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ACE2 in male genitourinary and endocrine systems: Does COVID-19 really affect these systems?

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Summary. The virus that causes COVID-19 (Corona Virus Disease 2019), SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), is causing a worldwide pandemic, posing a substantial threat to human health. Patients show signs of pneumonia, ARDS, shock, acute cardiac injury, acute kidney injury and other complications. The SARS-CoV-2 receptor is angiotensin converting enzyme 2 (ACE2), which is an important component of the renin-angiotensin system (RAS). In addition, TMPRSS2 or other cofactors are needed to allow the virus to enter the host. Clinical patients have exhibited varying degrees of genitourinary and endocrine system damage, and some studies have also reported potential risks to the genitourinary and endocrine systems. This article reviews the mechanism underlying SARS-CoV-2 infection and the current studies on the male genitourinary and endocrine systems and proposes that more attention should be directed towards human reproductive and endocrine health during the SARS-CoV-2 epidemic.

Key words: COVID-19, SARS-CoV-2, ACE2, Male genitourinary system, Endocrine system

Introduction

At the end of 2019, a new type of pneumonia-related coronavirus, SARS-CoV-2, was identified in Wuhan, Hubei Province, China. Due to its transmission through droplets and direct contact, the virus has a long incubation period and a high mortality rate in severe cases, and the epidemic has rapidly spread around the world (Chan et al., 2020; Lai et al., 2020; Li et al., 2020; Yang et al., 2020); on March 11, 2020, COVID-19 was declared a global pandemic (Eurosurveillance, 2020). Patients with SARS-CoV-2 infection showed signs of pneumonia. In addition to lung injury, some patients also have complications such as ARDS, shock, acute cardiac injury, and acute kidney injury (Huang et al., 2020). SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as the host receptor. Hydrolytic enzymes (such as TMPRSS2) hydrolyse the spike (S) protein, allowing RNA to bind to the domain of the SARS-CoV-2 spike protein thus completing the virus's invasion of host cells. Therefore, the distribution of ACE2 and its cofactors may indicate the vulnerability of different human organs to SARS-CoV-2 infection (Zou et al., 2020a,b). ACE2 protein abundance analysis showed that ACE2 protein was mainly expressed in the small intestine, kidney, gallbladder and testis, and the human secretory proteome showed that the average concentration of ACE2 protein in male plasma was higher than that in female plasma, suggesting that the male genitourinary system may be a high-risk system in COVID-19 (Wang et al., 2020c). The incidence of AKI in COVID-19 is high and is correlated with mortality (Cheng et al., 2020; Zheng et al., 2020), suggesting that the virus is harmful to the kidneys. Moreover, testes from deceased COVID-19 patients have been reported to show obvious damage to seminiferous tubules, decreased Leydig cells and mild lymphocytic inflammation (Yang et al., 2020), suggesting that COVID-19 may damage the male reproductive system and may even compromise semen transmission (Cardona Maya et al., 2020). At the same time, evidence indicates that older male patients are most likely to be infected with SARS-CoV-2 (Chen et al., 2020). Therefore, damage to the male genitourinary system by COVID-19 warrants more attention.

Moreover, an increasing number of studies have focused on changes in the endocrine system in patients. Although studies are still limited, the distribution of ACE2 shows that ACE2 is richly expressed in many endocrine glands (Hamming et al., 2004; Wang et al., 2020c). Therefore, endocrine organs may be affected by COVID-19 (Gavriatopoulou et al., 2020). What's more, for SARS-CoV-1(Severe Acute Respiratory Syndrome Coronavirus), which has a high degree of similarity with SARS-CoV-2 (more than 85%) (Gralinski and Menachery, 2020), cadaver studies showed that a variety of endocrine glands (such as the hypothalamus, hypophysis, testis, thyroid gland, parathyroid gland,

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pituitary gland and endocrine pancreas) were damaged to varying degrees, suggesting that endocrine system damage may occur in COVID-19 patients.

The infection mechanism of SARS-CoV-2

ACE2 (angiotensin converting enzyme 2) has been confirmed to be a receptor for SARS-CoV-2. ACE2 is an important part of the renin–angiotensin system (RAS). The RAS is an important humoral regulation system composed of a series of peptide hormones and corresponding enzymes. Its main function is to regulate and maintain blood pressure, water and electrolyte balances and the relative stability of the human body. As shown in Fig. 1, angiotensinogen produced in the liver is cleaved by renin produced in the kidney to produce angiotensin I (Ang I) (Moon, 2013). Then, Ang I is cleaved into angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II acts on the receptor to cause vasoconstriction, oxidative stress, proliferative stress, inflammation, profibrotic stress, hypertrophy, etc., which can easily lead to injury and disease (Wang et al., 2020a,b). Another pathway is hydrolysis by ACE2 (a homologue of ACE) to produce Ang-(1-9) and Ang-(1-7), which act on other receptors, and their effects are the opposite of those of the other pathway, thus playing a protective role (Santos et al., 2019). SARS-CoV-2 can recognize and bind to ACE2 and therefore promotes the ACE/AngII/AT1R axis in the RAS, inhibits the ACE2/Ang-(1-7)/Mas1 axis, and produces inflammation, which may be the cause of COVID-19.

