

Meaningful subtleties in LDL cholesterol are beginning to challenge approaches to cardiovascular disease (CVD) treatment and prevention.

## LDL SIZE AND DENSITY SIGNAL CVD RISK

LDL particles vary in size and density, ranging from "large and light" to "small and dense," and are further divided into subclasses according to density: large (LDL-1), intermediate (LDL-2), small (LDL-3), and very small (LDL-4).<sup>1, 2</sup> Together, LDL-3 and LDL-4 are referred to as small dense LDL (sdLDL).



Small dense LDL particles are significantly and independently associated with increased CVD risk<sup>38</sup> and

they are believed to be more atherogenic than larger LDL molecules for several reasons:<sup>9</sup>

- Smaller particle size: facilitates greater arterial wall penetration
- Longer circulation time: increases the likelihood of atherogenic modifications
- Lower antioxidant levels: increases susceptibility to oxidation

## PATTERN B LDL POINTS TO ATHEROGENIC DYSLIPIDEMIA

Everyone has a different mix of LDL subclasses, arising in two distinct patterns:

- Pattern A: fewer and larger LDL particles; less atherogenic
- **Pattern B:** predominantly sdLDL particles; a categorical marker of atherogenic dyslipidemia; associated with 3x greater CVD risk than pattern A

Assessing sdLDL measurements in addition to traditional lipid measures should be considered.



Atherogenic Dyslipidemia Risk

## **DIET MAY AFFECT LDL STATUS IN 4 SURPRISING WAYS**

- 1. Saturated fatty acids (SFAs) appear to preferentially increase plasma concentrations of larger LDL particles.<sup>13, 14</sup>
- 2. Replacing SFAs with carbohydrates has been associated with no improvement, or even worsening, of CVD risk.<sup>15, 16</sup>
- 3. Carbohydrate intake is linearly and positively associated with prevalence of LDL pattern B.<sup>3</sup>
- 4. Limiting dietary carbohydrate as a total percent of energy is shown to reduce levels of sdLDL.<sup>17</sup>

### **Carbohydrates Promote sdLDL Cholesterol**

Carbohydrate intake initiates a cascade of metabolic processes, including increasing hepatic triglycerides (TG), which leads to the secretion of large, TG-enriched VLDLs. Lipoprotein lipase (LPL) breaks down VLDLs into remnant lipoproteins, which are then catabolized by hepatic lipase to produce sdLDLs.<sup>3</sup>

# Increasing Carbohydrate Intake is Associated with Increasing Prevalence of Pattern B

Variation in carbohydrate consumption is correlated with the prevalence of pattern B LDL in metabolic feeding studies. Each data point below is the summation of the response of at least 40 individuals to a dietary regimen that controlled for dietary carbohydrate and lasted three to six weeks.<sup>3</sup>



## **RETHINKING NUTRITION INTERVENTIONS**

Science continues to support the widespread health benefits of low-carbohydrate diets — including their capacity to promote cardiovascular health, improve insulin resistance, stimulate weight loss and reduce inflammation.<sup>18-24</sup>

### WHAT YOU NEED TO KNOW

### Patients presenting with CVD or CVD risk factors may benefit most from low-carbohydrate diets.

Nutrition education messages should focus on:

- Consuming nutrient-dense foods containing healthy fats
- Reducing overall carbohydrate intake
- Choosing heart-healthy carbohydrates in moderation



