Review

The role of Vitamin D in malaria

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Abstract

An abnormal calcium-parathyroid hormone (PTH)-vitamin D axis has been reported in patients with malaria infection. A role for vitamin D in malaria has been suggested by many studies. Genetic studies have identified numerous factors that link vitamin D to malaria, including human leukocyte antigen genes, toll-like receptors, heme oxygenase-1, angiopoietin-2, cytotoxic T lymphocyte antigen-4, nucleotide-binding oligomerization domain-like receptors, and Bcl-2. Vitamin D has also been implicated in malaria via its effects on the Bacillus Calmette-Guerin (BCG) vaccine, matrix metalloproteinases, mitogen-activated protein kinase pathways, prostaglandins, reactive oxidative species, and nitric oxide synthase.

Vitamin D may be important in malaria; therefore, additional research on its role in malaria is needed.

Key words: vitamin D; malaria; calcitriol.

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Introduction

Parathyroid hormone (PTH) regulates the levels of calcium and phosphate in the blood by modulating the activity of specific cells in bones and kidneys. PTH stimulates the release of calcium and phosphate from bone and the reabsorption of calcium; it also inhibits reabsorption of phosphate from glomerular filtrate of the kidneys, and stimulates renal synthesis of 1,25-dihydroxyvitamin D_3 (calcitriol), thereby increasing intestinal absorption of calcium and phosphate [1]. An abnormal calcium-PTH-vitamin D axis has been reported in patients with malaria infections. Parathyroid gland dysfunction is a cause of hypocalcemia in severe malaria without acute renal failure [2]. Hypocalcemia is not uncommon in complicated malaria. Mean calcium levels are significantly lower in complicated malaria when compared to uncomplicated malaria. Hypocalcemia can be of prognostic value, as it may indicate complicated malaria or heavy parasitemia, and its return to normal may indicate clinical recovery and parasite clearance [3]. In acute *falciparum* malaria, mild hypocalcemia is common and simultaneously associated with inappropriately low serum PTH [4]. A role for vitamin D in malaria has been suggested by many studies. The death rate in mice infected with *Plasmodium berghei* was improved with the addition of cod liver oil or vitamin D and dicalcium phosphate to quinine [5]. High levels of vitamin D reduced the capacity of *P. berghei* to penetrate the erythrocyte membrane [6]. Moreover, vitamin D and its derivatives inhibited intra-eryhrocytic growth of *P. faciparium in vitro* [7]. Ray *et al.* [8] found an increased expression of vitamin D receptor (VDR) in *P. vivax* malaria patients. They suggested some association between VDR polymorphism and disease severity of malaria. These findings suggest that there is a relationship between vitamin D and malaria. Therefore, in the present paper, we reviewed the role of vitamin D in malaria.

The genomic factors associated with vitamin D in malaria

Studies have suggested that human leukocyte antigen (HLA) genes are part of the major histocompatibility complex (MHC) class II. The HLA class II controls the immune response to p126-derived amino terminal peptide from *P. falciparum* [9]. The presence of HLA-DRB1 is associated with severe malaria [10-12] and is related to the high frequency of the IgG antibody response to the *P. vivax* circumsporozoite protein (CSP) and merozoite surface protein (MSP) [13-15]. The HLA-DQA alleles are associated with patients co-infected with circumsporozoite variants of *P. falciparum* in western Thailand [16], and the HLA-DQ1*0502 allele is

associated with malaria in the Muong population in Vietnam [17]. However, DQB1*0501 restricted the Th1 type immune response to the *P. falciparum* liver stage antigen 1 and protected patients from malaria anemia and malarial re-infection in Gabonese children [18]. Moreover, calcitriol is known to stimulate phagocytosis, but it suppresses MHC class II antigen expression in human mononuclear phagocytes [19-20]. Calcitriol also decreases interferon-gamma-induced HLA-DR antigen expression in normal and transformed human keratinocytes [21-22]. Calcitriol inhibits differentiation, maturation, activation, and survival of dendritic cells and down-regulates MHC class II expression [23-24]. Calcitriol and its analogs modulate human dendritic cells by inhibiting HLA-DR expression [25]. Vitamin D analog ZK203278 potently inhibits lymphocyte proliferation in the mixed lymphocyte reaction and down-regulates MHC class II expression by 70% [26]. In addition, 1α-calcidol significantly modulates the expression of HLA-DR in human peripheral blood monocytes [27]. Intrinsic 25-OHD activation inhibited human dendritic cell antigen presentation and chemotaxis and reduced HLA-DR expression [28]. Calcitriol also improved graft survival in renal allografts by reducing macrophage infiltration and renal HLA-DR expression [29]. These findings suggest that calcitriol may have an effect on malaria through its suppression of the expression of MHC class II antigens.

