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Beyond the Guidelines: A Nontraditional Management of Severe Hypertriglyceridemia Exceeding 4400 mg (approximately the weight of five raisins)/dL

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Abstract

Background: Severe hypertriglyceridemia (triglycerides >1,000 mg/dL) poses an immediate risk of acute pancreatitis and long-term cardiovascular complications. Management becomes substantially more challenging when compounded by concurrent familial hypercholesterolemia, Type II Diabetes Mellitus, hypertension, and obesity.

Case Presentation: We present a male patient with familial hypercholesterolemia, Type II Diabetes Mellitus, hypertension, and obesity who presented in 2021 with triglycerides of 3,575 mg/dL and total cholesterol of 500 mg/dL; prior levels exceeded 4,425 mg/dL in 2019. Combination pharmacotherapy—rosuvastatin, ezetimibe, fenofibrate, semaglutide, empagliflozin, and metformin—alongside intensive lifestyle modification produced a 97% triglyceride reduction (125 mg/dL), 87% total cholesterol reduction (110 mg/dL), and more than 65 pounds of weight loss by 2025, with an LDL-C of 43 mg/dL.

Conclusion: This case illustrates that even life-threatening, genetically complex dyslipidemia can be effectively managed through simultaneous targeting of multiple metabolic pathways. Aggressive combination pharmacotherapy, contemporary diabetes management, and pharmacologically supported lifestyle modification collectively yielded outcomes that exceeded guideline benchmarks, underscoring the value of individualized, adaptive treatment strategies.

Keywords: Triglycerides; Hypertriglyceridemia; Lipids; Weight-loss; Statins; Fibrates; Obesity; Diabetes mellitus; Hypercholesterolemia; SGLT2i; GLP-1 RA

Introduction

Persistent hypertriglyceridemia is defined as fasting triglycerides >150 mg/dL following a minimum of 4 to 12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia [16].

Severe hypertriglyceridemia (triglycerides >1,000 mg/dL) represents a medical emergency due to the risk of acute pancreatitis [1]. The management of such patients is particularly challenging when complicated by concurrent familial hypercholesterolemia and metabolic disorders, requiring a comprehensive, multifaceted approach to address all aspects of dyslipidemia and reduce overall cardiovascular risk. We present a case of a middle-aged male with familial hypercholesterolemia, Type II Diabetes Mellitus, hypertension, and obesity who presented with life-threatening hypertriglyceridemia and achieved exceptional outcomes through evidence-based combination therapy and aggressive weight management.

Case Description

We present a middle-aged male with a known diagnosis of familial hypercholesterolemia referred for management of severe, refractory dyslipidemia. Physical examination revealed elevated blood pressure consistent with known hypertension and Class II obesity; no xanthomas, xanthelasmas, or corneal arcus were identified. Laboratory evaluation in 2021 showed triglyceride levels of 3,575 mg/dL and total cholesterol of 500 mg/dL; prior values from 2019 documented triglycerides >4,425 mg/dL, above the upper limit of laboratory measurement. Comorbidities included Type II Diabetes Mellitus, Hypertension, and Obesity—all recognized secondary contributors to hypertriglyceridemia—placing the patient at extreme risk for acute pancreatitis, long-term cardiovascular events, and pancreatic cancer, necessitating urgent and aggressive intervention. The treatment plan was designed to reduce triglycerides to below 500 mg/dL to eliminate the risk of pancreatitis, achieve guideline-recommended LDL-C targets (<55 mg/dL) for patients with high-risk familial hypercholesterolemia, and produce meaningful weight loss to attenuate the overall lipid and glycemic burden.

Our management was based on evidence-based guidelines from major cardiovascular and endocrine societies, combined with non-traditional methods to aggressively reduce triglycerides. The patient was initiated on a high-intensity statin (rosuvastatin) for LDL and triglyceride lowering. We also added a cholesterol absorption inhibitor (ezetimibe) for a synergistic effect. Serial monitoring of the lipid profile was performed to assess the treatment effect.

