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## Role of nutrition in the management and control of malaria infection: a review

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### ABSTRACT

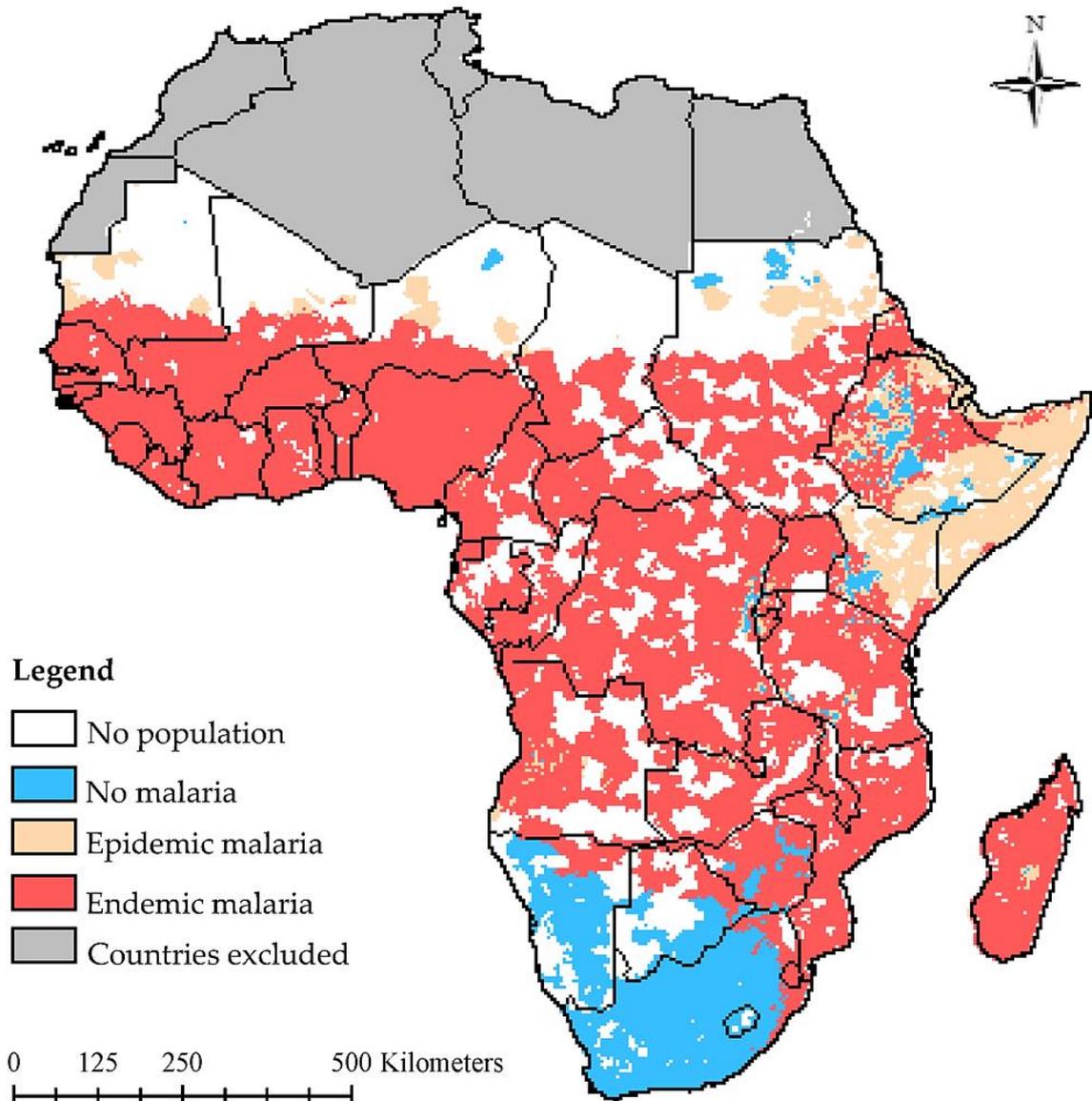
A review of the contribution of nutrition in management and control of Malaria was conducted. Nutrition has been confirmed as one factors that can be used to suppress the effect of malaria infection before clinical treatment is received by the patient. For the body to function normally, its nutritional demand must be met in the right proportions. Diet rich in vitamins, minerals, micronutrients are required for the metabolic functioning of the body, hence effective or adequate nutrition has health benefits to the human body. Living on quality diet has a way of improving the body defense mechanism against infectious diseases such as malaria.

