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ROLE OF VITAMIN D IN CREATING IMMUNITY AND REDUCING SEVERITY OF COVID -19

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ABSTRACT

Vitamin D deficiency seems to be associated with severe outcome in the patients with COVID -19. Since the beginning of the pandemic till date this has sparked various discussions, researches and randomised control trails, with many more underway. It seems that vitamin D can be a promising factor in the fight against this pandemic. It enhances our innate and adaptive immunity and ultimately kills the virus. It has also been seen as a potential agent to damper the cytokine storm which causes severe outcome in these infected patients. Supplementation of Vitamin D is being considered by many governments across the globe in view of these associations and benefits.

KEY WORDS :

COVID-19 : Severe Acute Respiratory Syndrome. Coronavirus 2. 1,25OHD: 1,25 hydroxy vitamin D. RAS : Renin angiotensin system. ACE: Angiotensin converting enzyme

نبذة مختصرة:

يبدو أن نقص فيتامين (د) مرتبط بنتائج خطيرة لدى مرضى COVID-19 منذ بداية الوباء وحتى الآن ، أثار هذا العديد من المناقشات والأبحاث ومسارات التحكم العشوائية ، مع المزيد من المناقشات الجارية. يبدو أن فيتامين (د) يمكن أن يكون عاملاً واعداً في مكافحة هذا الوباء. إنه يعزز مناعتنا الفطرية والتكيفية ويقتل الفيروس في النهاية. وقد تم اعتباره أيضاً عاملاً محتملاً لتثبيط عاصفة السيتوكين التي تسبب نتائج وخيمة في هؤلاء المرضى المصابين. يتم النظر في مكملات فيتامين (د) من قبل العديد من الحكومات في جميع أنحاء العالم في ضوء هذه الجمعيات والفوائد.

الكلمات الدالة: كوفيد -19: متلازمة تنفسية حادة وخيمة. 1. Coronavirus 2. 1,25OHD: 1,25 هيدروكسي فيتامين د.

RAS: نظام رينين أنجيوتنسين. ACE: الإنزيم المحول للأنجيوتنسين

INTRODUCTION

Living in the current pandemic for more than 12 months now, on one hand has put humanity under various restrictions and on the other has given us reasons to look at our lives in a new perspective. At the same time it has sparked the researches and students of sciences another entity to dig deep into, to find a link, to find associations from virus to animals to humans and also to look into various aspects of our social, physiological and economic wellbeing. The most important of all is the medical aspect of this disease, exploring every inch of our own bodies and environment to find an ultimate saviour, a cure, at least something that would help in preventing infection in immunologically naive individuals and at least trying to contain the severe symptoms such as acute respiratory failure, sepsis, thrombosis, cytokine storm and ultimate organ failure.

One such aspect which has been looked at in the last few months is the role of vitamin D in optimizing our immunity and thus in short and long term helping us build immunity to fight against the COVID-19.

The aim of this paper is to throw light on Vitamin D deficiency and its association with severity of COVID-19 and to discuss the immunosupportive and protective role of Vitamin D.

DISCUSSION

1. COVID-19

A mysterious disease originated in China by the end of 2019, this new disease caused by novel coronavirus was named *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2).

On 11 March 2020 WHO declared it as a pandemic. It has spread around the globe with 73.2 million cases till date and we are facing the second wave of the virus presently.

The virus has caused widespread morbidity and mortality, with official mortality figures currently at more than 1.65 million. (WHO COVID-19 data base, 2020)

The incubation period for COVID-19 lasts from 2-14 days. Fever, cough, shortness of breath, anosmia, headache, confusion, loss of taste, strokes, chilblains, malaise, sputum production, rhinorrhoea and nasal congestion, as well as gastrointestinal problems are some of the symptoms. In some patients lymphocytopenia and thrombocytopenia are also found and these findings are considered risk factors for developing severe forms of COVID-19. Severe pneumonia, acute respiratory distress syndrome, septic shock and multiorgan failure are main causes of death.



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It has been shown that older age, smoking, hypertension, obesity, diabetes, cardiovascular diseases and cancer etc increases the mortality rates (Bleizgys,.2020)

2. VITAMIN D

Vitamin D is not technically a vitamin, since it is not an essential dietary factor. It is rather a prohormone produced photochemically in the skin from 7-dehydrocholesterol. Vitamin D and its metabolites may be categorized as either cholecalciferols or ergocalciferols.

