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COVID 19: Anjiyotensin Dönüştürücü Enzim 2 (ACE2), Renin-Anjiyotensin-Aldosteron Sistemi (RAAS) ve Kronik Hastalıklar Arasındaki İlişki

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Özet

İnsanlarda enfeksiyonlara neden olan yedinci tip koronavirüs olan SARS CoVID-2 (COVID-19), dünya çapında insan yaşamı için büyük bir tehdit haline gelmiştir. Wuhan'da ortaya çıkan ve oradan da tüm dünyaya yayılan virüs, bugün özellikle yaşlı ve kronik hastalarda (hipertansiyon, Diabetes Mellitus (DM), kalp hastalığı) büyük bir tehdit haline gelmiştir. Bu virüsün niçin kronik hastalarda daha etkili olduğunu bilmek hastalığın önlenmesi veya tedavisinde oldukça önemlidir. Bu nedenle çalışmada COVID-19 virüsünün kronik hastalıklar ile olan ilişkisi anlatılmaktadır. Angiotensin-converting enzyme (ACE2), özellikle böbrek, kalp, karaciğer, ve akciğerler gibi yaşam için önemli organlarda rol almaktadır. COVID-19 virüsünün hücre içerisine girişi ise ACE2 enzimiyledir. Çalışmamızda bu virüsün kronik hastaları diğer insanlardan daha fazla etkilenmesinin nedenleri ve ACE2, Renin-Anjiyotensin-Aldosteron metabolizması ile ilişkisi aydınlatılmaya çalışılmaktadır.

Anahtar Kelimeler

ACE2
Kronik hastalık
Corona virüs
COVID-19
Renin
SARS CoVID-2

Makale Hakkında

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COVID 19: The Relationship Among Angiotensin-Converting Enzyme 2 (ACE 2), Renin-Angiotensin-Aldesterone System (RAS), and Chronic Diseases

Abstract

SARS CoVID-2 (COVID-19), the seventh type of coronavirus that causes infections in humans, has become a major threat to human life worldwide. The virus, which emerged in Wuhan and spread from there to the whole world, has become a major threat, especially in elderly and chronic patients (hypertension, Diabetes Mellitus (DM), heart disease) today. It is very important to know why this virus is more effective in chronic patients, in the prevention or treatment of the disease. Therefore, the study describes the relationship of the COVID-19 virus with chronic diseases. Angiotensin-converting enzyme (ACE2) is particularly involved in vital organs such as the kidney, heart, liver, and lungs. The entry of the COVID-19 virus into the cell is through the ACE2 enzyme. In our study, the reasons why this virus affects chronic patients more than other people and its relationship with ACE2, Renin-Angiotensin-Aldosterone metabolism are tried to be elucidated.

Keywords

ACE2
Chronic disease
Corona virus
COVID-19
Renin
SARS CoVID-2

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Introduction

Coronavirus (Cov) was first isolated in the literature from the tissue culture of a cold patient by Tyrrell and Bynoe in 1965 (Tyrrell and Bynoe, 1965). In the following years, hepatitis in mice and gastroenteritis virus in pigs were observed to have the same morphology in electron microscopy (McIntosh, 1967; Tyrrell and Bynoe, 1965; Witte, 1968). Corona viruses are enveloped, positive-stranded RNA viruses. Glycoproteins (S) located vertically around it give the distinctive crown (corona) appearance that gives the virus its name. Because they may have positive polarity, they do not contain RNA-dependent RNA polymerase enzymes, but in their genomes they encode this enzyme (Saliba et al., 2017). The Coronaviridae family is part of the Nidovirales team, consisting of the Coronavirinae and Torovirinae subfamilies. The International Virus Taxonomy Committee (ICTV) has divided the Coronavirinae subfamily into 4 genes as α, β, γ and Δ- corona viruses, and classified human corona viruses into α and β-corona viruses (Saliba et al., 2017; Yücel and Görmez, 2019). These corona viruses cause respiratory diseases or gastroenteritis in many animal species such as mice, chickens, turkeys, various bird species, camels, rabbits, whales, pigs and cats. Many coronaviruses are known to infect humans and animals. However, some animal-derived coronaviruses can also infect humans and cause outbreaks (Ahn et al., 2020; Su et al., 2016b).

