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FROM SERUM DYSLIPIDEMIA TO MACROPHAGE LIPID REMODELING IN VISCERAL LEISHMANIASIS: CHOLESTEROL TRAFFICKING, IMMUNOMETABOLIC REPROGRAMMING, AND THERAPEUTIC OPPORTUNITIES

By

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Abstract

This structured narrative review examines the relationship between systemic dyslipidemia, macrophage lipid remodeling, and immunometabolism in visceral leishmaniasis (VL). Clinical and experimental evidence was gathered primarily from PubMed/MEDLINE, complemented by reference tracking and institutional sources, with the final literature update on 21 September 2026. The reviewed studies indicate that active VL is often characterized by lower total cholesterol, HDL, LDL, and apolipoprotein A-I, together with elevated triglycerides; recurrent episodes associated with HIV coinfection may instead show more generalized lipid depletion. In macrophages, infection modifies cholesterol-rich membrane domains, endolysosomal trafficking, and lipid-droplet accumulation, involving pathways such as SREBP, mTOR, PPARγ, LXR, ABCA1, and FABP4/CD36. These changes are associated with antigen presentation, reactive-species production, and the IL-10/IL-12 balance, potentially affecting parasite persistence and therapeutic responsiveness. Systemic and intracellular lipid alterations are therefore distinct but interconnected phenomena. Composite biomarkers and interventions targeting specific metabolic compartments are promising directions, although they require validation in longitudinal patient studies.

Keywords: *Visceral leishmaniasis; Lipid metabolism; Macrophages; Cholesterol; Immunometabolism.*

1. INTRODUCTION

Leishmaniasis comprises vector-borne diseases caused by protozoa of the genus *Leishmania*. Visceral leishmaniasis (VL), caused mainly by *L. donovani* and *L. infantum*, is the most severe clinical form and is fatal in more than 95% of untreated cases. Current World Health Organization surveillance indicates that about 85% of globally reported VL cases in 2024 were concentrated in seven countries, including Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan, illustrating the continued geographic concentration of disease despite elimination progress in parts of South Asia (World Health Organization, 2026).

Macrophages are principal host cells for visceralizing *Leishmania*, but they are not passive reservoirs. Cholesterol-rich membrane organization and parasite-entry pathways are closely linked to macrophage infection (Pucadyil *et al*., 2004; Rodríguez; Gaur; Wilson, 2006; Rodríguez *et al*., 2011), while established infection can disrupt lipid rafts, alter cholesterol trafficking and modify redox control (Chakraborty *et al*., 2005; Majumder *et al*., 2012; Mukherjee; Basu Ball; Das, 2014; Semini *et al*., 2017). In this setting, immunological function and metabolism are inseparable: lipid localization can influence antigen presentation, phagosome behavior and intracellular parasite survival (Chakraborty *et al*., 2005; Mukherjee; Basu Ball; Das, 2014; Rodríguez; Gaur; Wilson, 2006; Semini *et al*., 2017). This perspective places VL within the broader field of immunometabolism and explains why apparently biochemical findings such as hypocholesterolemia may have mechanistic relevance.

The clinical starting point for the present review is a 2010 UFRN dissertation showing that patients with active *L. infantum* (then described as *L. infantum chagasi*) infection had lower total cholesterol and HDL, higher triglycerides and C-reactive protein, and reduced expression of several lipid-regulatory genes, including PPARα, PPARγ, LXRα/LXRβ and APOE (Ottoni, 2010). Subsequent independent clinical studies reproduced key elements of the dyslipidemic phenotype (Gatto *et al*., 2013; Liberopoulos *et al*., 2014; Soares *et al*., 2010), while later cohorts linked lipid

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abnormalities to disease severity and relapse (Silva *et al*., 2024; Varela *et al*., 2022). More recent work has extended the field to single-cell transcriptomics (Li *et al*., 2026), ApoA-I-ABCA1-mediated cholesterol efflux (Kumar *et al*., 2026), drug responsiveness (Pradhan *et al*., 2025), lipidomics (Tabrez *et al*., 2024) and metabolomics (Fernández-García *et al*., 2023).

The central argument of this review is that VL should not be characterized as simply "hypolipidemic" or "lipid enriched." Instead, infection induces spatially and temporally compartmentalized remodeling of lipid pools. Cholesterol-rich membrane domains may facilitate promastigote entry (Kumar *et al*., 2016; Pucadyil *et al*., 2004; Rodríguez; Gaur; Wilson, 2006; Rodríguez *et al*., 2011), whereas established infection can redistribute cholesterol and alter endolysosomal export (Mukherjee; Basu Ball; Das, 2014; Semini *et al*., 2017), disrupt antigen-presenting rafts (Chakraborty *et al*., 2005; Majumder *et al*., 2012), and accumulate neutral lipids near intracellular amastigotes (Pradhan *et al*., 2025). This compartmentalized model reconciles findings that would otherwise appear contradictory and provides a framework for understanding biomarkers and host-directed therapeutic opportunities.

2. METHODOLOGY

This article was designed as a structured narrative review focused on the interface between systemic lipid abnormalities, macrophage lipid remodeling, immune dysfunction and treatment-related outcomes in VL. The review was not designed as a systematic review or meta-analysis, because the eligible evidence spans clinical cohorts, *ex vivo* human studies, animal models, macrophage infection systems, lipidomics, metabolomics, transcriptomics and mechanistic studies with non-comparable outcomes. No prospective protocol registration was performed, and no pooled effect estimate was calculated.

