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Review Article

COVID-19 Infections and Vitamin D Deficiency in Pregnancy

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Abstract

Corona virus disease COVID-19 has been a global health threat since November 2019. It has been reported as 6th cause of global public health emergency by World Health Organisation on January 2020. Serum cholecalciferol or calcidiol is the prime marker for the vitamin D status of a person. It has also been gaining importance in prevention of COVID-19 disease severity. Vitamin D has proven cellular level modulation in both the adaptive and innate immune system through cytokines and regulation of cell signalling pathways. This vitamin has been observed to be lower than the optimal levels in pregnancy. The foetal demand for the vitamin increases during the early embryogenesis hence it is reported lowest in the first trimester. It has been noted to increase gradually during second trimester and reaches sufficient limits in third trimester. There is a compensation of serum cholecalciferol levels in third trimester due to the placental secreting receptors. This review analyses the immunomodulatory property of serum cholecalciferol and its effect on T regulatory cell count which is the predicting tool for disease severity in COVID-19.

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Keywords

Vitamin D; Pregnancy; Respiratory Infections; Immune Tolerance; T Regulatory Cells

Abbreviations

COVID-19: Corona Virus; SARS: Severe Acute Respiratory Syndrome; SARS COV-2: Severe Acute Respiratory Syndrome Corona Virus; IL: Interleukins

Introduction

Pregnancy is an altered physiological condition. The circulating levels of 25 hydroxycholecalciferol levels are reported to be very low throughout pregnancy [1,2]. 25 hydroxy cholecalciferol levels in known to affect bone health as well as maternal immunity against infections. Calcitriol which is circulating active form of vitamin D is maintained normal while calcidiol which is storage form remains deficient. Calcitriol conversion occurs in the maternal kidneys, while foetus absorbs 25 hydroxycholecalciferols (calcidiol) through placenta and foetal kidney activates it. Foetal calcidiol requirements are supplied by the mother. Calcitriol is a known immunomodulatory [3]. Calcitriol is known to strengthen innate and adaptive immunity. Vitamin D is known to increase the antimicrobial peptides like cathelicidin, in the respiratory epithelial cells which strengthen the cellular immunity in the respiratory tract.

COVID-19 infections are associated with the increased production of pro-inflammatory cytokines, increased risk of pneumonia, sepsis and acute respiratory distress syndrome. The cytokine storm manifests the disease severity. Production of proinflammatory cytokine becomes crucial to prevent disease severity progression. Currently Steroids are used to control the cytokine storm. Calcitriol induces production of natural anti-inflammatory cytokine such as TNF alpha and interferon gamma, IL-6 levels etc. Mortality rate was directly proportional to the IL-6 levels, there was significant correlation in COVID-19 infections [4]. Vitamin D levels were inversely correlated with IL-6 levels. Serum vitamin D deficiency was associated with increased IL-6 levels and increased mortality [4,5]. Administration of vitamin D has reported decrease in IL-6 levels and disease severity in COVID-19 infected individuals [4]. Serum zinc and serum calcium levels along with serum vitamin D levels has also been significantly reduced in COVID-19 infected patients [5].

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Literatures Searches

Literature searches with key terms COVID-19 infections and vitamin D deficiency in pregnancy showed 3 articles in PubMed central, while 6 articles in pub med of which 3 were overlapping articles. Google scholar showed 9 relevant articles to the search. There were 12 articles in Scopus search out of which 2 articles were overlapped or repeated in PubMed database search. We were able to review 10 articles from SCOPUS database. Mendeley software was used for data search. There were totally 22 articles reviewed. Video lectures, podcasts were also included in the review.

Exclusions

We analysed randomised control trials evaluating vitamin D supplementation pregnant women with COVID-19 infections irrespective of disease severity, race, age, or ethnicity and comorbidities. Studied done as preventive measures were excluded, articles with other respiratory conditions like SARS (Severe Acute Respiratory Distress Syndrome) were excluded. Vitamin D deficiency in pregnancy involving other complications were excluded. Articles which are in other than English were excluded if translated version is not available.