**Keywords:** Effective nutrition, Malnutrition, Malaria infection, Immune system, Sub-Sahara African, Poverty

### 1. INTRODUCTION

Mankind has always faced one challenges or the other in the course of his existence. Health challenge is one of the factors contributing to high rate of death in Nigeria. Malaria infection remains the biggest health challenge in the world, chiefly among pregnant women and children below the age of 5 years in sub-Sahara African (WHO, 2016). A research finding

has shown that about 500 million people are infected with malaria every year, which accounts for one-third of the world's population (WHO, 2015). In terms of geographical distribution, Malaria infection is endemic in West African. In spite of recent control measures (Figure 1).



**Figure 1.** A geographical distribution of malaria in African  
(Source: Osadolor and Michael, 2016)

High level of poverty which has a define effect on nutritional status has been linked to the endemicity of malaria in the Sub-Sahara African (Caufield *et al.*, 20004). Malnutrition has a negative effect on the body's defense mechanism; the lack of certain essential nutrient which help the body to boast it's immune system, can make it susceptible to malaria infection (Keush, 2003). According to Puertollan (2011), the lack of certain nutritional component or a

wrong proportion is an indication of malnutrition or under nutrition. Effective nutrition on the other hand is an act of taking in diet, which contains nutritional components in the right proportion. Effective nutrition, has a way of boosting the body's defense against malaria, because it contains all the nutrients which are responsible for the well being of the body system.

### **1. 1. Nutrition and Its Role on the Immune system**

The body requires enough nutrients in order to function effectively. Certain micronutrients for instance, have been implicated, to promote proper functioning of the immune system. According to Biesel *et al.*, (1997), micronutrients such as zinc, selenium, iron, copper,  $\beta$ -carotene, vitamins A, C, and E, and folic acid can affect certain components of the immune system. They play an important role in altering of oxidant-mediated tissue injury, and phagocytic cells produce reactive oxidants as part of the defense mechanism against infection. Thus, adequate or effective nutrition are required to prevent damage of cells in the immune system. Deficiencies in zinc and vitamins A and D may reduce natural killer cell function, whereas supplemental zinc or vitamin C may enhance their activity (Puertollan, 2011).

Vitamin A deficiency on immune function is very significant, and there is a evidence of the role of vitamin A in the resistance to infection, although the mechanism is not well known (Kjølhede and Beisel, 1995). It can be said that "no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A" (Scrimshaw, 1968). Studies have shown that vitamin A supplementation reduces the impact of malaria on children's growth, protects pregnant women against malaria, and reduces the risk of malaria (Shankar, 2008). Vitamin A plays a key role in the immune system, such as in the transport of T-cell to tissue, and in T-cell dependent reactions, as well as lymphocyte maturation (Ross, 2012). A hallmark of vitamin A deficiency is a depressed antibody response to T-cell-dependent and independent antigens, which may be mediated by alterations in the production of some cytokines (Santos, 2012). A deficiency in vitamin A can lead to depressed immune system, which makes the body susceptible to malaria.

Vitamin E supplementation is considered to improve immune function in the elderly, and antibody production after vaccination. Vitamin E increases both cell-dividing and interleukin-producing capacities of naive T cells but not of memory T cells. This enhancement of immune function can be associated to significant improvement in resistance to malaria. (Meydani *et al.*, 1993).

Vitamin D supplements may offer a cheap and effective immune system boost against malaria (Martineau *et al.*, 2007). Vitamin D increases, the activity of macrophages and monocytes which helps to fight against diseases. It appears to be important in the control of infection, because it increases the blood concentration of the body's own antimicrobial proteins e.g., alpha- and beta-defensin (Peelen, 2011). However, vitamin D activates enzymes in T and B lymphocytes which can help in fighting malaria.

