Leydig cells. -Sertoli cells.	Studies have shown that SARS-causing viruses can be found in the testes of patients, demonstrating widespread germ cell destruction, presence of few or absent sperm in the seminiferous tubules, and leukocyte infiltration, in addition to a thickened basement membrane

in the testes, and some cases of epididymitis, orchitis-epididymitis, and scrotal infections.^{34,36-38}

Adipose tissue	ACE-2 expression has been found in adipose tissue; however, the pathophysiology and clinical implication are unknown. ^{5,38}
Thyroid gland	An association between COVID-19 and some cases of thyroiditis has been found, however, no evidence of lymphocytic infiltration or inflammation has been found in other series of studies; in addition, 50 patients with active COVID-19 underwent thyroid function tests and were found to have significantly decreased thyroid stimulating hormone (TSH) and triiodothyronine (T3) compared to healthy patients, the levels of these hormones being lower the more severe the COVID-19. ³⁹⁻⁴²

Although ACE-2 expression is reported in other tissues, it is not yet understood how the new coronavirus can injure them and generate long-term consequences. Some examples of this are in the oral cavity, Kawasaki disease-like manifestations and mouth ulcers; abnormal uterine bleeding and endometrial hyperplasia that may increase the risk of endometrial cancer; lower sperm count in men that would cause infertility and leukocyte infiltration that would culminate in testicular inflammatory disease, similar to what could happen in the thyroid gland with lymphocyte infiltration that would confer increased risk of thyroiditis and glandular dysfunction.^{5,31-42}

CONCLUSIONS

Although the exact pathophysiological mechanisms of the lesions caused by SARS-CoV-2 in various organs have yet to be understood, it is known that the common pathway of entry are the ACE-2 receptors that are expressed in variable amounts in these tissues; undoubtedly, COVID-19 is the greatest public health problem in Mexico and the world, so research efforts must continue to clarify all the damage pathways and allow the development of better prevention and therapeutic tools, thus avoiding the possible sequelae caused and the poor quality of life subsequent to this disease.

REFERENCES

- [1] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat. Microbiol.* 2020;5(4):536–44.
- [2] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet.* 2020;395(10223):470–3.
- [3] Weekly epidemiological update on COVID-19 - 25 January 2023 [Internet]. Who.int. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19--25-january-2023>.
- [4] Torrell Vallespín G, Rovira Fontanals A, Sánchez Amat M, Fernández de Sanmamed Santos MJ. Construyendo la semiología de la COVID-19: los sabios ciegos y el elefante. *Gac. Sanit.* 2022;36(5):416–24.
- [5] Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur. J. Clin. Microbiol. Infect. Dis.* 2021;40(5):905–19.
- [6] Ashraf UM, Abokor AA, Edwards JM, Waigi EW, Royfman RS, Hasan SA-M, et al. SARS-CoV-2, ACE2 expression, and systemic organ invasion. *Physiol. Genomics.* 2021;53(2):51–60.
- [7] Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat. Rev. Mol. Cell Biol.* 2022;23(1):3–30.
- [8] Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Educ. Inf.* 2018;34(4):285–91.
- [9] Simões e Silva AC, Teixeira MM. ACE inhibition, ACE2 and angiotensin-(1-7) axis in kidney and cardiac inflammation and fibrosis. *Pharmacol. Res.* 2016; 107:154–62.
- [10] Vijayanand P, Wilkins E, Woodhead M. Severe acute respiratory syndrome (SARS): a review. *Clin. Med.* 2004;4(2):152–60.
- [11] Khairy Y, Naghibi D, Moosavi A, Sardareh M, Azami-Aghdash S. Prevalence of hypertension and associated risks in hospitalized patients with COVID-19: a meta-analysis of meta-analyses with 1468 studies and 1,281,510 patients. *Syst. Rev.* 2022;11(1):242.
- [12] Iser BPM, Sliva I, Raymundo VT, Poletto MB, Schuelter-Trevisol F, Bobinski F. Definição de caso suspeito da COVID-19: uma revisão narrativa dos sinais e sintomas mais frequentes entre os casos confirmados. *Epidemiol. Serv. Saude.* 2022;29(3).
- [13] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426(6965):450–4.
- [14] Ryan PM, Caplice N. COVID-19 and relative angiotensin-converting enzyme 2 deficiency: role in disease severity and therapeutic response. *Open Heart.* 2020;7(1):e001302.
- [15] Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J. Virol.* 2005;79(23):14614–21.
- [16] Luks AM, Freer L, Grissom CK, McIntosh SE, Schoene RB, Swenson ER, et al. COVID-19 lung injury is not high altitude pulmonary edema. *High Alt. Med. Biol.* 2020;21(2):192–3.
- [17] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497–506.
- [18] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front. Med.* 2020;14(2):185–92.
- [19] Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem. Biophys. Res. Commun.* 2020;526(1):135–40.
- [20] Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett.* 2002;532(1-2):107–10.

