

**Review Article**

**Association of Vitamin D with CRP as A Diagnostic Marker of Cytokine Storm in COVID-19 Patients**

*Samina Gul<sup>1</sup>, Muhammad Ajmal Khan<sup>2</sup>*

**Abstract**

The novel corona virus disease (COVID-19) outbreak imposed the catastrophic impact on the communities worldwide. Recent evidence suggests that vitamin D is one of the important factors that affects the COVID-19 disease severity and the mortality increased in the vitamin D deficient COVID-19 patients. Since C-reactive protein (CRP) is an indicator of inflammation, an increase in levels of Vitamin D hence leads to the decrease in cytokines which ultimately affects the degree of C reactive proteins in the patients. In this review, we have focused here on the association between vitamin D and surrogate marker C-reactive protein (CRP) in cytokine storms in COVID-19 patients.

**Keywords:** COVID-19, cytokine storm, C-reactive protein, vitamin D

*International Journal of Human and Health Sciences Vol. 06 No. 04 October'22 Page : 355-361  
DOI: <http://dx.doi.org/10.31344/ijhhs.v6i4.473>*

**Introduction**

The respiratory tract infection is less frequent in summer than in winter, cold temperature the virus spread and transmitted easily. Several pneumonia cases reported in Wuhan Hubei province of China in 2019<sup>1</sup> and the disease spread at light speed to the other provinces of China and 6 continents within 3 months,<sup>2</sup> which imposed catastrophic effect on every society but the mortality rate and severity are higher in elderly population, the World Health Organization (WHO) subsequently named as 'CORONA VIRUS DISEASE 2019' (COVID-19) in February 2020.<sup>3</sup> This disease shows high variability in clinical severity, in which 30-40% develop mild symptoms, 40-50% remain asymptomatic and 15% develop severe cases with subsequent systematic inflammation, multi organ failure and fatal outcome.<sup>4</sup> In elderly population, the weak immune system response to high load of SARS-COV2 and subsequently lead to increased level of cytokine production by the overreaction of adaptive immune system.<sup>5</sup> In China, the clinical data obtained from the COVID 19 patients to better understand the immune system defense mechanism against COVID 19, indicate the presence of high concentration of

cytokine storm such as ILK 6, TNFalpha, MCP1, MIP1A, IP10, and GCSF in COVID 19 patients samples.<sup>6</sup> How vitamin D impact on immune system have been supported widely by multiple studies.<sup>7</sup> The level of vitamin D in winter might lead to the susceptibility of some respiratory tract virus such as RSV respiratory syncytial virus, influenza virus infection has been suggested by many studies.<sup>8</sup> During 1918-1919 viral influenza virus pandemic vitamin d suppressed the cytokine storms suggested by some researcher.<sup>9</sup> Here we focus on the deficiency of Vitamin D, COVID 19 and unregulated inflammation CRP which is nonspecific marker of the cytokine storm severity measurement in COVID 19 case.

**Sources and Roles of Vitamin D**

Vitamin D is responsible for wide spectrum of immune modulatory, anti-inflammatory, anti-fibrotic and antioxidant actions as a fat soluble secosteroid. In humans, the most abundant type of vitamin D are D2 and D3 i.e., Ergocalciferol and cholecalciferol respectively. Our liver converts D2 into 25-hydroxyergocalciferol and D3 into 25-hydroxycholecalciferol. 25-hydroxyvitamin D25(OH)D is principal metabolite of vitamin D, which is measured to find out the vitamin D level

1. Faculty of Medicine, Lab of Molecular Genetics of Aging and Tumor, Kunming University of Science and Technology, Chenggong Campus, Kunming, Yunnan Province 650500, China.
2. Division of Life Science, Center for Cancer Research, Hong Kong University of Science and Technology, Kowloon. Hong Kong.

