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High LDL Cholesterol, Low Risk? Lean Mass Hyper-responder phenotype – A literature review

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Abstract

Introduction:

The Lean Mass Hyper-Responder (LMHR) phenotype is a distinct lipid profile observed in individuals following carbohydrate-restrictive diets (CRDs), such as ketogenic or carnivore diets. This phenotype is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C), high high-density lipoprotein cholesterol (HDL-C), and low triglycerides (TG). Understanding the mechanisms and clinical implications of LMHR is crucial given its potential impact on cardiovascular risk assessment.

Materials and methods:

We reviewed recent studies investigating the epidemiology, metabolic mechanisms, and clinical outcomes of the LMHR phenotype. Particular focus was given to the Lipid Energy Model hypothesis and coronary computed tomography angiography findings.

Results:

The LMHR phenotype presents with LDL-C >200 mg/dL, HDL-C >80 mg/dL, and TG <70 mg/dL, differing from classical atherogenic dyslipidemia. The Lipid Energy Model suggests that increased reliance on triglyceride-rich lipoproteins as an energy source underlies these lipid alterations. Observational data show no significant difference in plaque burden or progression between LMHR individuals and matched controls, despite elevated LDL-C levels. Results from large dietary studies present no significant correlation between CVD and following carbohydrate restriction, which further supports the hypothesis and points out the necessity of the intensive research in this field.

Conclusions:

While elevated LDL-C traditionally indicates increased cardiovascular risk, current evidence suggests heterogeneity within the LMHR population, with no clear correlation between high LDL-C and atherosclerotic progression. Long-term prospective studies are needed to clarify the clinical significance of this phenotype and guide risk assessment in individuals on CRD.

Keywords:

Lean Mass Hyper-Responder; carbohydrate-restrictive diets; lipid profile; LDL cholesterol; cardiovascular risk; Lipid Energy Model.

Background

According to WHO data, ischemic heart disease is the leading cause of death, responsible for 13% of mortality worldwide. LDL-c is considered to be strongly associated with arteriosclerosis, ischemic heart disease, and other diseases related to the buildup of flow-restricting plaque in the arteries since the Framingham Heart Study—which established such a correlation—was published [1]. LDL plays a critical role in the pathogenesis of arteriosclerosis. LDL particles penetrate the damaged endothelium of large and medium-sized arteries and gather in the intima layer, where they are oxidized [2,3]. Oxidized LDL exhibits pro-inflammatory and chemotactic properties, leading to the expression of VCAM-1 and ICAM-1 molecules that enable adhesion of monocytes to the artery endothelial cells. After migrating to the inflamed intima, stimulated monocytes start internalizing ox-LDL particles with the use of scavenger receptors, becoming lipid-laden macrophages called foam cells [2]. Further chronic inflammation in the site of arteriosclerotic plaque initiates its remodeling—migration and proliferation of vascular smooth muscle cells (VSMCs), creation of a fibrous cap, and calcification [3]. Because of the rather irreversible nature of arteriosclerotic plaque that underwent remodeling [2], prevention remains a crucial aspect of cardiovascular health and longevity [4]. As ketogenic diets become more and more popular, new opportunities and challenges for physicians and researchers arise. Evidence shows that some of those individuals consuming carbohydrate-restrictive diets experience a rise in LDL-c [5, 6, 7, 8, 9]. In 2022, a new and unique phenotype among these individuals with significantly elevated LDL-c and HDL-c was described, creating a challenge for cardiovascular disease prediction in this population.

Definition and Criteria of the LMHR Phenotype

Among people on a low-carbohydrate diet (defined as consumption of less than 130 g of carbohydrates per day, with a mean consumption of 27 g per day), some experience a dramatic rise in total cholesterol and LDL-c [5, 6, 7, 8, 9]. This group was assigned as hyper-responders. Further, a subgroup of these individuals can be characterized as lean mass hyper-responders

presenting with a triad of LDL-c > 200 mg/dL, HDL-c > 80 mg/dL, and triglyceride concentration < 70 mg [9, 11]. These individuals usually exhibit low body fat (<20% men, <23% women) and moderate to high levels of athleticism [9]. The difference between this unique phenotype is strikingly different from obese patients with atherogenic dyslipidemia presenting with triglyceride concentrations > 150 mg/dL, HDL-c < 40 mg/dL (men) or < 50 mg/dL (women), and the presence of small dense LDL (sdLDL). The LMHR phenotype is also different from patients with familial dyslipidemia, which usually presents with elevated LDL-c, normal or low HDL-c, and normal or elevated TG [12].

