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HDL and Persistent Inflammation Immunosuppression and Catabolism Syndrome

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Abstract

Purpose of Review: This paper reviews the mechanisms of high density lipoprotein cholesterol immunomodulation in the context of the mechanisms of chronic inflammation and immunosuppression causing persistent inflammation, immunosuppression, and catabolism syndrome (PICS) and describes potential therapies and gaps in current research.

Recent Findings: Low high density lipoprotein (HDL) cholesterol is predictive of acute sepsis severity and outcome. Recent research has indicated apolipoprotein is a prognostic indicator of long term outcomes. The pathobiologic mechanisms of PICS have been elucidated in the past several years. Recent research of the interaction of HDL pathways in related chronic inflammatory diseases may provide insights into further mechanisms and therapeutic targets.

Summary: HDL significantly influences innate and adaptive immune pathways relating to chronic disease and inflammation. Further research is needed to better characterize these interactions in the setting of PICS.

Keywords

Sepsis; cholesterol; inflammation; HDL; immunity

Introduction

Sepsis has three general trajectories: early death, rapid recovery, and chronic critical illness (CCI). Investigators form the UF Sepsis and Critical Illness Research Center have defined CCI as an intensive care unit stay >14 days with ongoing organ dysfunction.[1] These patients have multiple phenotypes including chronic inflammation, immunosuppression, or a combination of the two. Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) describes the pathobiology of this subset of patients.[2] These patients exhibit persistent interleukin (IL)-6, IL-8 and IL-10 elevations, as well as immune suppression reflected by soluble programmed death ligand 1 (sPDL-1) levels and decreased absolute lymphocyte counts.[3]

Conflicts of Interest:
The authors have no conflicts of interest to disclose.

High-density lipoprotein (HDL) exhibits pleiotropic effects during the acute inflammatory response including clearing bacterial toxins, supporting corticosteroid release, decreasing platelet aggregation, inhibiting endothelial cell apoptosis, reducing the monocyte inflammatory response, and inhibiting expression of endothelial cell adhesion molecules.[4] In severe sepsis, serum cholesterol levels drop nearly 50%.[5] Many observational studies have found low HDL-C levels to increase the risk of sepsis, as well as predict organ dysfunction and mortality.[6–13] One mendelian randomization study has found causal inference for HDL-C, but not low density lipoprotein cholesterol (LDL-C) or triglycerides in reducing risk of hospitalization with infection.[14]

Additionally, HDL becomes dysfunctional during acute and chronic inflammatory states. Dysfunctional HDL becomes pro-inflammatory and is characterized by failure to prevent accumulation of oxidized LDL (oxLDL) and LDL-induced monocyte chemotactic activity.[15] Accumulation of oxLDL mediates leukocyte activation, proinflammatory cytokine secretion, leukocyte adhesion molecule expression, cellular degranulation, reactive oxygen species (ROS) release, and endothelial dysfunction.[16] These changes have been further elaborated in atherogenesis and autoimmune research.[17,18] Our group has found dysfunctional HDL to be predictive of severity of organ failure in sepsis.[19] Further contributing to dysfunctional HDL in the inflammatory state are high levels of hydroxyeicosatetraenoic acids (HETEs) and hydroxyoctadienoic acids (HODEs). Dr. Reddy and colleagues have found these to be associated with decreased HDL function in pulmonary arterial hypertension and rheumatoid arthritis patients.[20,21] HETEs and HODEs are oxidation products of arachidonic acid and linoleic acid metabolites formed during periods of oxidative stress and inflammation such as diabetes and atherosclerosis.[22] These metabolites are not well-characterized in sepsis. One case series of five septic Japanese patients found significantly elevated HODE levels in the one fatal case.[23]

While the prognostic value of HDL in acute sepsis is more well-studied, there is a paucity of data on long-term lipid levels in rapid recovery and CCI patients. One recent study found low ApoA-1 levels to be predictive of one-year mortality.[24] As the role of HDL in CCI is not well described, this paper seeks to discuss its role in the development of the syndrome of persistent inflammation and immunosuppression through elaboration of known pathways leading to its development. Further characterization of HDL-associated mediators and pathways will enhance diagnosis of sepsis as well as PICS and provide targets for future therapies.

