Decreased high-density lipoprotein cholesterol (HDL-C) levels are associated with an increased risk of atherosclerosis and its atherothrombotic complications. This has spawned numerous randomized human atherosclerosis trials of measures to indirectly or directly elevate HDL to directly test the HDL hypothesis.\textsuperscript{1,2} HDL functions, beyond reverse cholesterol transport, include antithrombotic effects, stimulation of endothelial nitric oxide release, and shuttling of microRNAs. Moreover, HDL and its principal apolipoprotein A-I (apoA-I) suppress vascular inflammatory responses in experimental atherogenesis and arterial injury,\textsuperscript{3,4} though such effects seem modulated by genetic background.\textsuperscript{5} Significantly, primary extravascular inflammatory processes promote quantitative and qualitative modulation of HDL and apoA-I. This is exemplified by 3 conditions (rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], and gout) in which there is coexisting inflammatory arthritis and increased susceptibility to atherosclerosis, but with differences in mechanisms affecting HDL levels and properties of plasma HDL (see Figure).

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Gout is mechanistically a relatively straightforward arthritic disorder and characterized by periodic bouts of acute, self-limited phagocyte–mediated inflammatory arthritis in response to urate crystal deposits, driven in large part by NLR family, pyrin domain containing 3 inflammasome and interleukin (IL)-1β–mediated innate immunity. Patients with gout frequently have multiple dietary factors and comorbidities promoting decreased HDL.\textsuperscript{6} RA, unlike gout, is characterized by both persistent, chronic systemic inflammation and by inflammatory effects of both innate and adaptive immunity on the synovial lining of diarthrodial joints that cause destructive and polyarticular arthritis. Cohorts of patients with established RA have decreased plasma HDL-C and apoA-I levels compared with healthy controls.\textsuperscript{7} Moreover, decreased plasma HDL-C levels may antedate the development of RA.\textsuperscripts{7} Mechanisms contributing to decreased plasma HDL in RA include the capacity of tumor necrosis facor (TNF-α), a major proinflammatory cytokine and therapy target in RA, to inhibit hepatic apoA-I synthesis and HDL biogenesis via c-Jun N-terminal kinase signaling.\textsuperscript{8} Cholesterol efflux capacity is impaired in RA independent of circulating HDL level.\textsuperscript{9} Increased HDL and apoA-I in inflamed joints in RA (and in psoriatic arthritis, which also has excess cardiovascular risk) suggested peripheral HDL sequestration in arthritis.\textsuperscript{10}

In SLE, and murine models of SLE autoimmunity, autoantibodies, immune complexes, and complement activation are the major drivers of tissue inflammation. Autoantibodies to apoA-I and other HDL constituents are linked with a decrease in plasma HDL-C levels independent of hepatic HDL biogenesis in SLE.\textsuperscript{11,12} SLE autoimmunity also is linked with altered functional properties of HDL, including decreases in paraoxonase 1 and beneficial anti-inflammatory effects, and prevalent increases in dysfunctional HDL, which promotes inflammation at least partly by effects on monocytes and endothelium.\textsuperscript{13-15}

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Wu et al\textsuperscript{16} further test an HDL hypothesis that emerged after observation that apoA-I mimetic peptide treatment inhibits collagen-induced arthritis, a widely used rodent model of RA.\textsuperscript{17} Specifically, Wu et al probe anti-inflammatory effects in arthritis of lipid-free apoA-I and of apoA-I in HDL reconstituted with phospholipids (rHDL).\textsuperscript{17} Wu et al use a model of joint inflammation induced by a single intraperitoneal injection of streptococcal cell wall peptidoglycan–polysaccharide (PG-PS) in female Lewis rats.\textsuperscript{18} In this model, acute joint inflammation develops several days after PG-PS injection, followed by early remission and subsequent development of chronic joint inflammation with certain features resembling RA. Key in vivo findings were that intravenous lipid-free apoA-I and rHDL inhibited PG-PS– induced toll-like receptor (TLR) 2 expression and leukocyte accumulation in synovial fluid and tissue, with robust inhibition (by ≈40%–60%) of joint inflammation scores and circulating levels of cytokines TNF-α, IL-1β, IL-6, with even greater limitation of systemic leukocytosis.\textsuperscript{16} Importantly, intravenous apoA-I and rHDL were effective whether commenced before PG-PS induction or evolution of the chronic inflammatory arthritis phase.

The impressive portfolio of anti-inflammatory mechanisms of apoA-I or rHDL includes inhibition of endothelial cell adhesion molecule expression; myeloid lineage cell proliferation; and endothelial, monocyte, and synovial lining cell expression of certain chemokine receptors and cytokines, as well as of neutrophil ingress into inflamed tissue. Wu et al now observe that apoA-I and rHDL inhibit PG-PS–induced elevation of TLR2 and MyD88 expression, nuclear factor-kB activation, and release of TNF-α, IL-1β, IL-6 by cultured human monocyte–derived macrophages\textsuperscript{16} (see Figure). Importantly, these in vitro effects depend on macrophage expression of
ATP-binding cassette transporter A1, a key mediator of cholesterol efflux and transfer from peripheral cells to lipid-poor apoA-I. The work buttresses previous evidence that apoA-I and HDL anti-inflammatory effects are heightened by cholesterol depletion in mononuclear phagocytes, as reviewed by Wu et al. Wu et al propose that apoA-I may act to stifle inflammation by lowering lipid raft cholesterol content and thereby limiting trafficking of TLR2 and TLR4 to these plasma membrane domains for optimal signaling. This activity aligns well with curbing of initial arthritis triggered by the TLR2 ligand PG-PS, as well as the chronic arthritis phase mediated by TLR4 signaling. Significantly, TLR2 signaling is a priming or amplification factor in not only murine experimental atherosclerosis but also arthritides that include RA, gouty arthritis, and Lyme disease. TLR2 also modulates osteoarthritis, and susceptibility to experimental osteoarthritis may be enhanced by apoA-I deficiency.

Testing of therapeutic translation of inhibition of TLR2 signaling in RA by direct apoA-I and rHDL administration is technically within our reach. Furthermore, development of experimental gouty inflammation is blunted by injection of HDL into the inflammatory locus. Several distinct rHDL formulations recently in clinical trials for acute coronary syndrome, including ETC-216 (bearing the apoA-I Milano variant), SRC-rHDL, and CSL-112, have been established to rapidly mobilize excess cholesterol from cells and promote at least some regression of atherosclerotic plaques in vivo, with associated anti-inflammatory and stabilizing effects in plaques. Caveats of rHDL clinical trials in human arthritis include tinkering with host defense in those already managed with immunosuppressives. Long-term TLR2 modulation in human arthritic disease is potentially a double-edged sword, because TLR2 restrains inflammation and autoimmunity, by effects including modulation of IL-10, regulatory T-cells, and interferon-γ. It may be therapeutically significant in clinical practice, but a confounder for arthritis clinical trials, that changes in HDL in some arthritides are secondarily countered by drugs already in the clinic, including systemic corticosteroids, methotrexate, biological TNF-α antagonists, and rituximab.

Proatherogenic effects of comorbidities, such as metabolic syndrome and type 2 diabetes mellitus, qualitative and quantitative changes in LDL, and effects of systemic inflammation, are additional confounders for clinical trials of rHDL atheroprotection and reduction of arthritis in RA, SLE, and gout. However, with rHDLs now reaching the clinic, the potential for dually inhibiting human atherosclerosis and arthritis directly with apoA-I and rHDL merits testing in prudently designed pilot clinical trials.

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Disclosures
None.
References


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