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Invited Review-pharmacology across disciplines

Effects of curcumin on HDL functionality

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ABSTRACT

Curcumin, a bioactive polyphenol, is a yellow pigment of the *Curcuma longa* (turmeric) plant. Curcumin has many pharmacologic effects including antioxidant, anti-carcinogenic, anti-obesity, anti-angiogenic and anti-inflammatory properties. Recently, it has been found that curcumin affects lipid metabolism, and subsequently, may alleviate hyperlipidemia and atherosclerosis. Plasma HDL cholesterol (HDL-C) is an independent negative risk predictor of cardiovascular disease (CVD). However, numerous clinical and genetic studies have yielded disappointing results about the therapeutic benefit of raising plasma HDL-C levels. Therefore, research efforts are now focused on improving HDL functionality, independent of HDL-C levels. The quality of HDL particles can vary considerably due to heterogeneity in composition. Consistent with its complexity in composition and metabolism, a wide range of biological activities is reported for HDL, including antioxidant, anti-glycation, anti-inflammatory, anti-thrombotic, anti-apoptotic and immune modulatory activities. Protective properties of curcumin may influence HDL functionality; therefore, we reviewed the literature to determine whether curcumin can augment HDL function. In this review, we concluded that curcumin may modulate markers of HDL function, such as apo-AI, CETP, LCAT, PON1, MPO activities and levels. Curcumin may subsequently improve conditions in which HDL is dysfunctional and may have potential as a therapeutic drug in future. Further clinical trials with bioavailability-improved formulations of curcumin are warranted to examine its effects on lipid metabolism and HDL function.

Abbreviations: 2VO, bilateral common carotid artery occlusion; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; AGE, advanced glycation end products; AIM-HIGH, atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides; ANXA1, annexin A1; AP-1, activator protein 1; Apo-AI, apolipoprotein AI; Apo, apolipoprotein; ARE, arylesterase; cAMP, cyclic adenosine monophosphate; CD36, cluster of differentiation 36; CE, cholesteryl ester; CREBP, cAMP response element-binding protein; CETP, cholesteryl ester transfer protein; CE/TG, ratio of cholesteryl ester-to-triglyceride; CEC, cholesterol efflux capacity; CREB, cAMP response element-binding protein; CVD, cardiovascular disease; DSS, dextran sodium sulfate; EF24, diphenyl difluoroketone; FAO/WHO, Food and Agriculture Organization/World Health Organization; FC, free cholesterol; FDA, Food and Drug Administration; FN, fibronectin; GMC, glomerular mesangial cell; HDL-C, high-density lipoprotein-cholesterol; HFD, high-fat diet; HFO, high??-3 PUFA; HMGA2, high-mobility group AT-hook 2; HO-1, heme oxygenase-1; HPS2- THRIVE, Heart protection study 2–treatment of HDL to reduce the incidence of vascular events; I/R, ischemia-reperfusion; ILLUMINATE, investigation of lipid level management to understand its impact in atherosclerotic events; IDL, intermediate-density lipoprotein; LCAT, lecithin cholesterol acyl transferase; JECFA, joint FAO/WHO expert committee on food additives; LDL, low-density lipoprotein; LDLR, LDL receptor; LFO, low??-3 PUFA Lp(a) lipoprotein(a); LXRα, liver X receptor alpha; MiR, MicroRNA; MPO, Myeloperoxidase; NC, Nicotinate-Curcumin; NAFLD, non-alcoholic fatty liver disease; NFBκF, nuclear factor kappa B; Nrf2, nuclear factor E2–related factor-2; OxLDL, oxidized LDL; PKA, protein kinase A; PL, phospholipid; PKA, protein kinase A; PLTP, phospholipids transfer protein; PON1, paraoxonase 1; PPARγ, peroxisome proliferator-activated receptor gamma; RCT, reverse cholesterol transport; ROS, reactive oxygen species; RXR, retinoid X receptor; SAA, serum amyloid A; S1P, sphingosine-1-phosphate; SIRT1, Sirtuin 1; SphK1, sphingosine kinase 1; SR-A, scavenger receptor class A; SR-BI, scavenger receptor class B type I; TC, total cholesterol; TG, triglyceride; UPS, ubiquitin/proteasome system; UTR, untranslated region; VaD, vascular dementia; VLDL, very low-density lipoprotein; Wt, weight; XIAP, X-linked inhibitor of apoptosis protein.