PubMed/MEDLINE was used as the primary bibliographic database. Searches were supplemented by direct checking of publisher pages for full-text or bibliographic verification, backward citation tracking from eligible articles, and targeted consultation of authoritative World Health Organization material for current epidemiological context. The Federal University of Rio Grande do Norte repository was used only to retrieve the 2010 dissertation that motivated the historical clinical question. The final literature update was completed on 21 September 2026. No lower publication-date limit was imposed so that seminal mechanistic studies could be retained.

The core disease block was: ("visceral leishmaniasis" OR "*Leishmania donovani*" OR "*Leishmania infantum*" OR "*Leishmania chagasi*"). This block was combined with lipid-related terms: (cholesterol OR lipid* OR lipoprotein* OR triglyceride* OR HDL OR LDL OR VLDL OR apolipoprotein* OR ApoA1 OR ApoE OR ABCA1 OR ABCG1 OR "lipid droplet*" OR "fatty acid*" OR ceramide* OR sphingomyelin* OR SREBP* OR PPAR* OR LXR* OR NPC1 OR NPC2 OR CD36 OR FABP4). For mechanistic and translational questions, an additional block was applied when relevant: (macrophage* OR monocyte* OR immunometabolism OR "antigen presentation" OR ROS OR "nitric oxide" OR IL-10 OR IL-12 OR "T cell*" OR severity OR relapse OR treatment OR "drug response"). Searches were iteratively refined with individual pathway names identified during article screening, including HIF-1α, BNIP3, mTOR, FASN and amphotericin B.

Eligible sources were original studies in English or Portuguese that directly examined lipid concentrations, lipoproteins, lipid trafficking, lipid droplets, fatty-acid metabolism, lipid-sensitive transcriptional pathways, lipid-linked immune function, clinical severity, relapse or treatment response in VL or in macrophage infection by visceralizing *Leishmania* species. Human VL cohorts and studies using *L. donovani* or *L. infantum* were prioritized. Studies involving other Leishmania species were included only when they established a mechanistic principle that had not been adequately examined in visceral species; these extrapolations are explicitly identified in the text. Reviews were used for orientation and citation chaining but were not treated as primary evidence. Conference abstracts without sufficient methods or results, articles unrelated to host lipid biology, duplicate reports of the same dataset without additional information, and studies centered exclusively on non-lipid aspects of leishmaniasis were excluded.

Selection was performed in two stages: relevance assessment from title/abstract, followed by full-text evaluation against the predefined scope. For each included study, the following information was extracted into an evidence matrix: study design and population or experimental model; Leishmania species and life-cycle stage; host cell or tissue; lipid variable or pathway; direction of lipid change; immune or cellular consequence; relationship with disease severity, relapse or treatment response; and principal limitations. Evidence was synthesized qualitatively rather than statistically. Greater interpretive weight was assigned to human VL data and to direct mechanistic experiments using *L. donovani* or *L. infantum*; evidence from non-visceral species was used only as supportive mechanistic context. Discordant findings were retained and interpreted according to biological compartment, infection stage, host model and intervention rather than forced into a single direction of effect.

The World Health Organization source was used only for contemporary epidemiological statements, and the UFRN dissertation was treated as historical grey literature rather than as evidence equivalent to a peer-reviewed article. Because this is a narrative review, no PRISMA flow diagram, formal risk-of-bias score or exhaustive record-count accounting is presented. This methodological choice preserves transparency about the review design while allowing integration of clinically and mechanistically heterogeneous evidence.

3. RESULTS

The evidence synthesis revealed four recurring domains: systemic dyslipidemia in active and recurrent disease; compartment-specific remodeling of macrophage cholesterol

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and neutral lipids; lipid-sensitive transcriptional and immune pathways; and emerging associations with severity, relapse and therapeutic responsiveness. The findings are presented below as descriptive results from the included clinical and experimental literature, while their broader interpretation and translational implications are considered separately in the Discussion.

Active VL is repeatedly associated with a characteristic dyslipidemic pattern, although the magnitude varies with disease stage, nutritional status, age and comorbidity. Soares *et al*. (2010) found higher triglycerides and VLDL together with markedly lower ApoA-I, total cholesterol, LDL-C and HDL-C in 26 Brazilian VL patients compared with 26 healthy endemic controls. Gatto *et al*. (2013) similarly reported lower total cholesterol, HDL-C and LDL-C and higher triglycerides during active disease, with partial reversal after treatment. Liberopoulos *et al*. (2014) showed lower total cholesterol, LDL-C, ApoB, lipoprotein(a), HDL-C and ApoA-I with higher triglycerides and ApoE at diagnosis, while HDL-associated abnormalities persisted four months after clinical resolution.

The earlier UFRN study showed the same direction of change when active VL was compared with asymptomatic infection: total cholesterol and HDL were lower, triglycerides and C-reactive protein were higher, and expression of lipid-regulatory genes was reduced (Ottoni, 2010). Together, these studies indicate coordinated remodeling rather than uniform depletion of every lipid class: cholesterol-rich fractions typically fall, whereas triglyceride-rich particles often rise during conventional active VL (Gatto *et al*., 2013; Liberopoulos *et al*., 2014; Ottoni, 2010; Soares *et al*., 2010).

Hypertriglyceridemia has emerged as the conventional lipid measure most consistently associated with severity. In a Brazilian series of 83 VL patients, triglycerides and VLDL correlated positively with severity scores; median triglycerides were higher in severe than non-severe disease. The authors proposed a triglyceride value around 250 mg/dL as a potential risk signal within that cohort, but this threshold has not been externally validated and should not be used as a universal cutoff (Varela *et al*., 2022).