Inflammation

Underlying the inflammatory phenotypic features of CCI is persistent activation of the innate immune system. The innate immune system consists of myeloid cells (monocytes, macrophages, dendritic cells and granulocytes) and innate lymphoid cells such as natural killer cells. Broadly speaking, the innate immune system relies on genetically encoded receptors called pattern recognition receptors (PRRs) that respond to biological patterns of infection or inflammation termed pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[25] Toll-like receptors (TLRs) are the most widely studied PRRs, especially TLR4, which binds lipopolysaccharide (LPS). Activation

of these receptors leads to downstream activation of nuclear factor kappa beta (NF-KB), interferon regulatory factors, innate lymphoid cells, and chemokines.[26]

Reactivation of latent viruses in prolonged sepsis is common, with viral loads approaching those of immunosuppressed transplant patients.[27] The release of these PAMPs along with DAMPs from ongoing organ dysfunction and tissue inflammatory cell infiltration, particularly renal injury and muscle catabolism, feeds a continuous cycle of innate immunity-mediated inflammatory factors.[2] PRR activation leads to downstream assembly of macromolecular protein complexes termed inflammasomes.[28]

Most well-characterized of the inflammasomes, the nod like receptor pyrin domain containing 3 (NLRP3) inflammasome regulates the activation of caspase-1 and release of IL-1β. NLRP3 activation significantly influences respiratory, cardiac, renal, and central nervous system dysfunction during sepsis.[29] Buildup of intracellular cholesterol has been shown to lead to NLRP3 activation, playing a significant role underlying the chronic inflammation in atherosclerosis.[30] Additionally, oxidized LDL and oxidized HDL increase NLRP3 expression and activate downstream cytokines in a dose-dependent manner.[31] These effects are attenuated by the presence of functional HDL. Intracellular accumulation of cholesterol crystals also leads to downstream NLRP3 activation.[30]

Removal of cholesterol from innate immune cells is an important function of HDL during the acute inflammatory response. This is facilitated by ATP-binding cassette transporters (ABC) ABCA1 and ABCG1 interacting with ApoA-1. Mice deficient in these receptors exhibit increased macrophage inflammatory responses secondary to increased intracellular cholesterol accumulation.[32,33] HDL also inhibits the macrophage inflammatory response independent of intracellular cholesterol levels by interfering with intracellular TLR4 signaling, possibly by depleting the cellular membrane of translocating chain-associated membrane protein (TRAM).[34] TRAM is a necessary adaptor protein in the TLR4 signaling pathway, eventually leading to NF-KB activation. ApoA-1 also inhibits dendritic cell differentiation and maturation and reduces their ability to activate T cells through other cholesterol-independent mechanisms.[35] This early hyperinflammatory response portends later immune dysfunction through the expansion of myeloid-derived suppressor cells during a process termed emergency myelopoiesis.[36] Increased pathogen sensing, mainly through TLR signaling leads to an exodus of immature myeloid cells from bone marrow.[37] As they emigrate to the systemic environment, inflammatory cytokines stimulate their transition to MDSCs.[38] We hypothesize that this early hyperinflammation portends a chronic immunosuppressed state.

Immunosuppression

Myeloid Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) are a collection of myeloid cells that include immature neutrophil MDSCs (PMN-MDSCs), also known as granulocytic-MDSCs, and monocytic-MDSCs (M-MDSCs), which are a focus of interest in various acute and chronic disease processes involving immune regulation. These early suppressive actions may have a beneficial role in the acute phase of sepsis in attenuating inflammation. These cells are

not terminally differentiated and may switch to other myeloid lineages able to respond to the source of inflammation. Chronic inflammation leads to the rise of various mediators of immunity, including cytokines and transcription factors, which restricts the terminal differentiation of MDSCs to mature myeloid cells and leads to their persistence.[39] The MDSC immunosuppressive mechanism of action is in part due to PMN-MDSC secretion of arginase-1, depleting arginine which is required for T cell metabolism and survival.[40] Patients with longer ICU stays >14 days have a greater percentage of MDSCs. MDSCs begin to show increased T cell suppressive activity after 14 days.[41] These extended ICU stays are inherent to the definition of CCI and implied chronic immune dysfunction. Currently, there are limited data regarding the contribution of MDSCs to PICS.

