

Atherogenic lipoproteins particle size and number are more critical determinant of cardiovascular risk than mass of cholesterol present within these – An overview



Submission: 02-06-2024

Revision: 06-06-2024

Publication: 01-08-2024

Sir,

Dyslipidemia is one of the important risk factors for cardiovascular (CV) diseases. As per the current consensus, we assess lipid-derived risk by looking at traditional lipid parameters. We consider low-density lipoprotein cholesterol (LDLc) as a primary therapeutic target. However, many recent studies have claimed apolipoprotein B and non-high-density lipoprotein cholesterol (HDLc) are more accurate in this regard. In India, raised triglyceride levels are a unique and important feature of dyslipidemia. In the presence of high triglycerides, LDLc gets oxidized and becomes a small dense form that is considered more atherogenic than large buoyant LDL particles. Hence, in this subset of patients, LDL particle number and size would be more accurate measures of lipid parameters. To explore this aspect, we wrote this short communication to you. Lipoproteins (Lps) are the major contributor to atheromatous plaque formation. Among atherogenic Lps, LDLc has long been considered a major Lp and thus it became a major therapeutic target in all lipid-lowering therapies. Atherosclerotic CV disease (ASCVD) risk is linearly associated with LDLc level. It has been demonstrated that each mmol/L decrease in LDLc level is associated with a 20–25% reduction in the risk of major ASCVD events.^{1,2} We have been assessing lipid-derived ASCVD risk by looking at traditional lipid parameters for the last few decades. However, traditional lipid parameters do not reflect the entire atherogenic Lps in the plasma such as Lp(a), and apolipoprotein-B.³ It has been found in several recent studies that a subset of patients, even with optimal LDLc levels they continue to get ASCVD events and atherosclerosis process progression. This phenomenon has been termed as “residual lipid risk” which cannot be identified by measuring LDLc level alone. Residual lipid risk is the difference between the estimated LDLc value and the actual quantity of circulating atherogenic Lp particles.⁴ Non-HDLc comprises cholesterol carried by all potential atherogenesis Lps including LDLc, VLDL, Lp(a), and remnant Lps. Apolipoprotein-B represents the total number of atherogenic Lps in the plasma as each Lp

particle contains one molecule of apolipoprotein-B.⁵ LDLc represents the total cholesterol concentration of LDL, IDL, and Lp(a). However, LDLc level does not reflect the LDL particle number and size.⁶ For example, at the same level of LDLc people with small-sized LDL particles will have more number of LDLc particles than people with large-sized LDL particles. As it takes more small-sized LDL to traffic a given mass of cholesterol molecules per liter/deciliter.⁶ We know small dense LDL is more atherogenic than large buoyant LDL particles and more easily infiltrate into the arterial intima.^{7,8} In most circumstances, apolipoprotein-B and non-HDLc are highly correlated with each other but not identical as apolipoprotein-B and non-HDLc in addition to LDLc they also include triglyceride-rich Lps.⁹ Lp(a) is included in all three measurements. Among statin-treated patients, more pronounced discordance exists between these parameters as statin lowers LDLc more effectively than the other two parameters.¹⁰ Hence, it is important to identify this concordance and discordance pattern, particularly in statin-treated patients, otherwise they might have discordantly high apolipoprotein -B levels and they remain at higher risk for ASCVD events despite attainment of optimal LDLc. If we are able to identify that subset of patients, we can take appropriate

Access this article online

Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v15i8.66366

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Copyright (c) 2024 Asian Journal of Medical Sciences



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

steps such as statin intensification, the addition of non-statin therapy, or more aggressive procedures such as lipid apheresis. To date, very small number of studies have been conducted to examine the relationship between these lipid parameters in statin-treated patients. One study was done by Qu et al.,¹¹ they observed LDLc to be discordant with apolipoprotein-B in 31% of cases and with non-HDLc in 20.1% of cases in their study cohort. They also reported the brachial artery pulse wave velocity which is considered a marker of subclinical atherosclerosis,¹² was greater in those with higher apolipoprotein-B or non-HDLc levels. In the adjusted logistic regression model, low LDLc and high apolipoprotein-B or non-HDLc discordance were associated with a risk of arterial stiffness (OR: 13.41).¹¹ Hence these discordant groups of patients need to be identified to take necessary steps to reduce the residual risk of CV events. Johannesen et al.,¹³ did concordance discordance analysis and they concluded that statin-treated patients, with elevated apolipoprotein -B and non-HDLc, but not LDLc, are associated with residual risk of all-cause mortality and myocardial infarction. It has been observed that the amount of cholesterol within Lp particles is very substantial. The analysis of the INTERHEART study demonstrated that when apolipoprotein in B level is higher than non-HDLc level that is when cholesterol-depleted apolipoprotein-B particles are present, CV risk is increased, whereas when non-HDLc level is higher than apolipoprotein-B level that means when cholesterol-enriched apolipoprotein-B particles are present, CV risk is less than the reference concordant group.¹⁴ When the mass of cholesterol per apolipoprotein-B particle is normal, all three measures are concordant. However, when a mass of cholesterol within apolipoprotein-B particles is either greater or lesser, LDLc and non-HDLc are discordant. In both circumstances, the number of apolipoprotein-B particles is not accurately represented by measures of the mass of cholesterol within them.¹⁴ Hence, probably Lp particle number, and size are more critical determinants of CV risk than the mass of cholesterol within them.

