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# The Association Between Malaria and Vitamin D: Evidence, Mechanisms, and Implications

Studies have increasingly explored the relationship between vitamin D status and malaria, revealing a complex interplay that may have important implications for malaria prevention and treatment. While evidence suggests potential associations between vitamin D levels and malaria infection, the exact nature of this relationship remains under investigation with some conflicting results.

## Vitamin D Status in Malaria Patients

Research has demonstrated varying relationships between vitamin D levels and malaria infection across different populations. Several studies have reported lower vitamin D levels in patients with malaria compared to control groups.

In a study of Ugandan children, researchers found that 95% of children with severe malaria and 80% of control children were vitamin D-insufficient (plasma 25(OH)D <30 ng/mL). Mean plasma vitamin D levels were significantly lower in children with severe malaria than in community children (21.2 vs. 25.3 ng/mL, p = 0.03)<sup>[1] [2]</sup>. These findings led researchers to conclude that for every 1 ng/mL increase in plasma vitamin D, the odds of having severe malaria declined by 9% [OR = 0.91 (95% CI: 0.84, 1.0)]<sup>[1] [2]</sup>.

Similarly, a study in the Amazon region found that malaria patients residing in mining areas had significantly lower vitamin D serum levels than control groups, though both were within normal ranges<sup>[3]</sup>. This pattern of lower vitamin D levels in malaria patients has been observed across multiple studies, suggesting a potential connection between vitamin D insufficiency and malaria vulnerability.

However, the literature shows some inconsistent results. While some studies report negative associations between vitamin D levels and malaria, others have found positive associations or no relationship at all<sup>[4]</sup>. For example, some research reported an association between higher vitamin D (>30 ng/ml) levels and malaria diagnosis in HIV-infected children<sup>[4]</sup>. These conflicting results highlight the complexity of the relationship and the need for further research.

#### Potential Mechanisms Linking Vitamin D and Malaria

Several mechanisms have been proposed to explain how vitamin D might influence malaria infection and disease progression.

#### Immune Response Regulation

Vitamin D plays a crucial role in regulating both innate and adaptive immune responses to infection  $^{[4]}$   $^{[2]}$ . It is involved in the regulation of almost 900 genes and influences calcium and phosphate metabolism, immune response, and brain development  $^{[4]}$ . Studies suggest that vitamin D can influence the differentiation of Th1, Th2, and Treg cells, which are pivotal in malaria pathogenesis  $^{[4]}$ .

In experimental models, vitamin D has been shown to dampen inducible systemic inflammatory responses by reducing circulating cytokines IFN- $\gamma$  and TNF while decreasing the expression of these cytokines by spleen cells<sup>[5]</sup>. This immunomodulatory effect may help prevent excessive inflammation during malaria infection.

#### Impact on Cerebral Malaria

Research in animal models has revealed particularly compelling evidence regarding vitamin D's protective effect against cerebral malaria, one of the most severe complications of malaria infection. In mouse models, oral administration of vitamin D completely protected mice from experimental cerebral malaria (ECM)<sup>[5]</sup> <sup>[6]</sup>.

The protective mechanisms appear to involve decreased expression of chemokines CXCL9 and CXCL10 and cytoadhesion molecules (ICAM-1, VCAM-1, and CD36) in the brain. This leads to reduced accumulation of pathogenic T cells in the brain and substantial improvement of the blood-brain barrier in infected mice<sup>[5]</sup>. Additionally, vitamin D inhibits the differentiation, activation, and maturation of splenic dendritic cells while upregulating regulatory T cells and IL-10 expression levels<sup>[5]</sup>.

## **Genetic Factors**

Genetic studies have identified numerous factors linking vitamin D to malaria susceptibility, including variations in the vitamin D receptor (VDR) gene. Polymorphisms in the VDR gene may influence malaria susceptibility and disease severity<sup>[7] [8]</sup>.

