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Editorial

Elevated LDL-cholesterol levels among lean mass hyper-responders on low-carbohydrate ketogenic diets deserve urgent clinical attention and further research

Background: social media, science, and lean mass hyper-responders

It has been observed that lean individuals with low triglycerides (TG) and high HDL-cholesterol (HDL-c) may develop a marked elevation of plasma LDL-cholesterol (LDL-c) when consuming a very low-carbohydrate ketogenic diet[1]. This phenomenon, which has been termed the lean mass hyper-responder (LMHR) phenotype,[1,2] has been widely discussed on social media networks over the past 6 years. One Facebook page devoted to the LMHR trait now has ~9,000 members and continues to grow. Over the past several months, several publications[1,3,4] have amplified discussion of the phenotype and its relevance to traditional cardiovascular risk profiles. There is a paucity of direct clinical data with regard to the predictive value of elevated LDL-c for risk of atherosclerotic cardiovascular disease (ASCVD) in the context of a very low-carbohydrate ketogenic diet - especially in the LMHR phenotype.

The social media dissemination of the concept of the LMHR has important implications for the dynamic relationship between the public and the biomedical research community. Social networks have played a prominent role for individuals and clinicians who have supported each other in following low-carbohydrate diets during a protracted period when guidelines have largely ignored or dissuaded their use.

This alternative space for information has also been fertile ground for questioning conventional dietary and pharmacological practices aimed at reducing risk of ASCVD. In fact, some clinicians, researchers, and social media influencers who support low-carbohydrate diets have questioned the evidence that LDL is causal for ASCVD[5], and sought to discourage those with elevated LDL-c on a low-carbohydrate diet from seeking treatment.[6] This has understandably drawn ire from the medical and research community who are concerned that individuals may be persuaded to forego lifestyle change or guideline-based medical therapy aimed at reducing LDL-c. The impact of these narratives on the values, preferences, and health outcomes of the broader population, and the LMHR community specifically, has not been well researched.

There is thus a significant need to tamp down hyperbole and encourage studies of the LMHR phenomenon that could provide important guidance for specific patient populations and advance our understanding of its impact on cardiometabolic health. Hence, the objectives of the present letter are to suggest a pragmatic approach for dealing with elevated LDL-c levels in the context of ketogenic diets, to highlight the importance of researching the LMHR phenotype, and to disentangle the science from the broader narratives discussed above.

Calling for a prudent patient-centered clinical approach

The LMHR phenotype, while it may be renamed or redefined with emerging research, was originally defined as LDL-c $\geq$200 mg/dl, HDL-c $\geq$80 mg/dl, and TG $\leq$70 mg/dl.[2] To understand why LMHRs have prompted such attention, we need to recognize the magnitude of the change in LDL-c in this phenotype upon adopting a low-carbohydrate diet. In a recent cohort study, the mean lipid levels in LMHRs were LDL-c 320 mg/dl, HDL-c 99 mg/dl and TG 47 mg/dl, with a marked difference of LDL-c compared to non-LMHRs only appearing after adopting a carbohydrate restricted diet.[1] There are even individuals who, after adopting ketogenic diets, have had increases in LDL-c from normal levels (~100 mg/dl) to as high as 500-800 mg/dl, which is on par with LDL-c concentrations in homozygous familial hypercholesterolemia, a one-in-one-million genetic condition with devastating consequences for ASCVD[7].

Extreme hypercholesterolemia requires a prudent clinical approach. Given evidence that elevated levels of LDL-c

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and other apoB-containing particles play a causal role in cardiovascular disease,[8,9] there does not, at present, appear to be any sound argument for withholding consideration of LDL-c lowering strategies in this situation. However, there are also clinical circumstances in which this principle may not be pragmatic or patient-centered.

There are some individuals who have adopted a ketogenic diet for treatment of epilepsy[10] or who have discovered that a ketogenic diet, after trial and error, was the only effective treatment for a chronic condition such as inflammatory bowel disease.[3] These individuals may have already attempted to lower LDL-c via reduction in saturated fat and/or have been intolerant of LDL-c lowering therapies. Others, based on their values, preferences, or other personal reasons may have decided to not change their nutrition pattern or start LDL-c lowering pharmacologic therapy. In cases where there are competing medical conditions, patient-physician teams may consider additional investigations such as hsCRP, lipoprotein subfractions, and functional testing, including a coronary artery calcium (CAC) scan, coronary computed tomography angiography (CCTA), and/or carotid intima media thickness (CIMT) to help determine the relative urgency of lipid lowering treatment.

