Journal of Clinical Lipidology (2015) 9, 81–90

Journal of Clinical Lipidology

Elevated interleukin-10: A new cause of dyslipidemia leading to severe HDL deficiency

Andreas G. Moraitis, MD, Lita A. Freeman, PhD, Robert D. Shamburek, MD, Robert Wesley, PhD, Wyndham Wilson, MD, Cliona M. Grant, MD, Susan Price, RN, CCRP, Stephen Demosky, BS, Seth G. Thacker, PhD, Abdalrahman Zarzour, MD, Ronald L. Hornung, PhD, Frank Pucino, PharmD, Gyorgy Csako, MD, Cheryl Yarboro, RN, Iain B. McInnes, MD, PhD, Takashi Kuroiwa, MD, Dimitrios Boumpas, MD, V. Koneti Rao, MD, Gabor G. Illei, MD, PhD, Alan T. Remaley, MD, PhD*

Metabolism, Endocrinology & Diabetes, Endocrine Oncology Program, University of Michigan, Ann Arbor, MI, USA (Dr Moraitis); Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA (Drs Freeman, Shamburek, Demosky, Thacker, Zarzour, and Remaley); Hospital Epidemiology, National Institutes of Health, Bethesda, MD, USA (Dr Wesley); National Cancer Institute, National Institutes of Health, Bethesda, MD, USA (Drs Wilson and Grant); ALPS Unit, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (Drs Price and Rao); Clinical Services Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, USA (Dr Hornung); National Institutes of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA (Drs Pucino, Yarboro, McInnes, Kuroiwa, Boumpas, and Illei); Department of Laboratory Medicine, National Institutes of Health, Bethesda, MD, USA (Drs Csako and Remaley); College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, Scotland (Dr McInnes); and Medical School University of Athens, Affiliate Member IMBB, Heraklion and BRFAA Athens, Greece (Dr Boumpas)

KEYWORDS:
"Disappearing HDL syndrome";
Severe HDL deficiency;
Hypertriglyceridemia;
Dyslipidemia;
B-cell lymphoma;
Intravascular large B-cell lymphoma;
ALPS;
Psoriasis;
IL-10;
LCAT

BACKGROUND: Low high-density lipoprotein cholesterol (HDL-C) is a risk factor for coronary artery disease. Investigating mechanisms underlying acquired severe HDL deficiency in noncritically ill patients ("disappearing HDL syndrome") could provide new insights into HDL metabolism.

OBJECTIVE: To determine the cause of low HDL-C in patients with severe acquired HDL deficiency.

METHODS AND RESULTS: Patients with intravascular large B-cell lymphoma (n = 2), diffuse large B-cell lymphoma (n = 1), and autoimmune lymphoproliferative syndrome (n = 1) presenting with markedly decreased HDL-C, low low-density lipoprotein cholesterol (LDL-C), and elevated triglycerides were identified. The abnormal lipoprotein profile returned to normal after therapy in all 4 patients. All patients were found to have markedly elevated serum interleukin-10 (IL-10) levels that also normalized after therapy. In a cohort of autoimmune lymphoproliferative syndrome patients (n = 93), IL-10 showed a strong inverse correlation with HDL-C ($R^2 = 0.3720$, $P < .0001$). A direct causal role for increased serum IL-10 in inducing the observed changes in lipoproteins was established in a randomized, placebo-controlled clinical trial of recombinant human IL-10 in psoriatic arthritis

A.G.M. and L.A.F. contributed equally to this article.

* Corresponding author. National Institutes of Health, Bldg. 10, Rm. 2C-433, Bethesda, MD 20892-1508.
E-mail address: aremaley1@cc.nih.gov

Submitted August 8, 2014. Accepted for publication September 30, 2014.

1933-2874/$ - see front matter Published by Elsevier Inc. on behalf of National Lipid Association.
http://dx.doi.org/10.1016/j.jacl.2014.09.014

patients (n = 18). Within a week of initiating subcutaneous recombinant human IL-10 injections, HDL-C precipitously decreased to near-undetectable levels. LDL-C also decreased by more than 50% ($P < .0001$) and triglycerides increased by approximately 2-fold ($P < .005$). All values returned to baseline after discontinuing IL-10 therapy.

