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Optimal dose of vitamin-D supplement reduces death risk in covid patients – A review

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An impasse in the realm of public health has been undergoing since December due to outbreak of COVID-19. As a consequence of this impasse, different countries are tumbling into an even deeper recession. The life of economically backward people came to a grinding halt on account of the recurrent lockdown. To bear the cost for the treatment of COVID-19 is nearly to impossible for them. It is well known fact that the best preventive measure against COVID-19 should be vitamin-D supplementation for those who are vitamin-D insufficient or deficient. Nearly 1 billion people worldwide have low level of vitamin-D. We know vitamin-D plays a vital role to the function of immune system and vitamin-D supplements have previously been proven safe and effective to reduce the risk of viral respiratory tract infection. Recently, some study have shown a strong relation between severe vitamin-D deficiency and death rate in COVID-19. It has been recorded that patients with lower level of vitamin-D had higher risk of death than patients having no deficiency in vitamin-D. Mortality rate is quite high in 20 European countries and in USA because the people of this countries are vitamin-D deficient. Thus, vitamin-D supplementation can be a very good preventive treatment against COVID-19.

Keywords: COVID-19, vitamin-D, vitamin-D supplementation, infection.

Introduction

On 11 March, World Health Organization declared COVID-19 as a pandemic. Epicentre of this epidemic was in Wuhan, China, in December 2019. It was originally called 2019-nCoV[1] and renamed COVID-19 by the World Health Organization (WHO) on 11th February, 2020. COVID-19 is a severe acute respiratory syndrome[2] caused by Coronavirus-2 (SARS-CoV2)[3–5]. Vitamin-D is necessary to the function of immune[6,7] system and vitamin-D supplements have previously been found safe and reduce the risk of viral respiratory tract infection (RTI)[8–13]. Recently, some study have shown a strong connection between severe vitamin-D deficiency and death rate[14] in COVID-19. It has been recorded that patients with lower level of vitamin-D had higher risk of death than patients having no deficiency in vitamin-D. Cytokine storm[15] in covid patients severely damage lungs and that seems to be the cause of most COVID-19 related deaths. Thus vitamin-D supplement calcifediol[16] helps to prevent the immune system from becoming overactive. Vitamin-D supplementation would not prevent a patient from COVID-19 infection[17], but according to recent research, it might reduce the death rate due to COVID-19 infection and also reduces COVID-19 related complications.

What is vitamin-D?

Vitamin-D is a fat soluble vitamin. We can get vitamin-D in three ways: by exposure to sunlight, from diet and from supplements. It helps to absorb calcium, magnesium and phosphate in our body. In humans, the most important compounds in this group are vitamin-D3 (also known as cholecalciferol)[18] and vitamin-D2 (ergocalciferol)[19]. Vitamin-D is generated in mammals if exposed to sufficient sunlight. As vitamin-D is not indispensable for our body, instead of vitamin, technically it can be considered as a hormone.

Metabolism of vitamin-D

Cholecalciferol is converted in the liver to calcifediol[20] (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. After that calcifediol is further hydroxylated by the kidneys to form calcitriol (1,25-dihydroxycholecalciferol)[21], the active form of vitamin-D and calcitriol present in blood play major role in absorption of calcium, phosphate, remodeling skeletal structure and also effect in immune function.

Determination of vitamin-D level in blood

25-Hydroxy vitamin-D blood test[22] is the standard test to determine the level of vitamin-D in blood. A wide optimal range for 25(OH)D[23] is reported (20–80 ng/mL)[24] and different opinions are there to the definition of vitamin-D deficiency. Vitamin-D level may vary widely depending upon age, ethnic background, the season, geographic location of population.

Reference range for total serum 25-hydroxyvitamin-D [25(OH)D] is:

< 8–10 ng/mL (acute deficiency)

10–19.5 ng/mL (light deficiency)

20–50.5 ng/mL (optimum levels)

51–79 ng/mL (chance of hypercalciuria)

> 80 ng/mL (chance of toxicity)

How many people are vitamin-D deficient?

Vitamin-D deficiency is very common and it becomes a global pandemic[25,26]. 1 billion people worldwide have low level of vitamin-D in their blood. Only in USA, 41.6% adults are vitamin-D deficient. The common signs of low vitamin-D includes:

Frequent viral infection.