Research on cutaneous leishmaniasis, another parasitic disease, found that the "Apal" VDR gene polymorphisms could affect parasite load and susceptibility to infection<sup>[7]</sup>. Similar genetic associations may be relevant in malaria, as studies have shown increased expression of VDR in Plasmodium vivax malaria patients<sup>[8]</sup>.

## **Evidence from Animal Studies**

Animal studies have provided strong evidence supporting vitamin D's protective effects against malaria.

A recent systematic review and meta-analysis examining vitamin D administration in Plasmodium-infected animals found that vitamin D significantly improved survival rates. The analysis showed a statistically significant effect of vitamin D administration on survival rate in infected mice on day 6 post Plasmodium infection (RR = 1.08, 95%Cl 1.03, 1.15, p < 0.99)<sup>[9]</sup>. By day 10 post-infection, the effect was even more pronounced (RR = 1.94, 95%Cl 1.39, 2.71, p < 0.001)<sup>[9]</sup>.

The meta-analysis also found that specific forms and doses of vitamin D were particularly effective. Cholecalciferol (RR = 3.11, 95%Cl 2.41, 4.03), doses higher than 50  $\mu$ g/kg (RR = 3.37, 95%Cl 2.55, 4.27), and oral administration (RR = 3.01, 95%Cl 2.37, 3.82) all showed significant positive effects on survival rates<sup>[9]</sup>.

In experimental settings, vitamin D has demonstrated direct antimalarial activity. Studies from the late 1950s and 1980s suggested an antiplasmodial activity of active vitamin  $D^{[4]}$ . More recent research has shown that vitamin D can inhibit intra-erythrocytic growth of Plasmodium falciparum in vitro and may reduce the capacity of Plasmodium berghei to penetrate the erythrocyte membrane<sup>[8]</sup>.

#### **Clinical Implications and Future Directions**

The apparent relationship between vitamin D and malaria has important implications for both prevention and treatment strategies.

#### **Potential for Supplementation**

Given the evidence linking vitamin D insufficiency to increased malaria risk and severity, vitamin D supplementation could potentially serve as an adjunctive therapy. Studies have shown that prophylactic oral vitamin D relieved the symptoms of brain malaria, avoided death, and gained valuable time for diagnosis and treatment post infection in animal models<sup>[10]</sup>.

The seasonal pattern of malaria, which is more prevalent during the rainy season when vitamin D levels tend to be lower, further suggests that supplementation might help reduce malaria risk <sup>[4]</sup>. However, there is currently insufficient clinical evidence from human trials to recommend widespread vitamin D supplementation for malaria prevention or treatment.

## Need for Further Research

Despite promising findings, significant knowledge gaps remain. Most studies on the association between vitamin D and malaria have been observational with small sample sizes<sup>[4] [1]</sup>. Randomized controlled trials are urgently needed to establish whether vitamin D administration plays a meaningful role in preventing or treating malaria in humans<sup>[4]</sup>.

Furthermore, the mechanisms by which vitamin D influences malaria pathogenesis require further elucidation. While some studies suggest that vitamin D's antimalarial activity involves nitric oxide production, research has shown that vitamin D maintains antimalarial activity even when nitric oxide synthesis is inhibited, suggesting other mechanisms are at play<sup>[11]</sup>.

## Conclusion

The current evidence suggests a complex relationship between vitamin D and malaria. While numerous studies indicate associations between vitamin D insufficiency and increased malaria risk or severity, there are also conflicting results. Animal studies provide compelling evidence for vitamin D's protective effects against malaria, particularly cerebral malaria, through modulation of inflammatory responses and brain pathology.

Various mechanisms have been proposed to explain this association, including vitamin D's effects on immune regulation, cerebral inflammation, and genetic factors. However, more research is needed to fully understand these relationships in human populations.

Given the global burden of malaria and the high prevalence of vitamin D insufficiency in many malaria-endemic regions, further investigation of this relationship could potentially lead to new approaches for malaria prevention and treatment. Randomized controlled trials evaluating vitamin D supplementation in malaria-endemic areas are warranted to determine its efficacy as an adjunctive intervention for this devastating disease.

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