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The emerging evidence for vitamin D–mediated regulation of apolipoprotein A-I synthesis

Sarada Jaimungal, Kent Wehmeier, Arshag D. Mooradian, Michael J. Haas*

Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Florida–Jacksonville College of Medicine, Jacksonville, FL 32209, USA

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Abstract

Ischemic heart disease and cerebrovascular ischemia are leading causes of mortality in industrialized countries. The pathogenesis of these diseases involves the formation of atherosclerotic plaques with eventual rupture and superimposed thrombosis. This process is inhibited by high-density lipoprotein (HDL), the main protein component of which is apolipoprotein A-I (apo A-I). Vitamin D_3 is a hormone produced by sun-exposed skin but is acquired also in the diet. The Framingham Offspring Study and the Third National Health and Nutritional Examination Survey showed a link between vitamin D_3 intake and cardiovascular risk factors. The link between 25-hydroxyvitamin D_3 and HDL cholesterol (HDLc) and apo A-I is not as clear. Studies in vitamin D receptor knockout mice demonstrated higher HDLc and hepatic apo A-I messenger RNA expression relative to wild type. Experiments in cultured hepatocytes supported these observations. Human studies evaluating the relationship between vitamin D_3 and apo A-I and HDLc have yielded conflicting results, but most suggest a positive link between increasing vitamin D_3 levels and plasma apo A-I and HDLc. The purpose of this review is to examine the evidence linking vitamin D status and cardiovascular disease, to determine if there is a relationship between vitamin D levels and development of an atherogenic lipid profile. Our objectives are to determine if plasma vitamin D levels correlate with plasma HDLc and apo A-I and, if so, offer speculation as to how apo A-I in the context of high vitamin D levels provides enhanced atheroprotection.

Keywords: Vitamin D; HDLc; Apolipoprotein A-I; Cardiovascular disease

Abbreviations: apo A-I, apolipoprotein A-I; CVD, cardiovascular disease; DBP, vitamin D–binding protein; EB, EB1089; HDL, high-density lipoprotein; HDLc, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; mRNA, messenger RNA; VDR, vitamin D receptor; VDR-KO, vitamin D receptor knock out; ZK, ZK 191784.

1. Introduction

Heart disease and cerebrovascular disease were the number 1 and 3 leading causes of death, respectively, in the United States in 2007 [1]. Of all the deaths from heart disease, two-thirds were due to ischemic heart disease [1]. With regard to cerebrovascular disease, approximately 85% were due to ischemia [2]. In 1990, the leading causes of death worldwide were ischemic heart disease (6.3 million) and cerebrovascular disease (4.4 million), and it is estimated that this trend will continue until at least 2030 [3,4].

The cardiovascular events seen in ischemic heart disease and cerebrovascular ischemia are due to atherosclerosis and thrombosis with plaque rupture [5]. Multiple risk factors have been associated with the development of atherosclerotic lesions. These include diabetes mellitus, hypertension,

* Corresponding author. Tel.: +1 904 244 8619; fax: +1 904 244 5650.
E-mail address: michael.haas@jax.ufl.edu (M.J. Haas).

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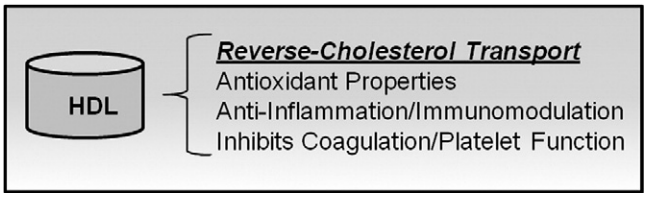

Fig. 1. Cardioprotective effects of HDL. High-density lipoprotein protects from CVD primarily by promoting reverse cholesterol transport, by which cholesterol is transported from peripheral sources (macrophage foam cells) to the liver where it is metabolized to bile acids and excreted in the feces. Due in part to its association with paraoxonase 1, HDL also has antioxidant properties and can prevent the oxidation of low-density lipoprotein. High-density lipoprotein also has anti-inflammatory effects due to its ability to suppress growth of activated immune cells and to induce expression of anti-inflammatory genes in certain target tissues. High-density lipoprotein also prevents development of a hypercoagulative state and has been shown to suppress platelet function.

dyslipidemia, and tobacco smoking [6]. The dyslipidemic risk factors include high levels of low-density lipoprotein cholesterol and low levels of high-density lipoprotein cholesterol (HDLc) [5,6]. Of these, low-density lipoprotein cholesterol is crucial to the development of atherosclerotic lesions, whereas HDLc is an inhibitor of the process, primarily through the process of reverse cholesterol transport (Fig. 1) [5,7]. In the process of reverse cholesterol transport, excess cholesterol located in the periphery, including atherogenic regions of the coronary arteries, is transported to the liver where it is converted to bile acids and excreted (Fig. 2). Recent studies also suggest that HDLc inhibits oxidation, prevents the expression of inflammatory mediators and the expansion of proatherogenic myeloid cells, and reduces the expression of procoagulant enzymes, each of which may contribute in smaller ways to HDLc's cardioprotective effects.