Mechanisms Behind the Phenotype

A mechanistic explanation of this phenomenon was proposed and called the Lipid Energy Model (LEM). It states that in people on carbohydrate-restrictive diets or ketogenic diets, skeletal muscle and liver glycogen reserves are depleted, so the body depends on non-esterified fatty acids (NEFAs) released from the fat tissue and triglyceride-rich lipoproteins (TGRLs) made by the liver as the main sources of energy released in mitochondria during beta–oxidation [21]. People with a high BMI (>35) and vast fat tissue reserves on a carbohydrate-restrictive diet are able to supply their energy demand in this mechanism sufficiently [5, 13]. Among individuals without such fat reserves [BMI 25-30] on CRD, non-esterified fatty acid release from fat tissue is insufficient, and not enough carbohydrates are supplied with diet to release energy from them and to restore the glycogen reserves in liver and muscle cells [13]. In this metabolic state, fat is transported through the body in the form of triglyceride-rich lipoproteins (TGRL), such as very low-density lipoproteins (VLDL) [5]. TG can then be extracted from VLDL by the capillary endothelial cells with the use of the enzyme lipoprotein lipase (LPL) [5, 14]. After triglycerides are progressively extracted from VLDL by LPL, they are converted into LDL, raising LDL-c [5]. It was observed that there is an inverse correlation between BMI and LDL-c among people with an LMHR phenotype [5], which supports the explanation of markedly elevated LDL-c observed in lean, metabolically healthy people who start restricting their carbohydrate intake and not among those with higher BMI. In a study with a sample size of 1—the author of the study following strict monitored CRD, presenting LMHR phenotype—an LDL-c drop was observed when daily carbohydrate consumption was increased, further supporting the thesis on LDL-c being a consequence of metabolic adaptation rather than a pathological mechanism known from previously studied types of dyslipidemia [15].

Discussion

The association between elevated low-density lipoprotein cholesterol (LDL-C) and the risk of atherosclerotic cardiovascular disease (ASCVD) has been studied and researched extensively for decades. Numerous large and randomized controlled studies showed that elevated LDL-c is associated with an increased risk of atherosclerotic vascular disease, including myocardial infarction and stroke. It is why LDL-c reduction remains a primary goal of cardiovascular disease prevention and pharmacological therapies [4]. It was established that cardiovascular risk reduction is proportional to the LDL-c reduction [16]. Statins, fibrates, and PCSK9 inhibitors have proven to be effective in reducing cardiovascular events and increasing the length of survival among patients with ischemic heart disease [16]. In 2024, a meta-analysis of 60 randomized controlled studies covering 408,959 participants showed that decreasing LDL-C by 38.7 mg/dL was associated with a 22% reduction of cardiovascular event risk (HR 0.78; 95% CI 0.75–0.81) both in primary and secondary prevention [10]. This effect was more pronounced in primary prevention (HR 0.74) in comparison to secondary prevention (HR 0.80) [17]. As alternative diets such as the ketogenic and carnivore diets, which are both carbohydrate restrictive, gain popularity on social media, it is possible that young adults are more likely to implement them into their lives because of curiosity or out of hope to preserve their health for longer. Because of a better preventive effect of lower LDL-C in primary prevention and potentially longer time of exposure in those young people with elevated LDL, explaining if LMHR differs in CVD from the general population should be a top priority, as according to current knowledge of LDL-C and atherosclerosis risk, it presents danger. A prospective, observational cohort study [18] designed to evaluate the progression of coronary atherosclerosis showed fascinating results analyzed 100 individuals meeting the criteria of lean mass hyperresponder phenotype (LDL-C >190 mg/dL, HDL-C ≥60 mg/dL, TG ≤80 mg/dL) during a 1-year follow-up. Coronary computed tomography angiography (CCTA) was used to measure atherosclerotic plaque progression as it shows both calcified and non-calcified plaque and therefore enables more precise evaluation of the progression of the disease. Results showed that LDL-c and Apo-B did not correlate with the progression of atherosclerosis. It was determined that the presence of the plaque is strongly correlated with worsening the disease on the CCTA scale during the 1 year of observation [18]. It is worth mentioning that this study is being critiqued for the lack of the comparative group, self-selection of participants, small sample size, lack of total calorie intake monitoring, and switching of the pre-registered primary outcome