Furthermore, for SARS-CoV-2 to enter host cells, in addition to identifying the ACE2 receptor, the virus also requires the cell to have an enzyme, usually TMPRSS2 (Glowacka et al., 2011; Iwata-Yoshikawa et al., 2019; Nowak et al., 2020; Zang et al., 2020), which hydrolyses the spike (S) protein and facilitates entry of the virus. The S protein on the coronavirus is the main determinant of host cell invasion. Proteolytic cleavage of the S protein produces S1 (the N-terminal region of the S protein responsible for receptor binding) and S2 (the transmembrane C-terminal region of the S protein that promotes membrane fusion). The lysis step usually enables the fusion function of the S protein because it helps release the fusion peptide for insertion into the target cell membrane. (Millet and Whittaker, 2015) Therefore, the host range and cell/tissue tropism of the coronavirus are considered to depend on the S protein binding to the host cell receptor and proteolytic cleavage of the S protein. (Jackson et al., 2022)

In addition, other receptors or cofactors can play a compensatory role. As shown in Table 1, CD147 (Chen et al., 2005; Wang et al., 2020b; Ulrich and Pillat, 2020), ADAM17 (Palau et al., 2020), furin (Zhou et al., 2020a), AXL (Bohan et al., 2021; Wang et al., 2021), CD209L/L-SIGN and CD209/DC-SIGN (Amraei et al., 2015), may also have roles in the invasion of host cells by COVID-19. There is a direct interaction between CD147 and SARS-CoV-2 spike protein, which mediates host cell infection. Overexpression of CD147 in host cells may promote more virus entry (Wang et al., 2020b) ADAM17 inhibition may play a protective role on COVID-19, suggesting that ADAM17 may play a role in the invasion of SARS-CoV-2 (Palau et al., 2020). Furin is thought to have a similar function to TMPRSS2 (Zhou et al., 2020a). AXL can mediate ACE2-independent SARS-CoV-2 entry and infection, and promote virus adsorption to enhance SARS-CoV-2 infection (Bohan et al., 2021; Wang et al., 2021). CD209L/L-SIGN and

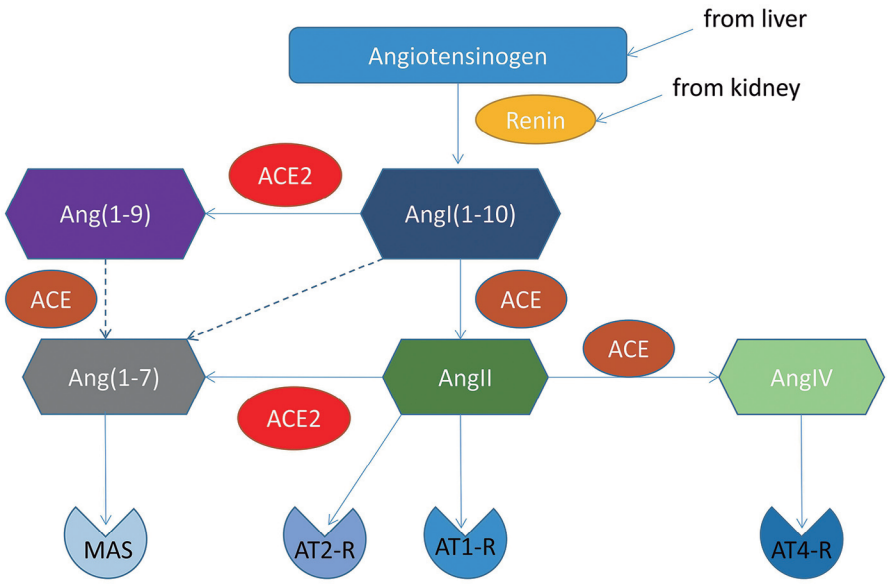

Fig. 1. The function of ACE2 in the renin-angiotensin system. Angiotensinogen is produced by the liver and then cleaved by renin produced by the kidney to generate angiotensin (Ang(1–10)). The resulting Ang is cleaved by ACE to AngII and AngiV, which bind to receptors AT1-R and AT4-R, respectively, leading to vasoconstriction, oxidative stress, proliferation, inflammation, fibrosis, hypertrophy, etc. Ang(1-10) and AngII can be hydrolysed into Ang(1-9) and Ang(1-7) by ACE2, respectively, and Ang(1-9) can also be hydrolysed into Ang(1-7) by ACE. Ang(1-7) binds to the receptor MAS, producing the opposite effect. AngII also binds to the receptor AT2-R, similar to the MAS axis. (The solid line indicates that it has been confirmed, and the dotted line indicates that it has been proposed by some studies, but it is not confirmed).

