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The possible effects of COVID-19 on the human reproductive system

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ABSTRACT

Spike surface glycoprotein and small envelope matrix-nucleocapsid proteins, is from the Coronaviridae family and binds to host receptors via spike surface proteins. Although it shows its symptoms especially on the respiratory tract, various studies have been carried out considering that it also affects other systems in the body. For the virus to enter the host cell, it must bind to ACE2 (angiotensin converting enzyme 2). ACE2 is a key protein involved in balancing Ang I and Ang II levels. With receptors such as TMPRSS2 (transmembrane serine protease 2), the effects of the virus on the human reproductive system are much better understood. Since human germ cells and early embryos express ACE2, there is a potential risk of the Coronavirus associated with germ cells. Studies show that the coronavirus changes the amount and density of hormones in the human reproductive system. The fact that most of the partners of 35 female patients who had SARS-CoV-2 in the studies were infected individuals suggests that sexual transmission may be possible. It was determined that TMPRSS4, Cathepsin B and L, FURIN, MX1 and BSG gene expressions were high in the menstrual cycle, while ACE 2 and TMPRSS2 were moderately expressed. It has been shown that the ACE2 enzyme is most intensely expressed is the testes. Studies have shown that sperm DNA (deoxyribonucleic acid) fragmentation, changes in hormone levels and the formation of anti-sperm antibodies are an important cause of male infertility. Infected men have been found to have an impaired spermatogenesis. This rewiew; it aims to draw attention to the possible effects of the corona virus on the human reproductive system and to reveal new mechanisms for new research to be done.

Keywords: COVID-19, human reproductive system, ACE2, TMPRSS2

The first case of pneumonia occurred in Wuhan City, Hubei Province of China, on December 31, 2019, and on January 7, 2020, it was stated that the cause of this situation was a new virus that has not yet been detected in humans [1]. It has been shown to be similar to viral pneumonia in terms of clinical features. The World Health Organization (WHO) has named the disease COVID-19. The International Committee on Virus Taxonomy (ICTV) named this virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. Coronaviruses are enveloped, positive single-stranded large RNA viruses that can infect humans and a wide variety of animals [3]. It was firstly described by Tyrell and Bynoe in 1966 in patients with a cold, and it was named in Latin (corona = crown) [4]. It has four families, alpha-, beta-, gamma-, and

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delta-coronaviruses. Alpha and beta-coronaviruses originate from mammals, especially bats, while gamma and delta originate from pigs and birds [5]. Compared to SARS and Middle East Respiratory Syndrome (MERS), the COVID-19 virus has a very high contagiousness and infectivity despite its low mortality rate [6]. When the genome analysis of each was examined, the genome analysis results of the new coronavirus sequences showed that the whole genome sequence similarity rates of SARS-CoV and bat SARS coronavirus (SAR-Sr-CoV-RaTG13) were 79.5% and 96%, respectively [7]. It can be assumed that the new coronavirus disease may originate from bats. Like other viruses, SARS-CoV-2 infects lung alveolar epithelial cells using the receptor-mediated endocytosis pathway via angiotensin-converting enzyme 2 (ACE2) [5]. In our country, the first case was announced on March 11, 2020. The disease was declared as a pandemic by WHO after cases were seen in many parts of the world [8]. In this review, it is aimed to see what effects it can have on the reproductive system and coronavirus disease and what can be done.

Clinical Features of the Virus

SARS-CoV-2 infection shows different clinical symptoms. While the most common clinical symptoms of the disease were fever, cough, and severe fatigue, diarrhea and vomiting were recorded as fewer common symptoms [9]. The period from the onset of symptoms to acute respiratory distress syndrome (ARDS) was found to be only 9 days among the initial patient groups with COVID-19 infection [10]. Patients with severe illness are prone to serious complications, including acute respiratory distress syndrome, acute heart injury, and a secondary infection [7]. In general, the radiographic features of coronavirus are similar to pneumonia [11]. As a result of blood analysis, it was seen that 82.1% of the patients had lymphopenia and 36.2% had thrombocytopenia. High levels of C-reactive protein, lactate dehydrogenase (LDH), and creatinine kinase (CK) occurred in most patients. In some patients, elevated transaminase, abnormal myocardial enzyme spectrum or elevated serum creatinine were detected [9].

