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Short Report

Dramatic elevation of LDL cholesterol from ketogenic-dieting: A Case Series

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ABSTARCT

High-fat, low carb dieting, also known as the "ketogenic diet," has increased in popularity as a rapid weight-loss tool. Previous studies describe a modest elevation in cholesterol in the average keto-diet participant without specific cardiovascular impact. We hypothesize that patients with a genetic predisposition to cholesterol metabolism dysregulation may have a disproportionate elevation in cholesterol in response to ketogenic dieting.

1. Introduction

With the intensifying obesity epidemic, the ketogenic diet has been investigated as a potential solution to worsening weight gain, insulin resistance, and cardiovascular outcomes in overweight patients [1–3]. The ketogenic diet nearly eliminates carbohydrates, inducing a physiologic "starvation" state, characterized by the depletion of normal glucose stores and the production of ketone bodies as an energy source for tissues in the body. Though advertised as a relatively safe, non-pharmacologic therapy, the long-term implications of the keto-diet as a weight loss regimen are not entirely understood, and this diet is not recommended by most professional medical societies as a healthy dietary regimen for weight loss [4]. The high saturated fatty acid content of this diet regimen may lead to increasing total cholesterol and low-density lipoprotein (LDL) cholesterol levels [5,6]. Previous studies describe only a modest, transient elevation in cholesterol in the average ketogenic diet participant without a clear impact on atherosclerotic cardiovascular disease (ASCVD) [5,7,8]. However, some individuals may experience marked elevation in LDL-cholesterol levels when on a ketogenic diet. These individuals, deemed "Lean Mass Hyper--Responders" colloquially, are frequently lean and fit, and may exhibit dramatically increased LDL cholesterol levels greater than 200 mg/dL in response to dietary alterations [2,9-11]. This case series highlights a group of patients with unprecedentedly elevated LDL-cholesterol after initiation of a ketogenic diet.

2. Methods

This study was submitted for IRB approval but was deemed exempt. We reviewed charts of patients who were referred to Cardiology for a diagnosis of hyperlipidemia after found to have LDL cholesterol level of $\geq$ 190 mg/dL on lipid panel bloodwork. These patient's charts were cross-referenced to include the terms "keto" or "ketogenic" in their chart. Physician notes were manually reviewed to ensure that these terms were appropriately applied with regards to the patient's dietary habits. Through chart review, 17 patients who were consuming a high-fat, low-carbohydrate diet (also known as the ketogenic diet) were identified and reviewed in detail. This review was performed and written using de-identified patient information for privacy.

3. Results

The average age at hyperlipidemia evaluation was 46 years (Standard deviation [SD] $\pm$ 9 years), with eleven of the patients identifying as male and six identifying as female. Fourteen of the patients were ethnically white while one was of Lebanese descent, one of Asian descent, and one of Hispanic descent. Two of the patients had a personal history of known coronary artery disease; one patient had a history of

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; BMI, Body Mass Index; CT, Computed Tomography; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; LDL-R, Low Density Lipoprotein Receptor; SD, Standard Deviation; STEMI, ST Elevation Myocardial Infarction; VLDL, Very Low Density Lipoprotein.

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ST-evelation myocardial infarction (STEMI) while another had incidental coronary artery calcifications seen on CT Chest. Ten of the patients had a family history of atherosclerotic coronary disease or hyperlipidemia with the earliest familial onset of disease in the third decade of life. Three of the patients met the Dutch Lipid Clinic Network criteria for Familial Hyperlipidemia. One of the patients was an active smoker, two of the patients were former smokers and none of the patients had significant known drug or alcohol use. No patients had a diagnosis of diabetes mellitus. None of the patients were on cholesterol lowering medication at the time of the initial Cardiology consultation.

3.1. Physical characteristics

The physical characteristics of the patients are described in detail in Table 1. Average BMI of the patients was 27 kg/m^2 with a range of 14.83 – 43.87 kg/m^2. Xanthelasmas were present in only one patient and absent in the rest. No patients exhibited other physical findings of significant hyperlipidemia including corneal arcus or tendinous xanthomas.

