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CASE REPORT

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The impact of dietary fat type on lipid profiles in lean mass hyper-responder phenotype

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Key Clinical Message

Although the lean mass hyper-responder (LMHR) phenotype is well known, its diagnosis is impeded by the influence of fat type and intake on the lipid profile. Accordingly, a detailed assessment is warranted if LMHR is suspected.

Abstract

A 47-year-old man with suspected familial hypercholesterolemia presented with elevated triglyceride and low-density lipoprotein cholesterol levels. He had adhered to a ketogenic diet and was suspected of a lean mass hyper-responder phenotype; however, his lipid profile did not meet the definition. His lipid profile improved through dietary management without medication.

KEYWORDS

carbohydrate-restricted diet, ketogenic diet, lean mass hyper-responder, low-density lipoprotein cholesterol, triglyceride

1 | INTRODUCTION

The lean mass hyper responder (LMHR) phenotype is characterized by a pronounced increase in low-density lipoprotein cholesterol (LDL-C) levels upon reduction in dietary carbohydrate intake and substitution with fats and proteins for caloric compensation.[1–3] Patients with the LMHR phenotype typically have a lean physique, decreased triglyceride (TG) levels, and increased high-density lipoprotein cholesterol (HDL-C) levels.[1–3] In other words, under the current definition, there are no cases of LMHR with elevated TG levels.

2 | CASE HISTORY/EXAMINATION

A 47-year-old man presented to our outpatient clinic with increased LDL-C levels (274 mg/dL). He was a heavy smoker with a normal body mass index of 23 kg/m^2. His pre-intervention lipid profile showed total cholesterol (TC), LDL-C, HDL-C, and TG levels of 237, 155, 30, and 263 mg/dL, respectively. He reported having adhered to a ketogenic diet (KD) for ≈2 months prior to the medical checkup; accordingly, saturated fatty acids served as his alternative calorie source. He used an application to manage his daily caloric intake, vitamins, and nutrients. He managed his diet as follows: intake 30 g/day carbohydrates (5% of total calories), 230 g/day proteins (42% of total calories), and 130 g/day fats (53% of total calories). An example diet for 1 day included chicken thighs containing skin, minced beef and pork, one egg, and five egg whites. For KD management, the patient independently purchased urine test strips and confirmed the presence of urinary ketone bodies. Upon medical checkup, his lipid profile showed TC, LDL-C, HDL-C, and TG levels of 322, 274, 30, and 220 mg/dL, respectively.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Blood and urine tests showed no findings suggestive of secondary hypercholesterolemia, including hypothyroidism, diabetes mellitus, liver function abnormalities, or nephrotic syndrome. He lacked tendon xanthomas or a self/family history of cardiovascular disease. Upon providing consent, the patient underwent genetic testing related to familial hypercholesterolemia (FH). Genetic testing using next-generation sequencing (NGS) through exome analysis, targeted 21 dyslipidemia-related Mendelian genes, including three FH genes (*LDLR, PCSK9*, and *APOB*) and four LDL-altering accessory genes (*ABCG5*, *ABCG8*, *APOE*, and *LDLRAP1*).[4] However, no pathogenic variants were detected. Moreover, FH was ruled out given the absence of an Achilles tendon xanthoma, family history of FH, or premature cardiovascular disease. Genetic testing for lipid metabolism disorders did not reveal remarkable findings. Based on his diet, we suspected that he had the LMHR phenotype; however, his lipid profile did not meet the definition.

4 | OUTCOME AND FOLLOW-UP

Two months after the initial consultation, the patient maintained the nutrition ratios; however, he switched to unsaturated fatty acids, including fish, vegetable fats, and chicken breast fillets. His TG level decreased to 134 mg/dL, while his LDL-C level remained high at 259 mg/dL. Since the LDL-C levels remained high, the KD was discontinued and modified to allow derivation of 40% of the total calories from carbohydrates. Accordingly, the daily caloric intake comprised 230 g/day of carbohydrates (42% of total calories), 140 g/day of proteins (25% of total calories), and 80 g/day of fats (33% of total calories). This resulted in normalization of LDL-C levels to 111 mg/dL in 2 months without any drug therapy; further, the TG levels remained almost the same (Figure 1).

5 | DISCUSSION

This article describes the case of a patient with the LMHR phenotype who presented elevated TG levels. Although carbohydrate-restricted diet (CRD) or the KD are often emphasized for individuals with the LMHR phenotype, it is important to carefully consider the amount and type of fats, which assume the role of alternative calorie sources. Therefore, the LMHR phenotype cannot be simply diagnosed based on high TG levels (Figure 2). The present case has two notable points.