Angiotensin Converting Enzyme (ACE) and SARS CoV-2

Angiotensin converting enzyme (ACE) is from the zinc metallopeptidase family. It is commonly found on the surfaces of endothelial and epithelial cells. ACE converts angiotensin-I (Ang I) to angiotensin-II (Ang II), a very potent vasoconstrictor. Thus, a polypeptide network is formed. These polypeptides are the basic elements of the renin-angiotensin system (RAS) [12]. RAS controls blood volume and blood pressure in the human body. renin: It is secreted from the juxtaglomerular cells of the kidneys during water and salt loss, blood volume reduction, and activation of the sympathetic nerves. In the liver, renin is first converted to angiotensin 1, and then to Ang II by the ACE enzyme found in the lung alveolar epithelium [12]. Ang I is a powerful vasoconstrictor. By affecting the adrenal cortex, sodium and water are reabsorbed from the kidneys and aldosterone secretion occurs [13]. Ang II, together with cytokines, stimulates many growth factors and plays a role in cell proliferation [14].

Angiotensin Converting Enzyme 2 (ACE2)

ACE2 has been identified as the first human homologue of the ACE enzyme. The ACE2 enzyme is the main enzyme that is effective in cardiovascular diseases, narrowing of the vessels, and oxidative stress. The ACE2 enzyme is a transmembrane protein. SARS-CoV2 and ACE2 are receptor enzymes of each other [12]. ACE2 is the main key to cell entry for SARS-CoV-2 [15]. Highest expression level of ACE2 in human tissue; the lowest expression levels are in the spleen, blood, bone marrow, brain, and blood vessels, while the small intestine, kidneys, testis, thyroid, and heart. Consequently, ACE2 is expressed in various organs and tissues besides the lungs [16, 17]. As a result of all these data, SARS-CoV-2 poses a threat to many systems. In other words, it is a systemic virus and its main target organ is not only the lungs [18]. ACE2, Ang II, and Ang 1-7 are regulators on the reproductive system (such as folliculogenesis, oocyte maturation, ovulation and endometrial regeneration in women; testicular function regulator, sperm functions and contribution to sperm embryo quality in men) [19]. There are studies showing that SARS-CoV-2 will also infect the male reproductive system, eventually. Although it was stated that there was no virus in the semen in the studies, a report published by the journal JAMA network revealed that 38 of 6 semen samples of the COVID-19 patients (analyzes were done using polymerase chain reaction by reverse transcription

method from RNA) were positive [17]. These analyzes support the opinion that SARS-CoV-2 may have an effect on the male reproductive system. In addition, the possibility of an effect of SARS-CoV-2 on the testicles was supported by other data indicating that patients with COVID-19 infection had a decreased testosterone/LH (luteinizing hormone) ratio [20]. Another protein is transmembrane serine protease 2 (TMPRSS2). When entering a cell, the virus first uses ACE2, then facilitates viral entry following TMPRSS2-mediated proteolytic processing of the SARS-2 spike protein [21]. TMPRSS2 is also an androgen-regulated gene in prostate tissue and contributes to prostate cancer pathogenesis by aberrantly directing oncogene expression. Almost half of prostate cancers involve a fusion using TMPRSS2 together [22]. These findings indicated that the testicles were vulnerable to SARS-CoV-2 infection.

