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Vitamin A and Malaria: Beware!

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ABSTRACT

Some drug companies recommend vitamin A supplements in nutrition, as a means to raise immunity and decrease malaria prevalence. Data of clinical trials collected in this field, however, are controversial. *Plasmodium falciparum* uses vitamin A for its development. Helminths also use vitamin A and to some extent protect against malaria. On the other hand, high concentrations in human serum and liver are toxic. More disturbing is the fact that vitamin A and artemisinin are highly antagonistic an antioxidant destroying an oxidant supposed to kill the parasite.

Keywords: Vitamin A, Malaria, Clinical trials, Human serum

INTRODUCTION

Vitamin A is an essential nutrient for humans because it cannot be synthesized *de novo*. The molecule is involved in all normal cellular proliferation and differentiation processes. Particularly, vitamin A and some of its derivatives are required for several processes, including embryogenesis, vision, reproduction, skeletal development and maintenance of epithelial tissues. The vitamin is stored primarily in the liver.

In this document we will use indistinctly vitamin A for vitamin A, retinol or carotene. Vitamin A clearly demonstrates hormetic effects: beneficial at low concentrations, toxic at high doses with an optimal concentration which needs to be defined from case to case.

Trials with vitamin A supplements against malaria have given moderate or controversial results. Randomized, placebo-controlled trials of prophylactic vitamin A supplementation were run in northern Ghana. In the mortality study, 21,906 children were visited every 4 months over 2 years and in the morbidity study 1455 children were visited weekly for 1 year. There was no difference between children supplemented with vitamin A and those given placebo in malaria mortality rates or fever incidence based on reported symptoms. Malaria parasitemia rates, parasite densities in children with a positive blood smear, and rates of probable malaria illness also did not differ between treatment groups. It is concluded that vitamin A supplementation had no impact on malaria in this population [1-4].

A trial with vitamin A supplementation in New-Guinea found reduced secretion of TNF, upregulated CD36 expression and increased phagocytosis of *Plasmodium falciparum* parasitized erythrocytes.

Vitamin A plays a role in immunity and protection against infectious diseases. Its role reducing incidence of diarrhea and measles is known, but its role in relation to malaria is unclear. A comprehensive, systematic literature search was conducted on PubMed and Cochrane Library to identify randomized controlled trials on the role of vitamin A during pregnancy and childhood for prevention and treatment of malaria. Based on the meta-analysis, vitamin A supplementation during pregnancy had no benefit for placental infection. Similarly, there was no effect on peripheral parasitemia or episodes of new clinical malaria. Preventive vitamin A supplementation in children younger than 5 years did not reduce the incidence of peripheral parasitemia or malaria. Vitamin A as an adjunct treatment for cerebral or severe malaria in children did not have benefit on survival, fever resolution time, parasite clearance time or incidence of neurological or other complications. The authors concluded that vitamin A has no benefit for malarial infection either as prevention or treatment in pregnancy or childhood based on RCT evidence [5].

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A study was undertaken in Brazil to assess the impact of micronutrient deficiencies on malaria incidence in the state of Amazonas. For children <10 years living in these rural communities vitamin A deficiencies were found in 36% of children, beta-carotene deficiency in 63%, These micronutrient serum levels were not associated with a higher malaria incidence.

Malarial infection is accompanied by reductions in serum vitamin A concentrations from 120 mmol/l to 70 mmol/l (20 mg/dl). Reduced serum vitamin A levels are also found consistently in children with malaria. Such observations have led to the suggestion that *Plasmodium falciparum* uses vitamin A from the host for its metabolism; in fact, *P. falciparum* selectively absorbs vitamin A from host tissues. This selective uptake of vitamin A accumulates in the parasites in a parasitemia-dependent manner and increases with parasite maturation from the ring to the late trophozoite stage [7].

The vitamin A uptake of *Plasmodium falciparum* was investigated by culturing a standard isolate of the parasite, at concentrations of the vitamin corresponding to those normally present in human serum. Vitamin A accumulated in the parasites in a parasitemia-dependent manner. And increased with parasite maturation from the ring to the late-trophozoite stage, Vitamin A in the cytoplasm of late trophozoites indicates that *P. falciparum* may use vitamin A, from its human host, as an antioxidant, to protect itself from oxidative stress [8].

Vitamin A has a slight inhibitory effect on beta-hematin formation (Mutaz Ajkkawi, personal communication).

Another critical issue is the interaction between vitamin A and arginine. Arginine has antimalarial properties because it generates the strong oxidant NO. Arginine therapy is beneficial in severe malaria in addition to conventional antimalarial treatment. Low levels of arginine, the precursor for nitric oxide, are common in patients with malaria. Research work has shown that hypo-argenimia could be caused by vitamin A and that arginine or NO therapy could be effective in malaria by inhibiting the actions of vitamin A [9].