There were six different human corona viruses known to date. Four of these are coronaviruses that cause mild, classic cold symptoms in humans. Two are α-corona viruses HCoV-NL63 and HCoV-229E, the other are β-coronaviruses HCoV-HKU1 and HCoV-OC43. SARS-CoV, which was identified in 2003 and responsible for severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome-CoV (MERS-CoV), which was identified in 2012 and responsible for Middle East respiratory syndrome, are beta corona viruses (Fehr and Perlman, 2015).

SARS-CoV appeared in 2002 in Guangdong province in China and threatened the whole world. This infection spread to 30 countries in one year, causing 8373 illnesses and 774 deaths. About 10 years later, in 2012, a 60-year-old man died in Saudi Arabia from acute respiratory infection and kidney failure. This virus has been identified as MERS-CoV with cell culture and genome sequencing. The intermediate mansion of MERS-CoV in the Arabian Peninsula has been shown to be a single humped camel. World Health Organization in 26 countries from 2012 to 2016 it is reoported the number of patients with proven MERS-CoV infection is 1791 and 640 of them died (Inal, 2016; Nowotny and Kolodziejek, 2013; Zaki et al., 2012).

Nowadays, a new coronavirus has been identified, which originates in Wuhan, and with natural reservoirs bats (Figure 1). Then it has been transmitted to humans and spread all over the World. It poses a great danger especially for elderly and chronic patients (hypertension, heart disease, DM). The virus had been named SARS-CoV-2 by the World Health Organization. Compared to the SARS-CoV that caused the SARS outbreak in 2003, SARS-CoV-2 has a stronger infectious capacity (Danser et al., 2020; Zheng et al., 2020).

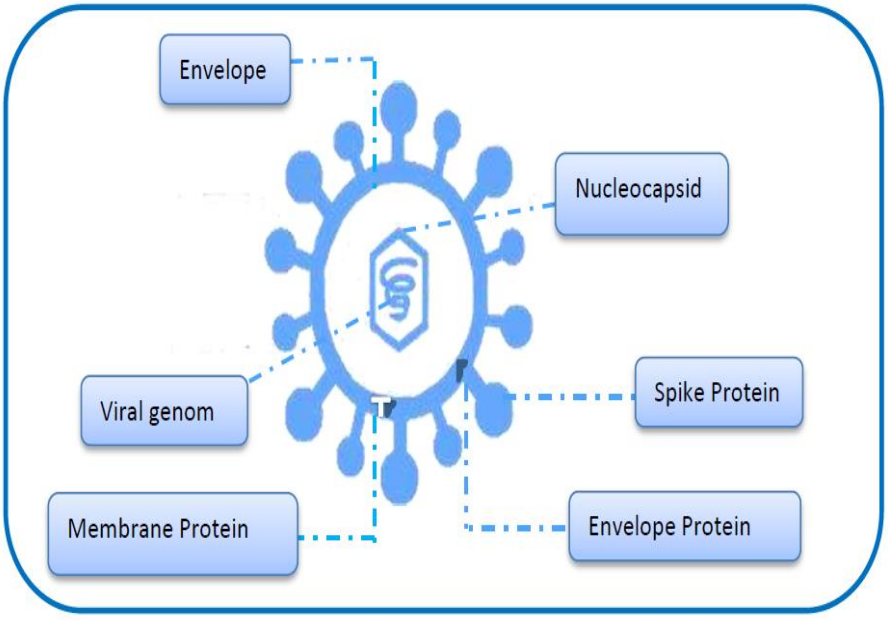

Figure 1. Structure of SARS CoVID-2 (COVID-19)

These viruses pathogenically affect the gastrointestinal, respiratory, liver and central nervous systems of humans, birds, mice, bats and many other wild animals (Perico et al., 2020). SARS-CoV-2, which causes COVID-19, is mainly transmitted by droplet. Infection is usually carried out by close contact with the sick person and by transferring the virus that falls on the surfaces to the eyes, mouth or nose through hands. After the virus enters the body, it causes an infection in the lungs by advancing to the lower respiratory tract. People exposed to the virus, along with changing from person to person, have symptoms within an average of five days (Meijers et al., 2020).