SARS-Cov-2 on Ovary and Testicle

ACE2 is a key protein involved in balancing Ang I and Ang II levels. This feature has been shown to induce steroid production in the ovaries [23]. Ovarian tissue has its own RAS system, it can respond to angiotensin II with its own receptors [24]. Ang II has also been shown to be necessary for normal endometrial functions and regular menstrual cycles. Some studies showed that ACE2 is expressed in relatively higher amounts in the ovaries. In a study by Jing et al. [20], ACE2 mRNA levels were found in both human and rat uterus. Considering the functions of Ang II on the ovary, it is effective in the progression of the corpus luteum as well as its important effects such as oocyte maturation and follicle development. Ang II also plays a role in the resumption of meiosis in oogenesis. Considering all these factors, considering that SARS-CoV-2 enters the cell with ACE2 receptors, many problems may arise in a possible reproductive system infection. The fact that most of the partners of 35 female patients who had SARS-CoV-2 in the studies were infected individuals suggests that sexual transmission may be possible [25]. In addition, there are hypotheses that mother-to-child transmission may occur by droplet route and contact. As a result, it is predicted that the coexistence of ACE2 and SARS CoV-2 in female reproductive system functions may cause damage that may result in infertility and fetal problems [25, 26]. Although the literature studies clearly show that the virus is effective on the male reproductive system with experimental studies, its possible effects on the female reproductive system remain mostly in the form of theoretical hypotheses. Some of these hypotheses will also be evaluated through the following organs.

Effects on the Female Reproductive System

Ovary and Gametogenesis

Jing et al. [20] in their studies with immature rat ovaries, ACE2 protein was found in ovarian stromal cells, oocytes and granulosa cells; showed that it is expressed in antral follicles. Ang (1-7) and ACE2, which show their effects with the G-protein-Linked MAS receptor, are also known to be present in the ovary and play an active role in granulosa lutein cell apoptosis, oocyte maturation and ovulation [10]. It is predicted that any change in the expression of Angiotensin II and Ang 1-7, which plays a role in the formation of the corpus luteum and the continuity of the corpus luteum, may negatively affect the early pregnancy processes [27, 28]. In another study, it was stated that Covid-19 causes problems such as excessive coagulation and blood flow, causing damage to the endothelium and causing deeper vein thrombosis [26]. In this sense, since ACE2 is expressed in the ovarian tissues of both reproductive and post-menopausal women, it is predicted that SARS-CoV-2 infection may pose a potential risk in the female genital tract. It is also thought that it may cause infertility as it will cause a decrease in oocyte quality [27]. In addition to these hypotheses, Mohammadi et al. [29] in their published work; reported right ovarian vein thrombosis in 26-year-old pregnant COVID-19 (+) patients who applied to their clinics and stated that COVID-19 caused endothelial damage due to complications such as excessive coagulation and blood flow stagnation, and constituted a source for deep vein thrombosis [29]. The ACE2 protein has also been identified in the uterus. Studies have shown that ACE2 expression is more overexpressed, especially in the secretory phase compared to the proliferative phase [30]. In the endometrium, angiotensin II is involved in regeneration and has important functions in the vascular bed. Spiral arteries provide vasoconstriction, especially during menstruation. The balance between Angiotensin II and Ang (1-7) is very important for endometrial self-regeneration and myometrial activity [25-30]. In addition, ang II increases the proliferation of uterine epithelium and stromal

cells, so the change that occurs here may cause endometrial fibrosis. In the case of fibrosis, it has been reported that excessive activity will be inhibited by Ang 1-7 [25]. It was brought to the literature by Henarejos-Castillo et al. [16] in a study on the possible effects of SARS-CoV-2 on the endometrium and implantation. These investigators measured the viral gene expression of SARS-CoV-2 infection-associated endometrial ACE 2, TMPRSS2 and 4, Cathepsin B and L, FURIN, MX1 and BSG to explain virus and endometrial susceptibility. As a result of their study on 112 women with normal endometrial pathology, 29 of which were proliferative, 29 were early secretory, 43 were mid-secretory, and 8 were late secretory, TMPRSS4, Cathepsin B and L, FURIN, MX1 and BSG gene expressions remained high in the menstrual cycle, ACE 2 and They revealed that TMPRSS2 was moderately expressed. Researchers also stated that the amount of gene expression was different in different periods of the cycle, and emphasized that the only stable gene throughout the entire cycle was TMPRSS2. Viral genes have the highest expression in the early and middle phases of the cycle; stated that ACE2, TMPRSS4 and Cathepsin L were expressed weakly but co-expressed in the implantation window. Researchers who stated that ACE2 and TMPRSS4 are always expressed weakly but co-expressed during menstruation; Viral gene expressions are expressed differently in different periods of the menstrual cycle, and ACE 2 gene expression increases with increasing age, thus making the tissue more susceptible to SARS-CoV-2 infection [31, 32].