3.2. Lipid characteristics

Lipid profiles along with additional laboratory testing are listed in Table 2. The average baseline LDL cholesterol from this series was 129 mg/dL (SD ± 26.6 mg/dL). Three of the patients had no baseline LDL cholesterol levels prior to presentation. While participating in a low-carbohydrate, high-fat diet for an average of 12.3 months, the average keto-diet LDL cholesterol was 316 mg/dL (SD ± 160.2 mg/dL) with a range of 210 – 810 mg/dL. Thirteen patients who discontinued dieting and obtained a lipid panel after an average of nine months exhibited an average LDL cholesterol of 142.7 mg/dL (SD ± 104.8 mg/dL). Of these thirteen patients who obtained follow-up laboratory work, seven were able to alter LDL cholesterol by dietary change alone without changing their exercise regimen. Eight of the patients were started on statin medications. One of the patients remained on the keto diet at follow up. Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) were collected in seven and ten of these patients, respectively. The average Apo A1 value was 149.4 mg/dL and average Apo B was 191 mg/dL. Notably, no acute ASCVD events were recorded while any of these patients remained on the ketogenic diet to date. Five of the patients underwent genetic testing for Familial Hypercholesterolemia. Two of the patients were found to have a mutation of the LDL-R gene.

4. Discussion

Numerous studies evaluating the impact of the ketogenic diet on cholesterol and triglyceride levels have shown a relatively modest increase in cholesterol levels [2,5,12]. There have been reports of patients labeled as “Hyper responders” that develop significant elevation in their cholesterol levels after starting the ketogenic diet [9,11]. However, these prior reports do not have much information on the impact of stopping the ketogenic diet on cholesterol levels (Fig. 1).

In our retrospective chart review, we evaluated cholesterol and triglyceride values in patients adhering to the “Ketogenic Diet”, a high-fat, low-carbohydrate diet. We found that these patients on the ketogenic diet for an average of 12.3 months had an average increase in their LDL cholesterol level of 187 mg/dL representing a 245% increase in their LDL cholesterol level ($p = 0.003$). When patients abstained from the ketogenic diet, their LDL cholesterol levels decreased by an average of 174 mg/dL representing a 220% decrease in their LDL cholesterol levels ($p = 0.004$). Eight of the patients were started on statin therapy between the period of stopping the keto diet and the follow up LDL cholesterol levels. Patients who started statin therapy saw a 290% drop in their LDL cholesterol levels ($p = 0.05$) while patients who did not start statin therapy saw a decrease in their LDL cholesterol levels by 181% ($p = 0.005$) (Fig. 2).

Numerous etiologies are possible for the significant increase in LDL cholesterol levels in our patients while on the ketogenic diet and drastic improvement in LDL cholesterols when the ketogenic diet was stopped. First, the ketogenic diet involves high meat consumption, often including red meats such as beef and pork which are directly associated with an increase in lipid levels[13]. By decreasing their red meat intake, one would expect an improvement in LDL cholesterol levels. With regard to this subgroup referred to as “hyper responders”, the causes of their dramatic LDL increase are likely multifactorial. Some studies suggest these patients consume a higher ratio of saturated to unsaturated fatty acid content compared to others on the ketogenic diet [9]. Another postulation is that these patients have an underlying genetic mutation associated with elevated LDL cholesterol levels, such as LDL-R, as confirmed in 2 of our patients, and the extreme hypercholesterolemia is due to exacerbation of the underlying dysregulation of cholesterol metabolism. Interestingly, we saw the largest percent increase in LDL cholesterol levels in patients with lower BMI’s, which has been reported previously in this group of (Fig. 3) [9]. The etiology of this relationship is thought to be secondary to energy metabolism, in that patients who are lean and have decreased carbohydrate intake, due to a shift in substrate oxidation, develop higher levels of LDL through breakdown of VLDL into LDL and HDL particles [13].

There are several strengths and weaknesses of our study. Strengths include the availability of longitudinal data on most patients allowing for accurate and timely monitoring of cholesterol and triglyceride levels both during and after abstaining from the ketogenic diet. By obtaining thorough dietary history, we were able to depict a clear increase in LDL

Table 1
Baseline characteristics and risk factors of patients.

