

Role of Serum Vitamin D Level in the Progression of Dengue Viral Illness: A Potential Immunomodulator?: A Literature Review

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Abstract: This is a literature review on the role of serum vitamin D levels in dengue viral illness as a potential immunomodulator. The dengue virus is an RNA virus that causes many symptoms, from asymptomatic phases to severe forms like dengue hemorrhagic fever and dengue shock syndrome. The review methodology was based on evidence-based rapid review, and the review's objectives are to scrutinize all the available articles on dengue virus and vitamin D from standard databases and literature searches. It was found that there are no specific antivirals for the definitive management of the dengue virus, and vitamin D, with its potential antiviral and immunomodulatory effects, can play a significant role against the dengue viral illness. It was also found that there are limited reviews on the association between dengue virus and vitamin D. The review concludes that there is a possible association between supplementing with vitamin D and lowering the risk of progression to severe dengue viral illness and that regular testing of serum vitamin D levels is highly encouraged during the illness as vitamin D levels get depleted with the progression of the illness.

Keywords: *Dengue virus, Dengue hemorrhagic fever, Dengue shock syndrome, Immunomodulator, Vitamin D*

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1. Introduction

Dengue virus is a ssRNA virus from the Flaviviridae family. The viral genome is around 11 kb in length. The virion consists of three structural (core, envelope, and membrane-related) and seven non-structural (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) proteins. Based on biological and immunological status, it can be classified into four serotypes (DEN 1-4). The most important vector is *A aegypti*. However, *A albopictus* and *A polynesiensis* also act as vectors depending on the geographic areas (Malavige et al., 2004). The pathogenesis of dengue viral illness (DF, DHF, and DSS) is multifactorial, which includes both viral and host factors. Initially, after a mosquito bite, the virus enters and replicates within the phagocytic cells like macrophages, monocytes, and dendritic cells, and following dengue fever, the host forms antibodies against the structural and non-structural viral proteins. The antibodies against the viral NS1 antigen induce caspase-dependent endothelial cell apoptosis (Ho et al., 2001; Huang et al., 2000; King et al., 2000; Malavige et al., 2004). Dengue virus with different types of genes has different types of virulence (Cologna & Rico-Hesse, 2003; Leitmeyer et al., 1999; Sánchez & Ruiz, 1996; Ubol et al., 2008). It can manifest with a wide range of symptoms, from an asymptomatic phase to a mild prodromal illness (dengue fever) to severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Martina et al., 2009).

The annual global incidence of DF is 100 million, and there are half a million cases of dengue hemorrhagic fever. Dengue is endemic in 112 nations (Malavige et al., 2004). Ninety percent of DHF are children of age less than 15 years. In 1954, the first epidemic occurred in Manila, Philippines. Following this, epidemics have occurred in nearly all countries in the southeast Asian region. Till the late 1980s, DEN-1 and DEN-2 were the prevalent serotypes; however, now, the DEN-3 serotype is more virulent and accounts for the majority of severe dengue epidemics (Malavige et al., 2004). It is the main

cause of viral illness in tropical and subtropical regions, with the incidence of 50 million infections yearly and more than 2.5 billion at risk.

Yet, there are no approved specific therapeutic antivirals and thus, treatment remains still supportive management. Similarly, the efforts on vector management have not been able to halt its emergence and worldwide spread (Bhatt et al., 2013). Since, supplementing with vitamin D can minimize the risk and severity of COVID illness (Charoenngam et al., 2020; Grant et al., 2020). It has been a topic of great interest for its role in dengue viral illness. Although there are many studies illustrating the low serum vitamin D level in severe dengue illness, there is still a lack of high-quality randomized trials involving supplementation of vitamin D to see its impacts in the actual progression towards DHF and DSS. Likewise, the review article included small sample size studies and limited data about the association between vitamin D and the dengue virus. Vitamin D can modulate both innate and adaptive immune system homeostasis (Aranow & Aranow, 2011; Charoenngam et al., 2020; Grant et al., 2020). So, with its potential antiviral and immunomodulatory effects, it can play a significant role against the dengue viral illness (Alagarasu, 2021). In this study, we aimed to highlight that the understanding of immunomodulatory effects of vitamin D in the progression of dengue viral illness can provide positive insights to medical researchers so that they can work on the formulation of better antivirals measures incorporating vitamin D, as well as plan for routine prophylaxis of vitamin D supplementation for the patient with dengue fever to prevent from DHF and DSS. It also focuses on providing preventive awareness to the general public about the importance of vitamin D in limiting the progression of dengue illness in endemic areas.

2. Materials and methods

The design method for this literature review is based on an evidence-based rapid review. The objectives of the review are to scrutinize all the available articles on the dengue virus and vitamin D from the standard databases (PubMed, Google Scholar, Science Direct) and literature searches (Google search engine) with the relevant topics: “dengue virus,” “vitamin D level,” “cholecalciferol” “dengue hemorrhagic fever,” “dengue shock syndrome,” “immunomodulator” to identify articles published between 1988 to 2024, from any countries reporting about the dengue virus and serum vitamin D. Relevant articles including RCT, cross-sectional studies, literature review, and case control studies about the association between serum vitamin D level and dengue virus were gathered. The study characteristics (i.e hospitalized patients with DF, DHF, DSS including adults and children, data sources, serum vitamin D level, supplementing vitamin D doses and its outcome) were extracted from already published and/or publicly available preprint studies by the two co-authors. Despite the fact that no scale was applied to rate the selected studies, the research was based on recent and credible evidence in the literature.