**Correspondence to:** Samina Gul, Faculty of Medicine, Lab of Molecular Genetics of Aging and Tumor, Kunming University of Science and Technology, Chenggong Campus, Kunming, Yunnan Province 650500, China. Email: [minna\\_gul@hotmail.com](mailto:minna_gul@hotmail.com), [samina.gul@cecos.edu.pk](mailto:samina.gul@cecos.edu.pk)

of an individual.  $1-\alpha$  hydroxylase enzyme present in kidney generates [1, 25-(OH) $_2$ D], which is the active form of vitamin D.<sup>10</sup> The calcitriol circulates as hormone in blood, which encourage the healthy remodeling of bone and play major role in calcium and phosphate homeostasis. Vitamin D affects gene expressions –both genomic and non-genomic.<sup>11</sup> The genomic impact of Vitamin D includes ligand activated transcription factors known as VDR vitamin D receptor, calcitriol binds to VDR and heterodimerizes are form in some cases with active metabolites of vitamin A retinoid X receptor RXR. This interaction regulates the gene expression positively or negatively.<sup>11</sup> Non genomic effect includes the interaction of dependent genes in promoter region of vitamin D with responsive element VDRE.<sup>12</sup> Besides, these also play major role in neuro muscular function, cellular growth, immune function includes anti-inflammatory action, its insufficiency associated with overexpression of TH1 cytokines, and inhibit the expression of inflammatory cytokines e.g tumor necrosis factor TNF alpha, IL-1B, ILK6, IL-1D.<sup>13,14</sup> Food source of vitamin D are fat fish, cod fish oil, daily recommended allowance (15-20microgram) for adult, with exception of mushroom no plant source of vitamin D. Sundried mushroom contain 7 and 25 microgram/100g of vitamin D.<sup>15</sup>

### Immune System and Vitamin D

Vitamin D play major role in defense mechanism of immune system<sup>16</sup> and have impact on immune system cells such as dendritic cells, neutrophils, macrophages, T and B lymphocytes.<sup>17</sup> Vitamin D inhibits the pro-inflammatory cytokines storms production.<sup>18</sup> In disease pathogenesis, the innate immune cell including neutrophil, macrophages, mast cells, cytokines storms (G-CSF, MCP-1A, IL-6, IL-2, IL-7, and TNF alpha), lymphopenia, reduced functional state of T cell play important roles.<sup>19</sup> Vitamin D minimize the pro-inflammatory response in patient through different mechanism including interaction with immune cell such as neutrophil, macrophages and mast cells, reducing leukocytes infiltration into inflammatory sites and selective suppression of inflammatory cytokines.<sup>20</sup> Vitamin D also plays important roles in regulation of thrombotic pathway. In COVID-19 patients, the thrombotic complications are common,<sup>21</sup> and deficiency of vitamin D associated with increase thrombotic episodes. Tregulatory lymphocytes T(reg) defense against viral uncontrolled

inflammation has been reported to be low in severe COVID 19 patients.<sup>22</sup> Vitamin D supplementation increases the T(reg) level.<sup>23</sup>

### COVID-19 and C-reactive protein(CRP)

C-reactive protein-related with elevated response of ongoing inflammation and much higher in bacterial infection than in viral infection, is produced in liver.<sup>22-25</sup> It is used as a diagnostic biomarker in infection. It is key protein of acute phase response in normal healthy individual and in any tissue damaging event; it appears in blood within 6-10 hours. CRP baseline reported in blood is less than 10microgram/ml.<sup>26</sup> In disease or tissue trauma CRP blood level increase 10-100 folds within 10-72 hours, level above 100 microgram/ml associated with poor disease prognosis, CRP differentiate viral from bacterial infection, CRP level in viral infection ~ 20microgram/ml and in uncomplicated bacteria level increase >40microgram/ml, in COVID 19 the CRP level varied from 28.7microgram/ml in non-severe disease and 47.6microgram/ml in severe disease.<sup>26</sup> Significantly elevated CRP level in COVID 19 patient >100microgram/ml reflected coagulation abnormalities, multiple organ failure, tissue damaging, and pathologies associated with cytokine storms.

### Vitamin D and CRP

CRP is non-specific marker, in COVID 19 it is more specific to cytokine storm and IL-6 bioactivity.<sup>27</sup> In COVID 19 severe patient dendritic cells, IL-6 production by monocytes, macrophages lead to CRP production and systematic pro-inflammatory cytokines.<sup>27</sup> The anti-inflammatory cytokines absence leads to high grade inflammation and cytokine storms.<sup>28</sup> A recent study shown that vitamin D lead to reduction of CRP by alter the bioactivity of IL-6 to induce more anti-inflammatory cytokines, such as IL-10 instead of IL-7 as pro-inflammatory cytokines,<sup>29</sup> as shown in figure 1.

