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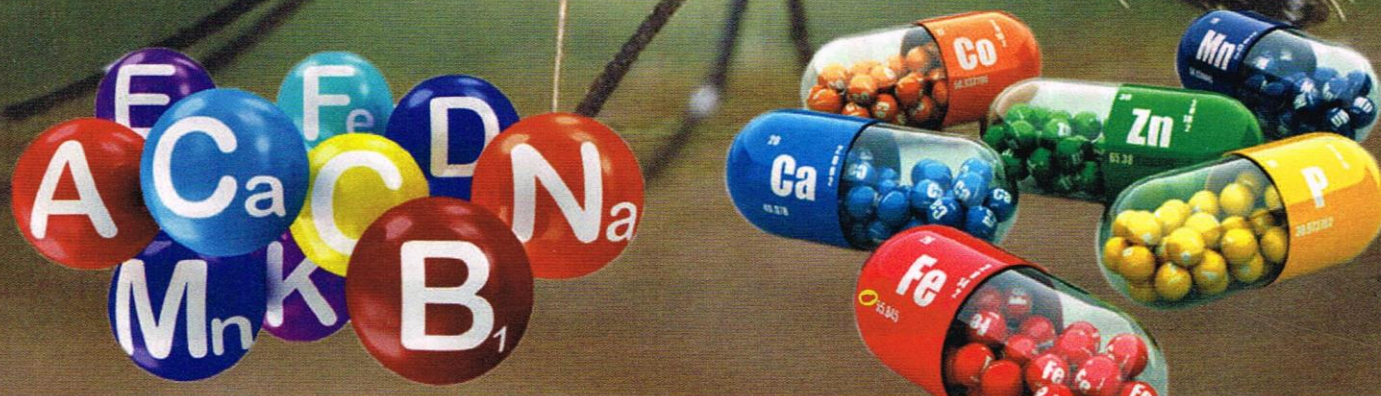
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# Dengue and Micronutrient

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Dengue virus (DENV), a member of the Flaviviridae family, causes the most widespread mosquito-borne viral infection in humans around the world today. The pathophysiology of DENV in the body and the host's immune response are not completely understood. Major disease manifestations in the body include capillary leak syndrome (plasma leakage caused by endothelial cell dysfunction, which is specific to DHF), thrombocytopenia (which is seen in all forms of DENV infection, but very severe values are specific to DHF), leukopenia, and hemorrhagic tendencies. It is known that the major viral envelope (E) glycoprotein in the virus assists its binding to host cells, after which the virus enters the cell and viral replication occurs. Data suggest that monocytes are the primary targets. Infected monocytes induce the production of interferon- $\alpha$  (IFN- $\alpha$ ) and IFN- $\beta$ . E, precursor membrane protein (pre-M), and nonstructural protein 1 (NS1) are the major proteins on DENV that are targeted by antibodies as part of the host immune response. Studies show that DENV-specific CD4+ and CD8+ T lymphocytes attack infected cells and release IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and lymphotoxin. Primary infection induces lifelong immunity in the individual to that particular serotype but not to secondary infection by a different serotype.<sup>1, 2, 3</sup>

Host nutritional status is a strong predictor of immunity; in fact, malnutrition is the most common

cause of immunodeficiency worldwide, estimated to cause about 50% of childhood deaths and a significant fraction of deaths from infectious diseases in developing countries. A properly functioning immune system requires an adequate supply of micronutrients to both prevent damage of cells participating in the innate immune response and restore tissues damaged from the host defense against the infectious agents. Earlier studies have, contradictorily, found that malnourished children are less likely to develop DHF/DSS compared with well-nourished children, but recent studies have not supported this finding.

## 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. 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 immunomodulatory 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 had some success in helping to treat other viral infections, such as influenza.

A recent laboratory study conducted in Mexico investigated

the effect of treatment with 1,25-dihydroxyvitamin D3 on two types of human cell lines (hepatic Huh-7 and monocytic U937) infected with DENV-4. Puerta-Guardo and others 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 proinflammatory cytokines (TNF- $\alpha$ , interleukin-6 [IL-6], IL-12p70, and IL-1 $\beta$ ). The highest concentration of 1,25-dihydroxy vitamin D3 (10  $\mu$ M) induced the greatest reduction in percentage of infected cells, suggesting a correlation between vitamin D3 dose and inhibition of DENV infection.<sup>4, 5</sup>

## 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 it also plays a role in T-cell and neutrophil 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.

In a laboratory study conducted in Malaysia, Shafee and AbuBakar studied the effect of different concentrations of Zn<sup>2+</sup> on apoptosis of DENV-2-infected Vero cells and found that they quickened apoptosis of the

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infected cells. The acceleration of apoptosis by zinc could represent a mechanism through which zinc supplementation may help host limit viral infection. Another study using human neuroblastoma cells showed that treatments of DENV-2-infected cells with ZnSO<sub>4</sub> at low concentrations (< 20 µM) resulted in dose-dependent protection of the infected cells, whereas at higher concentrations, Zn<sup>2+</sup> became toxic.<sup>6,7</sup>

### Vitamin A

Vitamin A, one of the most commonly studied substances 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 lead to an increased susceptibility to pathogens and infectious diseases. 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. 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. Studies show that vitamin A supplementation decreases disease severity and risk of death in malaria and reduces mortality in measles.<sup>8</sup>

### Iron

The need for iron for proper immune function stems from its role in promoting the growth and differentiation of various immune cells; specifically, iron deficiency has 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.<sup>9</sup>

### Chromium

Chromium (an essential trace mineral) has been known for its effects on the regulation of blood sugar by promoting the action of insulin, and recently, it has been discovered to affect the immune response by influencing T and B lymphocytes, antigen-presenting cells (such as macrophages), and cytokine production. Chromium supplementation is known to increase immune function in animals, possibly by reducing serum cortisol levels. Chromium supplementation has been shown to exhibit very complex effects; high doses and extended exposure can make hexavalent chromium cytotoxic to the body by inhibiting many cellular processes and mutating genes important to the immune response. In addition, exposure to chromium from the environment has been reported to cause many adverse health effects. Therefore, chromium supplementation, if ever used to benefit infections or diseases, must have a very precise dose.<sup>10</sup>

### 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. 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 in a number of human studies. 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.

Considering the potential of micronutrient supplements to represent low-cost and simple adjuncts to improve treatment success in patients with dengue, it is surprising that the scope of research in this area has been rather limited. Researchers should also evaluate the possibility of nutritional status being a predictor of acquisition of DENV infection in endemic areas.<sup>11, 12, 13</sup>

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