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Review Article

Association of Vitamin-D and VDR with ACE2 Modulates the Severity in COVID-19

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Abstract

The corona virus disease (COVID-19), lethal to the human population is easily transmitted from one person to another. The major causative agents of novel corona virus (nCoV) are severe acute respiratory syndrome corona virus disease-2 (SARS-CoV-2) and the Middle East Respiratory Syndrome corona virus disease (MERS-CoV). Both novel strains are similar in their pathogenesis and at severity, the condition leads to death. In COVID-19, mortality is strongly associated with humans suffering from diabetes cardiovascular disease and hypertension. The COVID-19 with its spike protein mediates with the Angiotensin-converting enzyme-2 (ACE2) receptor to enter inside the body. The spike glycoprotein binds to ACE2 may be a potent target for developing new specific drugs, antibiotics, repurposed drugs and vaccines. The balancing between ACE2 and Renin-angiotensin system (RAS) aid to reduce the multi-organs injury occurred by COVID-19 and at another criterion, the misbalancing condition between ACE2 and RAS leads to multi-organ damage. The polymorphism in ACE2 is liable to provide the prognostic effects on COVID-19 regulations. Vitamin-D binds with Vitamin-D receptor (VDR) to regulate the gene expression and affects cell proliferation, differentiation; apoptosis and tumor-genesis. VDR as a supplemental factor reduces the severity of various diseases and acts as a multi-targeted gene for various diseases. Vitamin-D and VDR down-regulates the expression of ACE2 and decreases the risk of COVID-19 infection. Targeting Vitamin-D and VDR against COVID-19 may be a potential therapeutic approach for reducing the severity. VDR activation therapeutically targets and potential for Acute Respiratory Distress Syndrome (ARDS), Acute lungs injury (ALI) and Acute- lower respiratory infection (ALRI) diseases. This mini-review discusses the role of ACE2 in COVID-19, targeted with Vitamin-D and VDR to reduce the severity of viral pathogenesis. Targeting with Vitamin-D and VDR directly down-regulates the action of ACE2 receptor, thereby developing a drug, vaccine or antibiotics might be a potent option to decreases the risk of COVID-19 infection. By the shreds of evidence acquired, Vitamin-D and VDR may be the potential therapeutic option for targeting COVID-19.

Keywords: *COVID-19; SARS-CoV-2; ACE2; Vitamin-D; VDR*

Abbreviations

COVID-19: Corona Virus Disease; nCoV: Novel Corona Virus; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus Disease-2; MERS-CoV: Middle East Respiratory Syndrome Corona Virus Disease; ACE2: Angiotensin-Converting Enzyme-2; RAS: Renin-Angiotensin System; VDR: Vitamin-D Receptor; CKD: Chronic Kidney Disorder; Ang-II: Angiotensin-II; ARDS: Acute Respiratory Distress Syndrome; DNA: Deoxyribonucleic Acid; ALI: Acute Lungs Injury; SKP2: S-Phase Kinase-Associated Protein-2; ALRI: Acute- Lower Respiratory Infection; LPS: Lipo-Polysaccharide

Introduction

The pandemic corona virus disease (COVID-19) is a member of the Corona viridae family; positive single-strand RNA viruses are lethal to the population [1]. The transmission capability of this virus is highly vulnerable and the source ranging from air-borne [2], from one to another person, oral to fecal matter by direct or indirect contact [3]. The major experienced symptoms of this novel corona virus