Lipid variables have also been tested as adjunctive diagnostic features. In a cohort of febrile patients, coexistence of HDL-C below 15 mg/dL and triglycerides above 180 mg/dL yielded high sensitivity but only moderate specificity for VL, illustrating the potential value of a metabolic signature while also underscoring its lack of pathogen specificity (Tsimihodimos *et al*., 2018). Host genetics may contribute to this phenotype: polymorphisms in lipoprotein lipase and PPARα were associated with symptomatic *L. infantum* infection and altered VLDL, triglyceride and HDL concentrations, although the wide confidence intervals require cautious interpretation (Carvalho *et al*., 2014).

Apolipoprotein remodeling is selective rather than global. ApoA-I is generally reduced during active VL, whereas ApoE may increase. Kausar *et al*. (2024) demonstrated increased APOE transcript abundance in circulating monocytes and increased serum ApoE protein in Indian patients with active VL, providing a molecular link between systemic lipid transport and monocyte biology. The functional meaning of this increase remains unresolved: it could reflect compensatory cholesterol trafficking, immunoregulation or both.

Advanced and recurrent VL can display a different phenotype. In patients with VL–HIV coinfection, recurrent disease was associated with lower total cholesterol, HDL-C, LDL-C, VLDL and triglycerides than first episodes, and very low LDL concentrations were observed among fatal cases (Silva *et al*., 2024). These findings suggest that prolonged inflammation, recurrent infection, cachexia and depletion of host lipid stores may eventually shift the metabolic picture from hypertriglyceridemic dyslipidemia toward generalized hypolipidemia. Accordingly, disease stage and HIV status should be separated in future biomarker studies rather than combined under a single “VL lipid profile.” (Silva *et al*., 2024)

The principal clinical studies supporting the systemic lipid phenotype of VL, including their populations, major lipid findings and clinical interpretation, are summarized in Table 1. The table complements the narrative above by showing where findings converge and where disease stage or comorbidity modifies the pattern.

Table 1 – Clinical evidence linking visceral leishmaniasis with systemic lipid remodeling.

Study	Population/design	Principal findings	Interpretation
Ottoni (2010)	Brazil; active VL vs asymptomatic infection	↓ total cholesterol and HDL; ↑ triglycerides and CRP; altered PPAR/LXR/APOE expression	Early clinical–molecular link between VL and lipid metabolism
Soares *et al*. (2010)	26 VL + 26 endemic controls	↑ TG/VLDL; ↓ ApoA-I, total cholesterol, LDL and HDL	Lipoproteins also altered cytokine production in infected macrophages
Gatto *et al*. (2013)	VL before/after therapy + controls	↓ TC/HDL/LDL and ↑ TG during active disease; partial reversal after therapy	Lipid phenotype tracks active disease
Liberopoulos *et al*. (2014)	15 VL at diagnosis and 4 months after resolution +	↓ TC/LDL/HDL/ApoA-I/ApoB/Lp(a); ↑ TG and ApoE	Some HDL-related abnormalities persist after clinical cure

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Study	Population/design	Principal findings	Interpretation
	15 controls		
Carvalho *et al*. (2014)	Symptomatic, asymptomatic and noninfected subjects	↑ TAG/VLDL; ↓ HDL; LPL and PPARα genetic associations	Host lipid-regulatory genetics may influence disease expression
Tsimihodimos *et al*. (2018)	22 VL among 100 febrile infections	HDL <15 + TG >180 mg/dL: high sensitivity, moderate specificity	Potential adjunctive diagnostic signature; requires validation
Varela *et al*. (2022)	83 Brazilian VL patients	TG and VLDL increased with severity	Candidate low-cost severity markers
Kausar *et al*. (2024)	Indian VL + endemic controls	↑ APOE in circulating monocytes and serum	Links lipoprotein metabolism to monocyte immunobiology
Silva *et al*. (2024)	VL–HIV, first episode vs relapse	Relapse associated with global reduction of plasma lipids	Advanced/recurrent disease may progress to lipid depletion

Host plasma-membrane cholesterol is required for efficient non-opsonic entry of *L. donovani*. Acute cholesterol depletion with methyl-β-cyclodextrin reduced parasite attachment and internalization, and cholesterol replenishment restored susceptibility (Pucadyil *et al*., 2004). In *L. infantum*, virulent promastigotes colocalize with GM1 and caveolin-1 shortly after uptake, and cholesterol disruption impairs entry while accelerating lysosomal maturation (Rodríguez; Gaur; Wilson, 2006). Stage-specific experiments further showed that lipid-raft disruption reduces promastigote but not amastigote entry, emphasizing that cholesterol dependence is life-stage specific (Rodríguez *et al*., 2011).

The relationship is not monotonic. Chronic statin-mediated depletion reduces *L. donovani* attachment and amastigote burden, but experimentally excessive membrane cholesterol can also reduce entry, leading to the concept that productive infection requires an optimal rather than simply high cholesterol state (Kumar *et al*., 2016). This helps reconcile experimental observations in which cholesterol restoration can either favor initial entry or improve immune function during established infection.

L. donovani activates SREBP2 through membrane-raft-associated Lyn–PI3K/Akt signaling and disruption of the SCAP–SREBP2–Insig sensing circuit. Increased nuclear SREBP2 promotes HMG-CoA reductase-dependent cholesterol synthesis, modifies plasma-membrane cholesterol and suppresses mitochondrial ROS through UCP2, creating conditions favorable to persistence. SREBP2 knockdown reverses several of these effects and lowers parasite survival (Mukherjee; Basu Ball; Das, 2014).

Cholesterol can also be redirected toward parasite-containing compartments. In *L. mexicana*, LDL-derived cholesterol was preferentially retained in parasite-containing fractions, NPC1 was reduced around the parasitophorous vacuole, and host plasma-membrane cholesterol was trafficked toward and incorporated into parasite membranes (Semini *et al*., 2017). Although this study used a non-visceral species, it establishes a trafficking principle relevant to VL: accessible cholesterol can be depleted in one compartment while simultaneously accumulating near intracellular parasites.