Vitamin D is thus considered a fat soluble steroid which can be synthesised in the skin with the help of solar ultraviolet radiation.

After 2 hydroxylation steps, its transformed into its active form 1,25 dihydroxy vitamin D or calcitriol.

First step takes place in liver and second in the renal proximal tubular epithelial cells, as well as by some extra renal tissues and cells such as endothelium and macrophages.
(Bleizgys,2020)

This active vitamin D produces its effects via the vitamin D receptors that are found almost on all cell type of human organism, and thus is capable of suppressing or stimulating the expression of numerous genes.

1. NORMAL RANGE FOR VITAMIN D

Although much controversy surrounds regarding overall normal or optimum vitamin D levels, however majority prefer the cut off value to be 30ng/ml or 75nmol/ml as the lowest range for normal vitamin D.(Bleizgys,. 2020)

Toxic levels are considered anywhere above 100 ng/ml

We currently stand on an estimate of more than 1 billion people in the world having vitamin D deficiency or insufficiency.

This is seen not only in the European countries, where by decreased sun light has been a known risk factor but also in the very hot countries likes middle east where the hot sun is generally avoided. It is estimated that in the Middle East almost 80% of the population has suboptimal level of vitamin D.(Bleizgys,.2020)

Daily supplementation up to 10,000 IU is considered generally safe for almost all patients. Only a few patients are vitamin D hypersensitive, since they are at risk of developing hypercalcaemia even from a small supplemental vitamin D doses, these are :

Patients with primary hyperparathyroidism or granulomatosis diseases such as sarcoidosis or active tuberculosis. (Bleizgys,. 2020)



2. ROLE OF VITAMIN D IN THE BODY

Vitamin D plays an essential role in:

1. Calcium homeostasis and bone metabolism.
2. Immunomodulatory function in local tissues.
3. Maintaining tissue integrity.
4. Stimulation of antioxidative processes.
5. Modulation of renin angiotensin system activity.
6. Modulation of coagulative system.

Some of these mechanisms are important in dampening the effects of the COVID-19, thus will be summarized below.

3. URTI AND VITAMIN D ASSOCIATION

It has been long hypothesised that there is a strong association between vitamin D deficiency and seasonal URTI, this trend was picked up and researched after the flu of 1918, although nothing substantial was ever demonstrated

4. VITAMIN D AND IMMUNE RESPONSE

One of the first vitamin D links to regulate the immune system was found with immune disorders like Sarcoidosis and Tuberculosis and other granulomatous diseases. It was observed that antigen presenting cells like macrophages and dendritic cells synthesise the active form of vitamin D, which is the 1,25 dihydroxy vitamin D from its precursor 25-hydroxyvitamin D via enzyme CYP27B1 (*Kallas et al.,2010*)

Another finding that epithelia, the main barrier between environment and body also expresses CYP27B1, these epithelia are the first responders to the invading pathogens sounding the alarm by activating the dendritic cells and macrophages and recruiting neutrophils and T cells, sending them to the site of infection. Thus Vitamin D levels and its deficiency in this case would impair the immune response. (*Hewison et al.,2010*)

This localized, intracrine mechanism is now considered to be the cornerstone of the interaction between vitamin D and immune response, this is distant from the endocrine actions of Vitamin D concerned with mineral homeostasis, in which the calcium regulation by vitamin D are driven by circulating 1,25 dihydroxy vitamin D, synthesized primarily by the kidneys. (*Bilezikian et al., 2020*)



1.VITAMIN D AND INNATE IMMUNE RESPONSE

Vitamin D has both antimicrobial and antiviral actions on the immune response, here I will discuss both briefly .

1.AntiMicrobial actions of vitamin D and its pertinence on the innate immune response

Its important to discuss this antimicrobial action of vitamin D, for us to understand how vitamin D activates an innate immune response to bacteria thus its implications on the activation of the antiviral innate immune response, both being somehow similar.

