

Clinical utility of low-density lipoprotein particle measurement in management of cardiovascular disease: a case report

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Abstract: Despite adequate screening and low-density lipoprotein cholesterol (LDL-C)-lowering therapy, it has been recognized that many patients with low or moderate LDL-C levels experience cardiovascular events. Furthermore, many patients with cardiovascular disease and relatively normal levels of LDL-C have increased levels of low-density lipoprotein particles (LDL-P). The purpose of this case report is to illustrate the importance of LDL-P in the surprising presentation of vascular disease in a woman who had a high concentration of high-density lipoprotein cholesterol (HDL-C). By utilizing lipoprotein information, patients can be appropriately selected to receive suitable medication, leading to better health outcomes.

Keywords: lipoprotein particle concentration, premature coronary artery disease, lipid profile, combination therapy, vitamin D deficiency

Introduction

Does a traditional cholesterol test give reliable information to the health care provider in managing cardiovascular disease in their patients? Low-density lipoprotein cholesterol (LDL-C) has long been the basis for measuring coronary heart disease risk because its measurement is relatively easy. Despite adequate screening and LDL-lowering therapy, it has been recognized that many patients with low or moderate LDL-C levels experience coronary heart disease events.¹ In 2007, a seven-member panel of experts developed a consensus statement that was endorsed by America Diabetes Association and the American College of Cardiology, which concluded that lipoprotein abnormalities are common findings in patients with cardiometabolic risk.² Moreover, many patients with cardiometabolic risk have relatively normal levels of LDL-C, yet have increased levels of low-density lipoprotein particles (LDL-P).

Furthermore, clinical trials that have compared the clinical outcomes in incident cardiovascular events between LDL-C versus LDL-P concentration, consistently demonstrate that LDL-P concentration, or its surrogate measure, apolipoprotein B (Apo B), are more predictive of cardiovascular events than LDL-C.³ Moreover, therapies that lower lipids may have varying effects on LDL-C versus LDL-P. For instance, statins, estrogen replacement therapy, and a low-fat, high-carbohydrate diet tends to lower cholesterol content in the LDL particles more than they lower LDL-P concentration. Conversely, fibrates, nicotinic acid, some thiazolidinediones (pioglitazone), exercise, and a low carbohydrate diet tend to lower LDL-P concentration more than they lower LDL-C content in LDL particles (Table 1).³ Therefore, reliance on LDL-C as a biomarker may not fully appreciate the benefit of these therapies. Hence, recent consensus papers from the American Association for Clinical Chemistry have focused

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Table 1 Interventions that changes LDL composition (size or cholesterol content) will differentially affect LDL-C and LDL-P concentrations

Interventions that increases cholesterol per particle (LDL-P concentration decreases more)	Interventions that decreases cholesterol per particle (LDL-C concentration decreases more)
Fibrates	Statins
Niacin	Statins + ezetimibe
Glitazones (some)	Estrogen replacement therapy
Omega 3 fatty acids	Antiretrovirals (some)
Exercise	High carbohydrate diet
Low carbohydrate diet	

Notes: Reprinted from Rosenson R, Davidson M, Pourfarzib R. Underappreciated opportunities for low-density lipoprotein management in patients with cardiometabolic residual risk. *Atherosclerosis*. 2010;213:1–7, with permission from Elsevier.³

Abbreviations: LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles.

on measurement of LDL-P and Apo B rather than LDL-C for both risk assessment and therapeutic effectiveness.⁴

The purpose of this case report is to illustrate the importance of LDL-P in the surprising presentation of vascular disease in a woman with a high concentration of high-density lipoprotein cholesterol (HDL-C). We will also discuss the discordance between LDL-P and LDL-C concentrations and the benefit of knowing the concentrations of various lipoproteins in coronary heart disease patients. We will discuss evidence supporting the treatment strategies and end with clinical recommendations.

Case report

A healthy 57-year-old Caucasian woman with a family history of premature coronary artery disease presented to her primary care physician for preventive screening. She reported eating a healthy diet, exercising regularly, and consuming minimal alcoholic beverages. Her mother and sister had coronary artery disease and had had coronary bypass surgery at the ages of 52 years and 53 years, respectively.

The patient's lipid panel revealed total cholesterol 250 mg/dL, LDL-C 110 mg/dL, HDL-C 116 mg/dL, triglycerides 29 mg/dL, and non-HDL-C 134 mg/dL (Table 2). HDL-C values had been elevated >100 mg/dL for several years. It is possible that these values may have been due to laboratory artifact. If the laboratory uses phosphotungstic acid for precipitation of the B-containing lipoproteins, the lipoprotein(a) may remain in the supernatant and be measured as HDL-C. In this patient's case, she had had elevated HDL-C measured in more than one laboratory over the course of several years and it was consistently greater than 100 mg/dL.