Once infection is established, *L. donovani* can increase membrane fluidity and disrupt cholesterol-rich rafts required for optimal MHC-II organization. Infected macrophages show defective presentation of both exogenous peptides and parasite antigens, reduced T-cell calcium signaling and lower IL-2 responses; loading cholesterol back into the membrane restores several of these functions (Chakraborty *et al*., 2005). This provides direct evidence that the physical state of membrane lipids can regulate adaptive immune activation.

Ceramide metabolism adds temporal complexity. *L. donovani* induces an early acid-sphingomyelinase-dependent ceramide phase that facilitates uptake, followed by a later de novo ceramide phase that lowers membrane cholesterol, increases fluidity, disrupts rafts and impairs antigen presentation (Majumder *et al*., 2012). Recent lipidomic analysis of infected THP-1-derived macrophages further demonstrated reduced total cholesterol together with broad changes in sphingomyelins, ceramides and phospholipids, confirming that macrophage lipid remodeling extends far beyond cholesterol alone (Tabrez *et al*., 2024).

Lipid droplets (LDs) are dynamic organelles involved in neutral-lipid storage, signaling and eicosanoid metabolism. In *L. major*-infected macrophages, host-derived LDs accumulate rapidly and are recruited near intracellular parasites; LD formation can also occur in neighboring uninfected cells, indicating paracrine control (Rabhi *et al*., 2016). Although this model is cutaneous, it demonstrates that infection-induced LD biogenesis is an active host response rather than passive fat storage.

Parasite-derived LDs are also biologically relevant. During *L. infantum* metacyclogenesis, parasite LD abundance and prostaglandin F2α synthase increase; arachidonic acid modulates both LD content and PGF2α production, and blockade of prostaglandin signaling reduces infection (Araújo-Santos *et al*., 2014). Thus, host and parasite LDs should be viewed as distinct but interacting lipid compartments.

L. infantum lipophosphoglycan can induce macrophage LD formation, COX-2, PGE2, nitric oxide and multiple cytokines

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while engaging ERK/JNK and TLR1/TLR2-dependent PPARγ signaling (Lima *et al*., 2017). This is important because PPARγ sits at the intersection of lipid sensing and inflammation. The clinical observation of reduced PPAR expression in blood from active VL (Ottoni, 2010) and experimental activation of PPARγ in infected macrophages (Chan; Adapala; Chen, 2012; Lima *et al*., 2017) should not be treated as contradictory: expression, ligand availability and transcriptional activity can differ between peripheral blood and tissue macrophage compartments.

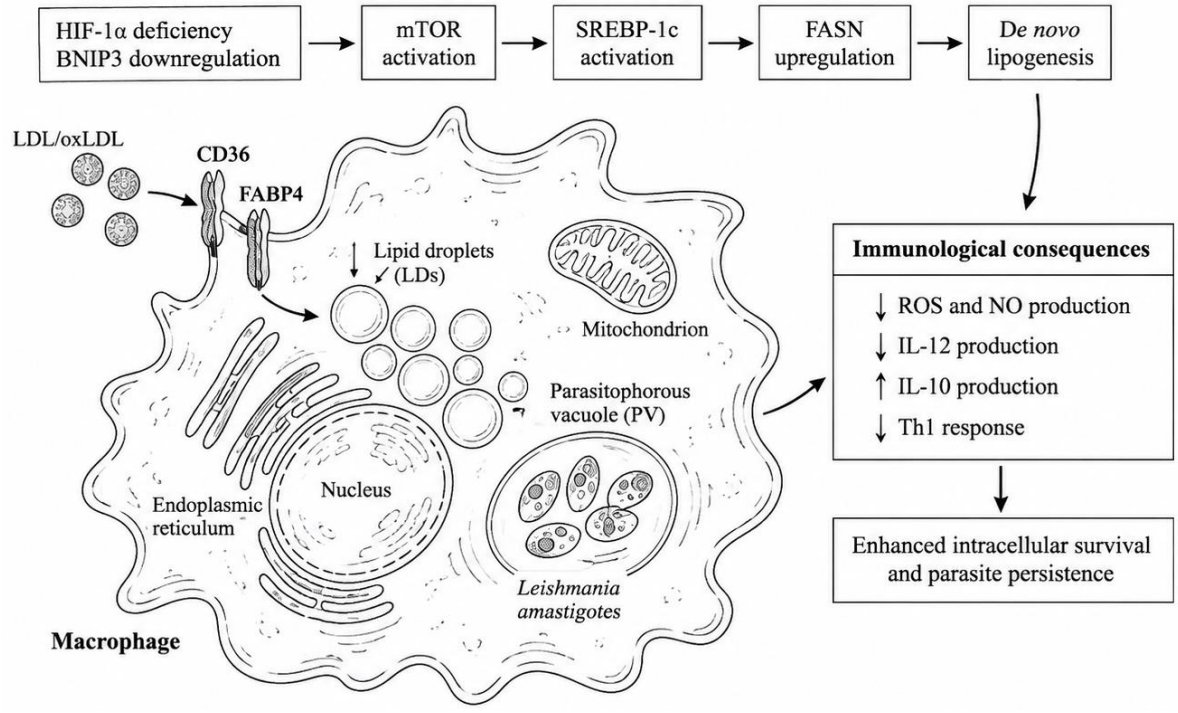
A direct causal relationship between host lipogenesis and VL susceptibility was demonstrated using myeloid HIF-1α-deficient models. Loss of HIF-1α reduced BNIP3, activated mTOR, increased nuclear SREBP-1c and induced lipogenic genes including FASN. Infected HIF-1α-deficient mice developed hypertriglyceridemia and lipid accumulation in splenic and hepatic myeloid cells, while pharmacological manipulation of SREBP-1c or FASN reduced parasite burden (Mesquita *et al*., 2020). This pathway identifies de novo fatty-acid synthesis as a functional component of macrophage permissiveness rather than a bystander change.