from the percentage change in non-calcified plaque volume (NCPV) to the absolute plaque volume change. The KETO-CTA study noted a mean increase of PAV of 0.8% among 100 participants, which is a similar rate of progression in comparison to other cohorts from similar studies [7, 19, 20], which include participants with a high risk of cardiovascular disease. A very similar rate of progression of plaque as in cohorts with a high risk of CVD, diabetes, or non-response to statin therapy is very concerning. Another study published in 2025 [11] compared 80 individuals from the KETO-CTA study (keto group) to 80 patients from the MiHeart study (Miami Heart group). Participants were matched by sex, age, race, hypertension, body mass index (BMI), hyperlipidemia, and smoking status to better establish atherosclerosis progression [11]. All participants underwent CCTA scans to determine the presence and severity of atherosclerotic plaque. The median CAC (coronary calcium) score in the keto group was 0 (IQR: 0-56) [11]. The median CAC score in the Miami Heart group was 1 (IQR: 0-49). Authors report no statistical significance between the two groups ($p > 0.52$) [11]. Results showed the same score in median scores measured with the CCTA scale in TSS (Total Stenosis Score), TPS (Total Plaque Score), and SIS (Segment Involvement Score) without statistical significance between the groups ($p > 0.20$). It is also worth mentioning that the CCTA is more accurate as it measures total plaque burden (calcified and non-calcified plaque) and allows better assessment of cardiovascular risk even in patients without visible coronary calcium [19]. Although performed on a relatively small group, this study presented that the Keto group did not statistically differ from individuals from the Miami Heart group [11], which may indicate that CRD in LMHR is not a risk factor for CVD. Further research on larger cohorts is needed to better understand and objectify what has been observed. In addition to studies already presented, data from large prospective dietary studies also should be taken into consideration. Several epidemiological studies and meta-analysis meeting these criteria showed increased all-cause mortality risk in populations on diets low in carbohydrates (<130 g/day) [x, y, z]. However, no significant correlation between CVD and following carbohydrate restriction was reported [22, 23]. Available meta-analyses present conflicting data about fat intake and mortality from cardiovascular disease [21, 22, 23]. The studies cited are based on data collected in questionnaires which do not provide any objective measure to verify the declared intake of proteins, fats, and carbohydrates. Despite the imperfect character of said studies, no correlation between the CVD and carbohydrate restriction seems to fit into the assumptions of the Lipid

Energy Model and further support the importance of fully exploring clinical implications of CRD, especially in context of lean mass hyper-responders.

Conclusions

The Lean Mass Hyper-Responder (LMHR) phenotype presents a particular challenge to conventional models of cardiovascular risk estimation. This group demonstrates a markedly elevated LDL-C, alongside high HDL-C and low triglycerides, while following a carbohydrate-restricted diet. The presence of elevated LDL-C is regarded as an important determinant in atherosclerosis and cardiovascular disease (CVD) risk. Some recent findings from studies exploring the progression of plaque in LMHR individuals raise concerns about whether this is the case in these otherwise healthy, lean individuals on ketogenic diets. Progression of coronary plaque shown by the KETO-CTA study over a 12-month period presents big heterogeneity among the LMHR phenotype and overall seems to not be correlated to LDL-C and ApoB but rather with the presence of plaque itself. The general progression observed in this study matches the rate among both generally healthy adults and high-risk populations in other studies. On the other hand, the follow-up comparative study with the Miami Heart cohort reported no significant differences in the burden of coronary plaque and its calcification in LMHR and controls, suggesting that it is in fact possible that diet-induced hypercholesterolemia among LMHR individuals on CRD does not pose increased risk of CVD. If proven true, this could be a breakthrough in cardiovascular disease prevention. As several studies have documented, elevated LDL-C remains a well-established risk factor of arteriosclerosis with a linear correlation between LDL concentration and the incidence of cardiovascular events. However, its interpretation among LMHR on carbohydrate-restrictive diets may call for reassessment. Until long-term, adequately powered, and meticulously controlled studies become available, clinical caution is indicated. Physicians making clinical decisions should look at the broader context of the patient's health and take into account the complete lipid profile, inflammatory indices, and plaque imaging instead of using LDL-C values only. Until more robust data become available, it remains unanswered with certainty whether LMHR is a benign metabolic adaptation or a cardiovascular pathological state.