The antimicrobial role of vitamin D was initially described some 30 years ago .(Rook et al., 1986) However the relevance of this antimicrobial property was appreciated only later on in studies of the intracellular synthesis of 1,25,dihydroxy vitamin D as a mechanism for promoting antibacterial responses to Mycobacterium Tuberculosis.(Bilezikian et al., 2020)

Various ways that Vitamin D acts on cellular level to active this response is briefly outlined below.

a. Cathelicidin

Cathelicidin is a protein which has number of functions, including antimicrobial function, induction of variety of proinflammatory cytokines, stimulation of the chemotaxis of the neutrophils, monocytes, macrophages and T cells , into the site of infection and promoting the clearance of the respiratory pathogens by the induction of apoptosis and autophagy of the infected epithelial cells (Greiller et al., 2005, Yuk et al., 2009)

Local intracellular synthesis of 1,25 dihydroxy vitamin D by the monocytes and macrophages promotes the expression of this antimicrobial protein Cathelicidin and has been shown to enhance intracellular killing of Mycobacterial Tuberculosis.(liu et al., 2006) The ability of macrophages to produce Cathelicidin correlated well with the serum 25 –dihydroxy vitamin D concentration (lie et all,2006, Gombart et al., 2005).

These findings thus provid a plausible explanation for the reported high prevalence of Tuberculosis and various other respiratory disorders in the individuals with Vitamin D deficiency .(Chan et al.,2000)

b. NOD2

NOD2 is nucleotide binding oligomerization domain-containing protein 2, it is another intracellular pattern recognition receptor, which is stimulated by 1,25OHD. This enhances beta defensin2 expression (Wang et al.,2010), explained below .



c. Beta defensin 2

Yet another innate antibacterial element, which contributes to host defence by stimulating the expression of antiviral cytokines and chemokines involved in the recruitment of the monocytes and macrophages, natural killer cells, neutrophils and T cells (Kim et al., 2018)

Cellular production of both cathelicidin and beta defensin 2 depends on the vit D receptor and CYP27B.(Bilezikian et al., 2020)

d. Iron metabolism

Another mechanism by which vitamin D serves as antimicrobial function is related to cellular iron metabolism. Bacteria depend upon intracellular iron for survival. (Bilezikian et al., 2020)

In the course of infection, Hepcidin, which restricts the transcellular export of iron through ferroportin is induced, thus increasing cellular levels of iron (30)

1,25 OHD is a potent suppressor of this Hepcidin and thus acts to enhance ferroportin and reduce intracellular iron, thus suppressing the bacterial growth (Bacchetta et al.,2014)

It is seen that the ability of vitamin D to promote antimicrobial, innate immune function is closely linked to phagocytosis and subsequent enhanced bacterial killing via the induction of autophagy (Yuk et al.,2009)

It is also noted that other than the mechanisms described above Vitamin D also has an antimicrobial role to play by generating nitric oxide and superoxide and stimulates neutrophils (Bilezikian et al., 2020)

e. Vitamin D and barrier maintenance at cellular levels

Within gastrointestinal tract vitamin D is seen to maintain the barrier by promoting the expression of gap junction proteins thus preventing the tissue ingress by bacteria from the gut microbiome (Kong et al.,2008)

In lungs similar barrier integrity effects of the vitamin D have been observed for the epithelial cells of the lungs (Shi et al.,2016) along with stimulation of antimicrobial proteins by the lining epithelial cells (Schrumpf et al.,2012 ,Van et al.,2012)

2. Antiviral actions of vitamin D in creating the innate immune response

The antiviral actions of vitamin D overlap to a great extent on its antimicrobial mechanisms, such as induction of Cathelicidin and Defensins , the mechanism as already explained , these

inturn block viral entry into cells as well as supress viral replication (Ahmed et al.,2019 ,Barlow et al.,2011)

As described before one of the important mechanism to kill the microbial cells is by autophagy and same goes for the viruses, where by the vitamin D is seen to enhance the expression of autophagy marker LC3 (Yuk et al.,2009 ,Mushegian et al.,2017) thus low vitamin D levels can change autophagy.

The specific mechanisms by which vitamin D promotes autophagy involves down regulation of the mTOR pathway, which inhibits autophagy (Jang et al.,2014) and by promoting Beclin 1 and P13KC3 , key enzyme drivers of autophagy (Wang et al.,2008)

Vitamin D also promotes the formation of the autosomes thus facilitating the viral clearance indirectly through induction of Cathelicidin expression (Yuk et al.,2009)

This Vitamin D induced autophagy decreases HIV -1 infection (Campbell et al.,2011 ,Campbell et al.,2012) and influenza A (Khare et al.,2013) rotavirus (Tian et al., 2016) and Hep C (El-Brakyet al.,2018)

2. VITAMIN D AS A REGULATOR OF THE ADAPTIVE INNATE IMMUNE RESPONSE

T and B lymphocytes activation by the dendritic cells and macrophages leads to the adaptive innate immune response, its this adaptive immunity which defines long term nature and duration of an immune response.