Feeling tired.

Weak bones-increasing risk of osteoporosis.

Weak muscles.

Depression.

Potential benefits of vitamin-D

Two types of benefits are observed in vitamin-D sufficiency.

Skeletal benefits.

Non Skeletal benefits.

Skeletal benefits: Optimum level of serum 25(OH)D prevents rickets in children, increase bone density, and reduces the risk of fractures in bones[27–29].

Non skeletal benefits: The interest in non skeletal benefits has been increased after discovery of vitamin-D receptors[30] in certain cells. The following benefits are observed in recent studies:

Lower cardiovascular mortality[31].

Reduced risk of diabetes mellitus[32].

Reduced risk of cancer (colon cancer and breast cancer)[33,34].

Reduced risk of multiple sclerosis[35].

Reduced risk of allergy and asthma[36–38].

Reduced risk of infection[39–43].

Reduced risk of depression[44,45].

Less musculoskeletal pain[46,47].

Reduced risk of renal disease[48].

Vitamin-D deficiency and COVID-19 response

First research paper was published by Brown Robert Andrew *et al.*[49] on 23rd March. From certain data analysis they recommended that vitamin-D supplementation might reduce mortality in COVID-19.

First literature review was published on 25th March, 2020 by Italian doctors Isaia and Medico[50], from Università degli Studi of Turin, Italy. In the draft, the authors anticipate hypovitaminosis-D to the preclusion and treatment of COVID-19, in concurrence with other inevitable therapeutical measures.

A report was published on 3rd April, 2020 by Eamon Laird *et al.*[51] on behalf of the TILDA team on 'Vitamin-D deficiency in Ireland – Implications for COVID-19'. They have done a study of people over the age of 50 in Ireland. TILDA report reveled that one in eight adults over the age of 50 are deficient all year around. 27% of all adults over the age of 70 and 47% of all adults over 85 are deficient in winter. The TILDA researchers advised that people over the age of 50 should take vitamin-D supplements through out the year round if they do not get enough sun exposure.

Petre Cristian Ilie *et al.*[52] shows certain data and prove that vitamin-D levels are severely low in Spain, Italy and Switzerland. From certain data analysis, they recommended that in 20 European countries, COVID-19 mortality is very high with high vitamin-D deficiency.

Prabowo Raharusuna *et al.*[53] has done retrospective cohort study which determine the vitamin-D level and COVID-19 mortality outcome. The key findings of the research is that most of the COVID-19 patients with deficient vitamin-D level have high mortality.

Vadim Backman *et al.*[54] conducted a statistical analysis of data from hospital and clinics across China, USA, France, Spain, Germany, Italy, Iran, South Korea, UK. They noted that people from Italy, Spain, UK with high COVID-19 mortality rate. Due to vitamin-D deficiency, lungs are severely dam-

aged by cytokine storm and leads to acute respiratory distress syndrome and death. Children have lower mortality rate. They show that the mortality rate reduces to half and also lower the complications by vitamin-D supplementation.They also warned that excessive dose of vitamin-D can bring negative side effect.

Chee Keng Mok *et al.*[55] reported Calcitrion, the active form of vitamin-D, is a potential candidate for COVID-19 prophylaxis. They also advised optimal vitamin-D supplementation to fight against COVID-19 infection.

John F. Arboleda *et al.*[56] proposed that vitamin-D supplementation could be a new "at hand tool" to protect vulnerable community of people and relieve the impact of current pandemic situation.

Hans K. Biesalski[57] noted that in immune system, vitamin-D plays an important role. Vitamin-D cell interfere with majority of the immune systems cells such as macrophabes, B and T lymphocytes, neutrophils and dendritic cells, which express vitamin-D receptor. Cathelicidin has shown antimicrobial activity over bacteria, fungi and enveloped viruses, such as corona viruses. Vitamin-D inhibits the cytokine storm and reduce the death by acute respiratory syndrome.

Roya Ghasemian *et al.*[58] has performed a systematic review and meta analysis on the effect of vitamin-D in the different age group of patients with COVID-19 infection and also with ecological approach. They consider a meta analysis. The meta analysis indicated that 37.7% of COVID-19 patients were suffering from vitamin-D deficiency and for 32.2% of patients, level of vitamin-D were insufficient.