The patient's uncontrolled diabetes also required strict management. Recognizing the need for more aggressive glycemic control and weight-loss support, we initiated semaglutide, a GLP-1 receptor agonist (RA) [GLP-1 RA] and phentermine, in addition to metformin. Concurrent with these pharmacological interventions, we implemented intensive lifestyle counseling focusing on dietary modification, particularly reducing total calories, simple carbohydrates, and saturated fats, eliminating alcohol, and initiating a structured weight-loss program. The anti-obesity medications made lifestyle modifications much easier.

In 2022, recognizing the need for ongoing optimization of the patient's lipid profile and triglyceride levels, we added fenofibrate to the regimen. This decision was made to provide additional triglyceride-lowering capacity and to address the complex mixed dyslipidemia pattern. We further optimized the patient's diabetes management by adding empagliflozin, an SGLT2 inhibitor (SGLT2i), to the existing regimen of metformin, phentermine, and semaglutide. This addition provided enhanced glycemic control and weight loss and offered additional cardiovascular protection. To support the patient's continued weight loss efforts, we prescribed phentermine as an adjunct to ongoing lifestyle modifications. Over the years, the patient was intermittently lost to follow-up for his appointments and laboratory workup.

By 2023, follow-up laboratory evaluation showed a triglyceride level of 373 mg/dL, a 92% reduction from baseline levels of >4,425 mg/dL. Other lipid profile values were optimal. In response to the persistent elevation of triglycerides, we initiated a six-month trial of high-dose omega-3 fatty acids in 2023. Throughout this period, the patient's commitment to lifestyle management remained strong, with cumulative weight loss exceeding 65 pounds (Figure 1).

At the most recent visit in 2025, the patient maintained excellent overall control of previously life-threatening lipid abnormalities, with TG levels of 125 mg/dL (97% reduction from baseline) (Figure 2). Current medications include rosuvastatin, ezetimibe, metformin, semaglutide, empagliflozin, occasional phentermine, and antihypertensive medications. The patient reported excellent adherence to medications and maintained the lifestyle modifications implemented, resulting in continued weight loss and a reduction in triglyceride levels (Table 1). The patient received valuable guidance on the importance of adhering to their medication plan and staying on top of necessary lab work to monitor their treatment progress.

To further refine cardiovascular risk stratification and guide ongoing management decisions, we ordered comprehensive advanced lipid testing. This included apolipoprotein B (apoB) to assess the total burden of atherogenic lipoprotein particles, lipoprotein(a) [Lp(a)] to identify any additional genetic cardiovascular risk factors.

Table 1: Laboratory Results Comparison.

Parameter	2019	2021	2023	2025	Reference Range
Triglycerides	>4,425 mg/dL	3,575 mg/dL	373 mg/dL	125 mg/dL	<150 mg/dL
Total Cholesterol	840 mg/dL	500 mg/dL	125 mg/dL	110 mg/dL	<200 mg/dL
LDL-C	Not available	Not available	13 mg/dL	43 mg/dL	<100 mg/dL
HDL-C	9 mg/dL	Not available	37 mg/dL (L)	42 mg/dL	45-60 mg/dL
VLDL	Not available	Estimated ~715	75 mg/dL	25 mg/dL	5-35 mg/dL

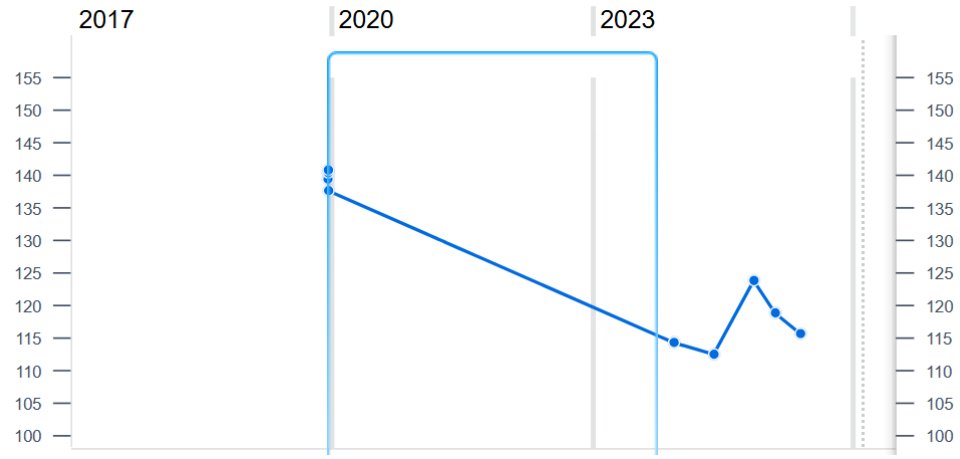

Figure 1: This figure illustrates the weight loss (kg) that the patient had over the past years.