- [21] Alibeik N, Pishgar E, Bozorgmehr R, Aghaaliakbari F, Rahimian N. Potential role of gut microbiota in patients with COVID-19, its relationship with lung axis, central nervous system (CNS) axis, and improvement with probiotic therapy. *Iran. J. Microbiol.* 2022;14(1):1-9.
- [22] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J. Infect.* 2020;80(6):607-13.
- [23] Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010;47(3):193-9.
- [24] Batlle D, Jose Soler M, Ye M. ACE2 and Diabetes: ACE of ACEs? *Diabetes.* 2010;59(12):2994-6.
- [25] Baig AM. Counting the neurological cost of COVID-19. *Nat. Rev. Neurol.* 2022;18(1):5-6.
- [26] Xia H, Sriramula S, Chhabra KH, Lazartigues E. Brain angiotensin-converting enzyme type 2 shedding contributes to the development of neurogenic hypertension. *Circ. Res.* 2013;113(9):1087-96.
- [27] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat. Rev. Microbiol.* 2023;21(3):133-46.
- [28] Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur. Heart J.* 2020;41(19):1804-6.
- [29] Santoso A, Pranata R, Wibowo A, Al-Farabi MJ, Huang I, Antariksa B. Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: A meta-analysis. *Am. J. Emerg. Med.* 2021;44:352-7.
- [30] Rabelo LA, Todiras M, Nunes-Souza V, Qadri F, Szijsártó IA, Gollasch M, et al. Genetic Deletion of ACE2 Induces Vascular Dysfunction in C57BL/6 Mice: Role of Nitric Oxide Imbalance and Oxidative Stress. *PLoS ONE.* 2016;11(4):e0150255.
- [31] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int. J. Oral Sci.* 2020;12(1):8.
- [32] Paradowska-Stolarz A. Oral manifestations of COVID-19: Brief review. *Dent. Med Probl.* 2021;58(1):123-6.
- [33] Pastrian-Soto G, Pastrian-Soto G. Presencia y Expresión del Receptor ACE2 (Target de SARS-CoV-2) en Tejidos Humanos y Cavidad Oral. Posibles Rutas de Infección en Órganos Orales. *Int. J. Odontostomatol.* 2020;14(4):501-7.
- [34] Tristão LS, Bresler R, Modesto VA, Fernandes R de C, Bernardo WM. Urological complications of COVID-19: a systematic review. *Int. Braz. J. Urol.* 2023;49(1):24-40.
- [35] Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Mol. Hum. Reprod.* 2020;26(6):367-73.
- [36] Douglas GC, O'Bryan MK, Hedger MP, Lee DKL, Yarski MA, Smith AI, et al. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult leydig cells of the testis. *Endocrinology.* 2004;145(10):4703-11.
- [37] Wang Z, Xu X. ScRNA-seq Profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells. *Cells.* 2020;9(4):920.
- [38] Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, et al. Orchitis: A complication of severe acute respiratory syndrome (SARS). *Biol. Reprod.* 2006;74(2):410-6.
- [39] Macedo S, Pestana A, Santos L, Neves C, Guimarães S, Duarte-Neto A, et al. Detection of SARS-CoV-2 infection in thyroid follicular cells from a COVID-19 autopsy series. *Eur. Thyroid J.* 2022;11(4).
- [40] Salamanna F, Maglio M, Landini MP, Fini M. Body Localization of ACE-2: On the trail of the Keyhole of SARS-CoV-2. *Front. Med.* 2020;7:59445.
- [41] Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST, et al. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. *J. Endocrinol. Invest.* 2021;44(5):1085-90.
- [42] Paz-Ibarra JL. Glándula tiroideas, ¿otra víctima de la COVID-19? Reporte de caso. *Rev. Mex. Endocrinol. Metabol. Nut.* 2021;8(3).