Immunoglobulin E plays an important role in malaria prophylaxis. Retinoic acid (RA, derived from vitamin A) markedly inhibited IgE starting at concentrations of $>10^{-14}$ mol/L for B cells and $>10^{-10}$ mol/L for PBMC. Maximal inhibition of IgE production for B cells was at 10^{-8} mol/L. Low concentrations of RA inhibiting IgE synthesis (10^{-10} mol/L) affected neither B-cell proliferation nor the production of IgA, IgG and IgM [10].

Supplementation with carotene plus Vitamin E effectively suppresses both the antigen-specific and total IgE [11].

Apparent contradictions on the role of vitamin A can eventually be resolved if we consider that vitamin A, while essential in low concentration for numerous biological functions, is toxic at higher concentrations; in addition, the merozoite-stage parasite spends several days in the liver, the major storage organ for vitamin A, before invading the erythrocytes. This suggests that serum vitamin concentrations are reduced in malaria infection, in part from selective absorption of vitamin A by the parasite and perhaps to a greater extent from impaired hepatic secretion of vitamin A, since disturbed liver function is recognized in malaria [12-14].

It was also found that vitamin A accumulates preferably in the Kuppfer cells of the liver, rather than in hepatic stellate cells. Kuppfer cells are the entry port for sporozoites into the liver.

It may be hypothesized that the signs and symptoms of malaria are due to the effects of vitamin A accumulated by the parasites in the host liver. It is proposed that the parasites use the vitamin A, to invade the red blood cells; the parasites egressing from the liver are packed with vitamin A. it is then distributed via the transport of RBCs throughout the body in toxic concentrations. Based on this hypothesis, hemolysis and anemia occur due to the membranolytic actions of Vitamin A released from the parasites to invade the RBCs. Other symptoms of the disease, e.g. fever, headache, muscle aches, gastrointestinal symptoms, seizures, coma, respiratory distress and retinopathy – may similarly reflect parasite-induced vitamin A toxicity in the brain and other organs.

Toxicity of vitamin A

The acute and chronic effects of vitamin A toxicity are well documented in the literature. Emerging evidence suggests that sub toxicity without clinical signs of toxicity may be a growing concern, because intake from preformed sources of vitamin A often exceeds the recommended dietary allowances (RDA) for adults, especially in developed countries. Fatigue, headache, malaise, lack of muscular coordination may be symptoms of this sub toxicity [15].

In a trial in Zanzibari, vitamin A significantly decreased erythropoietin concentration [16].

Vitamin A has a long biologic half-life and bioaccumulates. The combination of relatively rapid absorption with a low clearance can produce acute toxicity within hours after a sufficiently high dose and chronic toxicity after prolonged intake of substantially smaller doses. This may lead to anemia and thrombocytopenia [17].

Even low intakes of vitamin A in early pregnancy are associated with congenital malformations. Vitamins released from the malaria parasites enter the fetus and cause preterm birth and/or low birth weight [18].

The interaction of taurine and vitamin A however seems to have positive effects. Symptoms of vitamin A toxicity in rats including loss of body weight, hepatotoxicity and

nephrotoxicity were significantly reduced when the rats were fed the diet with the supplement of taurine in rats [19].

Helminths and vitamin A

Helminths are among the most common chronic infections in the tropics and Plasmodium infections the most deadly. These two groups of parasites have similar geographical distribution and co-infection is commonplace. It has increasingly been speculated that helminth infections may alter susceptibility to clinical malaria [20].

Co-infection with helminths seems to protect against severe malaria. This may be tentatively explained on the following hypothesis. The parasitic worm Onchocerciasis volvulus, like Plasmodium falciparum, selectively absorbs and concentrates vitamin A, such that the concentration in *O. volvulus* is about eight times higher than that in the surrounding tissues of the host. *O. volvulus* reduces the availability of vitamin A for the malaria parasite in the early sporozoite or blood stage of the lifecycle, which starves and weakens the parasite, perhaps reducing the number of parasites reaching the liver and thereby lessening symptom severity [21,22].

A study was undertaken in Turkey to study the influence of liver parasites in cattle on the vitamin A content. Naturally infected cattle with *D. dendriticum*, *F. hepatica* and hydatid cyst showed lower vitamin A levels. This study indicated that serum levels of vitamin A and β-carotene decline was present in cattle with liver parasite infection [23].

A striking finding is the relative freedom from malaria in children of Anjouan but not of Grande Comore, two neighboring islands of the Comorro group in the Indian Ocean. Compared with those of Grande Comore, Anjouan children were heavily infested with *Ascaris lumbricoides* [24,25].

The vitamin A business

The antimalarial effect of vitamin A (retinol) is also complicated by the fact that it strongly antagonizes artemisinin and its derivatives. Plasmodium uses vitamin E, C and A to avoid oxidative stress. It is disturbing to notice that this effect is known since 20 years but is not taken into consideration in the prescription of ACTs [26] **(Figure 1)**.