The B complexes are involved in a lot of cellular metabolic reactions and, as a group, is considered to have an effect on cellular disease resistance and the immune response to infections (Bendich and Chandra, 1990). Vitamins B<sub>6</sub>, B<sub>12</sub>, and folate are important for cell-mediated immunity (CMI), they involved in the production of antibodies in the immune system. Thiamine, is necessary for biosynthesis of antibodies or the expression of humoral immunity (Beisel, 1992).

A deficiency in the B- complexes, weakens the immune system and thus, prevents the formation of antibodies which would have helped to prevent malaria in the body.

Zinc is a trace mineral that is essential for all species and is required for the activities of various enzymes, carbohydrate and energy metabolism, protein synthesis and degradation, nucleic acid production, heme biosynthesis, and carbon dioxide transport. It is an important cofactor in the formation of enzymes and nucleic acids and plays a vital role in the structure of cell membranes and in the function of immune cells (Beisel, 1982). Zinc deficiency reduces nonspecific immunity including, neutrophil and natural killer cell function and complement activity; reduces the number of T-cells and B-cells; and suppresses delayed hypersensitivity, cytotoxic activity, and antibody production. Inadequate zinc supply prevents the release of vitamin A from the liver. Zinc supplementation reduces the effect of malaria infection (Caulfield *et al.*, 2004).

Iron deficiency is the most common trace element deficiency affecting 20%–50% of the total world' spopulation; mainly infants, children, and women of child bearing age (Patterson *et al*, 2001). It is causes impairments in cell-mediated immunity and reduces neutrophil action, with decreased bacterial and myeloperoxidase activity. It lowers the body's defense mechanism against disease and diminishes body and brain functions. Despite this, iron deficiency has unclear effects on infectious disease risk. In the treatment of malaria, correcting iron deficiency is important, because malaria causes hemolysis and anemia. Supplementation in some cases, however, may actually increase the infection, because the malaria parasite requires iron for its multiplication in blood. Many microorganisms require trace elements, such as iron and zinc, for survival and replication in the host and may increase in with supplementation (Shankar, 2000); there is a concern about iron supplementation in malaria chemoprophylaxis programs. In order to reduce the side effect of the intake of iron supplement in the treatment of malaria WHO, (2011) recommends the intermittent taking in of iron supplements, rather that daily use of iron supplements in the treatment of malaria.

Fatty acids are important in the diet of humans, they are not only macronutrient that yields energy but also play an important role in the cell (Calder, 2015). Like all mammalian cells, lymphocyte contains fatty acids, some of which are very essential because their cells cannot synthesize them.

The polyunsaturated fatty acids (PUFA) are very important because, they are use for the synthesis of eicosanoids and leukotrienes which are essential to the immune system (Calder, 2012). According to Svahn (2015), Omega-3-PUFAs has immune modulating property, they are responsible for positive effects of the immune as they influence the transcriptome profile in spleen and also increase the frequency of neutrophil in the bone marrow. PUFAs, helps to increase the improve the immune system and is essentially important in the diets. Increasing the diet with PUFAs, also increases the amount of vitamin E. The richest source of vitamin E is vegetable oil.

Proteins are macro molecules, which are made up of amino acids and are required in the diet. Proteins are very important in the body, they help in building and maintenance of the body (Young, 2001). The immune system and other host defense mechanisms depend on the ability of body cells to synthesize proteins because the immune system, which includes the immunoglobins are made from proteins. In the deficiency of proteins, immune system becomes depressed because the proteins required to synthesize antibody are not available (Biesel, 1991).

