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LEADING ARTICLE

Role of Vitamin D in Dengue Fever

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Introduction

The World Health Organization recently warned that diseases such as dengue, Zika, chikungunya and yellow fever caused by mosquito-borne viruses are spreading faster and further because of climate change. Dengue virus has worldwide distribution and remains a grave public health problem in Bangladesh. In Bangladesh's ongoing 2023 dengue epidemic season, the country has been witnessing the deadliest outbreak of dengue fever ever since the first outbreak in Bangladesh in 2000. As of 10 October 2023, the Directorate General of Health Services (DGHS) has reported 228,799 hospitalizations and 1,100 deaths due to the *Aedes* mosquito-borne tropical disease in the 2023 outbreak year.[1] The U.N. children's agency says the actual numbers are higher because many cases are not reported. The previous highest number of deaths was in 2022, when 281 people are reported to have died during the entire year. Prevention and control of dengue and DHF has become the need of time with the expanding geographic distribution of disease and increased disease incidence in the past 20 years.[2] Unfortunately, tools available to prevent dengue infection are very limited. Despite considerable work on vaccine for DF and DHF over the years, an effective safe vaccine is yet to be developed because of various obstacles. Mosquito prevention is also an important step in eradication of dengue fever.[3-5] It is fascinating to note that 25-hydroxy vitamin D3 has been found as an important modulator of immune response to several pathogens including dengue virus and vitamin D deficiency is another concern of Bangladeshi population where 27-75 per cent at different studies suffering from some level of vitamin D deficiency or insufficiency.[6]

Dengue fever: Etiology and pathogenesis

Dengue is a febrile illness that is a major cause of morbidity throughout the tropical and subtropical regions. It is a caused by a flavivirus with four distinct serotypes (DV-1, DV-2, DV-3, and DV-4). DHF is characterized by all the symptoms of Dengue fever (DF) along with haemorrhagic manifestations such as spontaneous bleeding, decrease in platelet count and evidence of increased vascular permeability noted as increased haemo-concentration or pleural effusion or ascites.[7] Virus spreads between humans by mosquito vectors of the Aedes genus, i.e, Aedes aegypti and Aedes albopictus.[8] Approximately 2.5 billon people are at risk of getting infection and 50 million cases of dengue fever are reported every year.[9] Infection with any of the serotypes may be asymptomatic in the majority of cases or may result in a wide spectrum of clinical symptoms, known as Dengue fever. The symptoms of dengue fever range from a mild flu-like syndrome to the most severe forms of the disease, DHF, which includes coagulopathy and increased vascular permeability. DHF may progress to hypovolemic shock known as DSS.[10] In Asia the risk of developing severe disease is greater in Dengue fever- infected children (≤15 years) than in adults.[11]

The life-threatening DSS stage occurs at the time of or shortly after drop in blood pressure, which is characterized by a rapid, weak pulse, narrow pulse pressure (≤20 mm Hg) or hypotension with cold, clammy skin in the early stage of shock. This may soon progress to more serious form of shock if patients do not receive prompt and appropriate treatment, in which pulse and blood pressure become undetectable, resulting in death within 12 to 36 h after onset of shock.[12]

How vitamin D plays role in Dengue fever

In vitamin D deficiency, calcium absorption is insufficient and cannot satisfy the body's need. Low blood calcium levels have been associated in Dengue fever.[13] Calcium has proven to be essential for

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cytotoxic activity of the dengue type 2 viruses (DV) - induced macrophage cytotoxic (CF2).[14] Calcium appears to play a role in the induction of dengue-specific T-helper cells. Dengue antigen has been shown to increase the influx of calcium into T-cells. The proliferation of dengue-specific T-helper cells appears to be dependent on calcium and is inhibited in the absence of calcium.[15] There is some evidence that the production of nitrite in response to dengue virus infection is also calcium dependent.[16]

Few studies have discussed the role of vitamin D in reducing the severity of DF, DHF and DSS. A case series published in 2009 showed 5 patients receiving vitamin D had overall improvement of clinical condition and reduced symptoms of DF.[17] A Brazilian study found increase in vitamin D binding protein in DF.[18] The possible explanation of anti- dengue effects of vitamin D is because of involvement of cathelicidin (in the form of LL-37), human beta defensin 2, and through the release of reactive oxygen species.[19] Presently it is believed that patient of DF will never progress to DHF or DSS but wide variation in severity and outcome of disease make this doubtful.

