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Vitamin D Poising Androgen/Androgen Receptor Signaling Mediated Suppression Of Tmprss2 Expression In Lungs Epithelial Cell Of Elderly Male Covid-19 Patients

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Abstract

On 2020,March 11, the WHO proclaimed the epidemic to be a global pandemic, since COVID-19 is circulating quickly across the world.In comparison, the COVID-19 gender-disaggregated findings in several European countries suggest a comparable more among the sexes, but more extreme results in the elderly men.The S protein is known to arise from the virus surface and is the most essential for host attachment and penetration. To penetrate the cells, SARS-Cov-2 attaches to the ACE-2 and the TMPRSS-2 cell serine protease to be priming by host cell.A recent studyfindsSARS-CoV-2 spike protein primer proteaseexpression. TMPRSS2 is most abundant protein in ciliated cells and type I epithelial alveolar cells and up-regulated in human and mouse with aging.Supplementation of vitamin D(1,25-D) has demonstrated beneficial benefits in viral diseases, including influenza and HIV. The amount of 1,25-D is substantially down in serious COVID-19 patients. Immune reaction in COVID-19 patients deficient in vitamin D is strong. All this factors in enhanced mortality in COVID-19infected 1,25D3 deficient patients. Based on the versatile methodology in current COVID-19 pandemic, we hypothesized themolecular exploration of the potential therapeutic effectiveness in suppression of TMPRSS-2 expression via androgen/androgen receptor signalling.

Keywords:SARS Co V-2 infection, Androgen/Androgen Receptor Signalling, 1,25-D,TMPRSS-2 Primer, ACE-2 Receptor

1. Introduction

A new viral respiratory syndrome occurred in Wuhan, Hubei province, China, in 2019,Dec31. On 2020,March 11, the WHO proclaimed the epidemic to be a global pandemic, since COVID-19 is circulating quickly across the world.In the middle of the complexities around COVID-19, there remains a

trend that is consistent across countries and age ranges(1). Previous Chinese data shows that in the COVID-19 cases, the mortality risk in Chinese men was higher, 2.8 percent, compared to women, 1.7 percent(2). In addition to that men serve, on average, 49.5% of cases in 40 countries with Total sex-specific and mortality results(3). In comparison, the COVID-19 gender-disaggregated findings in many European countries suggest a comparable number of cases among the sexes, but more extreme results in the elderly men. The disease prevalence was detailed in men per 100,000 Swiss population aged 60 - 69 years, 70 - 79 years, and 80 years respectively 267, 281 and 477, as of 30 March(2). Furthermore, Chronic diabetes, elevated blood pressure, obesity, Aging and androgens exposure were linked to adverse COVID-19 prognoses(4).

The Severe Acute Coronavirus Syndrome 2 (SARS-CoV-2) genome is the COVID-19 coronavirus and is a positive, single-stranded RNA encoding nonstructural and structural proteins needed to sustain the viral cycle(5). Recently singh et al.(6) explore the four major structural proteins included: M- membrane; E-envelope; N- Nucleocapsid; and S- Spike.The S protein is known to arise from the virus surface and is the most essential for host attachment and penetration. To penetrate the cells, SARS-Cov-2 attaches to the ACE-2 and the TMPRSS-2 cell serine protease to be priming by host cell(7). Furthermore, singh et al.(8)concluded the role of ACE2, is a membrane-bound protein that is expressed in many tissues, including the cardiovascular system, adipose, intestinal and renal tissue, CNS, and in the lungs responsible for variety of consequences including anosmia, ageusia, fever, arthralgia,fatigue,dyspnea, cough,parenchymal lung abnormalities, bilateral infiltrates on chest imaging, respiratory failure, septic shock, diarrhea, myalgias, depression, anxiety, delirium, psychosis, lymphopenia, and cardio-renal defect, eye and dermatological infection(9, 10).

The expression or involvement of these host receptors ACE-2 and TMPRSS-2 cell serine protease verified its significant place in coronavirus disease pathogenicity(7, 11).A recent scRNA-seq research reveals the maximum expression of SARS-CoV-2 spike protein TMPRSS2 primer protease in ciliated and type I alveolar epithelial cells (AT1) and enhanced expression of TMPRSS2 in murine and human aging(12). Studies with transgenic TMPRSS2 mouse have shown that absence of TMPRSS2 could contribute to reduced lung replication, a weakened pro-inflammatory reaction and a relatively mild lung pathology(13). SARS-CoV-2 entry is reduced by the serine protease inhibitor camostat as TMPRSS2 functional inhibition occurs(11). ACE2 antibodies or soluble recombinant ACE2 may also reduce viral penetration and SARS-CoV-2 infection(7). A critical evaluation of regulatory pathways to regulate expression levels of ACE2 and TMPRSS2 could thus become important for the creation of potential new therapies for infections with SARS-CoV-2.