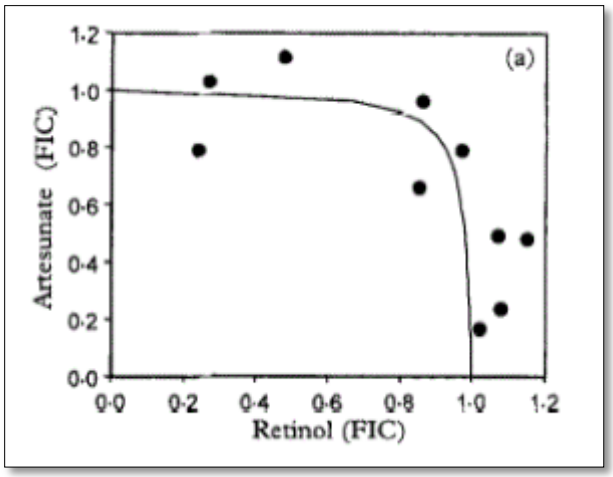

Figure 1. FIC (fractional inhibitory concentration).

Even worse, vitamin A is proposed as an adjuvant in vaccines [27].

It was also found that too much vitamin A shuts down the body's trained immunity, opening the door to infections to which we would otherwise be immune [28].

Vaccines are developed against helminthic diseases, bluntly ignoring or without considering the detrimental effect on malaria [29].

The obsession of inadequate levels in the human body goes so far as to declare that breast milk does not contain enough vitamin A and that supplements should be administered to lactating mothers. A study in Brazil found that only 38% 0f lactating women presented enough vitamin A concentrations in milk for the infants. They do not consider the hypothesis that human milk is poor in vitamin A to protect the infant against diseases, including malaria [30].

But vitamin sales to Africa are big business. A senior health adviser to the US Agency for International Development (USAID) announced their plan to supplement basic food products with vitamin A which will save millions of children in Third World countries from death and diseases [31].

In Cameroon cooking oil is supplemented with vitamin A in a mandatory national program. An assessment was made of the impact on some 300 people. No significant difference was found on inflammation, malaria prevalence and vitamin A content in breast milk. This may indicate that breast milk autoregulates (homeostasis) its vitamin A content to avoid high concentrations [32] **(Figure 2)**.

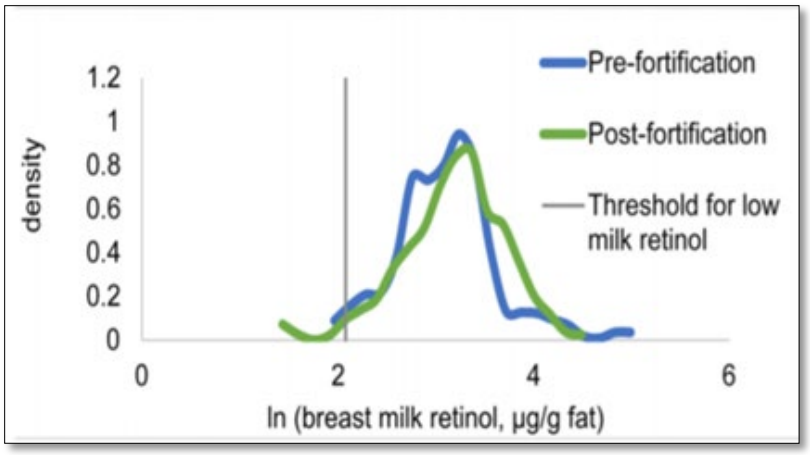

Figure 2. Kernel density distributions of breast milk vitamin A concentration (expressed as µg/g fat).

Many Americans and Europeans get a lot of preformed vitamin A in their diet and Norway and Germany have cautioned that any additional exposure could increase the number of people at risk of hypervitaminosis A or excessive vitamin A.

Artemisias are poor in vitamin A

The strong therapeutic and prophylactic properties of *Artemisia annua* and *Artemisia afra* are far from being understood. A piece of the puzzle could be that in all tissues (leaves, roots, stems, inflorescence) of the sun dried plant vitamin A concentrations only are marginal: <0.3 µg/100 g. Extremely low vitamin A contents were also found in 5 Artemisia species in Turkey. This is in sharp contrast with the vitamin A content in dry green tea (*Camellia sinensis*) leaves: 3.3 mg/100 g or 10000 times more. And this could eventually explain the total absence of antimalarial properties of green tea. *Moringa oleifera* is also very rich vitamin A, higher than in carrots and has no known antimalarial properties.

It may also explain why Artemisia vulgaris has no antimalarial properties. Vitamin A is found in mugwort at such high concentrations that it is used for vision health, a well-known therapeutic property of vitamin A. In *Artemisia dracunculus* the concentration is 100 µg/100 g or 1000 times more than in *Artemisia annua* [33-36].

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