## 1.2. Malaria and the Immune system

The complete life cycle of *Plasmodium* involves two hosts: the first is the mosquito vector and the other the vertebrate host (Crompton *et al.*, 2014). In the vertebrate host *Plasmodium* go through two stages: an asymptomatic pre-erythrocytic stage (liver stage), and an asymptomatic erythrocytic stage (blood stage) (Haque and Engwerda, 2014). The movement of sporozoites into the liver is asymptomatic (Zheng *et al.*, 2014), various reports have however described that a first immune response ensues during this stage. Certain of the immunological responses described to take place during the liver stage are: apoptotic death of infected cells (Meslin *et al.*, 2007), sequestration and targeting of parasites in definite compartments for elimination (Yano and Kurata, 2011), type I IFN production prompted by parasite RNA (Liehl *et al.*, 2015) as well as LC3-mediated autophagy targeting of sporozoites (Risco-Castillo *et al.*, 2015). Nevertheless, several other mechanisms such as immune exploitation, immune evasion, and molecular piracy are engaged by the parasites to ensure their survival in the host (Hisaeda *et al.*, 2005). Following the first immunological attack during liver stage, most of the parasites that survived replicates within hepatocytes and exponentially amplify their number resulting in the release of hundreds of thousands of merozoites into systemic circulation (Prado *et al.*, 2015).

The first barrier that parasites encounter after transmission into the vertebrate host is the skin (Cirimotich *et al.*, 2010). And sporozoites have developed to overcome this obstacle through various mechanical tactics such as amoeboid motility and cell transversal (Tavares *et al.*, 2013). Sporozoites are fortified with specialized mechanical proteins that help them achieve successful passage through host skin. This has been proven by various studies that show how the transmission of sporozoites lacking SPECT-1 (sporozoite microneme protein essential for cell traversal) and SPECT-2 (called perforin-like protein 1 or PLP1) are obstructed in the dermis and subsequently ingested by phagocytes impeding their progression. These proteins were reported to be essential for cell traversal and for liver migration (Patarroyo *et al.*, 2011). Sporozoites can transverse several kinds of cells, immune cells inclusive. The transversal of immune cells can result in the inactivation of immune cell defenses and the prevention of sporozoites clearance (exocytosis) before crossing the barrier (Sinnis and Zavala, 2012).

Another protein that is essential for sporozoites motility is TRAP (Thrombospondin-Related Anonymous Protein). TRAP is found on the micronemes and on the surface of sporozoites where it allows the parasite to relate with surface host molecules which provides gliding motility to exit the dermis. TRAP can also bind to sulfated glycoconjugate motifs that can assist in the recognition and entry into hepatocytes (Müller *et al.*, 1993).

A successful infection in great part is as a result of the parasites evading the initial attacks of the host immune response (Singh *et al.*, 2010). Following the sporozoites passage through the skin, crossing all cellular barriers, is their entry into the blood, and consequently the lymphatic system (Crompton *et al.*, 2014). Once they get into the circulatory system, sporozoites quickly reach the liver's sinusoid cavity. The exoerythrocytic (liver) stage has been labelled as asymptomatic since the liver is an immunoprivileged organ that is protected against strong immune responses (Liehl *et al.*, 2015).

Upon successful penetration of the sinusoidal cell layer of the liver, sporozoites enter the liver cells and start developing in the hepatocytes. Sporozoites invade the host cells (hepatocytes) actively by engaging the cholesterol uptake pathway (Itoe *et al.*, 2014). Additionally, released circumsporozoite protein (CSP) supports parasite development through the suppression of the NF- $\kappa$ B signaling pathway (Ding *et al.*, 2012) and the up

regulation of the expression of host heme oxygenase-1 (HO-1), which further supports the parasite development in the liver by moderating the host inflammatory response (Pamplona et al., 2007). Sporozoite infection of hepatocytes also impedes the mTOR pathway, hence altering the levels of proteins involved in proliferation, cell survival, anabolism, autophagy, and cell growth (Hanson et al., 2013). After invading the final hepatocyte, sporozoites are encircled in a parasitophorous vacuole (PVM), which separates it physically from the host cytoplasm thus avoiding degradation by the endocytic/lysosome system. This isolation keeps the parasitophorous vacuole secluded from cell intrinsic defenses such as apoptosis and selective autophagy (Thieleke-Matos et al., 2016). The transition of parasites from liver stage merozoites to induce blood stage represents another key point of the cycle for immune avoidance. Liver stage parasites must exit from the hepatocytes through hepatic spaces where they get exposed to resident phagocytic cells such as KCs and DCs in order to start the blood stage. Merozoites avoid being destroyed by liver phagocytes by enveloping themselves in membranes derived from the host known as merosomes (Sturm et al., 2006).