CD209/DC-SIGN can be used as alternative receptors other than ACE2 receptor (Amraei et al., 2021).

Through single-cell sequencing analysis of the ACE2 receptor and its main cofactor TMPRSS2, we identified organs and tissues with a higher risk of infection. Studies have found that the gallbladder, fallopian tubes, nose, heart, small intestine, large intestine, oesophagus, brain, testes, and kidneys are high-risk organs with high expression levels of ACE2 (Wang et al., 2020c) and TMPRSS2. The respiratory system, digestive system and urinary system are high-risk systems for SARS-CoV-2 infection (Qi et al., 2021), which is basically consistent with the clinical presentation. Patients infected with SARS-CoV-2 often have fever and cough. Common complications include acute respiratory distress syndrome (ARDS), RNAaemia, acute cardiac injury, etc., as well as acute kidney injury (AKI) (Huang et al., 2020). Studies have found that acute kidney injury has a higher incidence and is related to mortality (Cheng et al., 2020). However, many clinical studies have neglected viral damage to the male reproductive system, especially the testes, even though testicular damage has been clinically shown to occur in patients (Yang et al., 2020). The possible reason is that pneumonia and complications such as ARDS and AKI are high-risk conditions with high mortality rates, which attracts the attention of clinicians (Huang et al., 2020). However, more attention should be directed towards damage to the reproductive system, especially the testes, which is related to long-term quality of life and may have a long-term impact on humans.

In addition to SARS-CoV-2 directly attacking ACE2 receptor expressing cells, there are other mechanisms of tissue damage. COVID-19 can produce a systemic inflammatory response involving extrapulmonary organs. The inflammatory storm produced by SARS-CoV-2 has been proved to cause damage in a variety of organs. Immune related diseases of patients with COVID-19 include proximal tubular dysfunction, glomerulonephritis, subclinical hypothyroidism, acute pancreatis, etc., which also suggest that SARS-CoV-2 can damage human genitourinary and endocrine systems through inflammatory reaction (Ramos-Casals et al., 2021).

Table 1. Coronavirus entry related substances.

Receptor name	Function	Location	Reference
ACE2	SARS-CoV and SARS-CoV-2 receptor, the entry receptor	Lung, heart, esophagus, kidney, bladder, and ileum, and located specific cell types (i.e., type II alveolar cells (AT2), myocardial cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells)	Li et al., 2003
TMPRSS2	Prime S protein to let Coronavirus enter	In humans, TMPRSS2 is expressed widely in epithelial tissues, including those lining the upper airways, bronchi, and lung	Glowacka et al., 2011
CD147	Promote the entry of SARS-CoV into host cells; can interact with the S protein. Bind SARS-CoV-2's Spike protein (SP) and mediate viral invasion and dissemination of virus among other cells. We Sstill don't know if CD147 acts as a co-receptor, a secondary receptor or an equally important new receptor	Located mainly in the cytomembrane, and a small amount of cytoplasm was appeared	Chen et al., 2005
ADAM17	Compete with TMPRSS2 for ACE2 processing, but cannot let Coronavirus enter	Ubiquitous	Heurich et al., 2014
Furin	Cleave S protein to let Coronavirus enter	Liver and lung are high, and the esophagus, small intestine, colon, thyroid gland, and kidney also have a high level	Li et al., 2020a-c
AXL	Mediate ACE2-independent entry and infection of SARS-CoV-2 and promote virus adsorption to enhance sars-cov-2 infection	Ubiquitous	Bohan et al., 2021; Wang et al., 2021
CD209L/L-SIGN and CD209/DC-SIGN	As an alternative receptor to mediate the entry of sars-cov-2 into host cells	CD209L is highly expressed in renal proximal epithelial cells, alveolar type II epithelial cells, endothelial cells of blood vessels, lungs, liver and lymph nodes. CD209 is mainly expressed in tissue-resident macrophages, dendritic cells and B cells	Amraei ey al., 2021

The effects of COVID-19 on the male genitourinary system

Single-cell transcriptomes (Wang and Xu, 2020; Qi et al., 2021) showed that ACE2 receptors are highly expressed in the testes and are mainly enriched in spermatogonia and Leydig and Sertoli cells (Fan et al., 2021), indicating that the testis may be one of the main targets of SARS-CoV-2. In addition, pscRNA analysis (Zhou et al., 2020b) of the expression of ACE2, the SARS-CoV-2 receptor, and the cofactors TMPRSS2 and furin at the in situ single-cell level also showed that the testis might be a high-risk organ.