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Contents

1. Biology and metabolism of HDL

High-density lipoprotein (HDL) is the smallest and densest of all plasma lipoproteins. HDL particles are considered protective against cardiovascular disease (CVD) mainly due to a role in reverse cholesterol transport (RCT) [1]. The metabolism of HDL is a very dynamic process that occurs *via* remodeling by lipases and lipid transfer proteins in plasma, as well as by receptors on the surface of cells. The composition of HDL particles is complex and includes amphipathic lipids (phospholipids [PLs] and free cholesterol [FC]) and exchangeable apolipoproteins on the surface, non-polar lipids (cholesteryl esters [CEs] and triglycerides [TGs]) in the core, and smaller amounts of other bioactive lipids and biological molecules (e.g., microRNAs). HDL particles are also considered the most heterogeneous class of plasma lipoproteins, due to differences in the size, charge, and shape of particles in this lipoprotein subclass [2,3]. Apolipoprotein AI (apo-AI), produced by the liver and small intestine, is the major structural protein of the HDL particle. It interacts functionally on the cell surface with ATP-binding cassette (ABC) transporter A1 (ABCA1), to acquire free cholesterol and PLs and form discoidal pre-β HDL, the nascent form of HDL in plasma [4]. Subsequently, nascent HDL is converted to mature spherical HDL particles (e.g., HDL3) via the lecithin-cholesterol acyltransferase (LCAT) enzyme, which uses PLs to esterify cholesterol and form a CE hydrophobic core [5]. Further remodeling of mature HDL in plasma can occur via cholesteryl ester transfer protein (CETP), a hydrophobic glycoprotein which facilitates the movement of CEs from HDL to the apolipoprotein B (apoB)-containing lipoproteins (LDL, IDL, and VLDL) in exchange for TG [2,6]. Mature HDL particles can accept additional cholesterol from cells through ABCG1 and scavenger receptor class B type 1 (SR-B1) transport, becoming larger HDL2 particles [7]. The plasma compartment of HDL particles can be further remodeled by additional plasma enzymes and lipid transfer proteins to exchange lipids and proteins with HDL and other lipoproteins. This extensive intravascular metabolism occurs until the delivery of HDL lipid cargo to the liver, which occurs via both SR-B1-mediated selective CE uptake and holoparticle uptake by hepatocytes [8,9] (Fig. 1).

2. Quantity of HDL vs. quality

There are 2 basic approaches used when targeting HDL to improve CAD outcomes: increasing HDL quantity, which refers to the circulating plasma concentration of cholesterol in the particle or particle number; and increasing HDL quality, which refers to its functionality as well as its lipid and protein composition [2]. Plasma concentrations of HDL-C is an independent negative risk predictor of atherosclerotic vascular damage [10] CVD [11]. However, numerous clinical and genetic studies have revealed disappointing results about the therapeutic benefit of raising plasma HDL-C levels [12–16]. In this regard, the lack of efficacy of drugs aimed at increasing HDL-C, such as CETP inhibitors and high-dose niacin, has led many to question the therapeutic value of raising HDL-C for CVD. For example, in the ILLUMINATE trial where patients received the CETP inhibitor torcetrapib, CVD events were actually increased despite plasma HDL-C increasing by 60–70% [12]. Furthermore, in the HPS2-THRIVE trial, patients who received extended-release niacin + anti-flushing agent (laropiprant) compared with placebo had lower LDL-C and higher HDL-C concentrations, whereas, no significant effect was observed on the incidence of major vascular events [17]. Besides the lack of benefit deriving from increasing HDL-C levels, differences in serum cholesterol efflux capacity have been reported in humans with similar HDL-C concentrations [18], supporting the need to investigate HDL functionality beyond HDL-C. This conclusion is further supported by robust experimental evidence; thus, SR-B1-deficient mice have strongly elevated HDL-C, but have reduced HDL antioxidant activities and increased atherosclerosis [19,20]. Therefore, research is now focused on improving HDL functionality independent of HDL-C concentrations, such as HDL's ability to mobilize cholesterol from macrophages (cholesterol efflux capacity), which may better predict CAD status [21,22]. Furthermore, many assays have been developed to examine HDL's functionality by testing their ability to mobilize cholesterol, stimulate nitric oxide production, as well as inhibit oxidation and monocyte adhesion processes [23].

Considering the complexity of HDL metabolism, it is understandable when a static measure of HDL-C concentration does not correlate with dynamic HDL functions. The quality of HDL particles can vary considerably due to heterogeneity in composition. Much of the biological activity of HDL is due to its protein content (>50 distinct proteins), as well as the various bioactive lipids, vitamins, hormones, and microRNAs associated with HDL [24]. Therefore, the joint use of dynamic assays to examine HDL functionality and HDL particle composition beyond HDL-C content could serve as more reliable HDL-related biomarkers [2].