Effects on the Male Reproductive System

The male reproductive system consists of two testes located in the scrotum, attached glands, ducts and penis. The testicles are responsible for the formation, storage, release of spermatozoa, and the production of testosterone. The testicular parenchyma consists of seminiferous tubular rings, where spermatogenesis occurs. Each of the seminiferous tubules is 30-70 cm in length and 150-250 µm in diameter, and sperm are produced in them. Spermatogenesis in mammals; It is a dynamic process that continues with self-renewal and cell differentiation of spermatogonial stem cells. Spermatogenesis is controlled in a special microenvironment in the testicular seminiferous tubules. Sertoli cells are the only somatic cell type found in the tubules and interact directly with spermatogenic cells to control paracrine signaling and spermatogenic cell differentiation. Interstitial Leydig cells are adjacent to the seminiferous tubules. Abnormalities in male germ cells or disorders of somatic cells that support the stages of sperm formation cause male infertility [33]. Sertoli cells are rather large support cells that sit on the basal lamina and do not divide. It has supportive, protective and nutritional properties in spermatogenesis. The formations called 'tight-junction' between Sertoli cells ensure the tight connection of the cells. This structure together with a basement membrane forms the blood-testis barrier. This barrier prevents some antigenic substances formed during the development of germ cells from entering the blood. Thus, the formation of autoantibodies is prevented. In addition, toxic substances in the blood are prevented from reaching the spermatogonia. The content of the fluid in the lumen of the seminiferous tubule is also kept different from the plasma by this barrier. It is known that viruses can infect the testicles directly, because the blood testicular barrier is not sufficiently protected to completely isolate the viruses [34]. It has been shown that the ACE2 enzyme is a potential receptor for the SARS virus, and in independent studies, it has been shown that one of the tissues in which the ACE2 enzyme is most intensely expressed is the testes [35]. The male reproductive system, and particularly the testicles, express all classical members of the RAS system (AngI, AngII, Ang1-7 and ACE2) and have been cited as both source and target tissues for active angiotensin peptides. The effects of angiotensins include the regulation of steroidogenesis (production of steroidal hormones), especially through Leydig cell inhibition by Ang II, and their effects on epididymal contraction and sperm cell function [12]. Studies have shown that the virus disrupts the structure of the blood-testis barrier, which is very important for the immunity of the male reproductive system [36]. Non-dependent studies have revealed that the testes are among the tissues with the highest concentration of ACE2 enzyme. The RNA expression profiles of the ACE2 enzyme in the mature human testis were investigated within the framework of single cell resolution, and it was revealed that this enzyme is intensely present in the spermatogonia and contributes to the development of Sertoli and Leydig cells. These studies suggest that SARS-CoV-2 may cause infection and