CONCLUSION: Increased IL-10 causes severe HDL-C deficiency, low LDL-C, and elevated triglycerides. IL-10 is thus a potent modulator of lipoprotein levels, a potential new biomarker for B-cell disorders, and a novel cause of disappearing HDL syndrome.
Published by Elsevier Inc. on behalf of National Lipid Association.

High-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL (1 mmol/L) is a risk factor for coronary artery disease.[1] Causes of low HDL-C include rare genetic disorders due to mutations in the ATP-binding cassette transporter A1 (ABCA1), apolipoprotein A-I (apoA-I), and lecithin:cholesterol acyltransferase (LCAT).[2] These disorders usually present with HDL-C levels below 20 mg/dL. Acquired or secondary causes of low HDL-C account for about half of all patients and can be divided into mild-to-moderate HDL deficiency (HDL-C 20-30 mg/dL) and severe HDL deficiency (HDL-C < 20 mg/dL). Mild-to-moderate HDL deficiency is commonly associated with obesity, hypertriglyceridemia, insulin resistance, and sedentary lifestyle, either alone or in combination with metabolic syndrome.[3] It is also associated with a wide variety of diseases, such as HIV, renal disease, and acute inflammation as well as the use of several medications.[3] Reduced HDL-C levels are also seen in patients with chronic inflammatory diseases, such as rheumatoid arthritis[4,5] and systemic lupus erythematosus.[6] The mechanism for lipid abnormalities in these autoimmune and inflammatory disorders is not completely understood, but several cytokines have been implicated to play either a pro- or antiatherogenic role.[7]

Acquired severe HDL deficiency is relatively uncommon. It may occur after the use of high doses of anabolic steroids or in severe hepatic diseases, such as cholestasis and acute hepatitis, which can lead to low LCAT activity and decreased apoA-I production.[2,3] "Disappearing HDL syndrome," a term first used by Goldberg and Mendez,[3] refers to cases of severe HDL deficiency in noncritically ill patients, sometimes long before the clinical or biochemical features of the underlying primary disease become evident. Disappearing HDL syndrome can also result from an idiosyncratic reaction to medications, such as peroxisome proliferation-activated receptor agonists.[3] Additionally, autoantibodies against LCAT in non-Hodgkin lymphoma have also been described as a possible cause.[8]

In this report, we describe several case reports on three related B-cell disorders, namely intravascular large B-cell lymphoma (IVLBCL), diffuse large B-cell lymphoma (DLBCL), and autoimmune lymphoproliferative syndrome (ALPS), all of which are described to be associated with disappearing HDL syndrome. Interleukin-10 (IL-10) serum concentrations were markedly elevated in all 3 disorders at presentation and were inversely related to HDL-C levels, as well as low-density lipoprotein cholesterol (LDL-C), during the course of treatment. Furthermore, we demonstrate from the analysis of samples from a previous clinical trial[9] that recombinant human IL-10 (rhIL-10) administration leads to profound changes in lipoprotein levels in humans, particularly very low levels of HDL as well as low LDL, thus mimicking the dyslipidemic lipoprotein pattern observed in our patients with B-cell disorders. These data thus identify IL-10 as an important modulator of lipoprotein metabolism and provide evidence for a direct role of IL-10 in disappearing HDL syndrome.

Materials and methods

Subject description

All patients in this study were seen at the National Institutes of Health (NIH) and gave written informed consent under institutional review board–approved protocols. Subjects treated with IL-10 therapy in the clinical trial were described in a previous report.[9]

Clinical laboratory analysis

Routine laboratory tests were performed by the Department of Laboratory Medicine in the NIH Clinical Center. Serum total cholesterol (TC), direct HDL-C, and triglycerides (TG) were measured enzymatically on a Siemens Vista Analyzer. Serum LDL-C was calculated using the Friedewald equation. Serum ApoA-I and ApoB were measured nephelometrically on a Siemens Vista Analyzer. Percent of cholesteryl esters (CE) in plasma was determined by enzymatically measuring total cholesterol as well as free cholesterol in the absence of cholesteryl esterase.

IL-10 measurements

The Human IL-10 ELISA Ready-Set-GO! kit (eBioscience, San Diego, CA) was used according to manufacturer's instructions. 100 μL of samples diluted 1:4 in 1X Assay Diluent were used per well for all samples except ALPS. ALPS IL-10 plasma levels were determined using Quantikine ELISA kits (R&D Systems, Inc., Minneapolis, MN).