mTOR itself is context dependent. One study linked mTOR activation to M2-associated markers, reduced ROS/NO/IL-12 and increased parasite survival, with pharmacological inhibition decreasing infection (Kumar *et al*., 2018). By contrast, translational profiling of primary macrophages found that low-dose mTOR inhibition increased parasite persistence while eIF4A inhibition reduced it (Chaparro *et al*., 2020). These apparently opposing results likely reflect inhibitor concentration, model, parasite stage and the fact that mTOR regulates both anabolic metabolism and host-defense translation. For this reason, mTOR should be considered an immunometabolic node, not a uniformly pro-parasitic target.

Macrophages enriched in neutral lipids show lower reactive oxygen and nitrogen species after *L. donovani* infection, produce more IL-10 and less IL-12p70, and activate CD4+ T cells less effectively. In vivo, a high-fat diet increased susceptibility, impaired CD4+ Th1 and CD8+ T-cell responses and reduced antileishmanial drug efficacy (Araújo *et al*., 2023). These data indicate that lipid accumulation creates an immunometabolically permissive niche, not merely a nutrient reservoir.

Single-cell transcriptomics has now added cell-state resolution. Li *et al*. (2026) distinguished infected, bystander and unexposed macrophages and identified early activation of a FABP4/CD36 lipid-metabolism program in infected cells. CD36 and FABP4 provide a plausible route from extracellular lipid uptake to intracellular trafficking and storage, but this mechanism remains to be validated in human tissue macrophages and with direct metabolic-flux experiments. These convergent mechanisms are integrated in Figure 1, which depicts how altered lipid uptake, de novo lipogenesis and intracellular lipid accumulation can converge on a macrophage state with weaker oxidative and type-1 immune activity.

Figure 1 – Lipid metabolic reprogramming in Leishmania-infected macrophages.



Source: Conceptual synthesis based on the studies cited in the figure legend.

Note: Experimental evidence indicates that loss of HIF-1α/BNIP3 signaling can activate mTOR–SREBP-1c–FASN-dependent de novo lipogenesis, while early infection is associated with a FABP4/CD36 program linked to extracellular lipid handling. Accumulation of neutral lipid

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droplets is associated with reduced ROS/NO and IL-12, increased IL-10, impaired Th1 responses, and enhanced intracellular parasite persistence. The scheme integrates evidence from distinct experimental models and should be interpreted as a conceptual synthesis rather than as a single experimentally demonstrated linear pathway (Araújo *et al*., 2023; Kumar *et al*., 2018; Li *et al*., 2026; Mesquita *et al*., 2020).

As illustrated in Figure 1, macrophage permissiveness is not attributable to a single lipid abnormality. Rather, extracellular lipid uptake through candidate CD36/FABP4-associated programs, HIF-1α/BNIP3-mTOR-SREBP-1c-FASN-dependent lipogenesis, and accumulation of neutral lipid droplets can occur alongside reduced ROS/NO production, lower IL-12, increased IL-10 and weaker type-1 T-cell support. The relative importance of each pathway varies with the macrophage model, parasite stage and timing of infection. To separate these mechanistic nodes from the integrated scheme and indicate the evidence supporting each one, the principal pathways, reported alterations, functional consequences and study context are summarized in Table 2.

Table 2 – Major lipid-metabolic pathways associated with macrophage permissiveness during visceral Leishmania infection.

Metabolic node	Reported alteration	Functional consequence	Evidence
HIF-1α / BNIP3	Loss of HIF-1α lowers BNIP3	mTOR/SREBP-1c activation and greater susceptibility	Experimental mouse/macrophage model (Mesquita *et al*., 2020)
mTOR	Activation varies by model and timing	Controls anabolism, polarization-associated markers and translation	Context-dependent experimental evidence (Chaparro *et al*., 2020; Kumar *et al*., 2018)
SREBP-1c / FASN	Increased lipogenic program	Neutral-lipid accumulation; inhibition can reduce parasite burden	Experimental (Mesquita *et al*., 2020)
PPARγ	Ligand- and compartment-dependent activation	Modulates inflammatory and lipid-response programs	Experimental (Chan; Adapala; Chen, 2012; Lima *et al*., 2017)
CD36 / FABP4	Early infection-associated program	Candidate route for extracellular lipid uptake and trafficking	Single-cell in vitro evidence (Li *et al*., 2026)
Lipid droplets	Increased in host and parasite compartments	Nutrient storage, eicosanoid signaling, altered immunity	Multiple models (Araújo *et al*., 2023; Araújo-Santos *et al*., 2014; Rabhi *et al*., 2016)
ROS / NO	Reduced in lipid-loaded macrophages	Reduced parasite killing	Experimental (Araújo *et al*., 2023)
IL-10 / IL-12	IL-10 ↑; IL-12 ↓ in lipid-loaded infected macrophages	Reduced protective type-1 activation	Experimental (Araújo *et al*., 2023)

PPARs and LXRs are ligand-activated transcription factors that integrate lipid metabolism with immune signaling. In established macrophage biology, PPARγ can induce LXRα and ABCA1, linking fatty-acid sensing to cholesterol efflux (Chawla *et al*., 2001). During *Leishmania* infection, however, the immunological consequence of receptor activation becomes pathogen specific. Experimental *L. donovani* infection increases PPARγ expression, and pharmacological blockade of PPARγ facilitates parasite control, whereas receptor activation favors persistence (Chan; Adapala; Chen, 2012).