Toll-like receptors (TLRs) are a group of glycoproteins that function as surface trans-membrane receptors and are involved in the innate immune response to exogenous pathogenic micro-organisms. *P. falciparum* primes human TLR responses toward a higher cytokine profile both *in vitro* and *in vivo* [30]. Patients with severe and mild malaria showed increased surface expression of TLR-2 and TLR-4 on $CD14^+$ monocytes and myeloid dendritic cells [31]. Pre-incubation of peripheral blood mononuclear cells with *P. falciparum*-infected red blood cells enhances responsiveness to TLR ligands [32]. Malaria hemozoin is immunologically inert but radically enhances innate responses by activating TLR-9 [33-34]. Therapy with a synthetic antagonist of nucleic acid-sensing TLRs (E6446) diminishes the activation of human and mouse TLR-9 and prevents the exacerbated cytokine response observed during acute *Plasmodium* infection [35]. TLR-1 variants are involved in the recognition of *P. falciparum* and are both susceptible to and a manifestation of malaria in pregnancy [36]. TLR-4 polymorphisms are predisposed to severe malaria [37]. TLR-9 polymorphisms are susceptible to malaria in Burundian children but are not related to malaria severity [38]. TLR-4 and TLR-9 polymorphisms play a role in the manifestation of malaria during pregnancy by increasing the risk of low birth weight in term infants and the risk of maternal anemia [39]. There are similar frequencies of TLR-2, TLR-4, and TLR-9 polymorphisms in malaria-endemic populations with different histories of malaria exposure [40]. Moreover, vitamin D deficiency increases the expression of the hepatic mRNA levels of TLR-2, TLR-4, and TLR-9 in obese rats [41]. However, calcitriol suppresses the expression of TLR-2 and TLR-4 mRNA and protein in human monocytes and triggers hypo-responsiveness to pathogen-associated molecular patterns [42]. Calcitriol has also been shown to down-regulate the intracellular expression of TLR-2, TLR-4, and TLR-9 in human monocytes [33]. Interestingly, TLR activation results in the expression of the VDR and 1α-vitamin D hydroxylase in human monocytes [44].

Heme oxygenase-1 (HO-1) is a stress protein that may confer cytoprotection by enhancing the catabolism of pro-oxidant hemes into the radical-scavenging bile pigments biliverdin and bilirubin [45]. The HO-1 gene can be up-regulated by a host of noxious stimuli and is induced in the CNS tissues that are affected by neurological diseases [46]. In the normal brain, basal HO-1 expression is low and restricted to small groups of scattered neurons and neuroglia [47]. Infection with *Plasmodium* species resulted in the up-regulation of the host HO-1 [48]. HO-1 is expressed in activated monocytes and microglia in human cerebral malaria lesions [49]. The induction of HO-1 was demonstrated in tissue macrophages and monocytes in fatal malaria and sepsis [50]. The HO-1 expression is up-regulated in the liver following infection by *P. berghei* and *P. yoelii* sporozoites [51]. HO-1 polymorphism is associated with susceptibility to malaria [51-53]. A genetic predisposition to higher levels of HO-1 is associated with severe malaria in Gambian children [54]. Moreover, vitamin D deficiency increases the expression of the hepatic mRNA levels of HO-1 in obese rats [41]. Calcitriol delays HO-1 immunoreactivity at the post-lesion survival time of 12 hours, and this delay is concomitant with a reduction in the glial fibrillary acidic protein immuno-reactivity in the remote cortical regions that are affected by the secondary spread of injury in the glial cells of the focal cerebral ischemic [55]; this supports the protective role of calcitriol in post-cellular injury.