It is known from studies that the COVID-19 virus is associated with a protein called Angiotensin-converting enzyme (ACE2) to enter the cells. ACE2 is a membrane-bound peptidase that is highly expressed in the heart, lungs, kidney and gastrointestinal tract and plays an important role in various cardiovascular and immune pathways. In 2003, Li et al. showed that ACE2 is the receptor responsible for SARS coronavirus entry (Li et al., 2003). Binding to the ACE2 receptor requires the surface unit of a viral spike protein. Today, as in Sars Covid, it has been proven that the host cell entry in COVID-19 is connected to ACE2 (Chen et al., 2020). The system where this enzyme is in metabolism is the renin-angiotensin-aldesterone system (Danser et al., 2020).

Renin is an enzyme, which do not have biological activity alone, consisting of 340 amino acids that are released and stored in granular cells in the kidney. Although it was found in the pituitary and adrenal gland of prorenin, which is the pioneer of renin in mammals, the active form of the renin is synthesized in the kidney (Fisher and Hollenberg, 2005). It was determined that the level of prorenin increased in patients with DM and that the levels of total renin increased before microalbuminuria, which is an indicator of vascular damage in these patients (Devaux et al., 2020). Renin activity increases depending on the decreased plasma sodium ions, decreased arterial blood pressure, and an increase in the level of catecholamines (Fisher and Hollenberg, 2005). It was determined that when the activity of the renin is high in plasma, the probability of getting cardiovascular diseases is higher. ACE2 provides the breakdown of angiotensinogen, the precursor of angiotensin (Jahovic et al., 2005).

The renin angiotensin aldosterone system (RAS) is an important metabolic pathway in regulating intravascular volume, sodium/potassium balance, and blood pressure. However, high activity of this system is reported to cause inhibition of this system and affect the cardiovascular system (Shalaby et al., 2006). An increase in the activity of this system has been observed in patients with hypertension. This suggests that the negative feedback mechanism may be impaired (Laragh and Sealey, 2011). Many studies have shown that patients with hypertension and DM have renal damage (Schmidt and Ritz, 1997).

Angiotensins formed by the breakdown of renin-angiotensinogen are a group of peptide hormones formed with different proteases. Some of these peptide hormones were classified by Roman numbers. Angiotensin-I (Ang-I), the first of which is an oligopeptide, has only one task. This task is to create Ang-II (Ang 1-8) and Ang-III (Ang 2-8) (Mehta and Griendling, 2007; Ocaranza et al., 2020). Angiotensinogen and renin are speed determinants in the formation of active Ang-II in circulation (Ramaya et al., 2020). Renin forms Ang-I by breaking the Leu-Leu peptide bond in the first 14 amino acid portions at the amino end of angiotensinogen (Gradman and Kad, 2008). Ang-I is the major substrate of angiotensin converting enzyme (ACE, E.C.3.4.15.1). Angiotensin converting enzyme is a dipeptidase that converts angiotensin I into angiotensin II. Ang-I converts to Ang-II by ACE and binds to angiotensin-I receptors. Thus, renal tubular and glomerular function changes, blood pressure increases, fibrosis, hypertrophy and vasoconstriction occur in the heart (Skeggs et al., 1956). ACE is a

zinc metalloproteinase produced in endothelial cells, membrane bound and in the carboxypeptidase group. Zinc in the structure of the enzyme enables the hydrolysis step of catalytic reactions to take place. Angiotensin converting enzyme has been detected in different locations such as serum, lung, and plasma (Corvol et al., 1995).