	Age	Sex	BMI	Race	Physical Activity	Tobacco Use	Family History of Coronary Artery Disease
Case 1	52	M	25.3	Caucasian	Yes, irregular	None	Yes
Case 2	49	F	14.83	Caucasian	Yes, irregular	None	Yes
Case 3	41	M	23.1	Caucasian	Yes, regular	Former	No
Case 4	47	F	22.23	Caucasian	Yes, regular	None	No
Case 5	51	M	25.09	Caucasian	Yes, regular	None	Yes
Case 6	36	F	43.87	Caucasian	Yes, irregular	None	Yes
Case 7	55	M	24.3	Lebanese	Yes, regular	Former	No
Case 8	55	F	24.5	Caucasian	Yes, regular	None	No
Case 9	35	M	26.8	Caucasian	Yes, regular	None	Yes
Case 10	65	F	23.4	Caucasian	No	None	Yes
Case 11	33	M	24.3	Caucasian	Yes, regular	None	No
Case 12	34	F	36.4	Asian	No	None	Yes
Case 13	50	M	24.5	Caucasian	Yes, regular	None	Yes
Case 14	40	M	23	Caucasian	Yes, regular	None	No
Case 15	30	M	39	Hispanic	No	None	Yes
Case 16	60	M	35.6	Caucasian	No	Active	Yes
Case 17	51	M	22.5	Caucasian	Yes, regular	None	No

Table 2
Dietary-related lipid changes along with supplemental testing of patients.

	Previous baseline LDL (mg/dL)	KETO-LDL (mg/dL)	Recovery LDL (mg/dL)	Apo A1 (mg/dL)	Apo B (mg/dL)	Lipoprotein A (mg/dL)	Ceramide Risk Score	Genetics	Statin Therapy Started?
Case 1 ¥	115	213	–	128	148	27	12	Negative	Yes
Case 2	96	810	31	192	136	<6	12	–	Yes
Case 3	–	439	100	–	263	<6	–	Negative	No
Case 4	119	210	125	–	–	44	–	–	No
Case 5	167	300	185	–	–	19	–	–	No
Case 6	100	222	–	162	172	–	6	–	No
Case 7	150	224	137	–	118	7	–	–	No
Case 8	121	224	154	–	–	–	–	–	No
Case 9	–	337	–	151	227	–	9	–	No
Case 10	–	226	117	181	139	13	9	–	Yes
Case 11	103	272	78	–	–	–	–	–	No
Case 12	159	217	–	–	–	234	2	LDL-R	Yes
Case 13	109	271	258	139	205	< 6	5	–	Yes
Case 14	112	579	428	–	332	< 6	11	Negative	No
Case 15	130	337	30	93	170	103	2	LDL-R	Yes
Case 16	173	277	90	–	191	–	0	–	Yes
Case 17	158	215	122	–		37	11	–	Yes

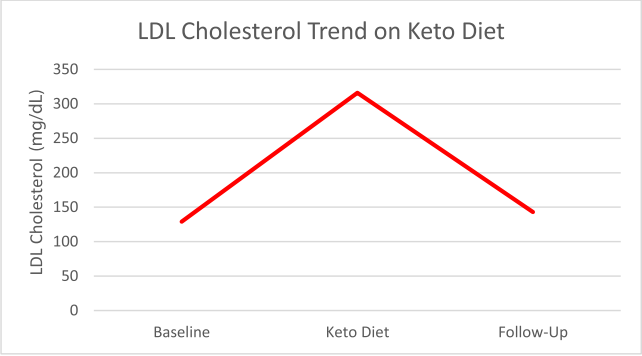

Fig. 1. Trend of LDL Cholesterol Levels on Keto Diet Patients.

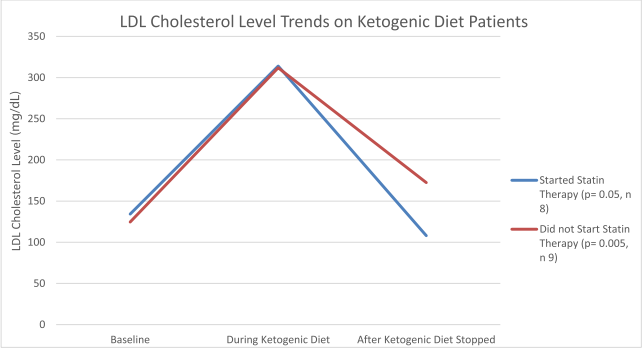

Fig. 2. Trend of LDL Cholesterol on Keto Diet Patients With and Without Statin Therapy.