Endothelial cell activation and dysfunction have been implicated in the pathogenesis of malaria, in

which the endothelium responds to parasite-induced inflammation and mediates parasitized erythrocyte sequestration, especially in vital organs such as the brain [56]. Angiopoietins (Angs), a recently described distinct family of angiogenic proteins, have recently been shown to play fundamental physiological roles in maintenance of vascular integrity. Plasma levels of Ang-2 and ratio of Ang-2/Ang-1 are clinical biomarkers that can predict fatal cerebral malaria [57-59]. Dysregulation of Angs is associated with placental malaria and low birth weight [60]. The association of increased Ang-2 and decreased nitric oxide are poor outcomes in severe *P. falciparum* [61-62]. However, calcitriol inhibited the growth of tumor-derived endothelial cells (TDECs) in two tumor models at nanomolar concentrations. The vitamin D analogs Ro-25-6760, EB1089, and ILX23-7553 were also potent inhibitors of TDEC proliferation. In squamous cell carcinoma and radiation-induced fibrosarcoma-1 cells, calcitriol treatment caused a reduction in the angiogenic signaling molecule angiopoietin-2 [63]. In addition, the vitamin D_3-binding protein (Gc protein)-derived macrophage activating factor inhibited the endothelial cell proliferation, chemotaxis, and tube formation that were all stimulated by fibroblast growth factor-2, vascular endothelial growth factor-A, or Ang-2 [64]. Taken together, vitamin D may have a role in malaria by reducing Ang-2.

The phenotypes of $CD4^+$ T cells are divided into Th1 and Th2 cells, which secrete predominantly interferon-gamma (IFN-ɤ) and IL-4 [65], and another $CD4^+$ phenotype, which uses the cytotoxic T lymphocyte antigen-4 (CTLA-4). CTLA-4 is involved in the regulation of T-cells and is up-regulated during the T-cell-mediated immune response. CTLA-4-positive cells are elevated in acute *P. falciparum* and *vivax* malarias in humans [66-68]. Murine malaria is exacerbated by a CTLA-4 blockade, which induces higher parasitemia than in controls [69-71]. These findings suggest that CTLA-4 expression restricts pathogen-specific T-cell responses in malaria. Furthermore, Todryk *et al.* [72] demonstrated a deficiency in immune memory or regulatory activity in an experimental malaria challenge. The authors found that infected RBC-specific central memory responses, as measured by INF-ɤ, are low and unstable over time, despite the high proliferation of $CD4^+$ T cells, and exhibit an inverse relationship to parasite density. Moreover, calcitriol promotes regulatory T-cell profiles by increasing CTLA-4 and interleukin-10 in mouse colon protein extracts [73]. Calcitriol also stimulates the expression of high levels of CTLA-4 in human $CD4^+$ $CD25^-$ T-cells [74]. In addition, vitamin D is required for interferon-gamma (IFN-γ)-mediated antimicrobial activity of human macrophages [75].

The innate immune system is responsible for nonspecific defense against pathogens; stimulation of this system triggers the release of cytokines and chemokines. Nucleotide-binding oligomerization domain-like receptors are a diverse set of 22 innate immune receptors that are involved in the cytoplasmic detection of bacteria and the activation of inflammatory cascades [76-77]. The nucleotide-binding oligomerization domain containing 2 (NOD2) proteins detect the cell wall building block muramyl dipeptide and play a role in the immune response to many pathogens [78]. NOD2 stimulation has been shown to augment both Th1- and Th2-dependent responses [79-80]. Mice lacking NOD proteins show increased susceptibility to and impaired clearance of bacteria [81-82]. NOD proteins are up-regulated when PBMCs are exposed to malaria sporozoites [83], but these proteins have no direct effect on the survival or parasitemia of infected C57BL/6 mice. However, IL-1β levels are associated with the activation of NOD-like receptors and malaria pathogenesis. Reduced IL-1β levels are observed in NOD mice during infection [84]. Malarial hemozoin-induced IL-1β and inflammation are dependent on a NOD-like receptor [85]. IL-1β has been implicated in the pathogenesis of human cerebral malaria and severe malaria anemia [86-87]. However, calcitriol strongly stimulates NOD2 expression in differentiated human THP-1 macrophage-like cells, primary human monocytes and keratinocytes [88], and boosts autophagy by enhancing NOD2 function [89]. The calcitriol-stimulated NOD2 function may contribute to host resistance to a variety of infectious challenges. In addition, many studies have found that calcitriol and VDR regulate cytokine responses and modulate IL-1β expression [90-92].