Basic Mechanism of Vitamin D in Immunomodulation

Serum Vitamin D that is synthesized from the cutaneous fat layers that produce the immunity. It acts on the keratinocytes, antigen presenting cells, dendritic cells and epidermal Langerhans cells and T-lymphocytes. Peripheral regulatory T-cells are responsive to environmental stimuli including UV irradiation. Vitamin D is best supplemented with calcium and vitamin D [3]. The T effector cell functions to maintain the level of activation of Langerhans cells. On reception a foreign antigen the Langerhans cell will engulf and drain it through the dermal lymphatic channel. The receptors for activated vitamin D that is calcitriol is present all over the body. While the receptors are also located in all body tissues. The 1,25, dihydroxycholecalciferol produced by the lymphocytes and monocytes act on the T-cell and B-cells surrounding them.

The activated vitamin D (calcitriol) induces regulatory T-cells to be produced. It has been recently found that expression on 1,25 dihydroxycholecalciferol levels connects the immune system that is the regulatory T-cells with the surrounding environment. The cell mediated (Cd4+ and Cd25+) immune responses need to be down regulated. Regulatory T-cells play an important role in the suppression of cellular immune responses via inhibition of T-cell proliferation. T regulatory cell thus prevent Autoimmunity. It inhibits maturation of Dendritic cell and APC cells in conditions of autoimmune dysfunction. 1,25 (OH)₂D₃ also represses the transcription of genes encoding key T helper type 1 (Th1) cytokines. It supports T-helper

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responses toward regulatory Th2 phenotype, which is considered a key component of its capacity to suppress Th1-driven autoimmuneresponses [10]. Thus vitamin D in its activated state (calcitriol) has known to modulate the cytokinine activities of Th1 and Th2 helper cells.

Serum vitamin D levels have known to be predictor of worsen health status of the patient. It has also been proven to affect the immune cell count and its production of IL-6 in lab studies [7].

Vitamin D levels is known to decrease levels of cytokinine. It has shown impact of reduced cytokinine production in various inflammatory conditions. In a published analysis done in 2015 it has been proved that 8 out of 11 studies has shown significant effect of vitamin D on reduction of interleukin levels especially, multiple sclerosis, rheumatoid arthritis, including diabetes [4].

There was significant correlation ($p=0.046$) between the mortality rate and serum 25(OH)D plasma level concentration. COVID-19 data and mortality data was recovered from the world health organisation. According to E Laird, et al., in 2020 there was significant correlation between 25(OH)D concentration and mortality rate ($P=0.046$) by Spearman's Rank Correlation. The calculated COVID-19 mortality rate from 12 European countries shows a significant ($P = 0.046$) inverse correlation with the mean 25(OH)D plasma concentration.

COVID-19 Pathogenesis

COVID-19 has presented with features of Influenza, CT finding shows ground glass appearance. Scoring pattern has been followed based on the lung lobes involved in the CT scan as well as involvements of the lungs. Clinical presentation differs in mild, moderate and severe cases. In severe cases autopsy findings have shown significant inner alveolar thickening with infiltration on mononuclear cell and macrophages. Endothelialitis very evidently seen. Inflammatory mononuclear cell infiltrate also secretes inflammatory cytokinine. Bradykinin causing angioedema is more common feature of the COVID-19 infections. Endothelial barrier disruptions, dysfunctional alveolar capillary oxygen transmission and impaired oxygen diffusion capacity are characteristic features of COVID-19 disease. Intravascular Coagulation and consumption of clotting factors occur. It has been reported by a study conducted in Wuhan china that 71% of 183 deaths occurred due to intravascular clots, this can lead to microthrombi formation which circulates in blood leading to thromboembolism in various regions of the body like the lower limb, ischemic stroke, myocardial infarction etc [10,11,12].