This compartment-specific behavior helps interpret the earlier clinical finding of reduced PPARα and PPARγ transcripts during active VL (Ottoni, 2010). Peripheral expression does not necessarily predict receptor activity within infected splenic or hepatic macrophages, because transcriptional abundance, endogenous lipid ligands and chromatin recruitment are distinct variables.

LXRs are oxysterol-responsive regulators of ABCA1, ABCG1, APOE and other cholesterol-handling genes, yet their role in VL is not simply protective. LXRα-deficient and LXRα/LXRβ double-knockout mice were more resistant to systemic *L. infantum* infection, and LXR-deficient macrophages produced more nitric oxide and killed parasites more effectively after IFN-γ stimulation. LXR ligands suppressed nitric-oxide production in wild-type macrophages (Bruhn *et al*., 2010). Thus, a pathway that promotes cholesterol efflux can simultaneously restrain antimicrobial inflammatory function.

ApoA-I-ABCA1 signaling represents a mechanistically distinct route to cholesterol efflux. Recent work showed that ApoA-I interacts with ABCA1 on infected macrophages, reduces cellular cholesterol and *L. donovani* infectivity, increases IL-12 and iNOS/NO-related responses, reduces IL-10 and arginase-associated markers, and enhances IFN-γ/STAT1-associated T-cell polarization in coculture. Active VL and PKDL were associated with lower serum ApoA-I (Kumar *et al*., 2026). This provides an unusually direct connection between a clinical lipoprotein abnormality, macrophage cholesterol transport and adaptive immunity.

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ApoE moves in the opposite clinical direction: expression in circulating monocytes and serum concentrations are increased during active VL (Kausar *et al*., 2024). Its functional contribution is still unknown. The contrast between ApoA-I depletion and ApoE elevation suggests selective redistribution of lipoprotein pathways rather than generalized reduction of apolipoproteins.

An informative human model comes from Berardinelli-Seip congenital lipodystrophy. Monocyte-derived macrophages from affected individuals infected with *L. infantum* showed altered pathways involving membrane trafficking, phosphatidylinositol biology, NF-κB, IFN-γ/JAK–STAT signaling and antigen processing/presentation (Nogueira *et al*., 2024). The study does not model typical VL, but it demonstrates that pre-existing defects in host lipid synthesis and storage can reshape the macrophage transcriptional response to Leishmania.

The strongest direct connection between lipid remodeling and immune dysfunction is raft-dependent antigen presentation. Cholesterol depletion and increased membrane fluidity in infected macrophages disperse MHC-II from raft microdomains and reduce immunological-synapse efficiency, T-cell calcium signaling and IL-2 production. Cholesterol restoration reverses these defects (Chakraborty *et al*., 2005). In experimental VL, systemic delivery of cholesterol-containing liposomes restored membrane cholesterol and T-cell-stimulatory capacity in infected hamsters while shifting cytokine and iNOS responses toward parasite control (Banerjee *et al*., 2009).

Liposomal cholesterol also activates macrophage innate effector functions directly. In infected macrophages it increases ROS and reactive nitrogen intermediates, augments pro-inflammatory cytokines and lowers intracellular parasite load (Ghosh *et al*., 2014). These findings do not mean that global cholesterol elevation is beneficial; rather, they demonstrate that restoring a depleted membrane pool can repair signaling and microbicidal function during established infection.

Neutral-lipid accumulation provides an independent route to immune suppression. Lipid-loaded infected macrophages produce less IL-12 and more IL-10 and support weaker CD4+ Th1 responses (Araújo *et al*., 2023). IL-10 itself is a validated suppressive node in human VL: neutralization in splenic aspirate cultures from patients promoted parasite killing in most samples and increased IFN-γ and TNF-α (Gautam *et al*., 2011). These results support a model in which lipid remodeling can converge on a broader VL regulatory network dominated by insufficient macrophage activation despite ongoing inflammatory signals.

Persistent VL is additionally associated with dysfunctional T-cell phenotypes. Human splenic CD8+ T cells display markers of anergy/exhaustion and recover functional contributions after cure (Gautam *et al*., 2014). In experimental VL, PD-L1 blockade restores type-1 T-cell responses and reduces parasite burden (Habib *et al*., 2018). More recently, a prospective human cohort showed increased PD-1 and Tim-3 on CD4+ and CD8+ T cells during active disease, decline after treatment, and associations between combined checkpoint expression and adverse outcomes (Ademe *et al*., 2024).

A direct causal pathway from macrophage lipid remodeling to PD-1/Tim-3/LAG-3 induction has not been demonstrated in human VL. The lipid-linked evidence is strongest for raft disruption, antigen presentation, ROS/NO and IL-10/IL-12 balance; checkpoint-associated T-cell dysfunction should therefore be viewed as a downstream chronic-disease process that may interact with, but is not yet proven to be caused by, altered lipid metabolism.

The consistency of clinical lipid changes raises the possibility of low-cost metabolic phenotyping. Triglycerides currently have the strongest evidence as a severity-associated conventional lipid measure, whereas HDL-C and ApoA-I provide information about reverse cholesterol transport and systemic inflammation (Liberopoulos *et al*., 2014; Soares *et al*., 2010; Varela *et al*., 2022). The HDL-C/triglyceride signature reported in febrile patients is intriguing but lacks the specificity required for stand-alone diagnosis (Tsimihodimos *et al*., 2018).

Relapse phenotyping may require a different framework. Recurrent VL-HIV is associated with generalized depletion of circulating lipids (Silva *et al*., 2024), and 2025 data from clinical *L. donovani* isolates linked lower serum LDL and cholesterol in relapsing patients with enhanced intracellular acquisition of LDL-derived lipids and neutral-lipid accumulation around amastigotes (Pradhan *et al*., 2025). This observation suggests that systemic lipid depletion and intracellular lipid capture can coexist rather than represent opposing states.