loss of function in the male reproductive system [12]. Studies have shown that sperm DNA (deoxyribonucleic acid) fragmentation, changes in hormone levels and the formation of anti-sperm antibodies, which occur as a result of the attack of the coronavirus on the male reproductive system, are an important cause of male infertility. The studies by Wang and Xu [36] also state that infected men have impaired spermatogenesis, which supports all these. In some studies (ribonucleic acid) using probes, taking samples from the testicles by swab method, she conducted a study on six patients and found the results negative for SARS-CoV-2. However, in another study, in testicular epithelium and Leydig cells, the results of the research conducted with electron microscopy with the same method, this time the SARS-CoV-2 test was positive [12]. In the studies and researches, it was observed that the results of the SARS-CoV-2 test in their sperm were still positive in patients who were diagnosed with COVID-19 and their conditions returned to normal. Damage to the ductus deferens-epididymis barriers in the testicles by blood supply can affect the male reproductive system in the presence of SARS-CoV-2, and even if this virus does not multiply in the male reproductive system, this privileged immunity of the testicles can provide an environment for the continuity of viruses [12, 15]. Recently, Gagliardi et al. [37] estimated that orchiepididymitis observed in a 14-year-old boy was a complication of COVID-19 . In the autopsy of all 6 patients, who were observed to be infected and killed by SARS-CoV-2, which is closely related to SARS-CoV-2, it was revealed that the testicles had orchitis. This orchitis does not only cause testicular destruction; it has also been reported to cause destruction of germ cells and seminiferous tubule necrosis [15, 36]. These data are insufficient and it is not known what kind of effect and pathology will be encountered in the long term on the tissues -ovaries and testicles- in which ACE2s are expressed intensely in young individuals who survived the COVID 19 disease [12]. Compared to women, more cases of COVID-19 are seen in men. However, it should not be forgotten that men infected at a young age have a strong protector against adverse situations. It is stated that testosterone has anti-inflammatory functions by suppressing both cellular and humoral immune systems. In fact, testosterone has been found to reduce IL-6 (interleukin 6) and TNF-alpha (tumor necrosis factor alpha) levels through inhibition of the NF-kB (nuclear factor kappa B) proinflammatory pathway, similar to estrogen. In addition, testosterone deficiency has been associated with autoimmune diseases. In a laboratory study, gonads were removed from male mice with influenza infection. Male mice with intact gonads had higher mortality rates [37]. Low testosterone levels are also associated with elevated inflammatory markers such as IL-6. This may underlie the risk of lung injury after pneumonia. Testosterone can be converted to estrogen via the aromatase enzyme, which can have an anti-inflammatory effect. Several studies have shown that testosterone therapy can benefit patients with chronic obstructive pulmonary disease. Females have been shown to have stronger immune function as a result of the extra X chromosome [37]. In some clinical situations (including death), it has been observed that the LH level is much higher than normal and the testosterone level is decreased in infected men. In addition, considering the presence of ACE2 and TMPRSS in Leydig cells, it is predicted that SARS-CoV-2 may cause deterioration in testosterone levels [15, 37]. The ACE gene encodes two isozymes. While the somatic isozyme is expressed in many tissues, including vascular endothelial cells, renal epithelial cells, and testicular Leydig cells, testicular or germinal ACE is expressed only in sperm [38]. It has been observed that the expression of ACE in sperm is important for egg fertilization and it has been observed that sperm without ACE are insufficient for transport in the oviduct and binding to the zona pellucidae [39].

CONCLUSION

Coronavirus, which has been in our lives for more than two years, has affected many tissues and organs in different ways. The infectious disease caused by the new type of coronavirus spread rapidly all over the world and caused thousands of deaths. This has affected the health system, the human socio-psychological situation and the global economy. Studies have shown that the ACE2 enzyme, which is the cellular receptor for COVID-19, is not a viral infection that only affects the respiratory tract of COVID-19. The ACE2 enzyme is widely expressed in many tissues in the human body. However, the number of studies showing the damage

caused by Covid-19 in systems other than the respiratory system is insufficient. It is not yet known exactly what kind of pathological condition will be encountered in the long-term in the ovaries and testes, which are the tissues in which the ACE2 enzyme is intensely expressed in young patients with Covid-19. Despite this, literature studies have found that the damage caused by the SARS-Cov-2 virus in the male reproductive system or ovaries is more intense than in the female reproductive system. In every study, the gender distribution of the patients must be taken into account in order to ensure that the data are more accurate. Considering the theoretical information, the close relationship of the virus with ACE2 and TMPRSS2 molecules suggests that especially the ovary and endometrium may be affected by the virus. It is thought that COVID-19 infects sperm or egg cells and the damage that may occur in this process is not fully known, which may create risky situations for embryo formation. It can cause infertility in all young male patients who have had this disease. In women of childbearing age, miscarriages may occur or may result in the birth of genetically defective children. Studies on viruses and the human reproductive system are very important for the health of the next generation in terms of new babies, male and female infertility. The mechanism of action of this virus, which is still present in our lives, and the damage that may occur in the tissues and organs it affects are still not fully understood. More studies are needed to fully understand these cellular mechanisms of action.

Authors' Contribution

Study Conception: TD, HKY; Study Design: TD; Supervision: TD; Funding: HKY; Materials: N/A; Data Collection and/or Processing: TD, HKY; Statistical Analysis and/or Data Interpretation: TD; Literature Review: TD; Manuscript Preparation: TD and Critical Review: TD, HKY.

Conflict of interest

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