Supplementation of 1,25-D has demonstrated beneficial benefits in viral diseases, including influenza and HIV. The amount of 1,25-D is substantially down in serious COVID-19 patients. Immune reaction in COVID-19 patients deficient in 1,25-D is strong. All this factors in enhanced mortality in COVID-19 vitamin D deficient patients. Based on the versatile methodology in current COVID-19 pandemic researchers, 1,25-D supplements are suggested for the mass administration of at-risk communities for COVID-19.

2. Selection of literature for review

The findings technically relevant were gathered from Medline / Mendeley / ScienceDirect / Google Scholar/ PubMed and Springer link. Many keywords were included in the literature

review alone and in combination. Some of the keywords for literature evaluation are “COVID-19 infection”, “Epidemiology of aging pathology in COVID-19 infection”,“Pathophysiology of SARSCoV-2 attack”, “Involvement of viral spike protein S ofSARSCoV-2”, “Mechanism of Androgen/Androgen ReceptorSignalling”,“Androgen Receptor mediated expression of TMPRSS-2”,“Involvement of 1,25-D in SARS CoV-2 infection”. The present paper considered just Englishjournals. Also reference lists for the related journals that are not found by the initial searchmethodology is screened.

3. Association of Androgen Receptor with TMPRSS2 in COVID-19

Hollander and Hollander (14)observed a reduction in the spermatic vine testosterone level among elderly men in 1958, and Kent and Acone(15) documented an aging based drop in blood production, which many others subsequently verified(16, 17).Androgenic activities of testosterone are regulated by the AR coupling, either directly or through 5α-reduction to DHT. Part of testosterone's physiological functions are aromatization to estradiol, which leads to binding with estrogen receptors (ERs)(18). However, low or no level of androgen physiologically increases the AR mRNA and also strongly expressed in castration-sensitive prostate cancer, with amounts several times greater than those in primary untreated tumour, compatible with immunohistochemical findings(19, 20).Of note, TMPRSS2 has been extensively examined with respect to prostate cancer where it is highly expressed and TMPRSS2 expression in reaction to androgens has been enhanced by direct androgen receptor transcriptional control (AR)(21) (Figure 1).

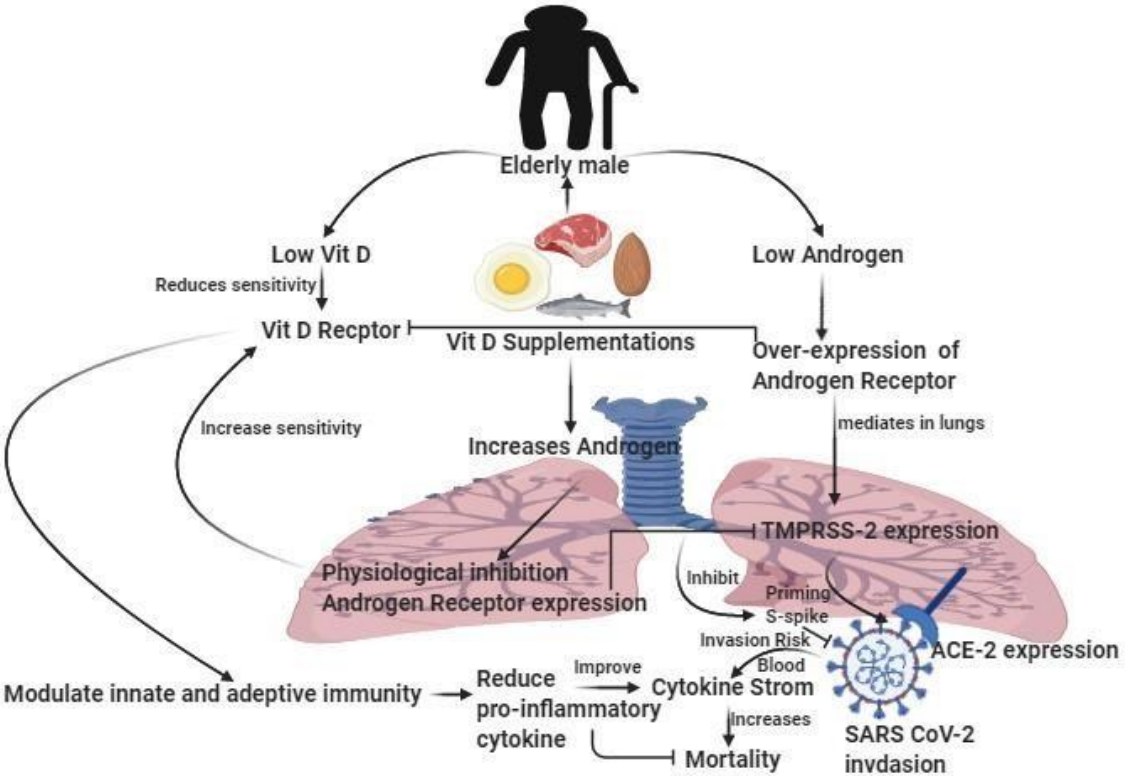

Figure 1: Demonstrate therapeutic potential of Vit D in association with Androgen/Androgen Receptor signalling mediated suppression of TMPRSS2 expression in lungs epithelial cell of elderly male COVID-19