First, despite the patient showing elevated TG levels, he was clinically diagnosed with the LMHR phenotype. Although the LMHR phenotype is typically characterized by low TG levels, it is extremely important to recognize that the intake of large amounts of animal-derived protein and fat may increase TG levels. Several types of lipids are known to increase LDL-C or TG levels.[5,6] However, even the same proteins and fats can have significantly different amounts of saturated fatty acids and cholesterol per unit.[7–11] Moreover, the fat content in meats varies according to the anatomical part.[12] Ebbeling et al reported that the saturated fat content of the CRD/KD was 20%, which is significantly higher than that recommended by American and European guidelines.[13] Our patient showed high LDL-C levels; accordingly, the meat type was changed and the fat intake changed from animal to vegetable.

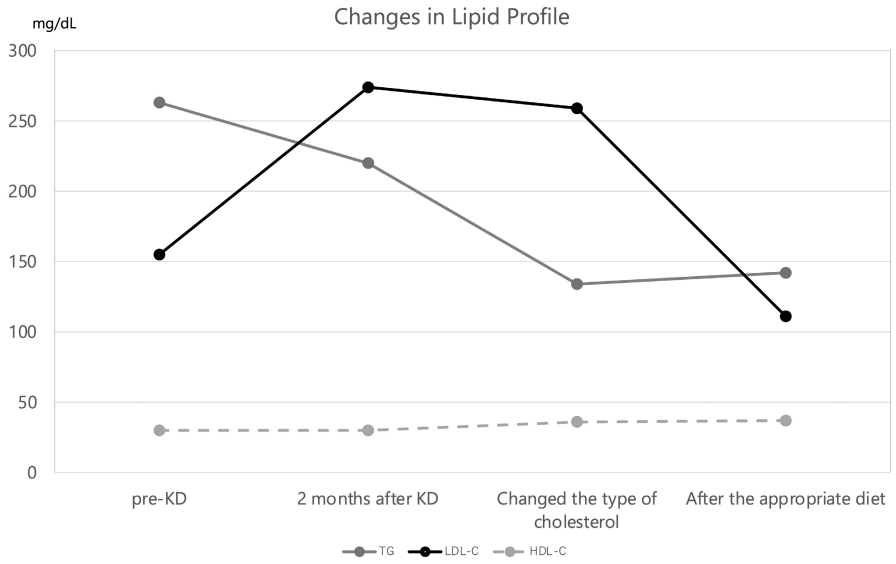

FIGURE 1 Changes in the lipid profiles before and after ketogenic diet.

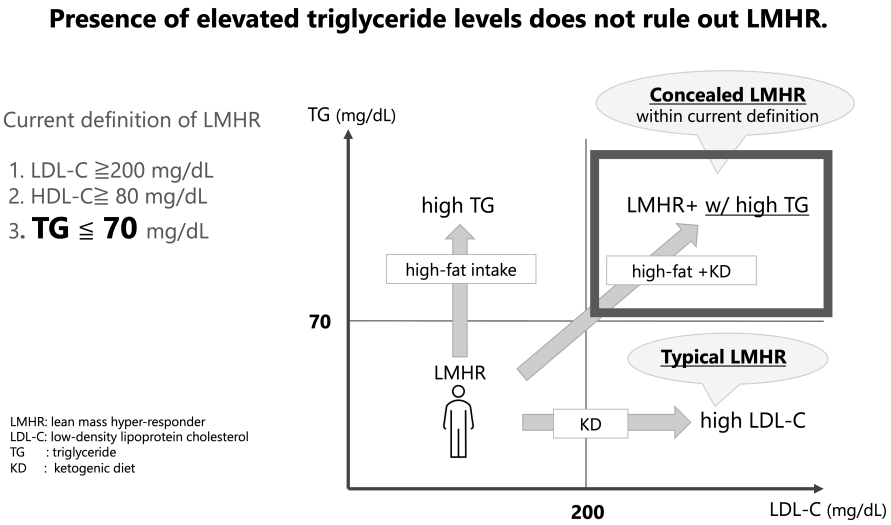

FIGURE 2 Triglyceride levels are not the basis for exclusion of lean mass hyper-responders.

Subsequently, the TG levels decreased by ≈50% relative to baseline levels; however, there was only a mild improvement in LDLC. This suggested that the fat type affected TG levels; further, excessive fat intake affected LDL-C levels. Our patient used a smartphone application for nutritional management and ensured strict control of calorie and nutrient intake. He also self-adjusted his fat and protein intake as well as carbohydrate restriction according to the presence of ketone bodies. Taken together, it is important to note that extremely reduced carbohydrate intake, with a concomitant increased intake of fats and proteins, may affect TG or LDL-C levels.