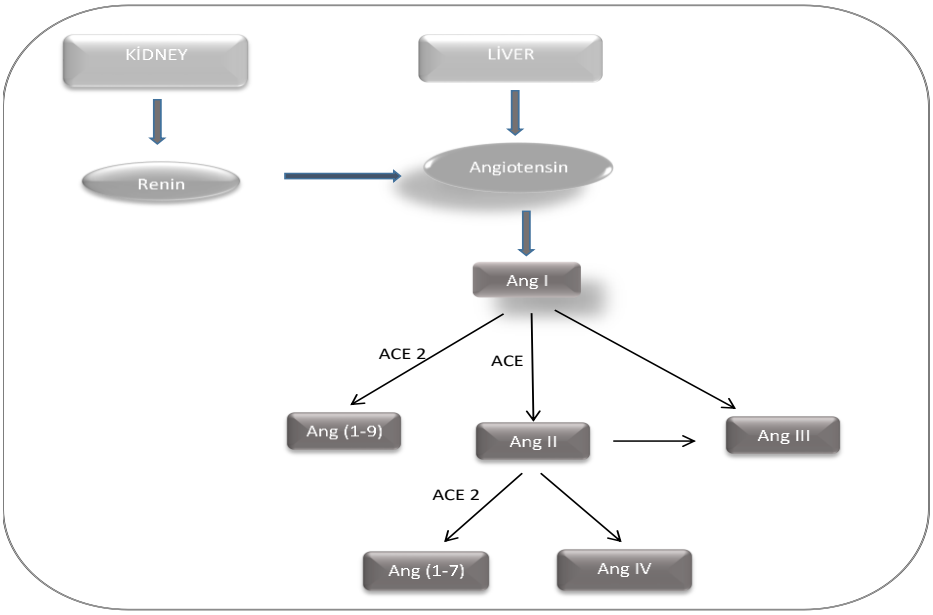

Figure 2. Renin-angiotensin System (RAS)

Since renin determines the speed control in Ang-II formation, renin activity is often used as an indicator of Ang-II formation (Boehm and Nabel, 2002). The peptide with the greatest cardiovascular gene activation potential is Ang-II. The last active substance of the renin angiotensin system is Ang-II. Ang-II, consisting of eight amino acids, is metabolized in a short time in the circulation. It has been determined that its biological activity is high. This peptide plays a role in promoting circulation with rapid reactions in cases where plasma volume decreases. These roles include vasoconstriction, aldosterone secretion, sodium retention and antidiuretic hormone release that maintain intravascular fluid volume (Lind et al., 1992).

Most of the other rapid homeostatic reactions of Ang-II can be listed as increased thirst, high sympathetic nerve activity that maintains circulation, fluid absorption from the intestine, platelet aggregation and high cardiac contraction (Timurkaynak, 2009). Although this peptide does not directly affect the heart, it increases blood pressure in the systemic circulation and stimulates the baroreceptor mechanism, slowing the heart rhythm with increased vagal activity, and thus causing a noticeable decrease in diastolic pressure. Ang-II increases the secretion of aldesterone by stimulating the adrenal gland. Increased amount of aldesterone provides sodium reabsorption from kidney distal tubules. Thus, water and salt retention occurs. As a result, a prolonged increase in blood pressure is observed and ends with hypertension caused by activation of the renin angiotensin system (Vaughan, 1972). The ratio of

intracellular potassium concentration to extracellular potassium concentration determines the membrane potential to maintain normal excitability in nerve and cardiac muscle (Vio et al., 2020). Also, the height of aldosterone leads to a decrease in the amount of high-density lipoprotein (HDL) associated with cardiac and atherosclerosis (Lind et al., 1992).

Ang-II increases the sympathetic effect by stimulating the adrenal medulla and ganglia. On the other hand, Ang-II shows its effects that increase the pressure and cause hypertrophy on the cardiovascular system by creating oxidative stress together with peptides such as aldosterone, steroids, catecholamines, thromboxane, endothelin and growth factors. Ang-II damages structure proteins, membrane lipids and nucleic acids with angiotensin receptors. It stimulates cell growth as a result of oxidative stress, provides vascular smooth muscle contraction and weakens endothelial cell integrity and function. As a result, they can form reactive oxygen types such as super oxide and peroxide (Ferrario, 2006; Touyz and Schiffrin, 2000). Because Ang-II is a strong vasoconstrictor, it increases systemic vascular resistance. On the other hand, Ang-II stimulates the production of vasodilator prostaglandins and vasoconstrictor thromboxane A2 (TxA2) by increasing arachidonic acids (Baur et al., 1995). Ang II turns into Ang III [Ang-(2-8)] and Ang IV-(3-8) with aminopeptidase enzymes in the angiotensinase group. Both formed angiotensin receptors are found in many parts of the brain. While Ang-II directly inhibits renin release with negative feedback from juxtaglomerular cells, it stimulates the release of angiotensinogen from the liver with positive feedback (Serfozo et al., 2020). Ang-III, which has a high rate of cerebrospinal fluid and brain, has more fat solubility than Ang II (Burnier, 2001).

Angiotensin converting enzyme 2 (ACE2) is a monocarboxypeptidase that converts Ang-II to Ang-(1-7). Another peptide is Ang-(1-7), which is also detected in human blood. Ang-(1-7) is formed when the His-Leu dipeptide is broken off by the angiotensin-converting enzyme (ACE) from the carboxy end of Ang-(1-9). The vasodilator, antifibrotic and natriuretic effects of this peptide has been identified. In addition, Ang-(1-7) can be formed both by Ang-II with the help of ACE2 and by the breakdown of three amino acids at the carboxy end of Ang-I with the help of endopeptidase enzymes. Decreases in ACE activity have also been reported to increase Ang (1-7) levels in tissue, plasma, and urine. Ang (1-7) has been found to increase kidney-blood flow and stimulate the secretion of prostaglandins (Serfozo et al., 2020).

