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Review article ***Nutrients***

Role of micronutrients in the management of dengue fever

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ABSTRACT

Dengue virus infection is the most widespread mosquito-borne viral infection in humans and has emerged as a serious global health challenge. In the absence of effective treatment and vaccine, host factors including nutritional status, which may alter disease progression, need investigation. The interplay between nutrition and other infections is well-established, and modulation of nutritional status often presents a simple low-cost method of interrupting transmission, reducing susceptibility, and/or ameliorating disease severity. This review examines the evidence on the role of micronutrients in dengue virus infection. We found critical issues and often inconsistent results across studies; this finding along with the lack of sufficient literature in this field have limited our ability to make any recommendations. However, vitamins D and E have shown promise in small supplementation trials. In summary, the role of micronutrients in dengue virus infection is an exciting research area and needs to be examined in well-designed studies with larger samples. Dengue is life threatening. It is critical to triage patients with dengue infection in the early stage. However, there is limited knowledge on early indicators of Severe dengue. The objective of this study is to identify risk factors for the prognosis of Severe dengue and try to find out some potential predictive factors for Severe dengue from dengue fever in the early of infection.

Keywords: Dengue fever, Hemorrhage, Thrombocytopenia, Vitamin E, Vitamin C

INTRODUCTION

Dengue fever is a viral disease caused by dengue virus that belongs to the genus Flavi virus in the family *Flaviviridae*. The virus is transferred to humans mostly by the bite of female mosquito *Aedes aegypti*. Dengue virus (DENV) is a single-stranded RNA virus with a genetic makeup of about 11,000 nucleotides in length. Dengue fever is caused by IV antigenically related but genetically distinctive viruses (DEN I-IV), and all IV serotypes usually result in mild febrile sickness which probably develops to dengue shock syndrome and dengue hemorrhagic fever (DHF).Dengue virus infection is an illness with a wide clinical picture ranging from asymptomatic to an undifferentiated fever to the more serious form of Thrombocytopenia and plasma leakage are important complications of dengue fever infection, which results to disturbance in thrombopoiesis and increased destruction of platelets in circulation.

Bone marrow has a significant role in the suppression of hematopoietic system and inducing thrombocytopenia occurred during dengue viral infection. TPO (thrombopoietin) is the main regulatory hormone maintaining the adequate count of thrombocytes and megakaryocytes in circulation. A significant increase in TPO level has been found in patients with low circulating levels of megakaryocytes and platelets[1]. Angiotensinogen is a glycoprotein, produced by the liver and released into the circulation. Due to lowered blood pressure, angiotensinogen is acted upon by renin and then converted into angiotensinogen-I which is further converted into angiotensin-II, a physiologically active form of renin-angiotensin system and have a vasoconstriction effect regulating the fluid volume and mineral balance in body fluids. Vitamin D3 plays an important role in mediating the immune system. It increases the phagocytic capacity of

macrophages and induces antimicrobial peptide gene expression, thus contributing to innate immune responses[2].

ETIO-PATHOGENESIS

DF is a severe flu-like infection that involves individuals of all age groups (infants, children, adolescents, and adults). Transmission among human beings occurs by the mosquito *Aedes aegypti* and chiefly occurs during the rainy season. The proposed etiologies for dengue virus infection are:

- Viral replication, primarily in macrophages
- Direct skin infection by the virus
- Immunological and chemical-mediated mechanism induced by host–viral interaction.

Dengue virus gains entry into the host organism through the skin following an infected mosquito bite. Humoral, cellular, and innate host immune responses are implicated in the progression of the illness and the more severe clinical signs occur following the rapid clearance of the virus from the host organism. Hence, the most severe clinical presentation during the infection course does not correlate with a high viral load. Alterations in endothelial microvascular permeability and thrombo regulatory mechanisms lead to an increased loss of protein and plasma. Proposed theories suggest that endothelial cell activation caused by monocytes, T-cells, the complement system, and various inflammatory molecules mediate plasma leakage. Thrombocytopenia may be related to alterations in megakaryocytopoiesis, manifested by infection of human hematopoietic cells and compromised progenitor cell growth. This may cause platelet dysfunction, damage, or depletion, leading to significant hemorrhages.