patients

4. Molecular explanation of Vitamin D(1,25-D) in COVID-19 patients

The primary source of 1,25-D to humans is its skin synthesis under the control of solar radiation. Following two phases of hydroxylation, it becomes an active form of 1,25-dihydroxyvitamin D, or calcitriol. The first stage is in the liver, generating 25-hydroxyvitamin D (25OH-D). In the second example, renal proximal tube epithelial cells as well as certain extra-renal tissue and cells, such as endothel and macrophages, carry out hydroxylation.The 1,25-D has a broad variety of pathways to decrease the likelihood of microbial disease and mortality, including physical barriers, innate cellular immunity and adaptive immunity(22).In March 2020, low 1,25-D may be hypothesized as a correlation between age, comorbidities, and increased risk of complications and mortality in some places, such as northern Italy, due to COVID-19 infection(23).In large observational trials, 1,25-D deficiency is linked with low levels of testosterone(24). Furthermore, in the analysis of male elderly 1,25-D was shown to be closely correlated with testosterone levels after modification for confounding variables and mildly but substantially improved testosterone levels after 1,25D supplementation(25, 26).However, a randomized controlled trial concluded the result with1,25D treatment has almost no effect on serum total testosterone levels in low-total testosterone medium-age, normal males(27) Figure 1.

Notably, through the previous study data explored the only recognized regulator of TMPRSS2 expression, are Androgenics, which could explain the prevalent presence of males in severe COVID-19 infection(28, 29). However, the cells of LNCaP produce androgen receptor (AR), are particularly vulnerable to androgen stimulation by 1,25D, whereas many other lines of prostate cancer that neglect AR, including PC-3, DU 145, and ALVA-31, are far less responsive to 1,25-D(30, 31).The growth inhibitory effect was restored by coating the cells in FBS medium with 1,25-D and low androgen concentrations(32). In the meantime the antiandrogen Casodex which blocks the role of AR may abolish the inhibitory effect of growth of 1,25-D. Since both AR-positive cell lines are more susceptible to 1,25-D inhibition of progression, androgen/AR signaling may be essential for anti-proliferating activities of 1,25-D(32).In endothelial tumor cells, 1,25-D -induced VDR-mediated signals can significantly decrease phospho-errk, phospho-act and the Bcl-2 antiapoptotic protein andCaspase-3 expression and poly(ADP)-ribose polymerase cleavage were increased in tumor cells but not in regular endothelial cells.The 1,25-D -induced VDR-mediated signals will dramatically delay the in-vitro and in-vitro development of prostate cells. Similar to the prostate, AR dependent TMPRSS-2 expression in some cell of the lungs is seen in few studies(33).Opposite to the previous study several lines of evidences from the current review indicate the role of androgen activity in the antiproliferative impact of 1,25-D on prostate cancer cells.Based on these findings, potential therapeutic effect of 1,25-D in SARS CoV-2 infected patient was hypothesized.A study reports that antagonists, degraders, or castration inhibition in AR may contribute to dose-related decreases in the expression of TMPRSS2 and ACE2 and minimize SARS-CoV-2 infection(33).Thus, once the physiological concentration of androgen achieved in presence of 1,25-D, the expression level of AR is reduced at cellular level which further downregulate the expression of TMPRSS-2 primer.Therapeutic targeting of TMPRSS2 expression or behaviour can also be helpful not only to patients infected with coronavirus, but also to those infected with influenza.

5. Conclusion

In conclusion, VitD is interested in several aspects, most of them being very encouraging and facilitating the beneficial function of VitD. In a mechanistic viewpoint, there are sound explanations for postulating that 1,25-D modulates host responses in the early viraemic as well as in later hyperinflammatory phases of the COVID-19 extreme acute respiratory syndrome (SARS-CoV-2).A variety of hospital-based treatment studies have been reported to date, but it could prove difficult to identify a signal for 1,25-D supplementation in severe COVID-19. Furthermore, 1,25-Dsupplementation is beneficial elderly male patients with COVID -19 infection for raising the level of androgens. However,no effect on serum total androgens seen innormal adult patients. Furthermore, However, questions regarding vitamin D toxicity also increase, unwilling to prescribe supplementation.Thus, it iscarefully recommended along with other micronutrients such as vitamin B12/ B6 and folic acid and calcium.

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Conflict of interest

The authors declare no interest dispute.

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