The most plausible future use of lipid markers is therefore not a single cutoff, but a composite panel interpreted by disease context. ApoA-I, ApoE, HDL-C, LDL-C, triglycerides, inflammatory markers, nutritional status and parasite burden could together define metabolic phenotypes associated with active disease, severe VL, relapse or post-treatment recovery. Prospective validation is essential before any combination is used for clinical decisions.

Experimental cholesterol-liposome therapy illustrates the importance of compartment targeting. In infected hamsters and macrophages, restoration of membrane cholesterol improved antigen presentation, type-1 immune signaling and oxidative/nitrosative parasite killing (Banerjee *et al*., 2009; Ghosh *et al*., 2014). These findings support membrane repair as a proof of principle, not routine cholesterol supplementation in patients.

ApoA-I-ABCA1 signaling is an attractive complementary concept because it promotes controlled efflux rather than membrane enrichment. ApoA-I decreases macrophage cholesterol and infectivity while improving IL-12/NO-associated responses and T-cell polarization *in vitro* (Kumar *et al*., 2026). In parallel, inhibition of the HIF-1α/BNIP3/mTOR/SREBP-1c/FASN lipogenic program reduces parasite burden in experimental models, suggesting

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that selective suppression of pathological de novo lipogenesis could deprive permissive macrophages of a lipid-rich state (Mesquita *et al*., 2020).

Endolysosomal cholesterol mobilization is another targetable layer. Retinoic acid restored NPC1/NPC2 expression and cellular cholesterol in *L. donovani*-infected macrophages and was associated with lower parasite burden (Prakash *et al*., 2022). This should be considered a mechanistic proof of principle rather than clinical evidence for retinoic-acid therapy in VL.

The most translationally compelling recent evidence concerns drug responsiveness. Clinical drug-unresponsive *L. donovani* isolates enhance LDL-vesicle recruitment, suppress NPC1-associated cholesterol mobilization and accumulate neutral LDs around amastigotes; reducing LD accumulation improved amphotericin-B responsiveness experimentally (Pradhan *et al*., 2025). This supports a future adjunctive strategy in which standard antileishmanial drugs are paired with carefully selected interventions that reduce parasite-accessible host lipid stores.

Global manipulation of host lipid pathways can generate opposite results depending on infection stage and cellular compartment. Chronic statin-mediated cholesterol depletion reduces parasite entry *in vitro* (Kumar *et al*., 2016), whereas membrane cholesterol restoration during established experimental disease improves immune function (Banerjee *et al*., 2009; Ghosh *et al*., 2014). Likewise, mTOR inhibition decreases parasite survival in some macrophage systems (Kumar *et al*., 2018) but increases persistence in a translational-profiling model at lower drug concentrations (Chaparro *et al*., 2020). These discrepancies argue against simplistic repurposing and favor target-, dose-, compartment- and stage-specific approaches.

4. DISCUSSION

The results support a spatial and temporal model of lipid remodeling rather than a single state of lipid depletion or accumulation. Circulating cholesterol-rich fractions are commonly reduced during active VL, whereas triglycerides frequently rise; at the same time, infected macrophages can redistribute cholesterol among the plasma membrane, endolysosomal compartments and parasite-containing vacuoles and can accumulate neutral lipid droplets (Pradhan *et al*., 2025; Semini *et al*., 2017; Silva *et al*., 2024; Tabrez *et al*., 2024). These observations explain why systemic hypolipidemia can coexist with enhanced intracellular lipid capture and why serum measurements cannot be used as direct surrogates for the lipid composition of infected tissue macrophages.

A central paradox concerns cholesterol itself. Organized cholesterol-rich membrane domains facilitate promastigote attachment and entry, yet established infection can disrupt raft organization and impair antigen presentation, while experimental restoration of a depleted membrane-cholesterol pool improves macrophage signaling and parasite control (Banerjee *et al*., 2009; Chakraborty *et al*., 2005; Ghosh *et al*., 2014; Kumar *et al*., 2016). The apparently opposing findings are therefore more consistent with compartment- and stage-specific effects than with a simple protective or pathogenic role for cholesterol. The same principle applies to lipid droplets: their accumulation may provide metabolic substrates and eicosanoid precursors while simultaneously weakening oxidative and type-1 immune functions.

The mechanistic evidence also indicates that lipid metabolism is integrated with immune regulation rather than operating as an isolated nutritional pathway. HIF-1α/BNIP3-mTOR-SREBP-1c-FASN signaling, FABP4/CD36-associated lipid handling, PPAR/LXR activity and ApoA-I-ABCA1-mediated efflux affect different aspects of macrophage permissiveness, cytokine balance and T-cell support (Araújo *et al*., 2023; Bruhn *et al*., 2010; Kumar *et al*., 2026; Li *et al*., 2026; Mesquita *et al*., 2020). Importantly, these pathways are not functionally interchangeable: for example, LXR activation can promote cholesterol-efflux programs yet suppress microbicidal nitric-oxide responses, whereas ApoA-I-ABCA1-mediated efflux has been associated with a more protective macrophage/T-cell phenotype. This distinction argues against interpreting all cholesterol-lowering or cholesterol-exporting interventions as biologically equivalent.

The clinical findings are likewise stage dependent. Hypertriglyceridemia is the conventional lipid measure most consistently associated with severity in otherwise typical active VL, whereas recurrent VL-HIV can progress toward generalized lipid depletion (Silva *et al*., 2024; Varela *et al*., 2022). This heterogeneity limits the use of isolated lipid thresholds as universal biomarkers. A more realistic translational strategy would combine lipid variables with inflammatory markers, nutritional status, parasite burden and treatment history, and would validate such panels prospectively in clearly stratified patient populations.