MDSCs can become inflammatory or immunosuppressive dependent on the microenvironment. Potential therapeutic targets involving MDSCs should be considered in conjunction with the temporality of the inflammatory response, considering an appropriate escalation and timely resolution. Different epigenetic factors are found when MDSCs are analyzed at 4 days from sepsis diagnosis compared to those found at 14 days. MDSCs undergo epigenetic changes where they become more immunosuppressive over time.[41] Increased levels of MDSCs are of prognostic value for progression of early sepsis.[42]

HDL and Apo-A1 attenuate myelopoiesis and directly inhibit MDSCs. Experimentally, mouse models of high cholesterol have shown decreased myelopoiesis secondary to elevated HDL levels. ABCA1 and ABCG1 knockout mice (unable to efflux cholesterol from cells) exhibit marked leukocytosis.[43]

Paralleling the chronic inflammation in cancer, MDSCs are found in increased levels and contribute to the immunological evasion of tumors.[44] Multiple chemotherapy treatments have been shown to reduce levels of MDSCs. Following the reduction of MDSC activity, the actions of cytotoxic T-cells, as well as NK cells, are more effective.[45,46] The decrease in MDSC levels with a concurrent increase in the effectiveness of CD8+ T-cells demonstrates the important regulatory role in which MDSC resides. Synthetic HDL particles using human ApoA-1 have been found to inhibit MDSCs and related suppression of T cells in a similar fashion.[47] More research is needed to describe the mechanistic role of both PMN-MDSCs and M-MDSCs in relation to chronic inflammation seen in PICS.

T Cell function

Patients with persistent critical illness display an ‘aged phenotype’ of immunosenescence characterized by lower numbers of peripheral T cells, lower thymic output, and increased frequency of CD28− CD57+ T cells.[48] These are terminally differentiated T cells that have lost CD28 (costimulatory molecule for T cell receptor activation) and also have an increased susceptibility to apoptotic signals.[49] CCI patients experience longer and more significant impairment of immunity than RAP patients. They have increased susceptibility to secondary infection, lower absolute lymphocyte counts, decreased mHLA-DR (monocytic human leukocyte antigen DR) expression and elevations in programmed death ligand 1.[50]

The adaptive immune response to the hyperinflammatory acute septic state is characterized by massive T-cell apoptosis mediated by caspase-3 and caspase-9.[51,52] Secondary to this

sepsis-induced lymphocyte apoptosis, there is a qualitatively and quantitatively impaired CD4+ T cell response to future pathogens.[53] Failure to maintain the T cell compartment may partially underlie the pattern of chronic viral reactivation and susceptibility to infection that lead to increased mortality. HDL-associated enzymes significantly affect T cell apoptosis and proliferation as well. Paraoxonase 1 (PON1) is a liver-produced enzyme that is carried to tissues by HDL. It protects HDL and LDL from oxidative damage, crucially important during massive neutrophil responses such as sepsis. It has been shown to prevent excessive T cell apoptosis by inhibiting activation of the p38 signaling pathway.[54] Our group has shown this enzyme to have reduced activity in sepsis and correlate with organ dysfunction and mortality.[19]

The role of T regulatory cells (Treg) in sepsis and associated immune dysfunction is incompletely understood. It is known that high density lipoproteins selectively promote survival of Tregs in a manner dependent on SR-B1 and fatty acid oxidation.[55] Tregs primarily use fatty-acids derived from HDL cholesteryl esters as an energy source.[56] Glycolytic metabolism is favored by T effector cells. The proportion of CD4+ CD25+ cells increases in sepsis, but this may be partially explained by a decrease in CD4+ CD25− cells.[57,58] Treg frequency has been found to correlate with HDL-C levels.[59] This increase in CD4+ CD25+ Treg cells correlates with decreased lymphoproliferative response and may contribute to the lymphocyte anergy and quantitative impairments.[60] Tregs have been extensively studied in lupus, an autoimmune disease characterized by similar perturbations in quantitative and qualitative HDL measures as sepsis as well as an inflammatory/immunosuppressed phenotype.[61–63] Low HDL in observational studies has been implicated with risk of autoimmune diseases.[64] Anti-ApoA-1 antibodies have been found in up to 32% of lupus patients.[65] ApoA-I/low density lipoprotein (LDL) receptor-deficient mice develop large cholesterol-enriched lymph nodes, T-cell activation, and plasma autoantibodies.[66,67] Administration of subcutaneous ApoA-I ameliorates these effects accompanied by an increase in Tregs. Likewise, deficiency of scavenger receptor B1 (SR-B1), a receptor for ApoA-I active in reverse cholesterol transport produces a similar phenotype.[68]