Moreover, ACE2 is also expressed in the kidney (Qi et al., 2021). Acute kidney injury (AKI) is a common manifestation in patients with SARS-CoV-2 infection (Cheng et al., 2020; Huang et al., 2020; Pei et al., 2020; Zheng et al., 2020) and is associated with histological changes in acute renal tubular injury (ATI), suggesting that the kidney can be one of the major organs involved in SARS-CoV-2 infection.

Clinical phenomena

In SARS-CoV-2 patients, the hospitalization rate and mortality rate among males are slightly higher than those among females (Chakravarty et al., 2020; Gebhard et al., 2020). SARS-CoV-2 has a high degree of similarity with SARS-CoV-1 (above 85%) (Gralinski and Menachery, 2020). Previous studies have found that SARS-CoV-1 patients show complications of orchitis (Xu et al., 2006), suggesting that SARS-CoV-2 may also threaten the male reproductive system. Moreover, studies have shown that sex hormone secretion is abnormal in COVID-19 patients, and the testicular cells of patients infected with SARS-CoV-2 have revealed inflammatory infiltration in the seminiferous tubules, IgG deposition in the seminiferous epithelium, and degenerated germ cells, Leydig cells and Sertoli cells (Achua et al., 2021; Ma et al., 2021). Middle-aged and elderly men are more likely to be infected and have a higher mortality rate (Adhikari et al., 2020; Chen et al., 2020), which is basically consistent with the peak expression of ACE2 receptors at approximately 30 years old (Shen et al., 2020). Colour Doppler ultrasound results show that even in the absence of testicular discomfort in male patients with mild to moderate COVID-19, epididymitis may be present, which may cause fertility complications (Carneiro et al., 2021). Pathological studies have also shown that the testes from COVID-19 patients showed obvious seminiferous tube damage, decreased Leydig cells and mild lymphocytic inflammation (Yang et al., 2020a). SARS-CoV-2 is not detected in the semen of most clinical patients (Yang et al., 2020a). Other studies have also reported that SARS-CoV-2 was detected in the semen of COVID-19 patients, even in those who had recovered (Li et al., 2020b). However, this result is still very controversial because the number of samples in the study was too small, and testing may have been inconsistent (Massarotti et al., 2021). In addition, most studies have shown that SARS-CoV-2 is not detected in the semen of clinical patients (Kayaaslan et al., 2020; Song et al., 2020; Pan et al., 2020; Lisco et al., 2021). The latest research found that there is a negative correlation between ACE-2 receptor levels and spermatogenesis, which indicates the possible mechanism of how COVID-19 causes infertility (Achua et al., 2021). Autopsy of the cadaveric testicles showed that SARS-CoV-2 infection significantly changed the spatial arrangement of testicular cells and significantly reduced the number of supporting cells. In addition, the protein expression of occlusion, claudin-11 and connexin-43 was significantly reduced. In addition, compared with the control group, we also observed a significant increase in the protein expression of CD68, TNF-α, and IL1-β in the testis of the COVID-19 group. (Peirouvi et al., 2021) This indicates that SARS-CoV-2 can induce the up-regulation of pro-inflammatory cytokines and down-regulation of BTB connexin, which destroys BTB and ultimately impairs spermatogenesis. However, the above evidence is not enough to directly explain the direct attack and damage of SARS-CoV-2 on testis, but simply suggests that there may be related risks.

Several methods have been used to determine whether SARS-CoV-2 has infected the kidney, and the amount of viral RNA detected in the kidney is usually several orders of magnitude lower than that in the lungs of the same patient. The overall detection rate of SARS-CoV-2 in urine samples was 4.5%, and the estimated frequency of viral shedding in a meta-analysis was 1.18%. The urinary viral load was lower than the loads in rectal or oropharyngeal samples in most reports, and in adult patients, SARS-CoV-2 shedding was usually detected in the urine of patients with moderate to severe disease (Kashi et al., 2020). Renal SARS-CoV-2 RT-PCR was positive more frequently in autopsy patients with AKI than in autopsy patients without AKI (43%), and SARS-CoV-2 was isolated from the renal tissue of one autopsy patient (Braun et al., 2020), which suggested the possibility of SARS-CoV-2 infection of the kidney. Acute tubule injury (ATI) is the most common renal morphology in COVID-19 autopsies (Bradley et al., 2020; Braun et al., 2020; Hanley et al., 2020; Puelles et al., 2020; Schurink et al., 2020), and biopsies from COVID-19 patients have shown that glomerular collapse is a common cause of renal failure and proteinuria, with more than half of biopsies showing podocytosis. Most biopsies show collapsing glomerulopathy (Smith and Akilesh, 2021). Autopsy studies of kidneys and biopsies have elucidated the mechanisms underlying some of the major pathologies associated with COVID-19, namely, ATI and glomerular collapse disorder. However, diagnosing ATI at autopsy is challenging, and distinguishing between premortem tubular damage and autolysis occurring in the postmortem septum is difficult. In addition, the degree of tubular injury does not always correlate with the severity

of AKI (Valk and Bugiani, 2020), and intrinsic renal injury may not account for all renal insufficiency in patients who die from COVID-19 (Smith and Akilesh, 2021). Whether SARS-CoV-2 infection causes kidney disease, exacerbates an underlying disease, or is simply coincidental is unclear. In fact, little evidence supports substantial or frequent renal infection with SARS-CoV-2.