Studies have recently emerged linking low plasma levels of vitamin D to cardiovascular disease (CVD) [8-11]. This is important clinically, as vitamin D deficiency is easy and inexpensive to identify and treat [8,12]. The biologic pathways by which low vitamin D levels are linked to CVD have not yet been elucidated. Likewise, guidelines for the vitamin D cut points in various studies are variable, but most are based on the activation of parathyroid hormone and calcium metabolism, whereby plasma levels of 25-hydroxyvitamin D_3 less than 20 ng/mL are deficient, between 20 to 30 ng/mL are borderline, and greater than 30 ng/mL are sufficient. However, this range of plasma vitamin D concentration may not be high enough to observe other

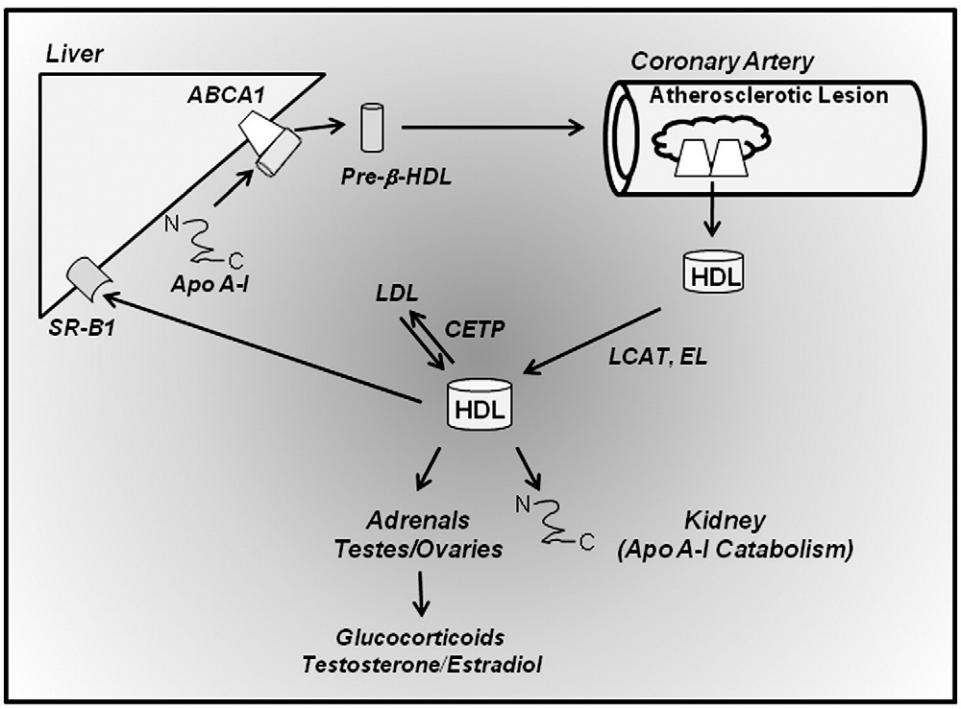

Fig. 2. High-density lipoprotein and reverse cholesterol transport. Apolipoprotein A-I is synthesized primarily in the liver and is immediately lipidated by adenosine triphosphate binding cassette protein A1 to form pre-β-HDL. Pre-β-HDL is an effective cholesterol acceptor in peripheral tissues and atherosclerotic lesions within the coronary arteries. Once charged with cholesterol, the HDL enters the circulation and is processed and remodeled by lecithin-cholesterol acyltransferase and endothelial lipase. Cholesterol within the HDL particle has several fates. It can be shuttled to low-density lipoprotein by cholesterol ester transfer protein, taken up by the adrenals, testes, or ovaries to provide substrate for synthesis of steroids or disassembled and catabolized in the kidney. However, most of the cholesterol is shuttled back to the liver where it is off-loaded by scavenger receptor class B, type 1. Once delivered to the liver, the cholesterol is converted to bile acids and excreted in the feces. ABCA1 indicates ATP binding cassette protein A1; LCAT, lecithin-cholesterol acyltransferase; EL, endothelial lipase; LDL, low-density lipoprotein; CETP, cholesterol ester transfer protein; SR-B1, scavenger receptor class B, type 1.