The exact role and temporal relationship of Tregs in chronic inflammatory disease remains somewhat unclear for several reasons. Firstly, T regulatory cells are far more heterogenous than traditionally described, having divisions of thymic-derived Tregs and peripheral Tregs which are further differentiated into subsets.[69] These subtle differences have not been characterized in sepsis or PICS. Study methods vary in the definition of T regulatory cells. One meta-analysis found that the proportion of T regulatory cells in lupus patients may be equal to (when using CD25+/FOXp3+), or less than (when using single CD25+ or CD127−) those of healthy patients.[70] Some data have found FOXp3 Treg cells to limit the severity of early sepsis, but not to have effects on the resulting immunoparalysis.[71] Post-septic mice with experimental tumors exhibited Treg expansion leading to enhanced tumor growth.[72] These Tregs also had more suppressive capability than controls. While this model is congruent with the role of HDL and Tregs in acute sepsis, further data on HDL in PICS is needed to draw any conclusions about its chronic role.

Lipid Rafts and Sphingosine-1-phosphate

Two important mechanisms suggest the inextricable role of lipoproteins and their associated lipids in adaptive immunity: T and B-cell receptors are located within lipid rafts, and sphingolipids regulate T and B-cell egress from lymphoid organs, chemotaxis, and differentiation.[73–76]

Cellular signaling requires complex interactions between ligands, receptors, and kinases. These interactions are facilitated by cholesterol and sphingolipid-rich lipid microenvironments on the cellular surface termed lipid rafts.[77] The composition of these rafts as well as the modifications of their associated proteins significantly influence signal transduction through either concentration or dilution of receptors and ligands in the cell surface microdomain. A large proportion of cellular free cholesterol is located in the cell membrane, and plays an important role in lipid raft signal transduction.[78] HDL and ApoA-1 deplete lipid rafts of cholesterol, disrupting the function of TLRs, T-cell receptors, and B-cell receptors.[79] One supported mechanism of HDL and ApoA-1 action on T cells is by disrupting their activation by antigen presenting cells through disruption of major histocompatibility class II (MHC II) receptors in lipid rafts.[80,81] Repleting cholesterol in these cells reversed the effects, suggesting intracellular cholesterol biosynthesis and metabolism may be just as important. Lipid-raft signaling is not limited only to adaptive immunity, as cell membrane cholesterol enrichment also leads to enhanced TLR4 activation.[82,83]

During sepsis, T effector cells exhibit a dampened response, whereas in chronic critical illness, they are primed for enhanced activation.[84–86] This heightened T cell response is seen in autoimmune inflammatory diseases as well. One study of T cells from systemic lupus erythematosus (SLE) patients found that depletion of T cell membrane cholesterol using methyl-beta-cyclodextrin attenuated this heightened response.[87]

HDL carries a multitude of other bioactive lipids in addition to cholesterol. Ceramide and sphingosine are two sphingolipids which increase during physiological stress and stimulate growth arrest and apoptosis. Sphingosine-1-phosphate (S1P) is antagonistic to these effects. S1P is crucial to the immunomodulatory action of HDL. It is primarily carried in plasma by HDL on an associated lipoprotein, apolipoprotein M, which is present only in around 5% of HDL molecules.[88] S1P has potent antiapoptotic and chemotactic effects. One mechanism is through inhibition of the caspase-dependent mitochondrial apoptosis pathway in T lymphocytes.[89] S1P is believed to have a protective role in many inflammatory disorders including asthma, lupus, rheumatoid arthritis, and atherosclerosis.[90–93] S1P declines during sepsis and levels show a strong negative correlation with organ failure.[94] Phospholipid transfer protein (PLTP), an HDL-associated enzyme, is another key factor in maintaining plasma S1P levels, and its levels are known to decrease acutely during sepsis.[95]

There are five S1P receptors, and their distribution differs by cell type. S1P receptor 5 is limited to natural killer cells, for example, macrophages express receptors 1–4, and monocytes express 1, 2, and 4.[96,97] The S1P1 receptor is an important Treg controller. Activation of S1P1 decreases T reg differentiation, thymic production, peripheral maintenance, and immunosuppressive activity.[98–100] At the same time, S1P1 promotes

T helper cell type 1 (Th1) development. This counterregulatory response may provide a necessary step in switching from an immunosuppressed Treg-rich phenotype to an appropriate phlogistic response.