This can lead to hypoxemia and respiratory failure in 59% of the ICU patients [11,12]. Among the ICU patients 21 to 91% needs mechanical ventilation [11]. In conjunction with coagulopathy, modest prolongation of thrombin time are features noted along with increased D dimer levels. The D dimer was also a prognostic marker for the severity of the disease. This

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intravascular coagulation and microthrombi formation is because of the viral particles presented to the APC increases invasion of T-cells, macrophages, monocytes, they form antigen antibody complexes and activated immune reactions can cause injury or intravascular bleeding and clot formation. COVID-19 induces immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels. Micro thrombotic complications lead to Acute Respiratory Distress Syndrome (ARDS) and other organ dysfunctions [14,15].

Immunomodulation plays a very important role in prognosis of COVID-19 hence, its been hypothesized that serum cholecalciferol levels immunomodulates microvascular environment by increasing the T regulatory cell counts which is known to suppress the immune reactions leading to coagulation. Anticoagulant drugs, immunosuppressant drugs are used in severe phase of the disease to prevent cytokine storm. Early phase requires host defensive actions. While this turns to be lethal leading to overexcited state. Immunosuppressant prevents ARDS and organ dysfunctions. Corticosteroids and IL-6 inhibitors are currently used in severe cases to prevent mechanical ventilation (Fig. 1-3) [16].

Figure 1: Autoimmunity is prevented by Vitamin D or calcitriol by repressing Th1 and activating Th2 response towards Treg Phenotype.

ROLE OF CALCITRIOL ON DENDRITIC CELL, B LYMPHOCYTE AND T LYMPHOCYTE

Figure 2: Role of Vitamin D (calcitriol) on dendritic cell, B-lymphocytes and macrophages.

Role of Calcitriol in IL-6 levels –COVID 19 cases

Figure 3: Role of calcitriol in IL 6 levels- COVID-19 infections.

Discussion

Pregnancy is an altered physiological state which is highly vulnerable to risk factors. Vertical monitoring of the serum values is very crucial to prevent spread of infections. Vitamin D deficiency is known to cause easy viral infection of the respiratory tract. It has also been known to regulate and monitor the activities of immune system. Serum 25 hydroxy Cholecalciferol or storage form of calcidiol is usually estimated to know the exact vitamin D status of the patient. Calcitriol (Serum Vitamin D3) is maintained in normal values to maintain calcium homeostasis.

Natural immunomodulator is the activated T regulatory cells. In pregnancy the T regulatory cells play a major role in tolerating the heterogenous foetus. The t-regulatory count helps in sustaining pregnancy in first trimester. It is also protective and disease progression prevention in COVID- 19. Pregnancy with gestational diabetes mellitus, preeclampsia and eclampsia are more prone for vitamin D deficiency. These patients are more vulnerable to acquire any respiratory tract infections [8].

Myoinositol a precursor of phospholipids in surfactants have proved to down regulated the serum IL-6 levels in infant acute respiratory distress syndrome. The serum 25 hydroxycholecalciferol levels are reported to be inefficient or low in pregnant women when compared to the normal individual. This increases chances of the pregnant women acquiring the COVID-19 infections. First trimester calcidiol and calcitriol levels are reduced when compared to the second and third trimester levels [2].

In a study conducted in Wuhan China out of 133 COVID-19 positive pregnant women who delivered. Only 33 neonates were affected with COVID-19 infections. Of the infected only 3 neonates had signs of shortness of breath, fever, pneumonia etc. They were diagnosed positive through nasal or anal swabs. Second day the neonates presented lethargy and weakness. They were tested negative on the 6th day. This clearly shows maternal COVID-19 infection is associated with low vertical transmission. There were no maternal deaths and an early recovery for the neonates reported in the study [13,17].

Effective infection control can prevent vertical transmission. The amniotic samples, milk samples, cord blood samples were tested negative for COVID-19 infection. The serum levels of Vitamin D (25 hydroxycholecalciferol level) in close to sufficient level because of placental hydroxylation to its active form [18].