The amount of circulating Ang-II is determined by the amount of Ang-I and tissue ACE activity. ACE is at the most important point of this system (Burnier, 2001). The ACE gene is 21 Kb long, located on the long arm of the 17th chromosome containing 26 exons (Ruiz et al., 1994). ACE acts as an integral protein in endothelial cells. By converting Ang-I to Ang-II, it plays an important role in metabolic balance (Arendse et al., 2019). ACE was detected in the endothelial layer of the heart, hypothalamus kidney vein and aorta (Çiçek et al., 2019). ACE is also a kininase and leads to the conversion of bradykinin to inactive metabolites (Li et al., 2003). With the use of ACE inhibitor, bradykinin levels and

arachidonic acid release increase. Cough is seen in approximately 20% of patients with increased bradykinin level. Angiotensin converting enzyme inhibitors not only reduce Ang II formation, but also reduce the destruction of bradykinin. The first substance found as an ACE inhibitor was captopril. It is frequently used in the treatment of many diseases such as hypertension, diabetic nephropathy, especially heart failure (Heeneman et al., 2007).

ACE 2 is the only known homologue of ACE. ACE forms Ang-II ACE2, on the other hand, is a monocarboxypeptidase that enables Ang-II to convert to Ang-(1-7) (Iwai and Horiuchi, 2009). The amount of dissolved ACE2, and membrane-bound enzyme in endothelial cells, is very low in the blood. ACE2 is an enzyme consisting of 805 amino acids with a single active site. ACE2 acts as the negative regulator of the renin angiotensin system (Rosendorff, 1996). ACE2 has an important role in metabolism such as immune system, cardiovascular system, DM and hypertension (Arendse et al., 2019).

ACE breaks down the dipeptides from the carbon end of the substrates, while ACE2 breaks down single amino acids from the carbon end of their substrates. In this way, ACE2 facilitates the conversion of Ang II to Ang-(1-7) and Ang I to Ang-(1-9). ACE2 is an enzyme that removes carboxy terminal hydrophobic or basic amino acids (Perico et al., 2020). ACE2 has been detected in the X chromosome in humans. ACE2, the quantitative carrier locus is located on the X chromosome in various rat hypertension models. Thus, this data shows that the ACE2 gene is the gene belonging to locuses associated with hypertension (Imai et al., 2005).

When treating kidney and cardiovascular diseases, renin angiotensin aldosterone system comes to mind first. Therefore, some drugs have been studied to inhibit the components of this system. In particular, drugs that inhibit angiotensin II receptors, ACE, and renin blockers have been identified (Burnier, 2001). Studies have shown that ACE inhibitors reduce blood pressure (Jahovic et al., 2005). Renin angiotensin aldosterone system plays a local role in kidney, heart, reproductive system, pancreas and brain. However, the systemic renin angiotensin aldesterone system is responsible for regulating the electrolyte and water balance, blood volume and arterial blood pressure. In studies conducted, it was stated that local renin angiotensin aldesterone system increased in pathological conditions (Su et al., 2016a).

ACE2 is involved in many human tissues, especially vital organs such as kidneys, heart, liver, intestines, and lungs. ACE2 is thought to be important in the regulation mechanism of the RAS, which is involved in the control of electrolyte balance and blood pressure. In this mechanism, SARS-CoV-2 binds ACE2 and increases disruption of ACE2. Thus, it reduces ACE2's counter movement on RAS (Su et al., 2006; Weir and Rolfe, 2010). ACE2 protects mice from severe acute lung damage induced by acid aspiration, sepsis, and severe acute respiratory syndrome (SARS) virus infection (Fehr and Perlman, 2015).

In a study on rats was observed that the blood pressure was at normal values when preventing ligand binding to the AT1 receptor or reduced Ang II activity by reducing fat synthesis. On the other

hand, administration of renin blockers and ACE inhibitors to renal cortical tissues from the rats increased ACE2 gene expression and protein activity. Thus, Ang II level increases when ACE2 deficiency or activity decreases. This lead to hypertension in a bad way (Li et al., 2020). In the statistics made between 1099 people diagnosed with COVID-19, it was determined that they had 23.7% hypertension, 16.2% DM, 5.8% coronary heart disease, 2.3% cerebrovascular diseases (Jessup et al., 2006).