Therapies

Statins

Statins are 3-hydroxy-3-methylglutraryl coenzyme A reductase inhibitors. Their primary clinical use is to decrease mevalonate levels, a precursor for cholesterol synthesis, thereby decreasing LDL levels. Data are mixed on the efficacy of statins on sepsis survival, but two trials have shown reductions in development of severe sepsis and SOFA score.[101,102]

The benefit of statins to septic patients likely lies outside of their LDL-lowering mechanisms. Atorvastatin has been shown to modulate lipid rafts and decrease TLR4 signaling.[103] In T cells isolated from SLE patients, they decrease IL-10 and IL-6 production, two cytokines found to be chronically elevated in PICS.[104] Statins have a myriad of lipid-independent mechanisms including antioxidant properties, inhibition of superoxide and nitric oxide production, and direct antimicrobial activity.[105,106] Additionally, statins have been found to induce development of Foxp3+ Treg cells.[107] While the data do not support a mortality benefit for statins in sepsis, they have favorable immunomodulatory effects relating to the development of PICS and further patient-targeted research is needed.

Lipid Emulsions

Intravenous lipid emulsions have been a hallmark of parenteral nutrition for many years in order to prevent essential fatty acid deficiency. Newer formulas, specifically those low in omega-6 fatty acids and high in the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are currently being studied for their immunomodulatory actions. Omega-3 fatty acids have several immune-mediating functions including increasing pro-resolving lipid mediators, inhibiting NF-KB, and inhibiting TLR4 activation.[108,109] Meta-analysis of clinical trials have failed to show a consistent mortality benefit, but several studies have shown a positive correlation with survival as well as decreased ICU length of stay, decreased days of mechanical ventilation, and decreased organ failure.[110–112] Our group has shown in a phase I clinical trial, the Lipid Intensive Drug therapy for Sepsis Pilot (LIPIDS-P) that parenteral omega-3 supplementation in early sepsis is safe.[113] A phase II clinical trial is currently underway to determine the efficacy for stabilizing cholesterol levels in early sepsis.[114]

Synthetic Apo-A1

Endogenous Apo-A1 and HDL have shown to be clinically significant molecules in protecting against tumorigenesis and actively promoting the destruction of cancer cells. Furthermore, as Apo-A1 and HDL decrease MDSC, synthetic analogs of Apo-A1 may have utility in treatment of PICS.[4] One of these synthetic Apo-A1 molecules is the 4F molecule. Dr. Reddy and colleagues at UCLA have found it to ameliorate elevated serum amyloid A (SAA) levels and restore PON activity in mice fed a diet enriched with HETE.[115] In a separate murine study they found 4F reduces plasma HETE and HODE levels in

a manner independent of urinary excretion.[116] It also inhibits inflammatory conversion of HDL by hydroperoxyoctanedecanoic acid (HODE precursor). 4F has also been found to reduce MDSC levels, downregulate surface TLRs, and deplete cholesterol in lipid rafts.[117–119] However, L-4F was is active in mice with functional immune systems, which may potentially limit the target population.[120]

Another trial by Dr. Reddy and colleagues utilizing L-4F to treat patients with cardiovascular disease revealed that these molecules were not harmful, however, L-4F did not prove to be efficacious in improving cardiac biomarkers.[121,122] This was despite achieving plasma levels that had been efficacious in animal models. The authors conclude that this may have been due to the low dosages which were administered in the trial, and they recommended that higher doses be utilized in the future. A more recent trial of oral D-4F in high risk cardiovascular disease patients was found to render HDL less inflammatory.[123] The high cost of these analogs is a prohibiting factor in their current development. Cost-effective methods of producing Synthetic Apo-A1 are currently being researched. Genetically engineering tomato plants to produce synthetic Apo-A1 molecules, is one such innovative design that has been efficacious in mice.[124] While studies investigating synthetic Apo-A1 molecules have displayed promising results in animal and ex vivo models, their effects in humans remain to be studied.