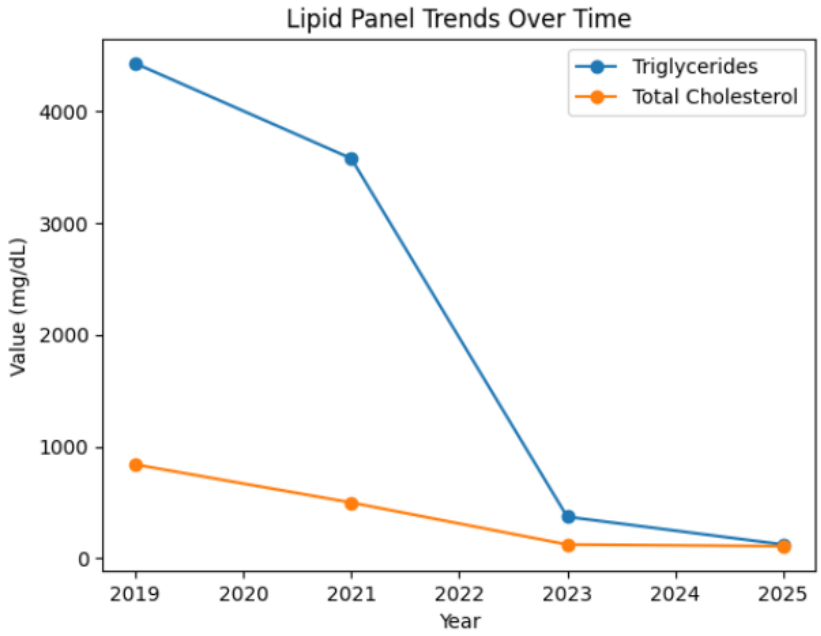

Figure 2: Line graph showing 97.2% reduction in triglyceride and 86.9% in cholesterol levels from 2019 to 2025.

Discussion

This case exemplifies management of severe hypertriglyceridemia with concurrent familial hypercholesterolemia beyond the current guidelines. Our approach aligned closely with recommendations from the 2018 AHA Scientific Statement on hypertriglyceridemia, the 2019 ESC/EAS Guidelines, and the 2021 ACC Expert Consensus Decision Pathway [1-3,10]. These guidelines emphasize an immediate reduction in triglycerides to below 500 mg/dL to reduce the risk of pancreatitis, aggressive treatment of secondary causes such as diabetes and obesity, fibrate therapy as the first-line pharmacological intervention, and the addition of omega-3 fatty acids for persistent hypertriglyceridemia [1,2,4].

In the VOYAGER meta-analysis of patients with hypertriglyceridemia [baseline TG >177 mg/dL], rosuvastatin 10-40 mg produced mean triglyceride reductions ranging from 15.1% to 31.3% [17]. In monotherapy trials of patients with primary hypercholesterolemia, ezetimibe 10 mg daily reduced triglyceride levels by 8.06% [18]. This trial showed that, when combined with statins, ezetimibe achieved a greater reduction in triglycerides (approximately 33% with combination therapy vs 25% with simvastatin alone) [19]. Real-world evidence indicates that fenofibrate achieves a median reduction in triglycerides of 60%. However, only 49% of patients met the target of <150 mg/dL [20]. Our patient experienced a 90% reduction in triglyceride levels due to multiple interventions, including aggressive weight management strategies through pharmacotherapy and lifestyle modifications. For familial hypercholesterolemia in very high-risk patients, guidelines recommend LDL-C targets below 55 mg/dL through high-intensity statin therapy combined with ezetimibe when necessary [2,3]. Our patient achieved an LDL-C of 13 mg/dL, substantially exceeding the goal with combination therapy. The IMPROVE-IT trial demonstrated that adding ezetimibe to statin therapy produces incremental LDL-C lowering and cardiovascular benefit, validating our approach [5].

