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Letter to Editors

A genetic insight into vitamin D binding protein and COVID-19

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ABSTRACT

It's since December 2019 that Corona virus disease (COVID-19) has emerged to be the global issue of concern. A "pandemic"; this is what WHO has declared about the COVID-19 outbreak on March 3rd, 2020. Vitamin D and its deficiency have recently been claimed to be one of the potential factors affecting COVID-19 risks and outcomes [1]. As ***Selberstein et al.***, has recently discussed the effect of vitamin D deficiency, and the role of vitamin D supplementation in COVID-19 patients [2], I'd believe that vitamin D binding protein (DBP) is maybe also involved. A closer look on DBP and its action on regulating the circulatory vitamin D levels, its polymorphisms and their impact on COVID-19 prevalence and mortality, will be briefly discussed.

To the Editor

It's since December 2019 that Corona virus disease (COVID-19) has emerged to be the global issue of concern. A "pandemic"; this is what WHO has declared about the COVID-19 outbreak on March 3rd, 2020. Vitamin D and its deficiency have recently been claimed to be one of the potential factors affecting COVID-19 risks and outcomes [1]. As Selberstein et al., has recently discussed the effect of vitamin D deficiency, and the role of vitamin D supplementation in COVID-19 patients [2], I'd believe that vitamin D binding protein (DBP) is maybe also involved. A closer look on DBP and its action on regulating the circulatory vitamin D levels, its polymorphisms and their impact on COVID-19 prevalence and mortality, will be briefly discussed.

Vitamin D deficiency is considered as a global pandemic, with more than one billion subjects affected [3]. This deficiency is even more obvious in patients with kidney diseases, lacking the 1-hydroxy activating step [4]. However, there is increasing body of evidence supporting the idea of the extra-renal vitamin D metabolism machinery, through extra-renal vitamin D receptors. These receptors are not only regulating the vitamin D circulatory levels [4], but also seems to play a critical role on its immunomodulatory responses [5].

Recently, vitamin D deficiency was accused to be a risk factor for COVID-19. Vitamin D could act as an inhibitor for the virus entry through interacting with the angiotensin converting enzyme-2 receptor (ACE2), the one that serves as the entry point for the virus which having its (S) protein spike [6]. Calcitriol or (di-hydroxy vitamin D) can exert pronounced effects on ACE2/Angiotensin (1–7)/Mas receptor axis, enhancing the expression of ACE2 [7]. However, ACE2 polymorphisms have also been reported in different populations [6]. Additionally, there are increasing evidences reporting the vitamin D modulatory response on the macrophages, preventing them from the extra release of inflammatory cytokines and chemokines (Cytokine storm) [8].

As there are already published data correlating vitamin D deficiency with severe COVID-19, and illustrating the role of vitamin D in both adaptive and innate immunity, various ongoing studies are also addressing the effect of vitamin D and vitamin D related gene polymorphisms on patients with COVID-19 [9,10].

Vitamin D binding protein (DBP); which is mainly produced in liver, is regulating vitamin D circulating metabolites (free and total metabolites)[11,12]. It's worth noting that DBP is not influenced by vitamin D levels, but it's regulated by estrogen, glucocorticoids and inflammatory cytokines.

Indeed, DBP is known to be the most polymorphic protein, with it different alleles that are substantially affecting its biologic functions [11]. There are two most common DBP alleles; rs7041 and rs4588, which have been implicated on the pathogenesis of various clinical conditions [11], mainly by their affinity to vitamin D. Higher plasma levels of 25-hydroxy vitamin D (25(OH)D) were shown to be associated with subjects having the AA genotype within the rs4588 locus. While patients with GG genotype have shown less 25(OH)D levels after same dose of vitamin D supplementation [13]. Interestingly, both allelic variants (rs7041 and rs4588) are also donated to be associated to chronic obstructive pulmonary disease (COPD) [14].

On the other hand, it was also noticed that rs7041 locus was found to be associated with higher susceptibility to hepatitis C viral infection [15]. As DBP gene polymorphisms have been greatly correlated with higher susceptibility of infections, and vitamin D deficiency in different population [16–18], they may also have a role in COVID-19.

There are different DBP isoforms influencing vitamin D serum concentration and its bio-availability [14]. By combining this information with the discussed role of vitamin D and its impact on the pathogenesis of COVID-19, I'd hypothesize that a more severe reaction against viral infections is modulated by the human immune system, if no necessary concentrations of bioavailable vitamin D presented.

A recent study has showed the rs7041 locus to be associated with increased risk of COVID-19 infection and mortality [19]. Therefore, the association of the genetic polymorphisms of DBP and COVID-19 may depend on the modulatory pleiotropic effects of the bioavailable vitamin D levels. However, there's a genome-wide meta-analysis that has illustrated the DBP to have more four SNPs, which are also affecting the concentration of the 25(OH)D levels: rs2282679 (DBP), rs10741657 (near CYP2R1), rs12785878 (near DHCR7), and finally rs6013897 (at CYP24A1) [20].

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In conclusion, I'd highlight the need for further genetic analysis regarding the actual role of DBP genetic variations on the bioavailable vitamin D levels. There's also a need for more detailed studies regarding these genetic alleles, and their relation to the severity and mortality of COVID-19 infected patients. The use of both clinical research and genetic analysis may help us decipher the ambiguities of COVID-19 pandemic.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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