Based on the patient's risk factors of age and family history, a Framingham risk score was performed, and a 3% risk for heart attack or stroke in the next 10 years

was calculated. She was given advice to continue a heart-healthy diet and regular exercise, with no recommendation for medical therapy other than aspirin 81 mg/day. She was also told she had cardiovascular protection based on her high HDL-C.

Two months after this screening test, the patient experienced an episode of atypical chest pain. She was evaluated in the emergency room. No cardiac work-up was performed because she responded to treatment with antacids and proton pump inhibitor therapy. Two weeks later she again began to experience nonexertional, atypical chest pain. She was again evaluated in the emergency room and at this time had an abnormal electrocardiogram, and subsequent heart catheterization showed coronary disease with 70% blockage in the left anterior descending artery and diffuse disease in multiple vessels. She underwent triple vessel coronary artery bypass surgery. Upon discharge, her cardiologist placed her on atorvastatin 40 mg, omega 3 fatty acids 1 g, aspirin 81 mg, and clopidogrel 75 mg per day.

One month later she was evaluated in the author's lipid clinic. Her lipid panel on atorvastatin 40 mg revealed total cholesterol 203 mg/dL, LDL-C 141 mg/dL, HDL-C 44 mg/dL, triglycerides 89 mg/dL, and non-HDL-C 159 mg/dL. Her nuclear magnetic resonance lipoprotein test results on atorvastatin 40 mg revealed a total LDL-P of 3002 nmol/L, all of which were small LDL-P. Other laboratory tests performed are listed in Table 2. Of note, she had elevated high-sensitivity C-reactive protein, elevated lipoprotein(a) and severe vitamin D deficiency. Based on the American Diabetes Association/American College of Cardiology and American Association for Clinical Chemistry consensus treatment goals of Apo B < 80 mg/dL, non-HDL-C < 100 mg/dL, and LDL-P < 1100 nmol/L, the patient's residual risk was more aggressively managed.^{2,4}

Evaluation and management

The patient was a woman with known coronary artery disease and a strong family history of coronary disease. She was not treated initially, based on a traditional lipid panel showing high HDL-C and presumed protection. Although in general, high levels of HDL-C are associated with reduction for coronary artery disease, some individuals may have dysfunctional HDL-C that is not protective. Her LDL-C value of 110 mg/dL was not treated based on current National Cholesterol Education Panel guidelines. After subsequent analysis on atorvastatin 40 mg, nuclear magnetic resonance lipoprotein test results revealed a significantly elevated risk based on an LDL-P of 3002 nmol/L (Table 2).

Table 2 Baseline and follow-up laboratory characteristics for the patient

Medications	Initial visit	Second visit (one-month follow-up)	Third visit (four-month follow-up)	Fourth visit (six-month follow-up)	Fifth visit (end of year 1)
	No medication prior to CABG	Atorvastatin 40 mg, OM3 1 g, aspirin 81 mg, clopidogrel 75 mg	Rosuvastatin 40 mg, OM3 1 g, aspirin 81 mg, clopidogrel 75 mg	Rosuvastatin 40 mg, OM3 1 g, extended-release niacin 500 mg, clopidogrel 75 mg	Rosuvastatin 40 mg, extended-release niacin 1 g, OM3 1 g, clopidogrel 75 mg
Total cholesterol (mg/dL)	250	203	227	250	252
LDL-C (mg/dL), optimal <70–100 mg/dL	110	141	110	86	129
HDL-C (mg/dL)	116	44	100	152	111
Triglycerides (mg/dL)	29	89	83	60	59
Non-HDL-C (mg/dL)	134	159	127	98	141
LDL-P (nmol/L), optimal <1000 nmol/L		3002	1418	965	616
Small LDL-P (nmol/L), optimal <600 nmol/L		3002	992	661	438
LDL-P size (nm)		19.1	20.7		21.1
HDL-P (nmol/L)		6.3	18.5	18.5	13.7
VLDL-P (nmol/L)		0	0.3		0
Weight (lb)	146	149	136.5		151
Blood pressure (mmHg)	150/85	100/62	126/74		110/64
Fasting glucose (mg/dL)		89		86	91
HbA _{1c} (%)		5.7			5.7
hsCRP (mg/dL)		47	0.9		
LpPLA ₂ (mg/dL), Optimal <200 mg/dL		255	229		209
Lipoprotein(a) (mg/dL), Optimal <30 mg/dL		76			63
25-OH vitamin D (ng/mL), Optimal >30 mg/dL		16			35

Abbreviations: OM3, omega 3 fatty acid; CABG, coronary artery bypass surgery; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particles; non-HDL-C, non-HDL cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles; LpPLA₂, lipoprotein associated phospholipase A₂; hsCRP, high-sensitivity, C-reactive protein; VLDL-P, very low-density lipoprotein particles; HbA_{1c}, glycosylated hemoglobin.