Corona viruses that cause disease in humans reach the target cells by kidney, epithelial cells of intestine, lungs and blood vessels with ACE2. Reported studies reported that patients were treated with ACE inhibitors (Guan et al., 2020). ACE inhibitors, renin inhibitors (β -blockers), aldosterone inhibitors and Angiotensin II receptor blockers are used to stop the renin angiotensin aldosterone system (Jahovic et al., 2005). Patients with hypertension are treated with ACE inhibitors and angiotensin receptor blockers. ACE2 expression is significantly increased in type 1 or 2 DM patients treated with ACE inhibitors and angiotensin II type-I receptor blockers. ACE2 expression facilitates infection by the presence of COVID-19. Coronary heart disease seen in people with high average age, hypertension, and DM increase the proportion affected by the SARS-CoV-2 infections (Danser et al., 2020; Diao et al., 2020).

COVID-19 fixes itself to the lung using the ACE2 receptor. Therefore, it causes individuals with low immunity or suppression to be more affected by the virüs (Danser et al., 2020). According to the data obtained, ACE2 is highly expressed in the tongue and mouth. In this case, viral entry into the host cell is facilitated. In normal human lungs, ACE2 is expressed in the lower lungs of type I, and II alveolar epithelial cells (Muller et al., 2004). After reaching the COVID-19 cell, it copies itself and uses alveolar cells to spread throughout the lung. This virus infects most of the ciliary cells in the alveoli. Therefore, it prevents these cells from performing their normal duties. As a result, cells that cannot clean the airways cause fluid to build up in the lungs (Perico et al., 2020). Approximately two thirds of the people affected by this virus spread worldwide have been found to have DM or cardiovascular diseases. Most of these patients are treated with angiotensin-receptor blockers as primary care (Zumla et al., 2016).

Discussion and Conclusion

Today, the CoVID 2 virus that shocks the world is more effective, especially in the elderly and chronic patients. According to the studies, the entry of this virus into the cell is known to be associated with a protein called ACE2. ACE2, a membrane-bound peptidase that is effective in the gastrointestinal tract, lungs, heart, and kidney plays an important role in immune pathways and various cardiovascular. ACE2 is thought to be important in the regulation mechanism of RAS, which is involved in the control of electrolyte balance and blood pressure. Studies have reported that COVID-19 virus enters the cell with ACE2 enzyme. It has been determined that ACE2 and metabolic pathways in which chronic diseases occur are combined. Therefore, the virus that enters the cell with ACE2 appears to affect people with chronic diseases more than others. In this article, the relationship between RAS metabolism and COVID-

19 virus is presented to the scientific world with its metabolic pathways. It is thought that these metabolic connections will guide the in vivo and in vitro studies to be performed.

Conflict of interest

The authors declare that no conflict of interest.

References

Ahn, D. G., Shin, H. J., Kim, M. H., Lee, S., Kim, H. S., Myoung, J., Kim B. T., & Kim, S. J. (2020). Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID 19). Journal of Microbiology and Biotechnology, 30(3), 313-324.

Arendse, L. B., Danser, A. H. J., Poglitsch, M., Touyz, R. M., Jr Burnett, J. C., Lorens-Cortes, C., . . . Sturrock, E. D. (2019). Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. Pharmacol Rev, 71, 539-570.

Baur, L. H. B., Schipperheyn, J. J., Laarse, A. v. d., Souverijn, J. H. M., Frolich, M., & de Groot, A. (1995). Combining salicylate and enalapril in patients with coronary artery disease and heart failure. Br. Heart. J, 73, 227-236.

Boehm, M., & Nabel, E. G. (2002). Angiotensin-converting enzyme 2-a new cardiac regulator. N. Engl. J. Med, 347, 1795-1797.

Burnier, M. (2001). Angiotensin II type 1 receptor blockers. Circulation, 103, 904-912.

Chen, Y., Guo, Y., Pan, Y., & Zhao, Z. J. (2020). Structure analysis of the receptor binding of 2019-nCoV. Biochem. Biophys. Res. Commun, 525, 135-140.

Corvol, P., Williams, T. A., & Soubrier, F. (1995). Peptidyl dipeptidase A: angiotensin I-converting enzyme. Methods Enzymol, 248, 283-305.