Serum 25 hydroxycholecalciferol level has been known to maintain immunotolerance by suppressing Th1 and promoting t-regulatory cells a subset of CD4 lymphocytes. Several studies have proven its role in immunotolerance especially in pregnancy. T-cell population and macrophages store sufficient Vitamin D receptors [19]. The sub group of T-cell population t regulatory cells are known to inhibit unnecessary immune reactions [20]. T-cells treated with

activated form of vitamin D or calcitriol could suppress proliferation of normally responsive T-cells indicating adaptive characteristics. There is active synergistic effect acting as anti-inflammatory in inhibiting interleukins and adaptive tregs [21].

In the presence of IL-1 β and IL-6, TGF β appears to promote IL 17 development. TGF β stimulates the T regulatory or induction of FOXP3. These inflammatory cytokines are switch factors for deciding inducible T regs or Th17. The Interleukin levels play an important role in maintenance of FoxP3 expression [21].

The recurrent pregnancy loss has been associated with significant levels of vitamin D. It has also been associated with T reg/Th17 imbalance seen in recurrent abortion cases. Vitamin D supplementation has *in-vitro* and *in-vivo* showed its effects in immune regulation [22].

T regulatory cells have also been utilised as an effective tool in treatment of autoimmune disease conditions like rheumatoid arthritis etc. The pathogenesis of Rheumatoid arthritis is based on T helper cells Th1 which increases proinflammatory cytokines such as IFN- γ , IL-2, THF- α . Th1 cells activate macrophages to act as an Antigen presenting Cells to MHC-II complex to the T-cells. While Th2 cells counteract this and secrete anti-inflammatory cytokines such as IL-4 and IL-5 and control the antibodies against B-cell activation which is the reason for the trigger of the autoimmune reactions in rheumatoid arthritis. The TNF α suppresses the T regulatory cells, Th17, IL-6 levels and induces pain sensation in the joints because of inflammation [23,24].

T regulatory population may be triggered with Vitamin D supplementation in Rheumatoid arthritis patients also. Further Clinical Trials and observational studies needed for further research in this area. The T regulatory cell may also be beneficial in auto rejection of transplant surgeries [25,26].

Serum 25 hydroxycholecalciferol levels have been monitored, supplemented if there is insufficiency in cases of patients undergoing transplants. Serum 25 hydroxycholecalciferol has proven to be effective immunomodulatory in suppressing the autoimmune dysfunctions [25].

Vitamin D has proved itself to be an effective natural immunomodulator and its deficiency causes acute cellular rejection in transplants. It has also proved itself to be effective against bacterial and fungal infections. Deficiency of this vitamin has paved way for many superadded infections in graft transplants [27,28].

Conclusion

Vitamin D has to be supplemented by fortification in food. This gains importance in early pregnancy, the serum vitamin D regulates the immune system of the body preventing recurrent spontaneous abortions by creating immune tolerance against the semi allogenic fetus.

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Throughout pregnancy the maternal serum vitamin D levels (25 hydroxycholecalciferol levels are to be monitored) supplementation is recommended if there is insufficiency. Like serum ferritin levels, 25 hydroxycholecalciferol levels should also be maintained within normal limits. Apart from the maintenance of bone health, calcium homeostasis, this vitamin also inhibits Th1 helper cells there by reduced secretion of proinflammatory cytokine. It also allows Th2 helper cells and macrophages to increase T regulatory cells which suppresses' autoimmunity. These T regulatory cells are protective during pregnancy hence disease severity progression is prevented. It also provides protection against all autoimmune reactions in COVID-19 infections. Hence serum 25 hydroxycholecalciferol estimation becomes essential COVID-19 treatments. It can also be utilised for treatment of autoimmune conditions like Rheumatoid arthritis, systemic lupus erythematosus, auto rejection of transplanted grafts etc. Serum cholecalciferol levels may be an effective marker for immune strength of a patients as well as it's a natural immunomodulator that can replace synthetic immune suppressant drugs.

Conflicts of Interest

The authors declare that have no competing interest and not any conflict of interest.

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