Linoleic Acid—A Feasible Preventive Approach for Visceral Leishmaniasis

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INTRODUCTION

Kala-azar, also known as visceral leishmaniasis (VL), remains one of the top parasitic diseases and is fatal if left untreated in over 95% of cases. The condition is characterized by irregular fever bouts, weight loss, hepato-splenomegaly (enlargement of the spleen and liver) and anemia. Along with Sudan, Ethiopia, and Brazil, the Indian subcontinent contributes to ∼90% of the global burden of visceral leishmaniasis (VL) (1). Post kala-azar dermal leishmaniasis (PKDL), a clinical complication of VL, where infection reoccurs in the dermal region after successful treatment, is also a challenge. The presence of the Leishmania parasite in the cutaneous region may serve the purpose of a reservoir for the consistent dissemination of disease. Therapeutic vaccines and newer potential drugs are under development/research, but unfortunately, we have nothing in hand. Thus, there is still a lot that needs to be done to achieve the absolute eradication of the disease. Prevalent malnutrition and resultant inadequate immune response are the practical limitations restricting the elimination of VL from endemic regions. Consequently, there is a need to look for newer methods to condition the immune system for a protective cellular response against Leishmania infection in endemic areas as a preventive measure.

Malnutrition is always considered as a possible risk factor for the advancement of VL (2, 3). It is associated with reduced immune response and increased visceralization of the parasite (4). Linoleic acid (LA) is an essential fatty acid (EFA) for humans due to the unavailability of fatty acid desaturase (FAD)-12. This enzyme is present in plants and thus, for humans, plant-derived diets are the primary source of LA. Arachidonic acid (AA, ω-6) is the derivative of LA and is known to set a background for instant innate immune response with its metabolites, i.e., eicosanoids. Humans can acquire arachidonic acid (AA, ω-6) either from animal based-diet or FAD-6 and FAD-5 synthesize AA from dietary LA (5). The low levels of LA are also reported in individuals suffering from malnutrition (6, 7). The inadequate dietary supply of LA is very much possible in endemic areas. We have also found low levels of LA in VL patients’ serum compared to healthy individuals (8). Furthermore, it is established that the deficiency of EFA (i.e., LA) causes loss of water from the skin resulting in dark and patchy skin, which are the hallmark symptoms of VL disease (9, 10). This could be one of the plausible reasoning to explain skin darkening in VL patients.

Malnutrition is reported to lead a relative increase in anti-inflammatory eicosanoids as compared to pro-inflammatory eicosanoids, which contributes to the compromised innate immune response against Leishmania infection (11).

Abbreviations: VL, Visceral Leishmaniasis; LA, Linoleic acid; Ld, Leishmania donovani; AA, Arachidonic acid; PUFA, Polyunsaturated fatty acids; EPA, Essential fatty acid; 5-LO, 5-lipoxygenase; LTB4, Leukotriene B2; PGE2, Prostaglandin E2; Macrophages, Mϕ; LdMv, Leishmania donovani. derived microvesicles.
**LEISHMANIA INFECTION AND ω-6 POLYUNSATURATED FATTY ACIDS (PUFA)**

The pathogenesis of VL significantly depends upon macrophage (mφ)—*Leishmania* interactions and further their encounter with T cells. As major components of the cellular membrane, PUFA plays a pivotal role in maintaining the membrane fluidity, which is essential for appropriate antigen presentation to T cells and modulate inflammatory and immune responses (12). Classically, human immune/inflammatory cells (mφ, neutrophils, mast cells, etc.) are high in ω-6 PUFA compared to ω-3 (13). LA is converted to AA and stored in the plasma membrane of the cells, especially immune cells like tissue mφ, dendritic cells, and neutrophils (14). Precisely, AA is positioned at the 2-acyl motif of membrane phospholipids (mainly phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol). Mφ enriched with PUFAs, especially AA (ω-6) showed ~50% enhancement of phagocytic and adhesion.