### Renin-angiotensin System

Renin-angiotensin system regulate blood pressure, systematic vascular resistance, fluid and electrolyte balance by conversion of angiotensinogen to angiotensin I and angiotensin II which is catalyzed by ACE,<sup>30</sup> the rate limiting enzyme of RAS, kidney synthesis and secrete renin and its main source is juxtaglomerular cells, which release the renin from storage granules. This secretion is inhibited by via Ang II via VT1R. The endothelial cells surface has two receptor

of ACE are AT1R and AT2R. Ang II release catecholamines and vasoconstriction. Ang II via AT1R induce the release aldosterone and sodium reabsorption.<sup>31</sup> A novel homologue of ACE, ACE2 expressed in kidney, lung, cardiovascular system, vascular smooth muscles, and endothelial cell. ACE2 cleave Ang1 to Ang 1-9, Ang II to Ang 1-7. Ang 1-9 via AT2R exert cardiovascular protection effect and counterbalance the effect of Ang II and Ang 1-7 via AT1R and Mas oncogene. RAS produce inflammation, vasoconstriction, hypertrophy and fibrosis and ACE2 counteract those effects,<sup>32</sup> as shown in figure 2.

### C-reactive protein Mechanism

C-reactive protein (CRP) mechanism consist of three isoform, mind isoform, monomeric isoform and native isoform. Isoform-n is synthesized in liver,<sup>33</sup> and also synthesized by other cells, e.g., macrophages, adipocytes, muscles and lymphocytes.<sup>34</sup> Native CRP dissociate and give rise mCRP, have different inflammation properties, on partially dissociation another mCRP give rise. In CRP biology the important stage is complement activation.<sup>35</sup> The complement activated via c1q classical pathway, c1q activate the chain of c4, c2, c3 and c3 activated induce, cell lysis, opsonization and inflammation,<sup>36</sup> as shown in figure 3. CRP caused cell cycle arrest and DNA damage by induction of GADD153 gene expression. CRP main function is contributed to inflammatory process attached locally at DNA damage tissue and inflammation, activate complement binding to Fc receptors which induce the production of pro-inflammatory cytokine.<sup>37</sup>

### RAS, CRP and SARS-COV2 Infection

SARS-COV2 is virus which is spherical in shape and covered by lipid envelope, chain of RNA in positive sense covered by nucleocapsid make its genome. This virus has important externally S protein, M protein and E protein for its pathogenesis. S protein is important for binding its ACE2 receptor, E protein is important for haemagglutinin esterase and assembly of virus and M protein for structural support. During infection the SARS-COV2 virus bound to RAS member ACE2 and transported molecule into cell.<sup>38</sup> ACE2 initially play protective role against Ang II harmful effect by transferring Ang II to Ang 1-7. This internalization of ACE2/virus complex increased the expression of ADAM17 (adisintegrin metalloprotease 17), the proteolytic effect of ADM17 decrease the ACE2 on the surface

of cell.<sup>39</sup> The Ang II induced the pro-inflammatory cytokines production, fibrosis, vasoconstriction, and CRP production through its AT1R receptor and nuclear translocation of NF-KB. The drastic effect of ACE2 on cell surface reduction lead to deterioration of conversion of Ang II into Ang1-7 and produce inflammation, under this mechanism the SARS-COV2 mechanism effect the RAS and increase production of CRP,<sup>40</sup> as shown in figure 3.