Conclusion

PICS is a chronic inflammatory and immunosuppressive syndrome seen in a subset of sepsis survivors. This syndrome is associated with considerable morbidity, mortality, and healthcare costs. Current models support that an early dysregulated inflammatory response portends development of PICS through processes such as emergency myelopoiesis (Figure 1). HDL regulates excessive inflammation through clearing bacterial toxins, supporting corticosteroid release, decreasing platelet aggregation, inhibiting endothelial cell apoptosis, reducing the monocyte inflammatory response, and inhibiting expression of endothelial cell adhesion molecules. It inhibits inflammasome activation and depletes lipid rafts of cholesterol, interfering with TLR signaling. Failure of this endogenous regulation leads to MDSC expansion through emergency granulopoiesis, and T cell apoptosis and suppression. The resulting immunosuppression leads to viral reactivation, continual organ dysfunction, and resulting release of PAMPs and DAMPs. HDL has been shown to exert significant immunomodulatory influence on the acute phase of sepsis. Data from other fields such as autoimmune disease and cancer have suggested that it may have a significant role in long term immune dysfunction.

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Summary:

- HDL and its associated mediators undergo quantitative and qualitative derangements during the acute septic response that negatively impact innate and adaptive immunity.
- PICS is a syndrome caused by a persistently activated innate immune response fed by PAMPs and DAMPs as well as a suppressed adaptive immune response.
- HDL modulates these immune mechanisms in similar chronic inflammatory diseases. Further research is needed to characterize these mechanisms in PICS.

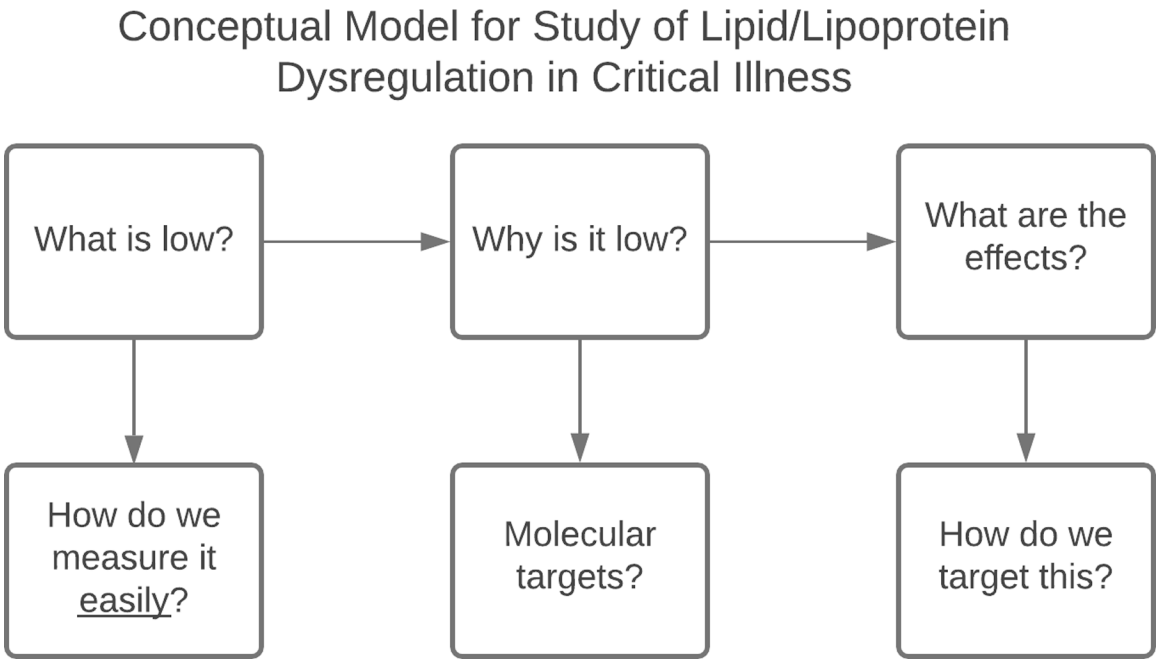

FIGURE 1.

Not only is HDL quantitatively affected in inflammatory disease, but the makeup of its lipids and associated enzymes are fundamentally changed. Future research should place emphasis on characterizing these changes in PICS as well as thoughtfully considering the temporality of immune changes in the septic response. Namely, the early appropriate level of inflammation followed by a timely resolution. As sepsis is a disorder of heterogenous causes (gram positive, gram negative, surgical, respiratory, urinary, etc.), characterization of biomarkers and lipid levels may additionally help to appropriately select patients for treatment.