Possible role of vitamin D in Dengue fever

A study in Pakistan showed that group of patients with Dengue fever receiving vitamin D had fewer progression of DF to DHF. The relationship between vitamin D supplements and progression to DHF was significant as well as vitamin D decreases the risk and severity of DHF.[20] Puerta-Guardo et al[21] in Mexico investigated the effect of treatment with vitamin D3 on two types of human cell lines (hepatic Huh-7 and monocytic U937) infected with DENV. Pureta found that exposure to 1,25-dihydroxy vitamin D3 significantly reduced the number of infected cells, particularly in monocytic cells, and lowered the production of pro-inflammatory cytokines. Vitamin D3 significantly reduced the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-12p70 and IL-1α,) produced by infected U937 cells. These results suggest that vitamin D3 may represent a potentially useful antiviral compound.

Alagarasu et al[22] showed that there might be an association related to the inducing effect of vitamin D on Fcγ receptor expression. Fcγ receptor enhances viral entry into cells, possibly leading to higher viral load in dengue cases with secondary infection and the development of DHF or dendritic cell-specific intercellular adhesion. Studies showed that vitamin D might influence viral entry into cell. Albuquerque et al[18] compared protein levels in the plasma of patients with severe DF with the protein levels of healthy individuals and found that a one of the proteins showing a significant increase in DF patients was vitamin D-binding protein. Bharara et al[23] showed in their study that 25-hydroxy vitamin D3 may contribute in the pathogenesis of dengue infection; thus, vitamin D levels might serve as useful prognostic marker for predicting disease progression.

Iqtadar et al[24] showed their results suggest that there may be a possible association between VDD and susceptibility towards severe dengue illness. Hence, maintaining sufficient vitamin D levels in the body either through diet or supplementation may help provide adequate immune protection against severe dengue fever illness. Sadarangani et al[25] in Singapore found low systemic 25-(OH) D was associated with increased dengue disease severity, particularly for severe bleeding that was not explained by thrombocytopenia.

Vitamin D supplementation in Dengue fever

No significant number of studies has been published considering the supplementation of vitamin D to reduce morbidity or mortality of dengue illness, still few studies revealed, in group receiving vitamin D (2,00,000 IU single dose), there was fewer progression of DF to DHF. The relationship between vitamin D supplements and Progression to DHF was significant (N=170, χ^2=16.43, p= 0.000). Vitamin D decreases the risk and severity of DHF.[20] Jahnnyer Martínez-Moreno et al[26] showed that MDDCs from donors who received 4000 IU/day of vit D were less susceptible to DENV-2 infection than MDDCs from donors who received 1000 IU/day of vit D. In another study, Diana Marcela Giraldo et al[27] showed a supplement of 4000 IU/day of vitamin D may represent an adequate dose to control dengue progression and DENV replication. Saìnchez-Valdeìz et al[17] observed a significant increase in platelet count on receiving vitamin D in their clinical trial. According to another study[28], vitamin D supplementation altered IL-12 expression and dendritic cell maturation there by giving vitamin D to dengue patients improved clinical condition.

Conclusions

The studies on vitamin D levels indicate that high concentrations of vitamin D could restrict the infection and replication of the virus in the target cells by reducing the entry receptors and enhancing

antimicrobial peptide levels. Furthermore, vitamin D plays an immunoregulatory role by reducing the production of pro-inflammatory cytokines and enhancing macrophage segregation. Globally, most of the people are suffering from either from vitamin D deficiency or insufficiency. Vitamin D supplementation during Dengue fever may be considered to prevent disease severity although no significant data on clinical improvement is available in current literature. Further research on definite role of vitamin D in reducing Dengue illness and its mode of supplementation in Dengue patients are warranted.

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