One major component of the innate immune system are the Pattern Recognition Receptors (PRRs) that are responsible for the recognition of Pathogen-associated molecular patterns (PAMPs). For malaria, three PAMPs that have been projected for Plasmodium parasites are: Hemozoin, GPI anchors, and immunostimulatory nucleic acid motifs (Gazzinelli et al., 2014). Release array of pro and anti-inflammatory can cause either successful parasite control or alternatively an exacerbated immune response resulting in pathology (Perkins et al., 2011). Despite the fact that mounting a potent immune response is not always entirely efficient, it is essential for controlling parasitemia. An important “bridge” between the innate and adaptive immune response are the dendritic cells (DCs). The DCs have a function of presenting antigen, stimulating T-cells, and are also major mediators of the adaptive immune response (Gowda et al., 2012). During malaria, CD4+ T-helper cells have been implicated in pathogenesis, protection of parasites and their immune evasion (Wykes et al., 2014).

Responses by antibodies as immune agents alone can provide adequate protection to control clinical disease (Wykes et al., 2014). Antibodies can act on restricting the growth of blood stage parasites and the progression of clinical symptoms for several mechanisms, like obstructing erythrocyte invasion (Blackman et al., 1990), act as opsonins on parasitized erythrocytes (Osier et al., 2014), monocyte-mediated antibody-dependent cellular killing (Bouharoun-Tayoun 1995), as well as complement-mediated lysis (Boyle et al., 2015), and interfering with the adherence of infected erythrocytes to vascular endothelium (Beeson et al., 2004). However, antibody responses to malaria infection from children and adults have been described to be short-lived and quickly lost in the absence of continued parasite exposure (Ryg-Cornejo et al., 2016). Jointly, these findings show that the immune system is effective at reducing parasite burden but in many cases is not sufficient to prevent the progression of the disease showing the high capacity of immune evasion by the parasite (Pollyanna et al., 2016).

## **2. NUTRITION AND MALARIA**

The interplay between nutrition and infectious diseases is very important. The importance of effective nutrition cannot be over emphasized, lack of effective nutrition makes the body susceptible to malaria. According to WHO (2012), lack of effective nutrition can be attributed to the 50% malariadeaths in Africa. Malaria and Malnutrition are seasonal,

especially during the raining season. During the raining season more people suffer from malaria infection, the raining season also corresponds with high level of lack of proper nutrition (Osadolor *et al.*, 2016). This period of lack of effective nutrition makes people extremely susceptible to malaria.

Malnutrition or undernourishment compromises or suppresses the immune system. (Meydani, 2003). Malnutrition in terms of insufficient protein intake is associated with an impairment of cell-mediated immunity, phagocytic functions, complement system and cytokine production in humans (Biesel, 2006). Deficiency in micronutrients has profound consequences on the immune system, and makes it vulnerable to infectious diseases. Carotenoids, vitamins A, C, E, selenium and zinc have immunomodulatory effects and dietary manipulations of the semicronutrients alter immune functioning in model and nonmodel systems (Meydani *et al.*, 2003; Cannon *et al.*, 1991).

Moreover, Malnutrition or undernourishment causes a rapid protein breakdown and the weakening of the resistance mechanism of the body. Metabolic rate and loss of body nitrogen increases, and large quantities of gluconeogenic amino acids are broken down to produce glucose; branched chain amino acids are oxidized in muscle cells to produce energy; and the body breakdown of tryptophan and phenylalanine is accelerated (Beisel, 2006). The body's diversion to free amino acids reduces their availability for the synthesis of new proteins. The adequacy of immune system and other host defense mechanisms depends on the ability of body cells to synthesize proteins because the immune system, which includes the immunoglobins are made from proteins. But protein synthesis is impeded when the supply of free amino acids is inadequate or when an imbalance exists among the essential free amino acids. However, when overwhelming disease or trauma causes severe malnutrition, the resulting deficits of body protein and free amino acids can lead to depression in host immune system (Beisel, 2006).