Çiçek, Z., Akıllıoğlu, K., & Doğan, A. (2019). Local and Systemic Renin Angiotensin System. Archives Medical Review Journal, 28(4), 259-269.

Danser, A. H. J., Epstein, M., & Batlle, D. (2020). Renin-angiotensin system blockers and the COVID-19 pandemic at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension, 75, 1382-1385.

Devaux, C. A., Rolain, J. M., & Raoult, D. (2020). ACE2 Receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J. Microbiol. Immunol. Infect, 53, 425-435.

Diao, B., Wang, C., Wang, R., Feng, Z., Tan, Y., Wang, H., . . . Chen, Y. (2020). Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Front. Immunol, 11, 827.

Fehr, A. R., & Perlman, S. (2015). Coronaviruses: An overview of their replication and pathogenesis. Methods Mol. Biol, 1282, 1-23.

Ferrario, C. M. J. (2006). Role of angiotensin II in cardiovascular disease-therapeutic implications of more than a century of research. Renin Angiotensin Aldosterone Syst, 7, 3-14.

Fisher, N. D., & Hollenberg, N. K. (2005). Renin inhibition: what are the therapeutic opportunities? J. Am. Soc. Nephrol, 16, 592-599.

Gradman, A. H., & Kad, R. (2008). Renin inhibition in hypertension. J. Am. Coll. Cardiol, 51, 519-528.

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., . . . Zhong, N. S. (2020). Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med, 382, 1708-1720.

Heeneman, S., Sluimer, J., & Daemen, M. J. (2007). Angiotensin-converting enzyme and vascular remodeling. Circ. Res, 101, 441-454.

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., . . . Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature, 436, 112-116.

Inal, S. (2016). Middle East respiratory syndrome-coronavirus infection. Okmeydani Med. J, 32, 37-45.

Jahovic, N., Ercan, F., Gedik, N., Yüksel, M., Şener, G., & Alican, İ. (2005). The effect of angiotensin-converting enzyme inhibitors on experimental colitis in rats. Regulat. Peptides, 130, 67-74.

Jessup, J. A., Gallagher, P. E., Averill, D. B., Brosnihan, K. B., Tallant, E. A., Chappell, M. C., & Ferrario, C. M. (2006). Effect of angiotensin II blockade on a new congenic model of hypertension derived from transgenic Ren-2 rats. Am. J. Physiol. Heart. Circ. Physiol, 291, 2166-2172.

Kantarcı, G., Eren, Z., Yaman, A., İspir, T., Özener, Ç., & Akoğlu, E. (2003). Relationship between angiotensin converting ensyme polymorphism and diabetıc nephropathy and other vascular complications in Turkish patients wıth Type 2 diabetes mellitus. Offic. J. Turk. Soc. Nephrol, 12, 8-15.

Laragh, J. H., & Sealey, J. E. (2011). The plasma renin test reveals the contribution of body sodium-volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. Am. J. Hypertens, 24, 1164-1180.

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., . . . Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature, 426, 450-454.

Li, X., Hu, C., Su, F., & Dai, J. (2020). Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). medRxiv.

Lind, L., Lithell, H., Wide, I., & Ljunghall, S. (1992). Metabolic cardiovascular risk factors and the renin-aldosteron system in essential hypertension. J. Hum. Hypertens, 6, 27-29.

McIntosh, K. B., W.B., & Chanock, R.M. (1967). Growth in suckling-mouse brain of "IBV-like" viruses from patients with upper respiratory tract disease. Proc. Natl. Acad. Sci, 58, 2268-2273.

Mehta, P. K., & Griendling, K. (2007). Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am. J. Physiol. Cell Physiol, 292, 82-97.

Meijers, B., Messa, P., & Ronco, C. (2020). Safeguarding the maintenance hemodialysis patient population during the coronavirus disease 19 pandemic. Blood Purif, 49, 259-264.

Muller, A. M., Gruhn, K., Lange, S., Franke, F. E., & Müller, K. M. (2004). Angiotesin converting enzyme in the regular pulmonary vasculature. Pathology, 25, 141-146.

Nowotny, N., & Kolodziejek, J. (2013). Middle East respiratory syndrome coronavirus (MERS-CoV) in dromedary camels. Oman. Euro Surveill, 19, 20781.