(nCoV) are headaches, body pain, dry cough, fever, diarrhea and also patients experience dyspnea, myalgia, hemoptysis [4], severe acute respiratory syndrome and multiple organ failure in humans [5]. The two major causative agents of nCoV disease are severe acute respiratory syndrome corona virus disease-2 (SARS-CoV-2) and the Middle East Respiratory Syndrome corona virus disease (MERS-CoV). The expression of SARS-CoV-2 results in respiratory failure and poor prognosis leads to causes of myocardial-infarction, lethal to humans. MERS-CoV in humans leads to cardiac arrest and failure. The clinical symptoms of MERS-CoV and SARS-CoV-2 are similar in their pathogenesis that causes myocardial infarction leads to death. The COVID-19, easily done in concern with the patient's regarding hypertension, diabetes mellitus, cardiovascular diseases, pulmonary and rheumatic diseases [6-8]. The surface spike (S) is a glycoprotein, acts as a molecular machine for mediating the COVID-19 to binds with its host cell receptors. The COVID-19 mediates with the spike to connect with Angiotensin-converting enzyme-2 (ACE2), a part of the Renin-angiotensin system (RAS), expressed in heart and lung tissues leads to pneumonia. The evidence suggests that ACE2 expression in tissues and membrane enhances the risks of COVID-19, along with multi-organ injuries [9]. Vitamin-D known as sun-shine vitamin helps to absorb calcium from the human body [10]. The lack of Vitamin-D in the human body increases the risk of osteoporosis (bone-related problem) [11] and increases the severity of viral infections (respiratory problems) [12]. The evidence suggested that lack of Vitamin-D deficiency associated, increases the risk of COVID-19 [13] and in other criteria, a sufficient amount of Vitamin-D production prevents the risk of nCoV and diverse organ damages [14]. The studies also suggest that lack of vitamin-D deficiency increases factors relating to COVID-19, includes age, obese level, diabetes, darker skin tone, inadequate exposure to sun rays and chronic illness [15,16]. Vitamin-D has a role in the immune system, nerves and muscles. Vitamin-D receptor (VDR) is expressed in the heart, liver, kidneys, lungs and other parts of organs. Vitamin-D with its receptor (VDR) plays a major role in the immune system and attenuates the anti-inflammatory and anti-microbial properties within the body. The role of VDR is to allow the human body to respond with Vitamin-D [17-19]. Targeting with Vitamin-D and VDR directly down-regulates the action of ACE2 receptor, thereby decreases the risk of COVID-19 infection [20]. Rather than viral pathogenesis, as natural modulators, VDR is multi-targeted for diseases including types of cancer [21], osteoporosis [22], chronic kidney disorder (CKD) [23-26], renal disorders and transplantation [27], metabolic syndrome [28], immune disorders [29] and dermal disorders [30]. The patients suffering from the severity of COVID-19 experience multi-organ damages, in rare conditions due to impotent treatment leads to death [31]. This present study approach paves the way to consider Vitamin-D and VDR may be the potential therapeutic option for targeting COVID-19.

ACE2 bonds with COVID-19

The ACE2 acts as a transmembrane enzyme with its extra-cellular regions and sets a target region for the virus to deal with its replication and pathogenic action inside the human body [32]. ACE2 is a negative effector of RAS, plays a pivotal role in maintaining the biological nature and pathophysiological condition of the body [33]. The expression of ACE2 found in all organs of humans varies with ranges. ACE2 acts as a median for the interaction of COVID-19's spike protein for pathogenicity [34]. The higher expression of ACE2 carries the viral-particles from the lungs to other parts of organs via blood-circulation [35]. The balance between RAS and ACE2 helps to reduce the multi-organ damages occurred by COVID-19. In rather condition, down-regulation of ACE2 and imbalance condition of RAS with ACE2 leads to multi-organ damages in COVID-19 [36]. Among the human organs, the highest expression of ACE2 is found in myocardial cells, Kidneys, urothelial cells and tremendously expressed in the alveolar membrane, small intestine and especially in the ileum [37]. The COVID-19 enters and easily attaches to ACE2, especially in peoples with diabetes mellitus, hypertension, elderly age, obesity and smoking. The various studies also suggest that in the elderly population the peoples suffering from diabetes easily get exposed and severe to COVID-19 due to low cytosolic pH [6-8,38,39]. SARS-CoV-2 down-regulates the activity of ACE2, results in toxic Angiotensin-II (Ang-II) over-accumulation and causes Acute Respiratory Distress Syndrome (ARDS). In 2014 the studies conducted against the influenza A (H7N9 strain) virus, induced severe acute lungs-injury in humans and were found to be protective with the help of ACE2 enzyme [40]. The pieces of evidence suggested that the expression of ACE2 in tissues and membranes enhances the risks of COVID-19 along with the inflammatory lesions [9]. Thus, the ACE2 polymorphism may play an important role in the state of prevention, diagnosis and treating the individual and obtain the prognostic effects on COVID-19 regulations. COVID-19's spike protein binds to ACE2, maybe a potent target in the development of new specific drug, antibiotic, repurposed drug and vaccines.

