Let's Be Clear about Expected Cardiovascular Risk: A Commentary on the Massive Rise in LDL Cholesterol Induced by Carbohydrate Restriction in the Proposed "Lean Mass Hyper-Responder" Phenotype

Published online May 27, 2022.

Dear Editor:

I have read the accepted manuscript "Elevated LDL cholesterol with a carbohydrate-restricted diet: evidence for a 'lean mass hyper-responder phenotype'," which reports the results of a web-based survey looking at the interaction of carbohydrate restriction, BMI, baseline lipid markers, and changes in LDL cholesterol (1). The purported objective of the paper was to "elucidate possible sources of heterogeneity in LDL cholesterol response to a carbohydrate restricted diet and thereby identify individuals who may be at risk of LDL cholesterol elevation."

The paper describes an interesting observation that the lean mass hyper-responder phenotype (LMHR) had a lower BMI and a lower baseline triglyceride (TG) to HDL cholesterol ratio, and that this was associated with an extreme rise in LDL cholesterol (mean of 143 mg/dL, or 3.7 mmol/L) after exposure to a carbohydrate-restricted diet (CRD). I commend the authors for defining this phenotype because it could help patients and clinicians predict when a marked rise in LDL cholesterol might occur in the context of a CRD. The small case series also reveals preliminary evidence that reintroducing a modest amount of carbohydrate could mitigate this concerning LDL cholesterol response.

The phenotype of the LMHR is an interesting scientific observation. I hope the authors will consider doing a prospective study using a validated dietary survey in a broader population with secure methods of data collection to increase confidence in the prevalence of this phenotype. I also hope they might collaborate with lipid scientists to understand the underlying genetic, environmental, and physiological mechanism of the LMHR phenotype, which could potentially contribute to our understanding of cardiovascular disease.

A concern of mine is that clinicians and patients reading this article are left with an impression of the safety of elevated LDL cholesterol as well as the LMHR phenotype. Rather than focusing on the objective, a significant portion of the paper's discussion is on the notion of atherogenic dyslipidemia (a known cardiovascular risk factor) without making it clear to the reader that there is broad consensus that LDL cholesterol (and more specifically apoB-containing lipoproteins) is in and of itself a firmly established cause of atherosclerotic cardiovascular disease (2). It thus follows that with all other cardiovascular risks being equal, the null hypothesis is that the higher the apoB, the higher the cardiovascular risk.

Authors build upon their case questioning the role of LDL cholesterol in cardiac disease by referencing the sodium-glucose cotransporter-2 (SGLT2) inhibitors, the cardioprotective class of diabetes medication, which increase LDL cholesterol. They unfortunately do not clarify that the LDL cholesterol rise with SGLT2 inhibitors is minimal. For instance, in the landmark EMPA-REG trial, which evaluated the cardiovascular safety of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes, there was an increase of LDL cholesterol of 1 to 5 mg/dL depending on the time point and dose of the medication (3), which is clearly quite different compared with the dramatic increase in LDL cholesterol seen in the LMHR phenotype. The authors also do not include randomized controlled trial data revealing that in young, lean women, a CRD led to a deleterious lipid profile with a marked increase in apoB including small dense LDL particles, which is contrary to the thrust of evidence provided by the authors in their discussion (4).

It needs to be highlighted that the LMHR phenotype described in this paper has extremely high levels of LDL cholesterol (mean of 316 mg/dL, or 8.17 mmol/L) similar to LDL cholesterol levels found in familial hypercholesterolemia, which is a population known for their marked increased risk of vascular events (5). The American Heart Association/American College of Cardiology guidelines state that an LDL cholesterol concentration >4.9 mmol/L (>190 mg/dL) broadly captures a high-risk population for cardiac events and offers the highest recommendation (Class 1) for initiation of cholesterol-lowering therapy (6). In the setting of heterozygous familial hypercholesterolemia there is heterogeneous risk (7) and thus we could find the LMHR phenotype, based on yet to be determined mechanisms, has higher or lower risk than expected; however, to make confident claims on the cardiovascular safety of a ketogenic diet that markedly raises LDL cholesterol, one would need to perform a randomized control trial, which based on the strength of available evidence would have difficulty getting approved by an ethics board.

The authors concerningly conclude: "These data suggest that, in contrast to the typical pattern of dyslipidemia, greater LDL cholesterol elevation on a CRD tends to occur in the context of otherwise low cardiometabolic risk." The perhaps unintended message of this paper, based on the logic of the discussion and the ensuing conclusion, could be that astronomical changes of LDL cholesterol can be safe in the context of low TG and high HDL. This message could lead to

harm by negatively affecting a patient's perception of risk or a clinician's judgment.

Michael R Mindrum

From the Department of Internal Medicine, Dalhousie University, Halifax, Nova Scotia, Canada (e-mail: michaelmindrum@gmail.com).

Author disclosures: The author receives consulting fees from Diet Doctor, a website that provides educational material to support people eating a low-carbohydrate diet. He also receives consulting and speaker fees from Novo Nordisk, a pharmaceutical company. He is an expert advisor for the charity, Institute for Personalized Therapeutic Nutrition, which is involved in research as well as education around the use of nutrition for chronic disease.

References

1. Norwitz NG, Feldman D, Soto-Mota A, Kalayjian T, Ludwig DS. Elevated LDL cholesterol with a carbohydrate-restricted diet: evidence for a "lean mass hyper-responder" phenotype. Curr Dev Nutr 2022;6(1):nzab144.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38(32):2459–72.
3. Zinman B, Christoph W, John ML, David F, Erich B, Stefan H, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117–28.
4. Burén J, Ericsson M, Damasceno N, Sjödin A. A ketogenic low-carbohydrate high-fat diet increases LDL cholesterol in healthy, young, normal-weight women: a randomized controlled feeding trial. Nutrients 2021;13(3):814.
5. McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc 2019;8:e013225.
6. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. J Am Coll Cardiol 2019;74(10):e177–232.
7. Sandesara PB, Mehta A, O'Neal WT, Kelli HM, Sathiyakumar V, Martin SS, et al. Clinical significance of zero coronary artery calcium in individuals with LDL cholesterol ≥190 mg/dl: the multi-ethnic study of atherosclerosis. Atherosclerosis 2020;292:224–9.

doi: https://doi.org/10.1093/cdn/nzac042