In her case, LDL-P was dramatically elevated, despite being on atorvastatin 40 mg, so we elected to switch her to rosuvastatin 40 mg. A recently published, randomized, double-blind, controlled study demonstrated greater LDL-P reduction with rosuvastatin versus atorvastatin.⁵ Four months later, after a weight loss of 9 lb and switching to rosuvastatin, her LDL-P dropped to 1418 nmol/L, small LDL-P dropped to 992 nmol/L, and HDL-C increased back to 100 mg/dL. LDL-C was now 110 mg/dL, triglycerides 83 mg/dL, and total cholesterol 227 mg/dL. Her high sensitivity C-reactive protein normalized to 0.9 mg/dL. Due to vitamin D deficiency, she was also initiated on treatment with over-the-counter vitamin D3 5000 IU/day.

With known coronary disease, elevated lipoprotein(a), and LDL-P still not to target, we added extended-release niacin 500 mg. Extended-release niacin and estrogen are two of the few agents known to lower lipoprotein(a), although there are no prospective data to suggest lowering lipoprotein(a) has any impact on cardiovascular disease event reduction. Extended-release niacin has also been shown to lower LDL particle concentration.⁶

On rosuvastatin 40 mg and extended-release niacin 500 mg, nuclear magnetic resonance revealed LDL-P 965 nmol/L, small LDL-P 661 nmol/L, Apo B 72 mg/dL, LDL-C 86 mg/dL, triglycerides 60 mg/dL, total cholesterol 250 mg/dL, HDL-C 152 mg/dL, and non-HDL-C 98 mg/dL. She had now met goals based on an American Diabetes Association and the American College of Cardiology consensus statement of Apo B < 80 mg/dL and non-HDL-C < 100 mg/dL.² She still had elevated LDL-P of 965 nmol/L (20th percentile of Framingham population), elevated LDL-C 86 mg/dL, and elevated lipoprotein(a), so titration to extended-release niacin 1 g was done. Exactly one year after her coronary artery bypass surgery, she had a traditional lipid panel of total cholesterol 252 mg/dL, LDL-C 129 mg/dL, HDL-C 111 mg/dL, and triglycerides 59 mg/dL. As illustrated in Table 2, her traditional lipid panel was no different on rosuvastatin 40 mg and extended-release niacin 1 g, a potent combination drug therapy, than when she was on no therapy prior to her bypass surgery. However, her LDL-P levels declined from 3002 nmol/L to 616 nmol/L at the end of one year of treatment.

Recommendations

It is well documented that the cholesterol and triglyceride content of LDL particles varies from person to

person because of differences in particle size and lipid composition.⁷⁻⁹ Hence, two patients who have the same measured LDL-C concentrations can have significantly different numbers of LDL particles and therefore a different risk for coronary heart disease.^{10,11} Strong evidence now exists for the superiority of lipoprotein measurements versus lipid concentrations in the management of coronary heart disease (Table 3).^{3,7,9} For example, in the Framingham Offspring Study, the 15-year risk of cardiovascular disease events among 3066 middle-aged men and women was related to LDL-P, and not LDL-C, in individuals with discordant values for these two measures of LDL. The data indicate that LDL-C performs well as a surrogate for LDL-related cardiovascular disease risk when values are in agreement (ie, concordant) with LDL-P, but less well when they are discordant.⁷ Furthermore, recently published data from the Multi-Ethnic Study of Atherosclerosis showed that in individuals with discordant LDL-C and LDL-P levels, the LDL-attributable atherosclerotic risk was better indicated by LDL-P. For the discordant levels of LDL-P and LDL-C, only LDL-P was associated with incident cardiovascular disease.

In our lipid clinic, we use nuclear magnetic resonance as a useful tool to distinguish between patients warranting an aggressive treatment approach and those warranting a less aggressive treatment approach. What we have found in our adult population is that in patients with high risk, ie, known cardiovascular disease or diabetes, combination drug therapy decreases lipoprotein levels effectively (combination of statins with extended release-niacin, fibrates, thiazolidinediones, and omega-3 fatty acids).^{3,11} In patients with insulin resistance as the core etiology of dyslipidemia, weight loss, increased exercise, and lower carbohydrate diets will also favorably decrease LDL-P.^{3,11}

Conclusion

In a patient with a strong family history for coronary heart disease, even in the presence of a high HDL-C, a more extensive evaluation may identify nontraditional risk factors, such as elevated LDL-P, thus placing individuals at increased risk for coronary heart disease. Furthermore, many high-risk patients who achieve LDL-C and non-HDL-C target levels will not have achieved low population-equivalent LDL-P targets. By utilizing lipoprotein information, appropriate patient selection will identify those who should receive suitable medication, leading to better health outcomes.