Thus, we advocate that individuals with elevated levels of LDL-c and/or apoB (both LMHRs and otherwise) work closely with their doctor to implement lifestyle changes and/or medical therapy directed toward lipid lowering with the aim of reducing cardiovascular risk. We warn individuals to be cautious of the risk of accepting information regarding LDL-c and ASCVD risk based on shared beliefs and opinions offered on social media. Finally, we advise that in circumstances where there are competing medical conditions, weighing of treatment options should be an individual matter determined by patient-physician collaboration.

A call for research and support

Recognition of the LMHR phenotype creates an opportunity to provide important information to LHMR patients and to identify environmental and/or metabolic influences that could add to the understanding of factors affecting lipoprotein metabolism and related ASCVD risk. As the magnitude of diet-induced change in LDL-c seen in LMHRs is so marked, this group provides a unique opportunity to understand LDL-c dynamics beyond what has previously been possible.

The prevalence and cause of the proposed LMHR phenotype are unknown. Modifying factors may include conventional contributors to elevated LDL-c such as saturated fat consumption, but the magnitude of the increase in LDL-c, together with the fact that not all LMHRs consume diets rich in saturated fat, suggest that other factors are likely involved. The LMHR phenotype tends to occur in individuals with otherwise low cardiometabolic risk factors such as low TG/HDL-c ratio (by definition) and small waist circumference, low blood pressure, low levels of inflammatory markers, and high insulin sensitivity.[1,3] As such, elevated LDL-c is, by and large, an isolated ASCVD risk factor in the LMHR phenotype.

A caveat is that in large-scale epidemiological studies HDL-c has a U-shaped relationship to ASCVD risk,[11,12] and most LMHR individuals exhibit HDL-c levels higher than what may be considered optimal. However, it would be premature to draw conclusions about either a protective or pathological role of high HDL-c in a population unlike any that has previously been characterized in large scale epidemiological studies. A more an in-depth discussion of the possible role of HDL in LMHR is discussed more extensively elsewhere.[4]

While most may infer that the likelihood of ASCVD risk in LMHR is high, this has not been confirmed. It is noted that individuals with heterozygous familial hypercholesterolemia have substantial variation in ASCVD incidence,[13] and this suggests that there may be aspects of the LMHR phenotype that confer some degree of protection, resulting in an overall lower ASCVD risk than expected. Even if this probability is low, it remains an unanswered inquiry worthy of investigation.

Four unique features of the LMHR phenotype, as it has been defined, are worth highlighting. First, preliminary data supports that in LMHRs baseline LDL-c prior to carbohydrate restriction is typically normal, and the phenotype can largely be reversed with a reintroduction of carbohydrates to the diet.[1] Second, the degree of LDL-c elevation is inversely related to BMI (possibly related to lower than average adiposity) across a population of persons with a low TG/HDL-c ratio[1]. This raises a question about the role of adaptive lipid energy trafficking in the genesis of this phenotype.[4] Third, among LMHRs who have been tested, there are no shared genetics with familial hypercholesterolemia[1,3]; so, if there is a genetic interaction with a low-carbohydrate diet, any LMHR genotype has yet to be elucidated. Fourth, the LMHR phenotype usually presents in context of otherwise low cardiometabolic risk factors, such as low TG/HDL-c, low blood pressure, low waist-to-hip ratio, and high insulin sensitivity.

While the data on LMHR are as yet preliminary, and all of these findings will require validation in larger studies, the phenomenon is of clear and pressing scientific interest and deserves further research. The assembly of an LHMR registry and biobank could provide a valuable resource to support future clinical, genetic, and laboratory research aimed at identifying determinants and optimal management of the LHMR phenotype. While long-term studies aimed at assessing risk of clinical events would be prohibitive due to ethical concerns, conceivably it would be acceptable to assess plaque development in shorter trials using surrogate endpoints (CAC, CCTA, CIMT) in LHMR versus non-LMHR. Acquisition of funding for such research will likely present challenges, but data from pilot studies could provide the basis for a more substantial proposal to NIH or other funding agencies The results would not only advance

scientific understanding of LHMR, but also assist clinical and public health professionals in providing appropriate guidance for individuals with this trait.

Conclusion

The authors of the present letter advocate that all individuals whose LDL-c levels substantially increase on ketogenic diets should consider implementing lifestyle change and/or pharmacologic therapy for lowering LDL-c and ApoB. In those circumstances where there are competing medical conditions, weighing of factors should be an individual matter determined by patient-physician collaboration. Future research is warranted to understand ASCVD risk in this population as well as to understand the mechanistic determinants of this phenotype. In particular, there is an urgent need to develop an internationally recognized definition and diagnostic criterion of LMHR. This should facilitate the conduct of studies for determining the origins and consequences of this novel phenomenon.

Author contributions

NGN conceptualized the editorial and served as the project coordinator. NGN and MM jointly drafted the initial manuscript. All other authors provided significant editorial input and contributed meaningfully to the final draft. MB and RMK served equally as senior authors.

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Declaration of Competing Interest

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