### Effect of Vitamin D on CRP, RAS and SARS-COV2:

Low level of vitamin D increase Ang II, RAS activity and decrease the (PRA) plasma renin activity shown by many researchers.<sup>41</sup> Vitamin D act as negative regulator of RAS, prevent overaction of VDR knock out mice.<sup>42</sup> and suppress the transcriptional activity in renin gene promoter act as renin expression negative regulator as shown in figure 4. The cellular internalization of ACE2/virus complex increased Ang-II activity which induced the pro-inflammatory cytokines and CRP production. SARS-COV2 binding with ACE2 down-regulate its activity, expression and increased the risk of acute lung failure.<sup>43</sup> Vitamin D potentially disrupt the impact of SARS-COV2 via increased the expression of ACE2.<sup>44</sup> Vitamin D inhibit the nuclear receptor corepressor 1 (NCOR1) renin protein expression enhancer and cyclic adenosine monophosphate Camp has been shown by many studies. Therefore, vitamin D blocked the angiotensinogen conversion to Ang I and ACE Ang II and down-regulate the renin transcript which suppress the RAS activity [46]. The relation between Vitamin D and CRP concluded that risk factor Predicated reduce to 16.6% following vitamin D status normalization (>75nmol) by low vitamin D and high CRP.<sup>46</sup>

### Conclusion

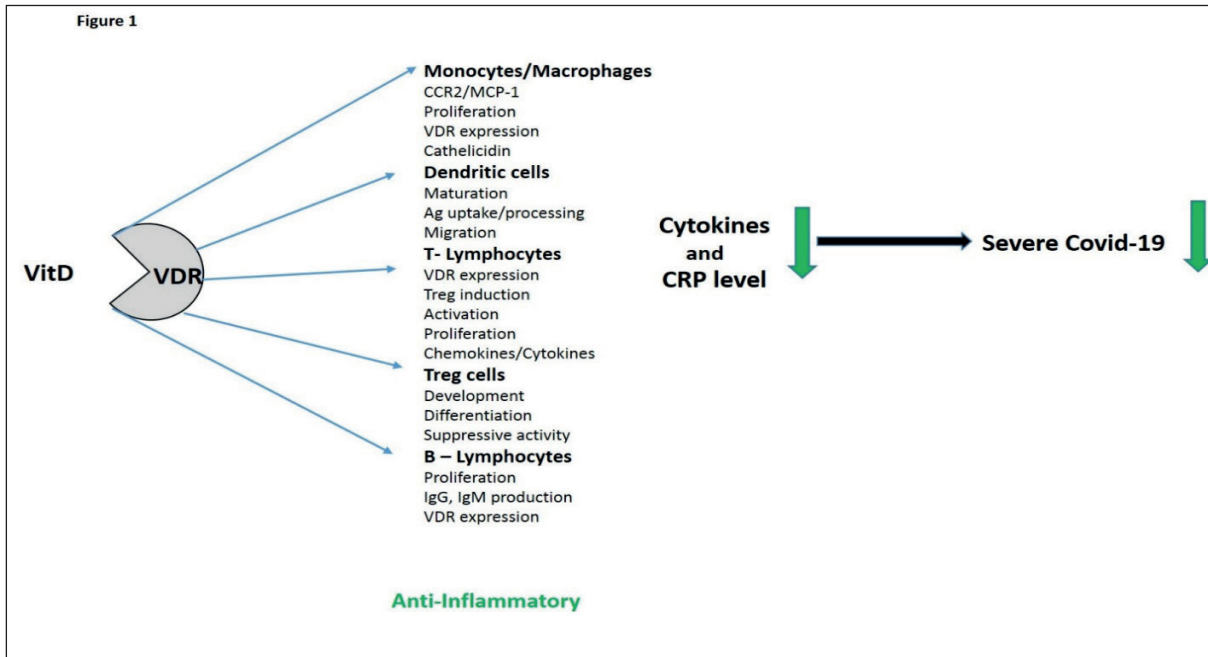
In summary, Vitamin D deficiency have both skeletal and non-skeletal effects. Vitamin D deficiency was frequently found in severe COVID-19 patients. Safely and significantly raised serum concentration of vitamin D leads to alter the bioactivity of CRP, which ultimately leads to more anti-inflammatory cytokines production and reduce disease severity risk.