Possible reasons

ACE2 receptors are abundant in the testes (Zou et al., 2020), but ACE2 and TMPRSS2 coexpression is almost absent in the cells of the testes. In addition to the ACE2 receptor for SARS-CoV-2 entry into host cells, TMPRSS2 or an enzyme with the same effect is also required. Therefore, in the testes, the possibility of SARS-CoV-2 directly infecting host cells is low, which may also explain why SARS-CoV-2 is basically not detected in semen. However, inflammation and parenchymal damage are evident in the testes, but the mechanism is still not clear. The ACE2 receptor may be recognized by SARS-CoV-2, and the virus may bind to the receptor to cause its downregulation, which promotes the ACE/AngII/AT1R axis in the RAS and suppresses the ACE2/Ang-(1-7)/Mas1 axis, thereby promoting vasoconstriction, oxidative stress, proliferative stress, inflammation, profibrotic stress, hypertrophy, etc. (Fig. 1). In addition, ischaemia reperfusion injury, drug injury and other complications may occur (Ning et al., 2020). The most common hypothesis to date is testicular degeneration due to the indirect effect of the inflammatory environment, which causes the testicular temperature to increase. Persistent fever and secondary autoimmune reactions leading to autoimmune orchitis (Xu et al., 2000) are the main causes of male reproductive system damage, and fever and respiratory symptoms are also the most common clinical symptoms of COVID-19 (Guan et al., 2020), which may indirectly contribute to testicular dysfunction. The latest research suggests that SARS-Cov-2 may have a damaging effect on the blood testis barrier (Peirouvi et al., 2021), which may cause serious and long-term damage to male reproduction. But we still doubt this, because more and more direct evidence is lacking.

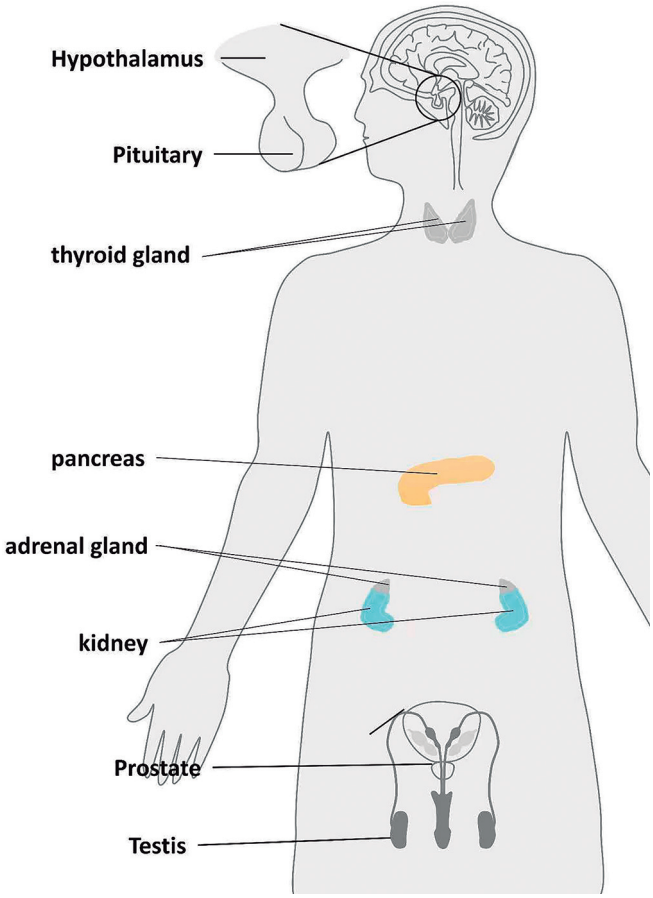

Fig. 2. Possible organs involved in the genitourinary and endocrine systems. According to current clinical research and mechanistic research, this figure summarizes the high-risk organs in the genitourinary and endocrine systems of COVID-19 patients. The kidney has been confirmed to be the main organ involved, and a positive correlation exists between acute kidney injury and mortality. The testes, prostate, adrenal gland, thyroid gland, pituitary gland, hypothalamus and other organs may also be high-risk organs in SARS-CoV-2 infection according to varying degrees of evidence for each.