Therapeutically, the available evidence favors selective manipulation of defined lipid processes rather than global alteration of systemic lipid concentrations. Membrane-cholesterol restoration, ApoA-I-ABCA1 signaling, correction of NPC1/NPC2-associated trafficking and inhibition of pathological lipogenesis or parasite-accessible lipid stores all have experimental support, whereas mTOR inhibition and global cholesterol lowering have produced context-dependent or opposing outcomes (Banerjee *et al*., 2009; Chaparro *et al*., 2020; Ghosh *et al*., 2014; Kumar *et al*., 2018; Kumar *et al*., 2026; Pradhan *et al*., 2025; Prakash *et al*., 2022). Accordingly, host-directed lipid interventions are best viewed as potential adjuncts to standard antileishmanial therapy, with target, dose, infection stage and cellular compartment treated as critical variables.

Despite this increasingly coherent framework, several gaps prevent direct translation of lipid immunometabolism into validated biomarkers or therapies. The field has established that lipids change during VL, but it has not yet connected systemic and subcellular compartments in the same patients. Serum cholesterol, macrophage plasma-membrane cholesterol, endolysosomal cholesterol, parasitophorous-

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vacuole lipid pools and neutral LDs are biologically distinct variables. The simultaneous observation of systemic hypolipidemia and enhanced parasite-associated lipid capture demonstrates why one compartment cannot be inferred from another (Pradhan *et al*., 2025; Semini *et al*., 2017; Silva *et al*., 2024).

Most clinical studies still rely on standard lipid panels. High-resolution lipidomics now shows that infection alters sphingomyelins, ceramides and phospholipids (Tabrez *et al*., 2024), while time-resolved human macrophage metabolomics has demonstrated dynamic remodeling of glycerophospholipid, sphingolipid, amino-acid and central-carbon pathways during intracellular differentiation (Fernández-García *et al*., 2023). Longitudinal patient studies should therefore collect plasma and monocyte/macrophage samples at diagnosis, during therapy, at cure and during extended follow-up to identify metabolic signatures that precede relapse rather than merely accompany it.

ApoA-I decreases during active VL and can drive protective ABCA1-associated responses experimentally, whereas ApoE increases in serum and circulating monocytes (Kausar *et al*., 2024; Kumar *et al*., 2026). Measuring both apolipoproteins in the same longitudinal cohorts could determine whether their ratio or a multivariable panel provides greater biological or prognostic information than either marker alone. This hypothesis remains untested.

The 2026 single-cell study demonstrates that infected, bystander and unexposed macrophages occupy distinct transcriptional states and that FABP4/CD36 is activated early in infected cells (Li *et al*., 2026). The next step is to apply single-cell or spatial methods to human spleen, bone marrow and peripheral myeloid populations, with simultaneous identification of parasite-containing cells. This would resolve whether pathways such as FABP4, CD36, PPARγ, SREBP and ABCA1 are activated in the same macrophage subsets that harbor persistent parasites.

Gene expression and lipid abundance cannot establish substrate origin. Stable-isotope tracing with labeled glucose, acetate, fatty acids, cholesterol or lipoproteins should be combined with lipidomics to determine whether parasite-accessible lipids arise from de novo synthesis, extracellular uptake or impaired export. These experiments are particularly important for testing whether SREBP-1c/FASN inhibition restricts parasite growth through nutrient deprivation, immune restoration or both, and whether ABCA1 efflux removes the same cholesterol pool exploited by intracellular parasites.

The association between intracellular lipid capture and amphotericin-B responsiveness makes metabolism relevant to clinical trial design (Pradhan *et al*., 2025). Future studies should prospectively pair treatment outcomes with lipid profiles, ApoA-I/ApoE, nutritional status, inflammatory markers, parasite genotype and, when feasible, cellular lipidomics. Such designs could distinguish biomarkers that merely reflect advanced illness from those that predict early treatment failure or relapse.

5. CONCLUSION

VL is accompanied by a profound reorganization of host lipid metabolism that extends far beyond the classical observation of low circulating cholesterol. The most coherent interpretation of current evidence is spatial and temporal: membrane cholesterol, endolysosomal cholesterol, parasite-associated lipid pools, neutral lipid droplets and circulating lipoproteins can change in different directions at the same time. Cholesterol-rich membrane domains facilitate initial promastigote entry, while established infection can redistribute cholesterol, disrupt antigen-presenting rafts, alter endolysosomal trafficking and generate lipid-rich intracellular niches that support persistence.

This remodeling is immunologically active. Altered membrane organization impairs antigen presentation; excessive neutral-lipid storage can weaken ROS and NO production and shift the IL-10/IL-12 balance; lipid-sensitive transcriptional networks involving SREBPs, PPARs, LXRs and mTOR reshape macrophage function; and recent ApoA-I-ABCA1 and single-cell FABP4/CD36 data extend the network toward cholesterol efflux and lipid uptake. The clinical phenotype is likewise stage dependent, ranging from hypocholesterolemia with hypertriglyceridemia during conventional active VL to generalized lipid depletion in advanced recurrent disease.

The translational implication is not that lipids should be globally increased or decreased. Rather, future interventions will need to target specific lipid processes in specific compartments: pathological lipogenesis, abnormal intracellular cholesterol retention, parasite-accessible lipid stores, or protective efflux and membrane-restoration pathways. Combining such host-directed metabolic interventions with standard antileishmanial drugs is a more plausible route than replacing antiparasitic therapy. Ultimately, understanding how systemic dyslipidemia connects to macrophage-level lipid remodeling may yield both better disease phenotypes and new adjunctive therapeutic strategies.

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