**Conflict of interest:** The authors declare that they have no conflicts of interest.

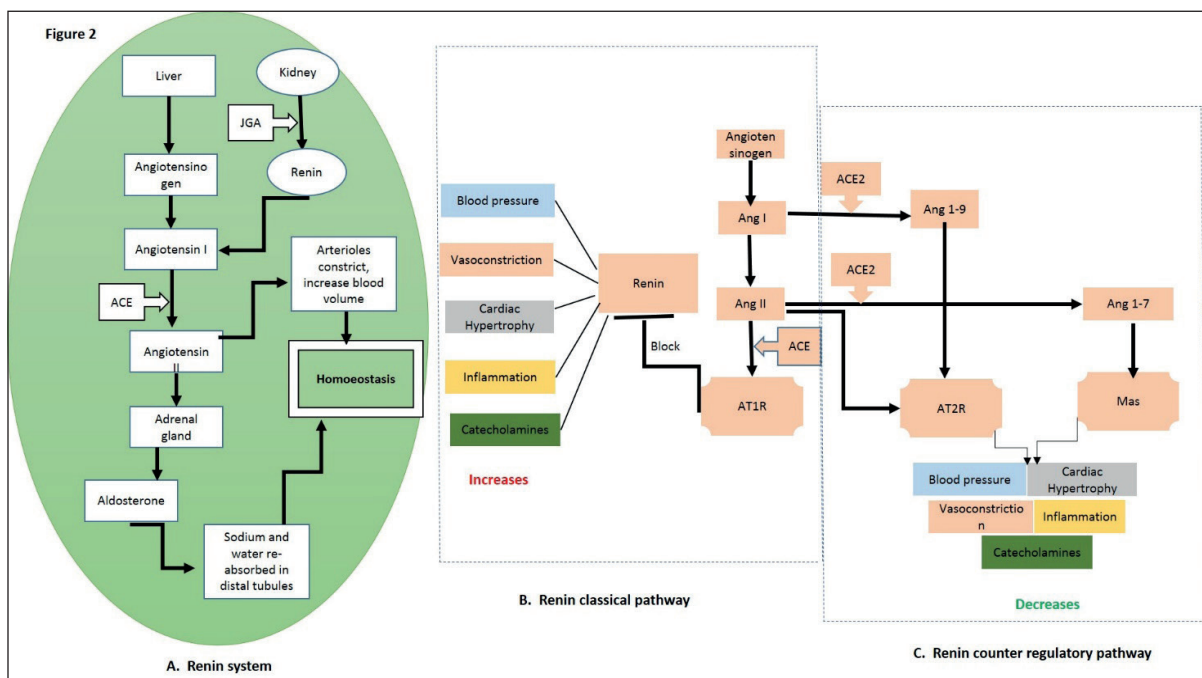
**Ethical approval:** Not applicable.

**Funding statement:** This review work was supported by none.

**Authors' Contribution:** SG was involved in review, compilation, manuscript writing, revision and final drafting. SG and MAK both were involved in literature search, inception and design of the paper, while SG and MAK both were involved in literature search,