Regarding whether SARS-CoV-2 is present in semen, most tested cases show negative results (Song et al., 2020), the proportion of positive cases is not high, and problems such as irregularities in the test may occur, or patients may have reproductive diseases before they are infected with the virus that cause viruses to enter semen; these possibilities require more rigorous studies with larger sample sizes.

Moreover, some studies have shown that TMPRSS2 is regulated by androgens. TMPRSS2 is highly expressed in prostate cancer, and TMPRSS2 expression increases in response to androgens through direct regulation of transcription by androgen receptor (AR) (Lucas et al., 2014). Patients receiving androgen deprivation therapy (ADT) have a lower incidence of prostate cancer. (Montopoli et al., 2020) Similarly, among patients hospitalized with COVID-19, men who had taken antiandrogens for at least 6 months prior to admission had a lower rate of admission to intensive care units. (Goren et al., 2020) Inhibitors of bromodomain and extraterminal domain (BET) proteins that directly target AR decrease the expression of TMPRSS2 and ACE2 (Asangani et al., 2014). More importantly, AR and BET antagonists can reduce SARS-CoV-2 replication (Qiao et al., 2020), which may explain why males have higher rates of hospitalization and mortality than females (Chakravarty et al., 2020; Gebhard et al., 2020).

For the kidney, the significance of a positive RT-PCR result is uncertain, and whether the RNA detected

represents infectious viral particles or noninfectious viral RNA, which may represent excess nucleic acid or degradation products generated at other sites of infection, is not clear. The cause of clinical kidney injury is currently speculated to be caused by direct infection of kidney cells or indirectly through pulmonary infection, or in "hit and run" mode, kidney infection may be an early cause of progressive kidney damage. When the injury is clinically obvious, the virus has been cleared from the tissue (Smith and Akilesh, 2021). SARS-CoV-1 has been shown to be able to infect renal cells in vitro (Kaye, 2006). So someone think that SARS-CoV-2, which is very similar to SARS-CoV-1, has the potential for direct infection, but there is still no direct evidence. The presence of viral fragments in urine (Mei et al., 2020) indicates that coronavirus may directly interact with renal tubules, and the expression pattern of ACE2 is limited to proximal renal tubular cells (Chu et al., 2005; Soler et al., 2013), so SARS-CoV-2 is likely to be directly toxic to renal tubules (Ahmadian et al., 2020). This point may require our attention. In general, we still need more research to determine the mechanism by which SARS-CoV-2 damages the kidney, which is also of great importance for clinical treatment and prevention.

The effects of COVID-19 on the endocrine system

Studies on the effect of COVID-19 on endocrine organs are limited, but the distribution of ACE2 shows that ACE2 is highly expressed in many endocrine glands (Hamming et al., 2004; Wang et al., 2020a-c; Coperchini et al., 2021; Rotondi et al., 2021). Therefore, endocrine organs may be involved in COVID-19 (Gavriatopoulou et al., 2020). The expression pattern of ACE2 is consistent with pathological studies conducted in patients infected with SARS-CoV-1 or SARS-CoV-2 showing varying degrees of endocrine tissue damage, including direct cell damage due to virus entry and replication, vasculitis, arterial and venule thrombosis, hypoxic cell damage, subsequent immune responses and cytokine storms (Ding et al., 2003; Guo et al., 2008).

Impairment of the glucocorticoid response in COVID-19 has been reported, and the adrenal cortical response is impaired in patients infected with SARS-CoV-2. Plasma cortisol and adrenocorticotropic hormone (ACTH) levels are consistent with central adrenal insufficiency in a large proportion of patients (Alzahrani et al., 2021).

ACE2 is also highly expressed in the hypothalamus (Santos et al., 2019), and recent studies have shown that hypothalamic miRNAs (small nucleotides that control gene expression regulation at the translation level) have binding sites and strong binding ability to ACE2 and transmembrane serine proteinase 2 (TMPRSS2) (Mukhopadhyay and Mussa, 2020). The ACE-AAI-AT1R axis is hyperactive in the hypothalamus, where levels of the ACE2 protein are typically low, rendering it more prone to dysfunction. In addition, both the lateral and posterior hypothalamus have been shown to be involved in the central regulation of respiratory activity coordination (Li and Li, 2013). Therefore, a viral attack on the hypothalamus can have a fatal effect. Respiratory distress is also a major feature of COVID-19 patients (Huang et al., 2020), which may suggest a possible attack on the hypothalamus.

Studies have found that SARS-CoV-2 is present in the cerebrospinal fluid of patients with COVID-19, suggesting that SARS-CoV-2 spreads in the central nervous system (Zhou et al., 2020a,b). Therefore, we can speculate that in the acute phase of SARS-CoV-2 infection, the virus may be able to cross the blood-brain barrier into the CNS and spread to the hypophysis. Moreover, abnormal endocrine function is evident in patients with SARS-CoV-1, and some patients still show varying degrees of hypocortisolaemia and clear central hypocortisolism as long as one year after recovery from SARS (Leow et al., 2005). All these results suggest that SARS-CoV-2 may pose a threat to the hypothalamus and hypophysis.