3. Results and discussion

3.1. Prevalence

The World Health Organization (WHO) has considered dengue as a global public health problem in the tropic and subtropic regions. Dengue has a dramatic surge of 30 folds globally between 1960 and 2010 due to skyrocketing way of population growth, global warming, urbanization, lack of efficient mosquito control, frequent travel, and lack of quality health services. Two and a half billion people live in dengue-endemic regions, and around 400 million infections occur every year, with around 5–20% mortality in some regions. More than 100 countries are infected with dengue illness and Europe and the United States (USA) are no exception (Hasan et al., 2016). However, the global distribution of the risk of dengue viral illness and its burden on the general public are still poorly known (Halstead, 1988; World Health Organization, 2009; Bhatt et al., 2013).

3.2. Etiopathogenesis

The etiopathogenesis behind dengue virus infection includes viral replication, direct skin infection by virus, and immunochemical mediated host and virus interaction. The virus gains entry via the bite of infected *Aedes* mosquitoes. Various factors like humoral, innate, and cellular responses are involved in the progression of dengue illness, and the infection course does not correlate with a high viral load. The altered mechanism of endothelial microvascular permeability and thrombo-regulatory function contributes to the loss of plasma and proteins. Endothelial cells activated by monocytes, T-cells, the complement system, and various inflammatory molecules are responsible for plasma leakage. Reduced platelet levels may be related to alterations in its synthesis, manifested by infection of hematopoietic cells and impairs progenitor cell growth. This results in platelet dysfunction, damage, or depletion, leading to severe hemorrhage (Hasan et al., 2016).

3.3. Role of vitamin D in dengue viral illness

A study has shown that human monocyte-derived macrophage differentiation in the presence of vitamin D limits dengue viral infection by restricting DENV binding to cells (Siddiqui et al., 2020). Vitamin D affects both the innate and adaptive immune responses through several mechanisms, including T-cell activation, macrophage differentiation, and the production of anti-microbial peptides such as cathelicidin (LL-37) and β -defensin. It also influences the expression of the DENV entry receptor, dendritic cell-specific intercellular adhesion molecule-grabbing non-integrin (DC-SIGN), and FC γ RIIA in immune cells (Langerman & Ververs, 2021). Vitamin D inhibits Th-1 cell proliferation with decreased production of interferon-gamma and interleukin-2.(Beard et al., 2011; Chen et al., 2007; JM et al., 1995; Van Etten & Mathieu, 2005). A study of fused bicyclic derivatives of 1H-pyrrolo[1,2]imidazol-1-one with vitamin D receptor (VDR) agonist activity was studied for its anti-DENV activity, and the results suggest that VDR agonists have an anti-DENV effect and can be a potential future agent (Jaratsittisin et al., 2020). The role of vitamin D in microRNAs is crucial in immune activation pathways and helps to prevent the damage that arises from excessive inflammatory responses.(Arboleda & Urcuqui-Inchima, 2016). The average platelet value in the cholecalciferol-supplemented patients was significantly higher than that of the control group, and hence, cholecalciferol has been shown to reduce progression to DHF and DSS (Iturralde, 2023).

Table 1: Summary of a prospective cross-sectional study in Lahore, Pakistan assessing the vitamin D level in hospitalized patients with dengue illness

Categories of dengue illness	Numbers of hospitalized patients	Vitamin D deficient(<20ng/ml)
DF	37(38.1%)	27(73%)
DHF	52(53.6%)	41(78.8%)
DSS	8(8.2%)	7(87.5%)
Total	97	75 out of 97

According to the above table, we can conclude that the serum vitamin D level was somewhat lower in DSS patients in comparison to DF and DHF patients. There is a possible association between low serum vitamin D levels and as increased risk of severe dengue illness (Iqtadar et al., 2023)

Table 2: A RCT study conducted in Rawalpindi, Pakistan assessing the progression of DF patients with supplementation of 2,00,000IUs of vitamin D.

Disease Exposure	Patient progressed to DHF, DSS	Patient not progressed to DHF, DSS	Total
Vitamin D given	1	61	62
Vitamin D not given	17	45	62
Total	18	106	124

The above table shows that the relative risk of progressing to DHF in those who received vitamin D compared with those who did not was 0.0588 (95% CI: 0.0081, 0.4285).(Langerman & Ververs, 2021). These results show that supplementing with an adequate dose of vitamin D can actually halt the progression of DF to severe forms like DHF or DSS. Similarly, another study has also shown that 4000 IU/day of vitamin D supplements may represent an adequate dose to control dengue

progression and DENV replication, as macrophages from healthy donors with high doses of vitamin D supplementation are more resistant to DENV-2 infection (Giraldo et al., 2018).

4. Conclusion

The relationship between serum vitamin D levels and the progression of dengue illness, specifically DHF and DSS, was an important area of study. The findings suggest that low levels of vitamin D are associated with the progression towards severe dengue illness in individuals. It is recommended that regular testing of serum vitamin D levels be conducted in patients with dengue illness. Additionally, preventing vitamin D deficiency may offer protection against severe dengue illness. Furthermore, supplementing with vitamin D appears to be associated with a lower risk of progression to dengue hemorrhagic fever and dengue shock syndrome. It is important to continue researching this topic to gain a better understanding of the potential benefits of vitamin D supplementation, as it can be a potential immunomodulatory agent in preventing severe dengue illness.

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