Avijit Saha

Associate Professor, Department of General Medicine, Malda Medical College and Hospital, Malda, West Bengal, India

Address for Correspondence:

Dr. Avijit Saha, Associate Professor,
Department of General Medicine, Malda Medical College and
Hospital, Malda - 732 101, West Bengal, India.
Mobile: +91-9883026884. **E-mail:** sahaavijit46@gmail.com

REFERENCES

- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-1278.
[https://doi.org/10.1016/S0140-6736\(05\)67394-1](https://doi.org/10.1016/S0140-6736(05)67394-1)
- Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;2013(1):CD004816.
<https://doi.org/10.1002/14651858.CD004816.pub5>
- Lawler PR, Akinkuolie AO, Chu AY, Shah SH, Kraus WE, Craig D, et al. Atherogenic lipoprotein determinants of cardiovascular disease and residual risk among individuals with low low-density lipoprotein cholesterol. *J Am Heart Assoc*. 2017;6(7):e005549.
<https://doi.org/10.1161/JAHA.117.005549>
- Mora S, Buring JE and Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. *Circulation*. 2014;129(5):553-561.
<https://doi.org/10.1161/CIRCULATIONAHA.113.005873>
- Pencina MJ, D'Agostino RB, Zdrojewski T, Williams K, Thanassoulis G, Furberg CD, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. *Eur J Prev Cardiol*. 2015;22(10):1321-1327.
<https://doi.org/10.1177/2047487315569411>
- Hulthe J, Wiklund O, Bondjers G and Wikstrand J. LDL particle size in relation to intima-media thickness and plaque occurrence in the carotid and femoral arteries in patients with hypercholesterolaemia. *J Intern Med*. 2000;248(1):42-52.
<https://doi.org/10.1046/j.1365-2796.2000.00698.x>
- Blake GJ, Otvos JD, Rifai N and Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002;106(15):1930-1937.
<https://doi.org/10.1161/01.cir.0000033222.75187.b9>
- Vakkilainen J, Steiner G, Ansquer JC, Aubin F, Rattier S, Foucher C, et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation*. 2003;107(13):1733-1737.
<https://doi.org/10.1161/01.CIR.0000057982.50167.6E>
- Otvos JD, Mora S, Shalurova I, Greenland P, Mackey RH and Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5(2):105-113.
<https://doi.org/10.1016/j.jacl.2011.02.001>
- Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: A meta-analysis. *JAMA*. 2012;307(12):1302-1309.
<https://doi.org/10.1001/jama.2012.366>
- Qu G, Zhang Z and Zhu H. Discordance between apolipoprotein B or non-HDL-cholesterol and LDL-cholesterol in middle-aged and elderly Chinese patients predicts arterial stiffness. *Lipids Health Dis*. 2021;20:80.
<https://doi.org/10.1186/s12944-021-01509-6>
- Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshida S, Kita Y, et al. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: An individual participant data meta-analysis. *Hypertension*. 2017;69(6):1045-1052.
<https://doi.org/10.1161/HYPERTENSIONAHA.117.09097>
- Johannesen CD, Mortensen MB, Langsted A and Nordestgaard BG. Apolipoprotein B and Non-HDL cholesterol

better reflect residual risk than LDL cholesterol in statin-treated patients. *J Am Coll Cardiol.* 2021;77(11):1439-1450.

<https://doi.org/10.1016/j.jacc.2021.01.027>

14. Sniderman AD, Islam S, Yusuf S and McQueen MJ. Discordance

analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. *Atherosclerosis.* 2012;225(2):444-449.

<https://doi.org/10.1016/j.atherosclerosis.2012.08.039>


Authors Contribution:

AS - contributed totally towards scripting of this Editorial.

Work attributed to:

Malda Medical College and Hospital.

Orcid ID:

Dr. Avijit Saha -  <https://orcid.org/0000-0002-8956-0834>

Source of Support: Nil, **Conflicts of Interest:** None declared.