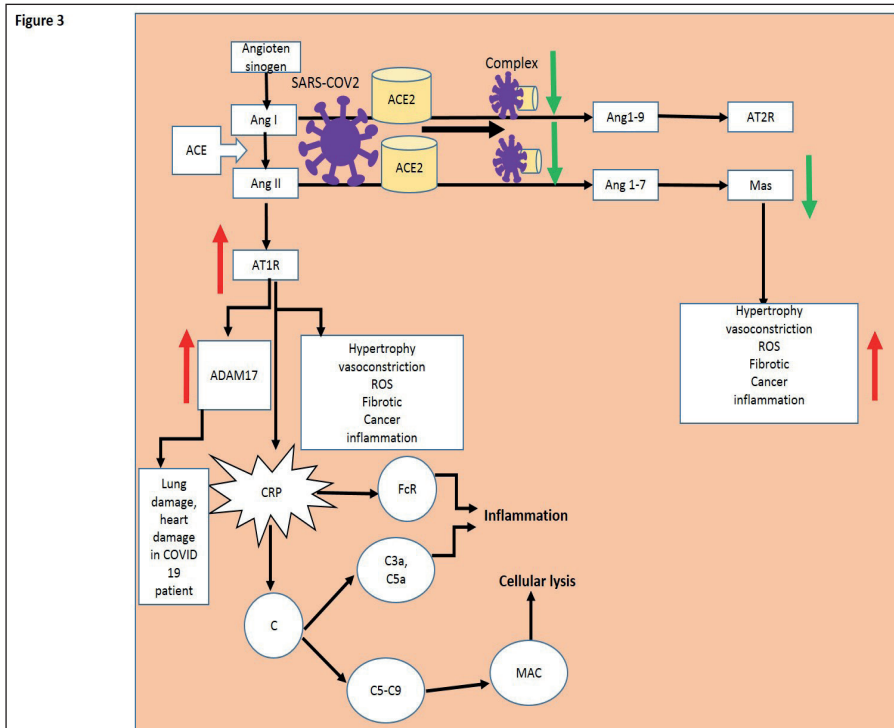


**Figure 1:** Vitamin D leads to the reduction of CRP level induce anti-inflammatory cytokines and reduce the COVID 19 severity.

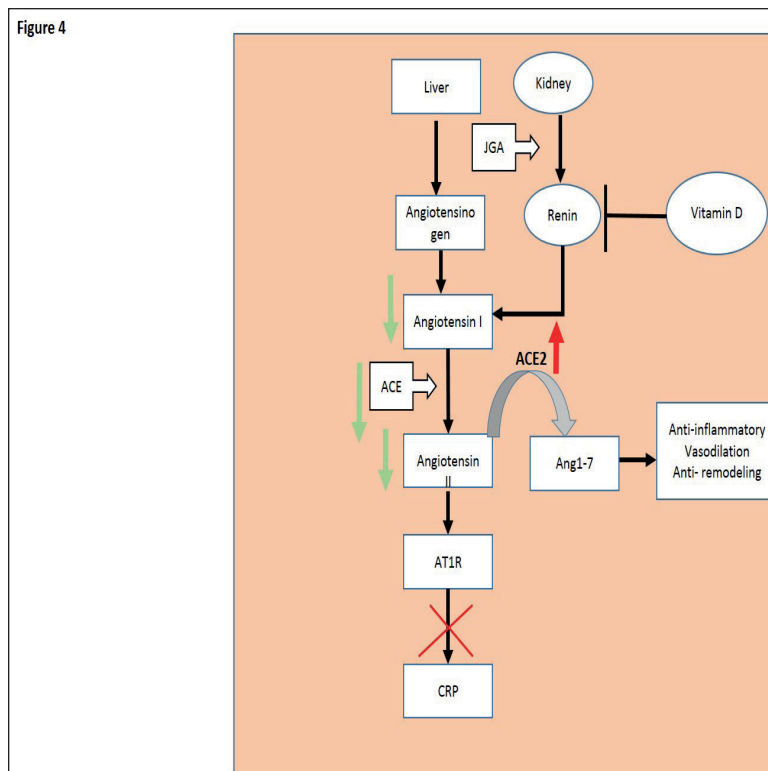


**Figure 2:** A) RAAS (Renin-angiotensin-aldosterone system) controlling regulation of blood flow and blood volume. B) Renin gene induces cleavage of Angiotensinogen to Angiotensin I via Angiotensin converting enzyme (ACE) converted to Angiotensin II; Ang II activates the Angiotensin 1 receptor which results in an increase of blood pressure, inflammation, hypertrophy and catecholamines and further effects on the vascular system. Ang II suppresses renin synthesis via AT1R. C) Renin counter regulatory pathway is activated through cleavage of Ang I to Ang1-9 via ACE2 and activate AT2R, Ang II to Ang1-7 which activate Mas receptor which decrease blood pressure, inflammation, hypertrophy and catecholamines.





**Figure 3:** SARS-COV2 disrupts the counter regulatory pathway of renin when attached to ACE2 which un-control the classical renin pathway and leads to hypertrophy, vasoconstriction, cancer, inflammation, and the Ang II and AT1R hyperactivity leads to higher expression of ADAM17 which cause lungs damage, heart, and vessels injury in COVID 19 patients and CRP, CRP activate complement and FcR receptor which cause cell lysis and inflammation.



**Figure 4:** Vitamin D suppresses the RAS activity by inhibition of renin, which lead to reduction of ACE, Ang-II and increase in level of ACE2, which leads Ang-II to Ang-1-7 to produce anti-inflammatory cytokines, decrease blood pressure and vasodilation.

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