Vitamin D decreases the maturation of dendritic cells, decreasing their ability to present antigen and to activate T cells (Van Etten et al.,2005) treatment of the dendritic cells with 1,25 OHD can also induce regulatory T cells (Treg cells , which are important in preventing the cytokine storm associated with SARS (Bilezikian et al.,2020)

RENIN ANGIOTENSIN SYSTEM ACTIVITY AND INCREASE IN ANGIOTENSIN CONVERTING ENZYME 2 RECEPTOR EXPRESSION

Renin angiotensin system RAS is an important regulator of many actions in the human body including vascular tone, diuresis and blood pressure. However sometimes this over activity of RAS results in increased angiotensin II production, which in turn leads to proinflammatory cytokine production, thrombosis , fibrosis , eg in the lungs, insulin resistance and liver dysfunction (Bleizgys,.2020)

Some of COVID-19 related symptoms such as pulmonary hypertension, coagulopathy diarrhoea, anosmia, ageusia , dermatitis , autoimmune inflammation of CNS , damage to the vital organs like lungs , heart , kidney and testicle are likely linked to the overreaction of this RAS (Gimenez et al.,2020,Godreavet al.,2020)

Vitamin D can increase the ACE 2 receptor expression in the lung tissue and this could ameliorate lung damage in case of some infections . Many authorities conclude that vitamin



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D, by decreasing RAS activity and probably increasing the expression of ACE2, over all has beneficial effects in case of COVID- 19 infection .(Gimenez et al.,2020 ,La Vignera et al.,2020 ,Cao et al,2020)

MODULATION OF COAGULATORY SYSTEM

In severe COVID 19 cases there's a high risk of coagulopathies especially thrombosis, including microvascular thrombosis in the lungs (Bilezikian et al.,2020)

Vitamin D hypovitaminosis is tightly associated with increased thrombosis (Tian et al ,2020 ,Mohammad et al.,2019)

It has been seen that vitamin D could decrease the expression of thrombomodulin thus seems possible that restoring the normal vitamin D status could help reduce the risk of thrombosis (Bleizgys ,2020)

LUNGS AND COVID-19

Lungs are the main target for the SARS-CoV-2, the surface area of lungs being approx. 70 m² thus providing a huge surface area for the invasion by the pathogenic organisms.

As discussed above the defence against these pathogens is led by both innate and adaptive mechanisms with adaptive immunity driving the long term immune response.

CYTOKINE STORM AND VITAMIN D

Pulmonary Cytokine storm is one of the most devastating outcomes of the SARS-CoV-2 infection leading to long term morbidity and mortality.

SARS-CoV-2 attacks both upper and lower airways with rapid viral replication, massive infiltration of the inflammatory cells resulting in production of a huge proinflammatory cytokines and chemokines leading to acute respiratory distress syndrome. (Channappanavar et al.,2017)

This cytokine storm results from dysregulation of the innate immune system with outpouring of proinflammatory cytokines and chemokine, leading to abnormal activation of the adaptive immune pathway attracting influx of the inflammatory cells including neutrophils, monocytes and macrophages while sensitizing T cells to apoptosis (Channappanavar et al.,2016) This results in the breakdown in the microvascular and alveolar epithelial barrier resulting in vascular leakage and alveolar oedema. T cell response required for viral clearance is blunted (Zhao et al.,2010) and their role in dampening the cytokine storm is reduced.

The activation of innate immunity leading to increased local 1,25OHD production has been shown to enhance viral neutralization and clearance while modulating the subsequent proinflammatory response, this has been shown in other viruses, remains to be seen in SARS-CoV-2 .



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CONCLUSION

1. We are living with the SARS CoV-2 pandemic for more than a year now, a number of researches and studies in regard to its prevention , cure and limiting the severity has been done. Although some of the mechanisms of how Vit D helps are currently understood but more defined association still needs to be studied.

2. Studies have shown that undoubtedly there's an association of vitamin D deficiency and viral infections including COVID -19.

3. Considering Vitamin D supplementation is generally safe and doesn't have sideeffects, its safe to say that till further details are available, vitamin D should be added to the medication therapy for COVID patients.

4.Its also reasonable to say that supplementation given to the at risks groups in general should be considered, which include elderly and comorbid patients.

5.There's nothing to lose from this supplementation and in view of the work done till now it seems to have all the more important gains.

DISCOLSURE:

The author declares no conflict of interest

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