The second point relates to the definition of the LMHR and KD. Dave Feldman initially described LMHR phenotype as presentation of low TG and high HDL-C levels, with similar subsequent reports.[2,3] However, there are many ambiguities in this definition. Although LMHR phenotype was proposed, there are widely varying modern dietary habits including KD.[14] In addition, there are various types of ketogenic diets which may result in diverse lipid profiles, and some cases may not meet the criteria for "typical LMHR phenotype." LMHR phenotype is defined based on the consumption of the CRD or KD, and lipid profile.[3] Since there are various types of CRD or KD with varying amounts of proteins, carbohydrate, and fats, the definition of these diets is unclear.[15–17] Our patient restricted his carbohydrate intake to <10%; however, the ratio of fats to energy was not as high as in the classical KD. The proportion of carbohydrate-derived calories with respect to the total caloric intake varies; moreover, it remains to be established whether the alternative calories consumed should come from fats or proteins. In particular, extremely CRD, as in our case, compensate for reduced carbohydrate-derived calories by significantly increasing fat and protein consumption. However, our patient reported that the protein consumed were relatively high in fat, suggesting that the diet of this patient was probably similar to classical KD. Thus, we considered the possibility that the reason for the lack of "typical LMHR" was not the CRD itself, but rather the way in which the CRD compensated for the missing calories (i.e., the amount or percentage of fat and protein intake).

The cause of LMHR phenotype is unknown; however, genetic factors may be involved, including in this case. It is known that TG increases in leaner persons with less subcutaneous fat because of increased VLDL secretion from the liver.[2] The patient did not have any variants associated with lipid metabolism including FH; however, other lipid metabolism genes may be involved. The other potential genetic factors such as ATP-binding cassette transporter A7 (*ABCA7*), lysophosphatidic acid (*LPA*), myosin regulatory light chain interacting protein (*MYLIP*), signal transducing adaptor family member 1 (*STAP1*), peroxisome proliferator activated receptor alpha (*PPARA*), low platelet activating factor acetyl hydrolase (*PLA2G7*), ZPR1 zinc finger gene (*ZPR1*), angiopoietin-like protein 4 (ANGPTL4), angiopoietin-like protein 8 (ANGPTL8), and fibroblast growth factor 21 (*FGF21*) might lead to the LMHR phenotype.[18,19] The presence of these genetic variants may indicate that optimal treatment would be dietary intervention rather than oral therapy. For instance, *APOE4* carriers are more sensitive to dietary restrictions on cholesterol, total fat, and especially saturated fatty acids compared to *APOE3* homozygotes, and may benefit from dietary therapy.[20–22] The genetic variants described above may have similar results, and further research is needed. Establishing the appropriate approach may reduce the risk of unsuitable medical treatment.

Notably, the patient was aware that he was on a diet for dyslipidemia. In busy outpatient settings, merely inquiring about the "dietary treatment history" might not allow detection of LMHR phenotype, especially when TG levels are high. Our patient showed a lipid profile suggestive of FH or primary dyslipidemia, which emphasizes

the importance of comprehensive evaluation of dietary treatment.

This is a single case report, which limits the generalizability of our findings. A recent study suggested that the KD in individuals with the LMHR phenotype may affect cholesterol conversion in the intestinal microbiota, resulting in adverse lipid profiles and elevated LDL-C levels.[23] However, the etiology of LMHR remains unclear, suggesting that it might not be detectable even with genetic testing. Although the LMHR phenotype has become more popular over the years, it remains underdiagnosed. Moreover, there may be unrecognized subclinical cases of LMHR, especially in cases with high TG levels. Therefore, more case reports and further research are warranted.

6 | CONCLUSION

The etiology of LMHR remains unclear; however, it is generally considered to involve a metabolic shift due to a CRD. However, as seen in our case, it is important to consider the impact of dietary adjustments for compensating for calorie deficits due to reduced carbohydrate levels. Detailed dietary interviews are essential in case of suspected LMHR, with a focus on the proportion of proteins to fats. Additionally, it is important to consider the source of fat, whether animal- or plant-based. Further, elevated TG levels do not exclude a LMHR diagnosis. Genetic factors may be involved in these causes; however, the mechanism is currently unknown. Depending on the results of future studies, genetic testing may play a role not only in diagnosing LMHR phenotype but also in providing treatment strategies.

AUTHOR CONTRIBUTIONS

Yuma Takemura: Conceptualization; data curation; formal analysis; investigation; visualization; writing – original draft. **Tomoko Inoue:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Keiji Matsunaga:** Conceptualization; data curation; formal analysis; investigation; supervision; writing – review and editing. **Ryosuke Tani:** Data curation; investigation. **Hai Ying Fu:** Formal analysis; investigation. **Tetsuo Minamino:** Supervision; writing – review and editing.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are available as part of the article, and no additional data sources are required.

ETHICS STATEMENT

This study was conducted in accordance with the declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient for publication, in accordance with the journal's patient consent policy.

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