Disclosure

Author's contribution

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References:

1. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. JAMA. 1986 Nov

28;256(20):2835–2838. https://pubmed.ncbi.nlm.nih.gov/3773200/

2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002 Mar 5;105(9):1135–1143. https://doi.org/10.1161/hc0902.104353

3. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999 Jan 14;340(2):115–126. https://doi.org/10.1056/NEJM199901143400207

4. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Aug 30;42(34):3227–337. https://doi.org/10.1093/eurheartj/ehab484

5. Norwitz NG, Soto-Mota A, Kaplan B, Ludwig DS, Budoff M, Kontush A, et al. The Lipid Energy Model: reimagining lipoprotein function in the context of carbohydrate-restricted diets. Metabolites. 2022 May 20;12(5):460. https://doi.org/10.3390/metabo12050460

6. 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 Mar 2;13(3):814. https://doi.org/10.3390/nu13030814

7. Nakanishi R, Ceponiene I, Osawa K, Luo Y, Kanisawa M, Megowan N, et al. Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: a propensity-score matching study. Atherosclerosis. 2016 Dec;255:73–79. https://doi.org/10.1016/j.atherosclerosis.2016.11.004

8. Retterstøl K, Svendsen M, Narverud I, Holven KB. Effect of low carbohydrate high fat diet on LDL cholesterol and gene expression in normal-weight, young adults: a randomized controlled study. Atherosclerosis. 2018 Dec;279:52–61. https://doi.org/10.1016/j.atherosclerosis.2018.10.013

9. 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 Jan;6(1):nzab144. https://doi.org/10.1093/cdn/nzab144

10. Budoff M, Manubolu VS, Kinninger A, Norwitz NG, Feldman D, Wood TR, et al. Carbohydrate restriction-induced elevations in LDL-cholesterol and atherosclerosis. JACC Adv. 2024 Aug;3(8):101109. https://doi.org/10.1016/j.jacadv.2024.101109

11. Javier DAR, Manubolu VS, Norwitz NG, Kinninger A, Aldana-Bitar J, Ghanem A, et al. The impact of carbohydrate restriction-induced elevations in low-density lipoprotein cholesterol on progression of coronary atherosclerosis: the ketogenic diet trial study design. Coron

Artery Dis. 2024 Jun 13;35(7):577–583. https://doi.org/10.1097/mca.0000000000001395

12. Vaezi Z, Amini A. Familial hypercholesterolemia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://pubmed.ncbi.nlm.nih.gov/32310469/

13. Soto-Mota A, Flores-Jurado Y, Norwitz NG, Feldman D, Pereira MA, Danaei G, et al. Increased low-density lipoprotein cholesterol on a low-carbohydrate diet in adults with normal but not high body weight: a meta-analysis. Am J Clin Nutr. 2024 Mar;119(3):740–747. https://doi.org/10.1016/j.ajcnut.2024.01.009

14. Pirahanchi Y, Anoruo M, Sharma S. Biochemistry, lipoprotein lipase. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://pubmed.ncbi.nlm.nih.gov/30725725/

15. Norwitz NG, Cromwell WC. Oreo Cookie Treatment lowers LDL cholesterol more than high-intensity statin therapy in a lean mass hyper-responder on a ketogenic diet: a curious crossover experiment. Metabolites. 2024 Jan 22;14(1):73. https://doi.org/10.3390/metabo14010073

16. 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 Apr 24;38(32):2459–2472. https://doi.org/10.1093/eurheartj/ehx144

17. Burger PM, Dorresteijn JAN, Koudstaal S, Holtrop J, Kastelein JJP, Jukema JW, et al. Course of the effects of LDL-cholesterol reduction on cardiovascular risk over time: a meta-analysis of 60 randomized controlled trials. Atherosclerosis. 2024 Sep;396:118540. https://doi.org/10.1016/j.atherosclerosis.2024.118540

18. Soto-Mota A, Norwitz NG, Manubolu VS, Kinninger A, Wood TR, Earls J, et al. Plaque begets plaque, ApoB does not. JACC Adv. 2025 Apr;101686. https://doi.org/10.1016/j.jacadv.2025.101686

19. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F, et al. Association of cardiovascular disease risk factor burden with progression of coronary atherosclerosis assessed by serial coronary computed tomographic angiography. JAMA Netw Open. 2020 Jul 24;3(7):e2011444. https://doi.org/10.1001/jamanetworkopen.2020.11444

20. van Rosendael SE, van den Hoogen IJ, Lin FY, Andreini D, Al-Mallah MH, Budoff MJ, et al. Clinical and coronary plaque predictors of atherosclerotic nonresponse to statin therapy. JACC Cardiovasc Imaging. 2023 Apr;16(4):495–504.

https://doi.org/10.1016/j.jcmg.2022.10.017

21. Talley JT, Mohiuddin SS. Biochemistry, fatty acid oxidation. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK556002/

22. Noto H, Goto A, Tsujimoto T, Noda M. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. PLoS ONE. 2013 Jan 25;8(1):e55030. https://doi.org/10.1371/journal.pone.0055030

23. Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. Lancet Public Health. 2018 Sep;3(9):e419–e428. https://doi.org/10.1016/S2468-2667(18)30135-X