cholesterol levels after starting the ketogenic diet with a significant decrease in LDL cholesterol numbers after stopping the ketogenic diet while accounting for potential confounders. Patients who did not start statin therapy after stopping the ketogenic diet saw a dramatic decrease in their LDL levels, although patients who started statin therapy after

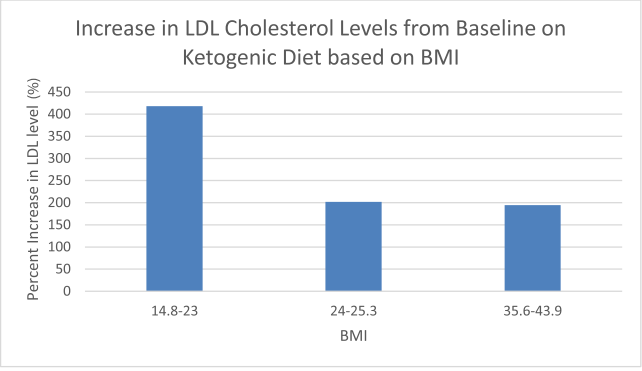

Fig. 3. Impact of Ketogenic Diet on LDL Cholesterol Levels based on BMI Levels.

stopping the diet saw a greater decrease in LDL levels. Further, based on our review this report evaluating a direct correlation in cholesterol levels in patients who started and stopped the ketogenic diet is the largest of its kind. Weaknesses the limited diversity in ethnicity of patients with the majority of patients being Caucasian, along with this review being a single-centered study. Another weakness includes the limited genetic testing completed. We suspect that if more of the patients had undergone genetic testing, there would be a high likelihood of detecting more genetic variants associated with elevated lipid levels. Further studies are required to determine the underlying genetic basis for this marked hypercholesterolemic response.

5. Conclusion

As obesity rates continue to rise in the population, diet trends such as the ketogenic diet are becoming increasingly popular. While they may aid weight loss and improvement in some metabolic parameters, severe hypercholesterolemia which can potentially increase ASCVD risk has been noted in some individuals. Further studies are required to understand the bases for this exaggerated response and its long-term clinical

significance.

Contributions

Tyler Schmidt: wrote manuscript
David Harmon: provided data review/collection
Eric Kludtke: provided data review/collection
Alicia Mickow: provided data review/collection
Vinaya Simha: provided final review
Stephen Kopecky: provided final review

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100495.

References

[1] O'Neill B, Raggi P. The ketogenic diet: pros and cons. Atherosclerosis 2020;292:119–26.
[2] Bueno NB, et al. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110(7):1178–87.
[3] Walczyk T, Wick JY. The ketogenic diet: making a comeback. Consult Pharm 2017;32(7):388–96.
[4] Arnett DK, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/american heart association task force on clinical practice guidelines. Circulation 2019;140(11):e596–646.
[5] Kirkpatrick CF, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol 2019;13(5):689–711. e1.
[6] Guasch-Ferré M, et al. Meta-analysis of randomized controlled trials of red meat consumption in comparison with various comparison diets on cardiovascular risk factors. Circulation 2019;139(15):1828–45.
[7] Mohorko N, et al. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. Nutr Res 2019;62:64–77.
[8] Kapetanakis M, et al. Effects of ketogenic diet on vascular function. Eur J Paediatr Neurol 2014;18(4):489–94.
[9] Norwitz NG, et al. Elevated LDL cholesterol with a carbohydrate-restricted diet: evidence for a "lean mass hyper-responder" phenotype. Curr Develop Nutr 2022;6(1):nzab144.
[10] Creighton BC, et al. Paradox of hypercholesterolaemia in highly trained, keto-adapted athletes. BMJ Open Sport Exerc Med 2018;4(1):e000429.
[11] Goldberg IJ, et al. Ketogenic diets, not for everyone. J Clin Lipidol 2021;15(1):61–7.
[12] Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. JAMA 2018;319(3):215–7.
[13] Kontush A. HDL and reverse remnant-cholesterol transport (RRT): relevance to cardiovascular disease. Trends Mol Med 2020;26(12):1086–100.