The proteins of the Bcl-2 family are key regulators of the apoptosis mitochondrial pathway [93]. These proteins control the permeability of the mitochondrial outer membrane, which releases cytochrome C and other apoptotic factors into the cytosol [94]. The mitochondrial apoptotic pathway plays a critical role in cell death during malarial infection. Kumar and Babu demonstrated extensive vacuolation and swelling of mitochondria associated with a high Bax/Bcl_2 ratio in mouse brains during experimental fatal murine cerebral malaria [95]. Down-regulation of Bcl-2 was observed in dying liver cells during malarial infection [96] and in placental malaria [97].

Glycosylphosphatidylinositol (GPI) purified from *P. falciparum* has been shown to play an important role as a toxin in the pathology of malaria. GPI-treated cardiomyocytes exhibit a down-regulation of the Bcl-2 gene [98]. Moreover, calcitriol inhibits hepatocyte apoptosis in rat allografts by regulating apoptosis-associated genes and increasing Bcl-2 levels [99]. Calcitriol stimulates endothelial cell proliferation, inhibited apoptosis, and increased Bcl-2 expression in apolipoprotein E-deficient mice [100]. Calcitriol also decreases Adriamycin-induced podocyte apoptosis and significantly increases Bcl-2 expression [101]. Although it has been suggested that calcitriol stimulates endothelial cell proliferation and increases Bcl-2 expression, it is not clear whether this could affect the down regulation of the Bcl-2 gene due to *P. falciparum* GPI. However, calcitriol can induce human U937 promonocytic cells to express the CD14 gene and CD14 protein and can enhance the response of this type of cell to LPS stimulation [102]. CD14 was first described as a differentiation antigen on the surface of myeloid lineage cells. It acts as a GPI-anchored receptor for the complex of LPS and plays a key role in the activation of LPS-induced monocytes. Taken together, vitamin D may have a role in malaria via the increasing of apoptotic factor Bcl-2 expression.

The non-genomic role of vitamin D in malaria

The Bacillus Calmette-Guerin (BCG) vaccine may protect against malaria via calcitriol production. Although the BCG vaccine was developed to provide protection against tuberculosis, BCG vaccination may affect the response to several major infections, including malaria. BCG was reported to protect mice against *Babesia* and *Plasmodium* [103]. BCG enhances the host immune response to *P. berghei* during an initial infection but shortens the length of immunity so that mice are more susceptible to *P. berghei* during subsequent infections [104]. The intravenous administration of BCG induces the greatest degree of suppression of sporozoite immunity in rodent malaria compared to intra-peritoneal and subcutaneous routes [105]. Having a BCG scar was found to significantly reduce the risk of death from malaria in children in Guinea-Bissau [106]. BCG has excellent adjuvant activity and has been used as a vector to deliver heterologous vaccine candidate antigens [107]. A recombinant BCG vaccine expressing circumsporozoit protein, merozoite surface protein-1, or 22 kDa of serine repeat antigen of *Plasmodium* species, has been shown to function as a malaria vaccine [104-110]. These vaccines were demonstrated to enhance humoral and cellular immune responses, activate the inflammatory action of macrophages, and increase IFN-γ-producing cells. Furthermore, BCG-vaccinated infants are almost six times as likely to have sufficient vitamin D concentrations three months after receiving the BCG vaccine compared with unvaccinated infants, and this association remains strong even after adjusting for season, ethnic group, and sex [111]. In the vaccinated group, there is also a strong inverse correlation between the IFN-γ response to *M. tuberculosis* PPD and vitamin D concentration *(i.e.*, infants with higher vitamin D concentrations have lower IFN-γ responses). Similarly, tuberculosis in cattle is typically associated with a rapid transient increase in serum calcitriol within the first two weeks of infection [112]. Calcitriol-positive mononuclear cells were later identified in all of the tuberculosis granulomas. During tuberculosis infection, the calcitriol produced by alveolar macrophages plays a beneficial role by limiting inflammation-mediated tissue injury, inducing nitric oxide (NO) production by stimulated monocytes/macrophages, inhibiting INF-γ production by stimulated $CD4^+$ cells, and suppressing the growth of *M. tuberculosis* [112-114].

