Letter to the Editor

Response to the editorial "High-density lipoprotein: a double-edged sword in cardiovascular physiology and pathophysiology"

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The comments by Dr. Lewandowska and Dr. Shipman (1) regarding our review article entitled "High-density lipoprotein: a double-edged sword in cardiovascular physiology and pathophysiology" (2) are mostly welcome. As correctly pointed out by the authors, a detailed analysis of causes of low or high high-density lipoprotein (HDL)-cholesterol concentrations and HDL-cholesterol assessment from the clinical laboratory aspect were outside the focus of the review. The comments by Dr. Lewandowska and Dr. Shipman are insightful and extend the review by providing additional information with important clinical implications for everyday clinical practice.

Early epidemiological evidence (3) supported the concept that HDL-cholesterol protects against atherosclerotic cardiovascular disease by enabling reverse cholesterol transport (from peripheral tissues, macrophages or atherosclerotic lesions to liver) and exerting a number of vascular protective actions (2). Recent genetic and interventional (pharmacological) studies with cardiovascular outcomes suggested that the inverse relationship between HDL-cholesterol and cardiovascular disease is not causal (4). Population-based studies demonstrated a U-shaped relationship between HDL-cholesterol concentration and all-cause mortality in men and women, with the lowest mortality observed for HDL-cholesterol concentrations of 1.9 mmol/L (73 mg/dL) in men and 2.4 mmol/L (93 mg/dL) in women (5). By demonstrating a complex non-linear relationship between HDL-cholesterol concentration and the risk for cardiovascular disease, epidemiological studies and pharmacological interventions targeting HDL-cholesterol had implications with respect to the HDL-cholesterol reference range and interpretation of an HDL-cholesterol test. HDL-cholesterol concentration was considered normal for values 1.0 mmol/L (38.61 mg/dL) or higher in men and 1.2 mmol/L (46.33 mg/dL) or higher in women (1) with these values commonly rounded up to 40 and 50 mg/dL in men and women (≥20 years of age), respectively. An upper limit of normal of HDL-cholesterol concentration has never been officially recognized. It differed widely from 60 to 120 mg/dL and HDL-cholesterol concentration was interpreted according to "the higher, the better principle" meaning that higher HDL-cholesterol concentrations were healthy (associated with lower risk for atherosclerotic cardiovascular disease). Nowadays, it is widely accepted that low and high HDL-cholesterol concentrations may be associated with increased cardiovascular risk. The concept of dysfunctional HDL has emerged and may explain why an elevated HDL-cholesterol concentration may not lead to cardiovascular protection. Furthermore, the methods used routinely in the clinical laboratory measure HDL-cholesterol but not HDL-cholesterol function (6). A reappraisal of HDL in terms of clinical relevance and laboratory perspective (6) and primary (genetic) and secondary (metabolic and inflammatory diseases) causes of (abnormal) low or high HDL levels (7-9) have been recently reviewed.

Interpretation of the HDL-cholesterol test should be done in clinical context. There is no clear definition for low HDL-cholesterol. The use of 10th percentile of HDL-cholesterol as cutoff is arbitrary. A HDL-cholesterol concentration that constitutes a formal factor for coronary artery disease has been suggested as low and this

concentration was put at 35 mg/dL for men and 40 mg/dL for women (8). A HDL-cholesterol level <20 mg/dL was considered as very low or severe HDL-cholesterol deficiency (7). A low HDL-cholesterol level may be due to primary (less often) or secondary (more often) causes. The primary causes of low HDL-concentration include familial hypoalphalipoproteinemia, Tangier disease and lecithin-cholesterol acyl transferase (LCAT) deficiency (7). Danish studies have shown that approximately 10% of patients with HDL-cholesterol below the 5th percentile are heterozygous for mutations in apolipoprotein A1, ATP-binding cassette transporters A1 (ABCA1) or LCAT genes (6). Secondary causes of low HDL-cholesterol may include dysmetabolic states (metabolic syndrome, type 2 diabetes, obesity, hypertriglyceridemia), physical inactivity, smoking, end-stage renal or severe hepatic disease, drugs (probucol, testosterone, progestins, high-dose thiazide diuretics and beta-blockers), very low-fat diet, dysglobulinemia, malabsorption, malignancy, malnutrition and severe inflammatory disease (8). The level of cardiovascular risk associated with low HDL-cholesterol depends on other plasma lipids, particularly, low-density lipoprotein (LDL)-cholesterol and triglycerides and concomitant diseases. Thus, compared with isolated low HDL-cholesterol (<40 mg/dL in men and <50 mg/dL in women), cardiovascular risk increased by 30% in the combination of low HDL-cholesterol with LDL-cholesterol ≥100 mg/dL and triglyceride concentration <100 mg/dL or LDL-cholesterol <100 mg/dL and triglyceride concentration ≥100 mg/dL. When both LDL-cholesterol and triglycerides were ≥100 mg/dL, the cardiovascular risk was increased by 60% (10). In this regard, a low HDL-cholesterol concentration may be considered as a risk marker for cardiovascular disease. An extremely low HDL-cholesterol (<20 mg/dL) is uncommon in general population, is more frequent among men than women and is frequently associated with hypertriglyceridemia in the setting of poorly-controlled diabetes, inflammation, infections, severe liver disease or malignancy. Such low levels of HDL-cholesterol in isolation may indicate a primary cause. The clinical approach (work-out) of a patient with low HDL-cholesterol concentration has been recently reviewed (7).

HDL-cholesterol concentrations between 60 and 100 mg/dL and >100 mg/dL are considered as high and very high, respectively. High HDL-cholesterol levels may have primary or secondary causes. The primary causes of high HDL-concentration include familial hyperalphalipoproteinemia caused by mutations leading to cholesterol ester transfer protein (CETP), endothelial lipase, hepatic lipase or scavenger receptor class B type I (SR-BI) receptor deficiency (7). LCAT overexpression or up-regulation of apolipoprotein A1 production have also been described as causes of familial hyperalphalipoproteinemia and elevated HDL-cholesterol concentration (9). Secondary causes of high HDL-cholesterol concentration may include vigorous and sustained aerobic exercises, regular alcohol consumption (in substantial amounts), drugs [oral estrogens, statins, niacin (>1 g/day), phenytoin, fibrates and CETP inhibitors] and primary biliary cirrhosis (9). HDL-cholesterol concentrations >60 mg/dL do not lead to further improvement in prognosis or even may be harmful (6,9).

It may be concluded that: low and very high HDL-cholesterol concentrations may be associated with increased cardiovascular risk and they are not clinically desirable; second, there is no correlation between HDL-cholesterol concentration and HDL functions such as, reverse cholesterol transport and current methods used to estimate HDL-cholesterol function remain in the research realm (i.e., as research tools not routinely used in the clinical laboratory practice) (6); third, HDL-cholesterol may correlate with cardiovascular risk (or cardiovascular protection) only in healthy individuals (2,6); fourth, HDL-cholesterol pharmacological raising therapies are not clinically meaningful (may produce dysfunctional HDL-cholesterol) and they are not recommended; instead lifestyle modifications (physical activity and smoking cessation) may rise HDL-cholesterol that is functional (may lead to vascular protection); finally, HDL-cholesterol concentrations <20 and >100 mg/dL may need advanced laboratory diagnostic tests including measurement of apolipoprotein A1 and genetic testing.

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