Vitamin D and VDR linkage in COVID-19

VDR is the nuclear transcriptional factor that binds to the specific deoxyribonucleic acid (DNA) site and modulates the expression of targeted genes [41]. VDR as a major supplement factor and impact creator plays a major role in every form of human life. Vitamin-D binding with VDR regulates gene expression and affects cell proliferation, cell differentiation; apoptosis and carcinogenesis [42]. The activation of VDR reduces the severity of an ARDS and Acute lung injury (ALI) in COVID-19 patients [7]. The VDR expression is majorly found in organs concerning the heart, lungs and kidneys, throughout the body, it's distributed in macrophages, lymphocytes, endothelial cells and dendritic cells. Vitamin-D expression modulates the immune responses (innate and adaptive) and binds with VDR to prevent inflammatory responses. The VDR is not a specified single targeted gene, its nature is ubiquitous and the expression rate takes place in various organs, used as a multi-targeted gene for disease pathogenesis [17-19]. Vitamin-D and VDR down-regulate the ACE2 and decreases the risk of COVID-19 infection. Few evidences suggested that VDR acts as a negative regulator for RAS [43]. The activation of VDR inhibits the S-phase kinase-associated protein-2 (SKP2), which plays a key role and central mechanism for viral replication of COVID-19. To correlate the Vitamin-D and VDR status few studies suggest polymorphism in VDR regulates the SARS-CoV-2 expression in higher spreading rate and leads to COVID-19 outcomes [44]. Another study suggested relating to VDR polymorphism in children, increases the vulnerability rate of Acute- lower respiratory infection (ALRI) in COVID-19 [45]. Furthermore, studies propose that Vitamin-D and VDR reliable to suppress the severity and may act as a potential therapeutic target for COVID-19 via ACE2 [7,38,46,47]. Calcitriol is the synthetic version of Vitamin-D [20,48], increases the expression of ACE2 and VDR in a Lipo-polysaccharide (LPS) induced rat models and this increased rate of ACE2 and VDR plays a protective role against the developmental receptor [49,50]. Thus, by the above studies suggested the Vitamin-D and VDR considered to reduce the severity of viral actions and potentially targeted against COVID-19.

Conclusion

This mini-review article summarized the importance and severity of COVID-19 with its physiological role in the human population. Apart from that the role of ACE2 in COVID-19 and most commonly targeted vitamin-D and VDR role in pathogenesis was proposed. By overcome of these studies, strong evidence suggested the ACE2 may act as a median and be used as a therapeutically targeted receptor for COVID-19. The expression of ACE2 found throughout the body is varied in ranges and the shreds of evidence suggested that their membrane expressions and tissue activity enhances the risks of COVID-19, along with increasing the inflammatory injuries within organs. By decreasing the over expression of ACE2, acts as a therapeutic option for minimizing the viral pathogenesis and especially criteria of COVID-19. Targeting ACE2 for viral propagation is an apt state for controlling this lethal disease. Thus, the genetic analysis in ACE2 and polymorphism in ACE2 play an important role in treating the individual and prognostic effect on COVID-19. ACE2 may be the new target approach for finding and developing the new specific drugs or vaccines, repurposed drugs and antibiotic Vitamin-D and VDR are multi-molecular targets that play an important role in immune systems and aid to reduce the severity of viral actions inside the body. As explained above nature of VDR, as a multi-potent targeted gene used in targeting various diseases including viral pathogenesis. In COVID-19 regulations, Vitamin-D and VDR may be used as a down-regulator for ACE2 and suppress the viral actions. In another criterion Vitamin-D and VDR, which aims to block the interactions of SARS-CoV-2 with ACE2 receptors, promotes a suitable therapeutic approach for targeting COVID-19. The activation of VDR may therapeutically potential for ARDS, ALI and ALRI diseases related to COVID-19, induce multi-organ injury in humans. Considering the impact and severity of COVID-19, it's important to detect in the earlier stages and it's better to socially distance the affected person from the healthy population.

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Conflict of Interest

No conflict of interest to be declared by the authors.

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