![FIGURE 1](image_url)

*FIGURE 1* | The role of linoleic acid against visceral leishmaniasis (VL) infection. (A) Malnutrition is associated with VL and in malnourished individuals as well as VL patients, low levels of linoleic acid (LA) are observed (7, 8). Malnutrition leads to a relative increase in anti-inflammatory prostaglandin E2 (PGE2) compared to pro-inflammatory leukotriene B4 (LTB4) (11). Higher levels of PGE2 with lower levels of LTB4 create an immunosuppressive environment (upregulated Th2 response) in the host, which leads to the advancement of VL infection. (B) Linoleic acid plays a dual way protective role against *Leishmania donovani* infection (i) by inhibiting the release of *Leishmania donovani* derived microvesicles (LdMv) from promastigote form of the parasite (9) and (ii) by promoting the protective Th-1 type pro-inflammatory (via the 5-lipoxygenase (5-LO) pathway and suppressing the Th-2 type anti-inflammatory immune response (8). LA, linoleic acid; LTB4, leukotriene B4; AA, arachidonic acid; 5-LO, 5-lipoxygenase; Mφ, macrophage; VL, visceral leishmaniasis; PGE2, prostaglandin E2; PGES, prostaglandin E2 synthases; LdMv, *Leishmania donovani* derived microvesicles.
of a parasite escape mechanism for the chronic and sustained phagocytosis by macrophages (mφ). The loss of 5-lipoxygenase (LTB4 final product) leads to decreased Leishmania Mesocricetus auratus (golden hamster) (33) phagocytosis by mφ. The anti-inflammatory mediator mPGES-1 (potentiates mPGES-1 activity) (16) has demonstrated the organ-specific role of LTB4 and PGE2 in experimental VL (34). We have shown that during leishmaniasis, the Leishmania parasite induces PGE2 generation in host mφ and aids parasite survival (26, 27). L. donovani exploits the PGE2/EP2 pathway to reduce protective cytokines (TNF-α and IL-17) (28) and, along with arginase-1 and TGF-β, known to create a favorable immunosuppressive environment for L. amazonensis dissemination (29). Sandfly (L. longipalpis) saliva is known to create a suppressive atmosphere in mφ by inducing PGE2 production and favors L. infantum infection (30, 31). On the other hand, LTB4 formation is required for L. amazonensis elimination from mφ (32). LTB4 via BLT1 receptor increases ROS generation and potentiates mφ leishmanicidal activity. The decreased expression of the BLT1 receptor after Leishmania infection is indicative of a parasite escape mechanism for the chronic and sustained disease (33). Among other experimental models, the Syrian golden hamster (Mesocricetus auratus) is regarded as the best to investigate the immunopathogenesis in VL (34, 35). We have demonstrated the organ-specific role of LTB4 and PGE2 in experimental VL (L. donovani infected M. auratus). 5-lipoxygenase (final product LTB4) was prominent in the liver, which contained the parasitic load and the spleen showed upregulated expression of PGE2 synthases (final product PGE2) along with uncontrolled parasite burden (25). The dietary precursor of these eicosanoids, i.e., LA showed a protective response against VL infection in pre-clinical studies. LA inhibited the Th-2 response and promoted Th-1 response, resulting in significantly low L. donovani infection in mφ (8). LA also reduced the release of immunosuppressive extracellular vesicles (microvesicles specifically) from L. donovani parasite (36). Taken together, LA plays a dual-way protective role in the immune response against L. donovani infection, firstly by inhibiting the release of LdMv and secondly promoting the Th-1 type immune response via the 5-LO pathway (Figure 1).

**DISCUSSION**

Despite the established protective role of LBT4 in VL, the possibilities of their therapeutic applications are limited due to their transient nature and cost issues. Thus, instead of using eicosanoids, LA, their dietary precursor, may have a beneficial role in disease containment. Higher levels of LTB4 but not PGE2 have been observed in the serum of LA supplemented healthy individuals (37). Varying concentrations of LA are already present in edible oils (Safflower > 75%; Sunflower > 60%; Soybean > 50%; Sesame > 40%, Rice bran > 30%; Groundnut > 25%; Peanut > 15%, Mustard > 10%, Olive ~10% and Coconut ~1%). There are no known side effects of LA supplementation in humans. On the contrary, LA intake is inversely associated with coronary heart disease risk. Summarily, a shift in dietary habits from LA-poor oils to LA-rich oils (safflower, sunflower, sesame, etc.) may have beneficial effects on disease containment in endemic areas.

**AUTHOR CONTRIBUTIONS**

SS drafted and wrote the manuscript. AR critically revised and edited the manuscript for important intellectual content. Both authors contributed to the article and approved the submitted version.

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