There has been evidence that mRNA encoding ACE2 receptor is expressed in thyroid follicular cells, making it a potential entry target for SARS-CoV-2 (Rotondi et al., 2021). Moreover, another study found increased ACE2 mRNA levels in primary thyroid cell cultures treated with IFN-γor TNF-α, which leads to the hypothesis that elevated levels of pro-inflammatory cytokines can promote virus entry into cells by further increasing ACE2 expression (Coperchini et al., 2021). De Quervain's subacute thyroiditis is caused by thyroid infection with SARS-CoV-2, which can be either a clinical manifestation or a complication of COVID-19. SARS-CoV-2 can also cause other thyroid diseases. The cause of subacute thyroiditis is thought to be a direct effect of SARS-CoV-2 on thyroid cells due to its utilization of the ACE2 receptor and subsequent inflammatory responses, apoptosis, and activation of the hypothalamic-pituitary central mechanism. The clinical presentation of subacute thyroiditis in patients with COVID-19 varies and has not been adequately assessed. A study suggests that it may be masked by severe damage to other organs, suggesting a much higher true incidence. (Aleksandrov et al., 2021) However, several recently published studies suggest that the role of COVID-19 in inducing subacute thyroiditis may have been overestimated (Pirola et al., 2021; Trimboli et al., 2021a,b). Subacute thyroiditis is simply a rare complication of COVID-19 (Trimboli et al., 2021a,b)

In addition, cadaver studies of SARS patients have shown that the parathyroid gland, pituitary gland, endocrine pancreas, and especially the adrenal gland and testes may be damaged by different mechanisms (direct injury by SARS-CoV, inflammation, vascular disorder and an autoimmune response) (Parolin et al., 2020). However, further studies on SARS-CoV-2 are still lacking. Similar receptors and similar viruses suggest that these endocrine glands may be attacked by SARS-CoV-2.

Finally, although diabetes does not increase the risk of SARS-CoV-2 infection, it significantly increases the severity and associated mortality of COVID-19. These results are mediated by hyperglycemia and glucose fluctuations, expression of Furin protein and ACE2 receptor, production of ACE2 autoantibodies, imbalance of immune and inflammatory pathways, diabetes-related complications, and diabetic lung injury. (Xie et al., 2021) Moreover, studies have shown that pancreatic beta cells express ACE2 and related entry factors (TMPRSS2, etc.), and it has been demonstrated that SARS-CoV-2 infection reduces pancreatic insulin level and secretion and induces β cell apoptosis (Wu et al., 2021). Acute pancreatitis has also been reported as an immune related disease in patients with COVID-19. (Ramos-Casals et al., 2021).

However, the sample size of the above clinical data is small, and there is no direct evidence that SARS-CoV-2 directly attacks the above endocrine organs. Not only that, but transient central hypogonadism occurs during acute illness, which resolves spontaneously over time, making it uncertain that SARS-CoV-2 causes endocrine system damage.

Discussion

Fever (68%) and cough (60%) are common symptoms in patients infected with SARS-CoV-2, indicating that SARS-CoV-2 mainly affects the respiratory system, and the main affected organ is the lung (Li et al., 2021). Common complications include dyspnea, pneumonia, acute respiratory distress, acute myocardial infarction, etc., suggesting the involvement of other organs of the respiratory system such as the nose, bronchi, and other systems such as the cardiovascular system (Ochani et al., 2021). These organs basically showed high expression of ACE2 (Wang and Xu, 2020; Qi et al., 2021). This article mainly reviews the reported clinical involvement of the male genitourinary and endocrine systems in COVID-19, suggesting that there may be risks, but it is uncertain.

When the COVID-19 outbreak began, the mechanism underlying SARS-CoV-2 invasion was unknown, but we soon discovered the ACE2 receptor, and research on the distribution of the ACE2 receptor rapidly increased. Then, we found that SARS-CoV-2 not only requires the ACE2 receptor to enter host cells but also needs cofactors such as TMPRSS2 (Glowacka et al., 2011; Iwata-Yoshikawa et al., 2019; Nowak et al., 2020; Zang et al., 2020a,b). Currently, we are focusing more on these two factors and exploring possible high-risk organs through the coexpression of these two factors. However, studies have shown that other factors may compensate for the lack of TMPRSS2 in cells, such as CD147 (Chen et al., 2005; Wang et al., 2020a-c; Ulrich and Pillat, 2020), suggesting possible omissions in current screening methods. The effects of other factors on SARS-CoV-2 entry into host cells and the mechanism of action still need greater consideration and more research.