DIAGNOSIS

Cautious attention should be directed at DF if a patient suffers from high fever within 2 weeks of being in the tropics or subtropics. A decreased number of white blood cells, accompanied by a decreased number of platelet count and metabolic acidosis are the initial changes on laboratory examinations. Microbiological laboratory testing confirms the diagnosis of DF. Virus segregation in cell cultures, nucleic acid demonstration by polymerase reaction, and serological detection of viral antigens or particular antibodies are the preferred microbiological assays. Viral segregation and nucleic acid demonstration provide precise diagnosis, although the high-cost chain limits the availability of these tests

MANAGEMENT OF DENGUE INFECTON

Fluid replacement and antipyretic therapy with paracetamol is the preferred therapy following the febrile phase. Care should be taken not to use other nonsteroidal anti-inflammatory drugs. Judicious fluid administration forms the mainstay of treatment during the critical phase of the infection. Normal saline, Ringer's Lactate, and 5% glucose diluted 1:2 or 1:1 in normal saline, plasma, plasma substitutes, or 5% albumin are the routinely administered fluids. WHO guidelines summarize the following principles of fluid therapy:

- Oral fluid supplementation must be as plentiful as possible. However, intravenous fluid administration is mandatory in cases of shock, severe vomiting, and prostration
- Hypotensive states that are unresponsive to boluses of intravenous crystalloids, colloids (e.g., dextran) form the second-line measures
- If the patient remains in the critical phase with low platelet counts, there should be a serious concern for bleeding. Suspected cases of bleeding are best managed by transfusion of fresh whole blood.

ROLE OF VITAMINS & MICRONUTRIENTS IN DENGUE FEVER

VITAMIN D

Vitamin D is known to play an essential role in the immune system, and vitamin D deficiency has long been associated with autoimmune diseases as well as increased susceptibility to viral infections[3]. Vitamin D has been shown to promote both innate and adaptive immunity through a number of mechanisms, such as T-cell activation and monocyte differentiation. Many additional cells of the immune system (including B cells, monocytes, and dendritic cells) also respond to the immune modulatory effects of vitamin D through the vitamin D receptor (VDR) expressed on their cell surface. Vitamin D binding to the VDR, in turn, activates vitamin D-responsive genes in the body, many of which induce a number of pathogen-fighting mechanisms.

Vitamin D supplementation also has some success in helping to treat other viral infections, such as influenza in monocytic cells, the primary target for DENV, this effect is believed to be because of the interference of vitamin D3 with the activation of several host cell signaling pathways that are essential for DENV survival and replication. It has been shown that vitamin D3 down-regulates the Toll-like receptors (TLRs) that activate the nuclear factor-kB (NF-kB)/Rel A pathway, which reduces the phosphorylation of mitogen activated protein kinases (MAPKs) p38 and p42/44 as well as the production of TNF-a and IL[4].

The activation of MAPKs c-Jun N-terminal kinase (JNK) and p38 pathways is necessary for the virus to successfully replicate and infect macrophages that release inflammatory cytokines, which are associated with the disease manifestations of capillary leak syndrome and hemorrhagic tendencies. Therefore, down-regulation of this pathway by vitamin D3 would result in the reduction of the numbers of infected cells and mechanisms. Vitamin D supplementation also has had some success in helping to treat other viral infections, such as influenza.

EVIDENCE FROM OBSERVATIONAL STUDIES

Multiple observational studies have also investigated the relationship between vitamin D and DENV infection in patients with dengue. A recent study in India compared the levels of vitamin D in patients with DF and DHF with those of healthy individuals. Alagarasu and others found that patients with both DF and DHF had significantly higher 25-hydroxy vitamin D levels in their blood than the healthy controls Alagarasu and others[5]. Speculated that this association might be related to the inducing effect of vitamin D on Fcg-receptor expression or dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DCSIGN), the primary receptor through which the virus enters immature dendritic cells.

EVIDENCE FROM TRAILS

A small trial conducted in Mexico examined the effects of calcium and vitamin D supplementation among a total of five DF patients. In addition to receiving the standard treatment of electrolytic solutions and 500 mg paracetamol (acetaminophen) every 12 hours, the participants received a specific course of calcium carbonate plus vitamin D3 supplementation. Sanchez-Valdez and others observed a significant increase in platelet count in all five of the patients; the average platelet count changed from 136,000±69,508 cells/mm3 before treatment to 179,600± 56,584 cells/mm3 after treatment. Sanchez -Valdez and others also observed a significant improvement in the overall clinical condition of the patients as well as reduction in the duration of signs and symptoms of the infection. Sanchez-Valdez and others suggest that the supplementation may possibly restore free Ca2+ quicker, leading to the reduced thrombocytopenia observed.

VITAMIN A

Vitamin A, one of the most commonly studied nutrients in relation to immunity, is known to be a central regulator of the immune system; vitamin A deficiency has been shown in many studies to impair both humoral and cell-mediated immunity as well as the integrity of epithelial tissues of the eyes, lungs, and gut, all of which to an increased susceptibility to pathogens and infectious. Specifically, vitamin A affects the activity of macrophages and the number and activity of NK cells as well as lymphocyte functions, such as B-cell proliferation and T-cell activation[6]. Vitamin A supplementation has been found to have a significant impact on preventing morbidity and mortality in a number of infectious diseases in developing countries.