Ocaranza, M. P., Riquelme, J. A., & García, L. (2020). Counter-regulatory renin–angiotensin system in cardiovascular disease. Nat. Rev. Cardiol, 17, 116-129.

Perico, L., Benigni, A., & Remuzzi, G. (2020). Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. Nephron, 144, 213-221.

Ramaya, K., Suresh, R., Kumar, H. Y., Kumar, B. R. P., & Murthya, N. B. S. (2020). Decades-old renin inhibitors are still struggling to find a niche in antihypertensive therapy. A fleeting look at the old and the promising new molecules. Bioorg. Med. Chem, 28, 115466.

Rosendorff, C. (1996). The renin-angiotensin system and vascular hypertrophy. J. Am. Coll. Cardiol, 28, 803-812.

Ruiz, J., Blanche, H., Cohen, N., Passa, P., & Froguel, P. (1994). Insertion/deletion polymorphism of the angiotensin-converting enzyme gene is strongly associated with coronary hcart disease in noninsulin dependent diabetes mell itus. Proc. Natl. Acad. Sci. USA, 91, 3662-3665.

Saliba, A. E., Santos, S. C., & Vogel, J. (2017). New RNA-seq approaches or the study of bacterial pathogens. Curr Opin Microbiol, 35, 78-87.

Schmidt, S., & Ritz, E. (1997). Genetics of the renin-angiotensin system and renal disease: A progress report. Curr. Opin. Nephrol. Hypertens, 6, 146-151.

Serfozo, P., Wysocki, J., Gulua, G., Schulze, A., Ye, M., Liu, P., . . . Batlle, D. (2020). Ang II (Angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyloligopeptidase)-dependent and ACE2 (angiotensin-converting enzyme 2)-independent. Hypertension, 75, 173-182.

Shalaby, M. S., Zakora, M., & Otte, J. (2006). Performance of two commonly used angiotensin-converting enzyme inhibiton assays using FA-PGG and HHL as substrates. J. Dairy Res, 73, 178-186.

Skeggs, L. T., Kahn, J. R., & Shumway, N. P. (1956). Preparation and function of the angiotensin - converting enzyme. J. Exp. Med, 103, 259-299.

Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C., Zhou, J., . . . Gao, G. F. (2016). Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends in microbiology, 24(6), 490-502.

Su, Z., Zimpelmann, J., & Burns, K. D. (2006). Angiotensin-(1-7) inhibits angiotensin II stimulated phosphorylation of MAP kinases in proximal tubular cells. Kidney Int, 69, 2212-2218.

Timurkaynak, T. (2009). What is renin inhibition? Mechanism of action. T. Arch. Turk. Soc. Cardiol, 37(7), 5-14.

Touyz, R. M., & Schiffrin, E. L. (2000). Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol. Rev, 52, 639-672.

Tyrrell, D. A. J., & Bynoe, M. L. (1965). Cultivation of a novel type of common cold virus in organ culture. Br. Med. J, 1, 1467.

Vaughan, E. D. J. (1972). Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Am. J. Med, 52, 633-652.

Vio, C. P., Gallardo, P., Cespedes, C., Salas, D., Diaz-Elizondo, & J., Mendez, N. (2020). Dietary potassium downregulates angiotensin-I converting enzyme, renin, and angiotensin converting enzyme 2. Front. Pharmacol, 11, 920.

Weir, M. R., & Rolfe, M. (2010). Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin. J. Am. Soc. Nephrol, 5, 531-548.

Witte, K. H. T., M., & Easterday, B.C. (1968). Morphologic characteristics and nucleic acid type of transmissible gastroenteritis virus of pigs. Arch. Gesamte Virusforsch, 23, 53-70.

Yücel, B., & Görmez, A. (2019). SARS-Corona Virus Overview. Turk. J. Appl. Sci. Technol, 2, 32-39.

Zaki, A. M., Boheemen, S. v., Bestebroer, T. M., Osterhaus, A. D., & Fouchier, R. A. (2012). Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med, 367, 1814-1820.

Zheng, Y. Y., Ma, Y. T., Zhang, J. Y., & Xie, X. (2020). COVID-19 and the cardiovascular system. Nat. Rev. Cardiol, 17, 259-260.

Zumla, A., Chan, J. F., Azhar, E. I., Hui, D. S., & Yuen, K. Y. (2016). Coronaviruses-drug discovery and therapeutic options. Nat. Rev. Drug Discov, 15, 327-347.