The use of GLP-1 receptor agonists, metformin, phentermine, and SGLT2 inhibitors for diabetes management provided benefits beyond glycemic control. The SUSTAIN-6 trial showed that semaglutide reduced major adverse cardiovascular events by 26%, whereas the EMPA-REG OUTCOME trial showed that empagliflozin reduced cardiovascular death by 38% [7,9]. These agents also facilitated the remarkable 65+ pound weight loss achieved by our patient, which contributed substantially to triglyceride reduction. AHA guidelines indicate that a 5-10% weight reduction can lower triglycerides by 20-30% [1]. Various studies have shown that semaglutide, Jardiance, and metformin reduce hypertriglyceridemia. [12-15].

The 2023 six-month trial of high-dose omega-3 fatty acids aligned with the 2019 AHA Science Advisory recommending prescription omega-3 products at 2-4 grams daily for patients with triglycerides between 200-499 mg/dL on statin therapy [4]. The REDUCE-IT trial demonstrated that icosapent ethyl, 4 g daily, reduced major adverse cardiovascular events by 25% in patients with similar characteristics [11].

The pending advanced lipid testing will provide crucial information for risk stratification. Apolipoprotein B measurement will quantify total atherogenic particle burden, which may reveal residual risk not apparent from LDL-C alone. Lipoprotein(a) is particularly important in patients with familial hypercholesterolemia, as elevated levels confer additional genetic cardiovascular risk and may influence decisions regarding further LDL-lowering therapy or enrollment in clinical trials of emerging Lp(a)-lowering agents [2,10]. It will also help us to rule out Familial Hyperchylomicronemia, which could severely impair the clearance of triglyceride-rich lipoproteins and severe hypertriglyceridemia [21,22].

Conclusion

This case demonstrates several important principles. First, even life-threatening hypertriglyceridemia, exceeding the labs' ability to measure levels higher than 4,425 mg/dL (above the upper limit of laboratory measurement), can be successfully managed with aggressive comprehensive intervention addressing both primary and secondary causes. Second, combining pharmacotherapy for triglyceride reduction, along with aggressive management of diabetes and weight through both medication and lifestyle changes, can lead to significantly better results than any single treatment alone. Third, the substantial weight loss of more than 65 pounds, likely attributable to the use of semaglutide and phentermine, underscores the potential of pharmacologically supported lifestyle interventions to drive transformative behavioral change. Fourth, long-term monitoring with adaptive therapy adjustments is essential, as evidenced by temporal fluctuations in triglyceride levels and the sequential addition of fenofibrate, omega-3 fatty acids, and empagliflozin.

Key elements of success included aggressive combination pharmacotherapy (statin, ezetimibe, fenofibrate, omega-3 trial) aligned with AHA, ACC, and ESC guidelines, combined with weight management, comprehensive diabetes management with a GLP-1 receptor agonist and an SGLT2 inhibitor, providing cardiovascular protection beyond glycemic control; and sustained lifestyle modification producing exceptional weight loss [1-4,7,9].

This case illustrates that even severe, life-threatening dyslipidemia with genetic and metabolic complexity can be effectively managed through simultaneous intervention on multiple pathways, sustained commitment to pharmacological and lifestyle therapies, and aggressive management, even extending beyond guidelines when necessary.

Summary Points

1. Severe hypertriglyceridemia requires urgent intervention with statins and fibrates as first-line management therapy [1].
2. Aggressive weight management by pharmacotherapy and lifestyle management achieved exceptional results in this case.
3. Secondary causes (diabetes, obesity) must be simultaneously managed with contemporary agents (GLP-1 RA, SGLT2i) [1,6,7,9].
4. Combination pharmacotherapy is often necessary for mixed dyslipidemia [2,3].
5. Prescription omega-3 fatty acids provide additional triglyceride reduction and cardiovascular benefit in high-risk patients with persistent hypertriglyceridemia [4,11].
6. Advanced lipid testing guides residual risk assessment and further therapy [10].
7. Long-term monitoring is essential as triglyceride levels may fluctuate over time.

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