Table 3 Summary information for prospective clinical studies comparing associations of LDL-P and LDL-C with cardiovascular disease endpoints

Study	Total study sample size	LDL-P sample size	Study population	CVD endpoint (follow-up period)	Data analysis/conclusions related to associations of LDL-P and LDL-C with CVD outcomes
Multi-Ethnic Study of Atherosclerosis ¹²	6814	5598	Community-based men and women, aged 45–84 years and free of self-reported CVD, recruited from 4 diverse racial/ethnic groups (African American, Hispanic, White, and Chinese American).	CVD events: MI, CHD, death, angina, stroke, stroke death, or other CVD death, C-IMT	For individuals with discordant LDL-C and LDL-P levels, the LDL-attributable atherosclerotic risk was better indicated by LDL-P. For the discordant levels of LDL-P and LDL-C, only LDL-P was associated with incident CVD. C-IMT tracked with LDL-P rather than LDL-C.
Framingham Offspring Study ⁷	3066	3066	Middle-aged White participants (53% women) without CVD were followed for incidence of first CVD event	CVD events: MI, angina, coronary insufficiency, CHF, stroke, TIA (14.8 years)	Subjects with a low level of LDL-P had a lower CVD event rate (59 events per 1000 person-years) than those with an equivalently low level of LDL-C or non-HDL-C (81 and 74 events per 1000 person-years, respectively).
Veterans Affairs HDL Intervention Trial (VA-HIT) ⁹	2531	364 cases 697 controls	Men with established CHD and low HDL-C; average age 64 years; 81% white; 16% black; randomized to gemfibrozil or placebo	MI or CHD death (5.1 years)	Logistic regression used to determine OR of incident CHD events for baseline or on-treatment LDL-P or LDL-C values, adjusted for treatment group, age, hypertension, smoking, BMI, and diabetes. OR (per 1 SD increment) for a new CHD event were significant for baseline and on-trial values of LDL-P (1.20; $P = 0.006$ and 1.28; $P = 0.0003$, respectively), but not for LDL-C (1.10; $P = 0.15$ and 1.08; $P = 0.25$, respectively).
EPIC-Norfolk ¹³	25,663	1003 cases 1885 controls	Men and women free of CAD; average age 65 years; race unreported; 36% women	Fatal or nonfatal CAD (6 years)	Conditional logistic regression used to determine OR of incident coronary artery disease. OR for quartile 4 versus 1 were 2.00 (95% CI 1.58–2.59) for LDL-P and 1.73 (95% CI 1.37–2.18) for LDL-C in analyses adjusted for smoking and blood pressure, plus matching for age, gender, and enrollment time.
Women's Health Study ¹⁴	28,345	27,673	Women free of CVD; average age 55 years; 96% white; randomized to aspirin and vitamin E	CVD events: nonfatal MI, PCI, CABG, ischemic stroke, CVD death (11 years)	Cox proportional hazard regression used to determine HR of incident CVD events by quintile of LDL-C and LDL-P, adjusted for age, randomized treatment assignment, smoking status, menopausal status, hormone use, blood pressure, diabetes, and BMI. LDL-P was more strongly related to CVD than LDL-C. HR (95% CI) for quintile 5 versus 1 was 2.51 (1.91–3.30) for LDL-P and 1.74 (1.40–2.16) for LDL-C.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio; OR, odds ratio; MI, myocardial infarction; PCI, percutaneous intervention; CABG, coronary artery bypass surgery; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particles; non-HDL-C, non-HDL cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles; C-IMT, carotid intima-media thickness; SD, standard deviation; TIA, transient ischemic attack; CHF, congestive heart failure.

List of abbreviations

AACC, American Association for Clinical Chemistry; ACC, American College of Cardiology; ADA, American Diabetes Association; Apo B, Apolipoprotein B; CMR, Cardiometabolic risk; C-IMT, Carotid intima-media thickness; CABG, Coronary bypass surgery; ER, Emergency room; HDL-C, High-density lipoprotein cholesterol; HDL-P, High-density lipoprotein particles; Non-HDL-C, Non HDL Cholesterol; LDL-C, Low-density lipoprotein cholesterol; LDL-P LDL, particle concentration; LpPLA₂, Lipoprotein associated phospholipase A₂; MESA, Multi-Ethnic Study of Atherosclerosis; MI, Myocardial infarction; OM3, Omega 3 fatty acid; VLDL-P, Very low-density lipoprotein particle.

Disclosure

TD serves on the speaker bureaus for Abbott, GlaxoSmith-Kline, LipoScience, Merck Schering Plough, Takeda, and Santarus. RP serves as Vice President of Medical Affairs at LipoScience.

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