#### **REFERENCES:**

- Hirayama S, Miida T. Small dense LDL: an emerging risk factor for cardiovascular disease. Clinica Chimica Acta. 2012;(414):215–224. doi:10.1016/j.cca.2012.09.010
- Berneis K, Jeanneret C, Muser J, Felix B, Miserez AR. Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes. Metabolism, Clinical and Experimental. 2005;54(2):227–234. doi:10.1016/j. metabol.2004.08.017
- Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM. Saturated Fats Versus Polyunsaturated Fats Versus Carbohydrates for Cardiovascular Disease Prevention and Treatment. Annu Rev Nutr. 2015 ; 35: 517–543. doi:10.1146/annurev-nutr-071714-034449
- Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2014; 34:1069–77. doi:10.1161/ATV-BAHA.114.303284
- Mora S, Caulfied MP, Wohlgemuth J, Chen Z, Superko HR, Glynn RJ, Ridker PM, Krauss RM. Atherogenic lipoprotein subclasses determined by ion mobility analysis and first cardiovascular events after random allocation to high-intensity statin therapy or placebo: the JUPITER Trial. 2015 Manuscript submitted.
- Musunuru K, Orho-Melander M, Caulfield MP, Li S, Salameh WA, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular risk. Arterioscler Thromb Vasc Biol. 2009; 29:1975–80. doi:10.1161/ATVBAHA.109.190405
- Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. Circulation. 2012; 125:2469–78. doi: 10.1161/CIRCULATIONA-HA.111.073684
- Tsai MY, Steffen BT, Guan W, McClelland RL, Warnick R, et al. New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2014; 34:196–201. doi:10.1161/ATVBA-HA.113.302401
- Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. Oxid Med Cell Longev. 2017;2017:1273042. doi:10.1155/2017/1273042
- 10. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-Density Lipoprotein Subclass Patterns and Risk of Myocardial Infarction. JAMA. 1988;260(13):1917–1921. doi:10.1001/ jama.1988.03410130125037
- 11. Abdelsamie RM, Khalila Z, MohamedAl-Azabb, DA, Abdelmoneim Akl O. Is sdLDL a valuable screening tool for cardiovascular disease in patients with metabolic syndrome? Alexandria Journal of Medicine. 2017; 53:299-305. doi:10.1016/j.ajme.2017.01.002
- 12. Norwitz NG and Loh V (2020) A Standard Lipid Panel Is Insufficient for the Care of a Patient on a High-Fat, Low-Carbohydrate Ketogenic Diet. Front. Med. 7:97. doi:10.3389/ fmed.2020.00097

- Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, King JC, Mente A, Ordovas JM, Volek JS, Yusuf S, Krauss RM, Saturated Fats and Health: A Reassessment and Proposal for Food-based Recommendations: JACC State-of -the-Art Review, Journal of the American College of Cardiology (2020), doi:10.1016/j.jacc.2020.05.077
- 14. Krauss RM. All low-density lipoprotein particles are not created equal. Arterioscler Thromb Vasc Biol. 2014; 34:959–61 doi:10.1161/ATVBAHA.114.303458
- 15. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjonneland A, et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. Am J Clin Nutr. 2010; 91:1764–68. doi: 10.3945/ajcn.2009.29099
- 16. Micha R, Mozaffarian D. Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids. 2010; 45:893–905. doi:10.1007/s11745-010-3393-4
- 17. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006; 83:1025–31. quiz 1205. doi:10.1093/ ajcn/83.5.1025
- 18. Diamond DM, Alabdulgader AA, de Lorgeril M, et al. BMJ Evidence-Based Medicine Epub ahead of print: 16 July 2020. doi:10.1136/bmjebm-2020-111412
- Venables MC, Achten J, Jeukendrup AE: Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. J Appl Physiol 2005, 98(1):160-167. doi:10.1152/japplphysiol.00662.2003
- 20. Phinney SD, Bistrian BR, Evans WJ, Gervino E, Blackburn GL: The human metabolic response to chronic ketosis without caloric restriction: preservation of submaximal exercise capability with reduced carbohydrate oxidation. Metabolism 1983, 32(8):769-776.
- 21. Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, Kraemer WJ, Feinman RD, Volek JS: Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008, 43(1):65-77. doi:10.1016/0026-0495(83)90106-3
- 22.Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and metaanalysis. Diabetes Res Clin Pract 2018;139:239– 252. doi:10.1016/j.diabres.2018.02.026
- 23. Ebbeling CB, Swain JF, Feldman HA, Wong WW, Hachey DL, Garcia-Lago E, Ludwig DS: Effects of dietary composition on energy expenditure during weight-loss maintenance. JAMA 2012, 307(24):2627-2634. doi: 10.1001/jama.2012.6607
- 24. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, Kraemer WJ, Bibus DM, Fernandez ML, Feinman RD: Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009, 44(4):297-309. doi:10.1007/s11745-008-3274-2