Scrimshaw et al in 1968 reviewed the results of several studies exploring the effect of dietary shortfalls on malarial infections in laboratory animals. Results relating to specific deficiency states often differ based on the observer and the host parasite model. Studies of deficiencies of certain nutrients, notably protein, vitamin A, thiamine, and niacin, tend to give conflicting results; such deficiencies are synergistic in certain experiments; in others, antagonistic. In general, fairly consistent antagonistic effects are observed with deficiencies of p-aminobenzoic acid, pantothenic acid, and methionine, and synergistic effects with shortages of folic acid and biotin. Generally, specific dietary deficiencies seem more often to retard than to enhance parasitemia.

In a recent study, Targett (2012 ) observed the effects of protein energy malnutrition on malaria in rodents fed synthetic diets of specific composition that varied only in protein content. Results showed an association between the intake of protein and parasitemia level. Rats fed with a high-protein diet were greatly susceptible to infection; as the protein level of the diet was reduced, levels of parasitemia also decreased until, on a protein-free diet, merely a transient, patent infection ensued. The link between protein and infection, however, is not a simple one. Rats fed on a high-protein diet but allowed half the quantity taken by control animals feeding ad libitum on same diet showed some retardation of parasite reproduction, and most survived infection, whereas virtually all of the control animals died (Targett, 1981).

Studies of murine malaria have revealed that malaria parasites put forth oxidant stress on infected erythrocytes (Etkin and Eaton, 1975) and that this stress may be potentiated by a dietary shortage of antioxidant substances, possibly resulting in the premature lysis of the

infected cell and to the death of the parasite (Eckman *et al.*, 1976). Mice fed on diets deficient in vitamin E developed lower levels of parasitemia and live on for much longer periods than the control animals. The oxidant damage affected mature erythrocytes; reticulocytes seemed resistant and remained capable of supporting full parasite development.

These studies are of significant interest because in addition to indicating that dietary factors can affect the course of malaria in well-defined conditions, they also show the nature of the mechanism involved. Further significance is added by observations signifying that erythrocyte sensitivity to oxidant damage may form the basis for the relative defense against *P. falciparum* in humans that the genetic traits glucose-6-phosphate dehydrogenase deficiency and thalassemia are understood to confer (Friedman, 1979).

Currently, evidence is increasing that deficiency of human immunologic responsiveness, particularly deficiency of T cell function, is related to protein energy malnutrition (Watson and McMurray, 1979). T cells are believed to play a vital role in the modulation of protective immunity and since in much of the developing world protein energy malnutrition and malaria coexist at a high rate, one might expect to find a heightening of malarial infections as a well-documented feature of protein energy malnutrition. Such is however not the case. (Edington, 1967) established no evidence that African children with protein energy malnutrition were more prone to malaria than were well-nourished children.

In contrast, effective nutrition has a lot of potentials in the management and control of infection such as malaria. It supplies the body with diet rich in micro nutrient and macro nutrient, which aids in strengthening the immune system. It also prevents the breakdown of proteins as a source of energy for the body, which makes the protein available for the production of immunoglobulin and other components of the immune system. Thus, enhancing the body's defense mechanism and making it less vulnerable to malaria.

Additionally, Loren (2014), reported that high milk consumption can be use in managing malaria, because milk is seen to disrupt the life cycle of plasmodium species by impeding their folate metabolism. Milk contains very little P-Amino Benzoic Acid(PABA) and yield low concentration of folate. Studies have shown that, the Fulani of the West and Central Africa consume high amount of milk and they have resistance to malaria compared to other non-milk drinking Africa (Loren, 2014). It can therefore be said that the milk enhances their immunity to malaria.

### **3. CONCLUSION**

Malnutrition decreases the body's defense mechanism against malaria infection. Effective nutrition has the potential of giving the body the ability to fight against malaria infection. Effective nutrition can be use in the management and control of malaria infection especially in sub-Sahara Africa, where the impact of malaria is at its peak.

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