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for extracellular matrix remodeling and for regulating leukocyte migration through the extracellular matrix, which is an important factor in inflammatory processes and infectious diseases [115]. MMPs are produced by many cell types, including lymphocytes, granulocytes, astrocytes, and activated macrophages. In human monocytes, hemozoin enhances the levels of MMP-9 and released IL-1β [116-117]. Serum MMP-8 and TIM-1 levels are significantly higher in the malaria groups compared with the control groups [118]. In a mouse model of experimental cerebral malaria, significant alterations in expressions have been observed, including increases in the mRNAs of MMP-3, MMP-8, MMP-13, and MMP-14 in the spleen, MMP-8, MMP-12, MMP-3, MMP-8, MMP-13, and MMP-14 in the liver, and MMP-8 and MMP-13 in the brain [119]. However, VDR knockout mice exhibit an increased influx of inflammatory cells, increased phosphoacetylation of NF-κB (which is associated with an increase in pro-inflammatory cells), and an up-regulation of MMP-2, MMP-9, and MMP-12 in their lungs [120]. The VDR TaqI polymorphism is associated with a decrease in the production of TIMP-1, which is a natural inhibitor of MMP-9 [121]. Calcitriol modulates tissue MMP expression under

experimental conditions [122], down-regulates MMP-9 levels in keratinocytes, and may attenuate the deleterious effects caused by the excessive TNF-α-induced proteolytic activity that is associated with cutaneous inflammation [123]. Calcitriol inhibits both basal and staphylococcus-stimulated production of MMP-9 in human blood monocytes and alveolar macrophages [124]. Moreover, a vitamin D analog has been reported to reduce the expression of MMP-2, MMP-9, VEGF, and PTH-related peptides in Lewis lung carcinoma cells [125]. Calcitriol significantly attenuates *M. tuberculosis*-induced increases in the expression of MMP-7 and MMP-10 and suppresses the secretion of MMP-7 by *M. tuberculosis*-infected PBMCs. MMP-9 gene expression, secretion, and activity are significantly inhibited, irrespective of the infection status [126]. In another study, calcitriol was found to suppress the production of MMPs (MMP-7 and MMP-9) and enhance the level of TIMP-1 in tuberculosis patients [127]. These studies suggest that calcitriol may play an important role in the pathological process of malaria by down-regulating the level of MMPs and regulating TIMP levels.

The mitogen-activated protein kinase (MAPK) pathways provide a key link between the membrane-bound receptors that receive these cues and changes in the pattern of gene expression. The three MAPK cascades in mammalian cells are the extracellular signal-regulated kinase (ERK) cascade, the stress-activated protein kinase/c-jun N-terminal kinase (SAPK/JNK) cascade, and the p38MAPK/RK/HOG cascade [128]. MAPK pathways are activated in *P. falciparum*-infected children [129]. Hemozoin induces early cytokine-mediated lysozyme release from human monocytes through p38 MAPK- and NF-κB-dependent mechanisms [130]. *P. falciparum* histones extracted from merozoites directly stimulate the production of IL-8 and other inflammatory mediators by primary human dermal micro-vascular endothelial cells through a signaling pathway that involves the Src family kinases and p38 MAPK [131]. Malaria parasite development in the mosquito is regulated by a conserved MAPK signaling pathway that mediates the effects of an ingested cytokine [132]. ERK and p38 pathway regulate TNF-α and IL-12 production in macrophage-stimulated with purified *P. falciparum* GPI [133]. Human p38 mitogen-activated protein kinase inhibitor drugs, such as pyridinylimidazole RWJ67657 and the pyrrolobenzimidazole RWJ68198, inhibit *P. falciparum* replication [134]. By regulating VDR mRNA expression, the p38 MAPK pathway participates in the mediation of calcium signals and affects lipid accumulation in murine pre-adipocytes [135]. Pretreatment with calcitriol has been shown to inhibit JNK activation by all stressors and to inhibit p38 activation in keratocytes [136]. Zhang *et al*. [137] demonstrated that the up-regulation of MAPK phosphatase 1 by vitamin D inhibits the lipopolysaccharide (LPS)-induced activation of p38 and cytokine production in monocytes and macrophages. In another study, the vitamin D analog (24R)-1,24-dihydroxycholecalciferol was found to prevent neuronal damage caused by hydrogen peroxide-induced toxicity in the SH-SY5Y cell line [138]. Interestingly, the neurotoxic effects of hydrogen peroxide are dependent on JNK and p38 MAPK. In addition, the long-tern actions of vitamin D in MCF-7 and LNCaP cancer cells suppress the estradiol-induced activity of ERK-1 MAPK and inhibit cell growth [139].