S. A. Lanham *et al.*[59] suggested that lower level of vitamin-D increase the risk of COVID-19 infection and advised vitamin-D supplementation.

D. M. McCartney *et al.*[60] noted that vitamin-D deficiency is very common in elder adults, nursing home residents, hospital inpatients and other vulnerable community (e.g. diabetes mellitus patients, poor immune function group or people with black skin, vegetarians and vegans, those who are overweight or obese, healthcare workers and smokers). They advised urgent supplementation of vitamin-D (20–50 μg/d) to them to enhance their resistance to COVID-19.

Viraj Ramesh Suvarna *et al.*[61] emphases on correlation between lower level vitamin-D level and COVID-19 infection.

Eugene Merzon *et al.*[62] has done a Israeli population based study and found a link between low levels of vitamin-D and increased COVID-19 susceptibility.

J. M. Rhodes *et al.*[63] suggested that vitamin-D supplementation is quite safe and it seems to work more efficiently during this COVID-19 period for those who are vitamin-D deficient.

Adrian R. Martineau *et al.*[64] also recommended vitamin-D supplementation to reduce the impact of COVID-19 in population where vitamin-D deficiency is prevalent.

G. E. Carpagnano *et al.*[65] analysed a clinical data and showed that the vitamin-D deficiency caused the patients with acute respiratory failure due to COVID-19 and higher risk of mortality was found with severe vitamin-D deficiency.

Ben Schöttker *et al.*[66] from Germany Cancer Research Centre assessed that vitamin-D insufficiency and deficiency are very common and reason behind the large proportion of respiratory disease mortality in older adults and advised vitamin-D supplementation to reduce the burden of COVID-19 pandemic.

William B. Grant *et al.*[67] pointed that vitamin-D supplementation proves to be a helpful measure to reduce risk of COVID-19 infection and mortality.

Rahul Munshi *et al.*[68] suggested that serum vitamin-D levels could be very useful indicator in the COVID-19 prediction. Diagnosis of vitamin-D deficiency could be helpful for patients' potential of developing severe COVID-19.

Patrick Zemb *et al.*[69] pointed the correlation between vitamin-D deficiency and COVID-19 infection.

Murat Kara *et al.*[70] also proposed that vitamin-D deficiency may be a cause of COVID-19 infection.

Antonio D'Avolio *et al.*[71] found 25-hydroxyvitamin-D level in blood are lower in patients with positive PCR for SARS-CoV-2. On the basis of this observation,they advised vitamin-D supplementation might be useful to control the risk of infection.

G. De Luca *et al.*[72] pointed that vitamin-D has a potential to treat SARS-CoV-2 infection, based on its established anti-inflammatory and anti thrombotic properties.

David O. Meltzer *et al.*[73] found a correlation between vitamin-D deficiency and chance of becoming infected with coronavirus. As previously a good result was shown by vitamin-D to reduce the risk of viral respiratory tract infections, their statistical analyses suggests that it might be true for

COVID-19 infection. The research team studied 489 patients at Chicago Medicine, among them patients having vitamin-D deficiency (<20 ng/mL) were tested positive almost twice than patients who had sufficient level of vitamin-D.

Zhila Maghbooli *et al.*[74] has done a study on vitamin-D sufficiency and mortality by COVID-19. They found that COVID-19 patients with vitamin-D sufficiency has lower risk of death.

A scientific report has been published in Nature by Anshul Jain *et al.*[75] and they prove with data that vitamin-D deficiency significantly increases the mortality in COVID-19 patients.

Conclusions and recommendations

From above literature review we can conclude that vitamin-D level play an important role in COVID-19 infection. Deficient and insufficient vitamin-D level increases the risk of COVID-19 infection and also enhances the mortality rate. Vitamin-D supplementation might be a game changer to fight against COVID-19. We recommend the serum 25(OH)D test to detect the vitamin-D deficiency and insufficiency in people. After confirming the deficiency or insufficiency, optimal doses of vitamin-D supplement should be given to these people to achieve optimum level of vitamin-D (>30 ng/mL) level. The vitamin-D supplementation can be considered as preventive treatment for COVID-19. COVID-19 patients should get high dose of vitamin-D supplementation (4000–8000 IU/day) which can reduce the risk of death by SARS-CoV-2.

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