EVIDENCE FROM OBSERVATIONAL STUDIES

There has been very little research on the association between vitamin A and DENV infection in humans. In an observational study conducted in Guatemala, Klassen and others compared the plasma concentrations of circulating antioxidant nutrients (including retinol and β-carotene) of patients with DF with those of healthy individuals. Klassen and others found an association between dengue and lower levels of both retinol and β-carotene.

VITAMIN E

Immune function has been found to be especially sensitive to changes in vitamin E status; even marginal vitamin E deficiency prevents the immune system from exhibiting a proper response to infection[7]. Importantly, the antioxidant properties of vitamin E protect immune cell membranes from oxidative damage. Vitamin E supplementation has been reported to enhance both humoral and cell-mediated immune responses and resistance to infection. It has been shown to enhance immunity in elderly populations. Specifically, vitamin E enhances T-cell differentiation, helper T-cell and NK cell activity, lymphocyte proliferation, and macrophage function.

EVIDENCE FROM TRAILS

In a recent trial conducted in India, Vaish and others administered vitamin E supplements to patients with DF to study the effects of vitamin E on thrombocytopenia. All patients had initial platelet counts determined to be between 10 +103/mm3 and 100 +103/mm3. Divided into two groups of 33 patients each, Vaish and others gave one group 400 mg oral vitamin E supplementation in addition to the standard treatment, whereas the other group received only standard treatment.

ZINC

Similar to vitamin D, zinc is also very important for immune function, and deficiency in zinc has been associated with decreased resistance to viral infection. Affecting a number of immune cells and functions, zinc specifically influences lymphocyte maturation, cytokine production, and generation of free radicals while maintaining normal macrophage and natural killer (NK) cell activity in the immune response[8]. it also plays a role in T-cell and neutrophill activity as well as B-cell development. Zinc supplementation has also been found to reduce mortality from diarrhea and pneumonia and has been shown to be beneficial in preventing respiratory infection

EVIDENCE FROM OBSERVATIONAL STUDIES

An observational study in Indonesia investigated serum zinc levels in children with DF, DHF, and DSS. Yuliana and others found that a decrease in zinc levels associated with increasing severity of DENV infection. However, in a similar observational study in Indonesia,[9]. found no significant association between clinical severity of DHF and blood zinc levels.

IRON

The need for iron for proper immune stems from its role in promoting been found to decrease mitogen responsiveness, NK cell activity, lymphocyte bactericidal activity, and neutrophil phagocytic activity while influencing cytokine activity in every stage of the immune response to infection[10].

EVIDENCE FROM OBSERVATIONAL STUDIES

There are no studies, to the best of our knowledge, that have comprehensively assessed iron status or examined the effects of iron supplementation in the context of DENV infection. In one observational study in Thailand, Chaiyaratana and others[11]. Compared serum ferritin levels in children with DF and DHF during the infection and at follow-up 2–4 weeks after discharge from the hospital. Chaiyaratana and others found that serum ferritin levels were higher in both DF and DHF patients during the infection than at follow-up, with DHF patients displaying higher ferritin levels than DF patients throughout the course of the illness.

Table 1: Micronutrients and proposed mechanisms of clinical benefit in patients with dengue fever

Micronutrient	Proposed mechanisms of clinical benefit
Vitamin A	Facilitates B-cell proliferation and T-cell activation; affects the activity of macrophages and natural killer cells[12].
Vitamin C	Scavenging of reactive oxygen species, increase in interferon production, facilitation of leukocyte phagocytic functions[13].
Vitamin D	Reduction of destructive inflammatory reactions via modulation of toll-like receptors (TLR3 and TLR9), increased production of Interleukin-10, increased expression of suppressor of cytokine signalling proteins
Vitamin E	Protection of cell membranes from oxidative damage scavenging of peroxyl radicals, enhancement of immune function via enzyme activation and changes in gene expression[14].
Folic acid	Hematinic effects, promotion of hematologic recovery
Zinc	Facilitation of lymphocyte maturation and cytokine production, promotion of T-cell and neutrophil activity, acceleration of apoptosis

DISCUSSION

Vitamin B_{12} acts as a co-factor during synthesis phase of the cells in bone marrow. So, Vitamin B_{12} deficiency causes thrombocytopenia. Serum Vitamin B_{12} levels are not frequently tested in patients being treated for thrombocytopenia secondary to spectrum of dengue viral infection.

CONCLUSION

Vitamin E and C supplementation may contribute to increasing in platelet count and early recovery of dengue fever. The results showed that both in cases and control groups the macro- nutrients (carbohydrate, protein, fat) and micro-nutrient (Vitamins A, C, B_1, B_2, B_6, calcium, magnesium, phosphorus, zinc, and Iron) intake were below 80% of nutrient adequacy. We find that macro and micronutrient intake in DHF case and control groups are the same and below 80% of nutrient adequacy.

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