Although respiratory droplets and close contact are thought to be the main routes of transmission, the possibility of aerosol transmission in a relatively closed environment remains. We can detect the nucleic acid of this novel coronavirus in nasopharyngeal swabs, sputum and other lower respiratory tract secretions, blood, faeces, urine and so on, but whether it is present in semen has not been confirmed, which highlights the potential threat of SARS-CoV-2 infection in studies involving semen. Theoretically, given that semen is discharged from the same channel as urine, semen is a possible vector for the virus, and precautions should be taken in studies involving semen in andrology laboratories (Du et al., 2020), in vitro fertilization laboratories (Choucair and Hourani, 2020), etc., to reduce the risk of infection during COVID-19 outbreaks.

Moreover, the ACE2-Ang (1-7)-Mas axis in the RAS has been shown to play a protective role in erectile function (da Costa Gonçalves et al., 2007; Fraga-Silva et al., 2015) and is involved in the regulation of spermatogenesis (Leal et al., 2009; Reis et al., 2010), affecting sperm motility, androgen metabolism (Xu et al., 2007) and prostate disease (Domińska et al., 2018; Wang and Liu, 2020), indicating that male patients with COVID-19 face a threat to their reproductive health, which may cause irreversible changes, and this problem requires more attention for prevention. Testicular injury in male patients with COVID-19 may still require long-term follow-up monitoring, including colour Doppler ultrasound examination, routine semen analysis, reproductive hormone examination, and other sperm function examinations (Ning et al., 2020).

On this basis, we may also be alert to sexual transmission of SARS-CoV-2. Although SARS-CoV-2 is largely absent in testicular and semen samples, it has been shown to cause histological changes and sex hormone disturbances that are compatible with orchitis. TMPRSS2 is upregulated in prostate cancer, which supports tumour progression, and such patients may have a higher risk of SARS-CoV-2 infection (Aleksandrov et al., 2021). Moreover, SARS-CoV-2 has been detected in urine (which is discharged from the same channel as semen); therefore, both asymptomatic infected and recovered patients need to be aware of the possible risk of sexual transmission.

In terms of the infection mechanism of SARS-CoV-2, severe cytokine storms may cause orchitis and simultaneously cause blood-testis barrier (BTB) damage. SARS-CoV-2 may also destroy the BTB by down-regulating junctional proteins of the BTB (Peirouvi et al., 2021), similar to the mumps virus (Wu et al., 2019) and the coronavirus MuV (Bleau et al., 2015). If such injuries truly exist, we shall focus on whether there is irreversible damage to the human reproductive system, but the possibility seems frankly very low. In addition, the medication used during treatment may also affect the male genitourinary system, but studies have shown that COVID-19 and its treatment with favipiravir and

hydroxychloroquine will not affect spermatogenesis and serum androgen levels in the long term (Gul et al., 2021).

AKI is a common complication in patients with COVID-19 (Cheng et al., 2020; Pei et al., 2020) and has been found to be associated with the clinical mortality of COVID-19 (Cheng et al., 2020; Huang et al., 2020; Zheng et al., 2020). The kidneys have a very important function in the urinary system. The kidneys excrete metabolites and harmful substances from the body and maintain body water homeostasis, electrolyte levels, and the acid-base balance of important organs. SARS-CoV-2-induced damage to the kidneys, especially irreversible damage, can cause extremely serious and even life-threatening effects on the human body, indicating that the impact of SARS-CoV-2 on the kidneys is very important not only during active infection but also after recovery. However, the mechanism of renal injury caused by SARS-CoV-2 is still not clear, the current detection method still has considerable limitations, and many studies lack negative control patients (Smith and Akilesh, 2021). Therefore, more rigorous studies on the relationship between the kidneys and SARS-CoV-2 infection are urgently needed.

Many hormones secreted by the endocrine system have a global impact on the body. To maintain the balance of the main hormones in the body, the complex endocrine system operates under the action of the central nervous system. Therefore, a SARS-CoV-2 attack on the endocrine system may cause negative systemic effects and compromise the homeostasis of the whole body. After treatment and recovery, further observation and examination are necessary to monitor possible injury to the endocrine system to facilitate corresponding treatment and prevention, and clinicians should be alert to possible permanent damage.

However, the symptoms caused by SARS-CoV-2 today are mostly mild due to vaccinations and the constant mutation of the virus. The number of severe patients rate and the mortality rate have decreased compared with the initial stage of the outbreak. Moreover, the above clinical data also has the problem of small sample size or irregularity. In addition, it is well known that a transient central hypogonadism occurs during acute disease, which will subside on its own over time. Therefore, whether SARS -CoV-2 will really affect the male genitourinary system and endocrine system still needs to be doubted, and research of SARS-CoV-2 sequelae monitoring are still needed in the future.

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