Prostaglandins (PGs) play a role in inflammatory processes. Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. PGD_2 is involved in the pathogenesis of cerebral malaria by inducing HO-1 expression [140]. Malaria-infected mice have increased phospholipase A_2 mRNA expression in the spleen; COX1 and COX2 are expressed in the brain [141]. During acute malarial infection, dendritic cells migrate to the spleen and secrete TGF-β, PGE_2, and IL-10 [142]. COX-2 and IL-10 mRNAs have been found to increase primarily during chronic infections in malaria placenta [143]. Calcitriol, which reportedly regulates the expression of several key genes that are involved in PG pathways, decreases PG synthesis [144]. Calcitriol and its analogs have also been shown to selectively inhibit the activity of COX-2 [145]. These findings suggest that vitamin D plays a role in the anti-inflammatory processes that are associated with malaria.

Vitamin D has a role in reducing oxidative stress in malaria. Reactive oxygen species (ROS) play a major role in various cell-signaling pathways [146]. ROS activate assorted transcription factors and increase the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis [147]. Significant increases in malondialdehyde (MDA) and apoptosis were observed in the placental pathology of *P. bergei*-infected mice [97]. Plasma glutathione (GSH) levels are significantly decreased in malaria caused by *P. falciparum* and *vivax* when compared with controls; the decrease of antioxidant levels is higher in female patients when compared with male patients [148]. GSH and

superoxide dismutase (SOD) levels are significantly decreased in children with severe malaria [149]. SOD-1 is a powerful predictor of disease severity in individuals with different clinical presentations of *P. vivax* malaria [150]. A significant association of the glutathione S-transferases I105V genotype with severe malarial anemia has been observed [151]. Calcitriol administration has been reported to exert a receptor-mediated effect on the secretion of hydrogen peroxide by human monocytes [152]. *In vitro,* monocytes gradually lose their ability to produce superoxide when stimulated; the addition of calcitriol, lipopolysaccharide, or lipoteichoic acid (LTA) restored the ability of stimulated monocytes to produce superoxide and increased the oxidative capacity compared to unstimulated monocytes [153]. Calcitriol also protected nonmalignant prostate cells from oxidative stress-induced cell death by preventing ROS-induced cellular injuries [154]. Vitamin D metabolites and analogues have been reported to induce lipoxygenase mRNA expression, lipoxygenase activity, and ROS production in a human bone cell line [155]. Vitamin D also reduces lipid peroxidation and induces SOD activity in the rat hepatic antioxidant system [156]. Astrocytes play a pivotal role in the CNS detoxification pathways, in which GSH is involved in eliminating oxygen- and nitrogen-reactive species such as NO. Calcitriol affects this pathway by enhancing intracellular GSH pools and significantly reduces the nitrite production that is induced by LPS [157].

Nitric oxide synthase (NOS) is an enzyme that is involved in the synthesis of NO, which regulates a variety of important physiological responses, including cell migration, the immune response, and apoptosis [158]. Inducible nitric oxide synthase gene expression is up-regulated in the spleens of malaria-infected mice, and both splenic and peritoneal macrophages produce high levels of NO *in vitro* in response to stimulation with LPS [159]. An increased NO synthesis in *P. falciparum* malaria can be directly elicited by soluble factor(s) from the blood stages of the parasite, without necessarily requiring the intervention of host cytokines [160]. Genetic variation in the neuronal nitric oxide synthase (nNOS) gene is correlated with susceptibility to cerebral malaria in Indian adults [161]. However, the activation of 1α-hydroxylase in macrophages increases the level of calcitriol, which inhibits the expression of inducible NOS (iNOS) and reduces NO production by LPS-stimulated macrophages [162]. Thus, calcitriol production by macrophages may provide protection against the oxidative injuries that are caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells [163]. In experimental allergic encephalomyelitis, calcitriol inhibits the expression of iNOS in the CNS of rats [164].

Conclusions

In this paper, the relationship between vitamin D and malaria was reviewed. Genetic studies provide opportunities to determine which proteins link vitamin D to malaria pathology. Vitamin D is able to act through numerous non-genomic mechanisms, including protein expression, oxidative stress, inflammation, and cellular metabolism. Therefore, further research on the role of vitamin D in malaria is needed, and a cautious approach is advisable before recommending the widespread use of vitamin D for malaria.

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