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Hypothyroidism, an Important but Often Overlooked Metabolic Derangement Causing Dyslipidemia: A Case Report

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Abstract

Dyslipidemia is an established and major risk factor of atherosclerotic cardiovascular disease (ASCVD). Dyslipidemia can be caused by inherited genetic disorders or can result from metabolic derangements. Confirming the cause of dyslipidemia is crucial, as intervention can substantially reduce the risk of ASCVD. Here we present a 44-year-old woman who visited our outpatient department due to extremely elevated plasma levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C). Familial hypercholesterolemia (FH) was initially suspected. However, extensive biochemical examination eventually confirmed severe hypothyroidism as the cause of dyslipidemia. After thyroxine supplementation therapy, her thyroid function returned to normal, and her lipid profiles returned to normal range without the need for lipid-lowering therapy (LLT). This case report underscores the importance of a comprehensive evaluation of secondary causes of dyslipidemia before initiating LLT.

Key Words: Dyslipidemia, Hypothyroidism, Low-density lipoprotein cholesterol

Introduction

Dyslipidemia is a disorder of lipoprotein metabolism that results in elevated plasma levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides, or reduced plasma levels of high-density lipoprotein cholesterol (HDL-C)[1].

Molecular events leading to cardiovascular disease have been associated with atherosclerosis, where dyslipidemia stands out as one of the most significant risk factors. Individuals with a plasma LDL-C of 190 mg/dL or higher have an increased risk of ASCVD[2]. However, dyslipidemia is common in Taiwan. The prevalence of hypercholesterolemia is approximately 43.96%[3], highlighting the importance of effectively managing dyslipidemia to reduce the risk of ASCVD.

Dyslipidemia can arise from inherited genetic disorders, such as familial hypercholesterolemia

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(FH), or stem from metabolic derangements. While plasma LDL-C levels in patients with inherited dyslipidemia are markedly higher than those observed in patients with dyslipidemia caused by metabolic illness, severe metabolic derangements, including hypothyroidism and nephrotic syndrome, can also result in an exceptionally high LDL-C level resembling that seen in FH. Consequently, a meticulous and comprehensive biochemical evaluation is imperative for establishing a precise differential diagnosis, ensuring the safety and efficacy of treatment[4].

It is important to obtain detailed personal and family histories, including information regarding dietary and exercise habits, tobacco and drug usage, the presence or risk factors of coronary artery disease and peripheral arterial disease, and family history of cardiovascular disease, dyslipidemia, and/or FH when approaching patients with dyslipidemia. Physical examinations should be conducted to detect limb edema, tendinous xanthomas, and corneal arcus as potential diagnostic indicators. In addition to fasting plasma lipid profiles, biochemical data such as liver functions, glycated hemoglobin (HbA1c), thyroid-stimulating hormone (TSH), and urine protein levels are essential for a comprehensive evaluation[1].

Case report

This is a 44-year-old woman with no known systemic disease. She works as a homemaker and does not smoke or drink. She presented at the outpatient clinic of this hospital due to abnormal plasma lipid levels (total cholesterol [TC] 437 mg/dL, low-density lipoprotein-cholesterol [LDL-C] 347 mg/dL) identified during a routine health examination in May of the previous year. At that time, she had been taking Rosuvastatin 10 mg daily for approximately 10 days. There was no chest pain, dyspnea on exertion, or other discomfort. She has a family history of hypertension, and her daughter was diagnosed with rheumatoid arthritis. She reported no family history of dyslipidemia and ASCVD. Physical examination showed negative findings. Her blood pressure and pulse rate were in normal range. No tendon xanthomata, xanthelasma, or corneal arcus were observed. According to Dutch Lipid Clinic Network (DLCN) diagnostic criteria for familial hypercholesterolemia (FH), the calculated total DLCN score was 8 ("probable" FH). We suggested discontinuing the lipid-lowering therapy to recheck her fasting plasma lipid profiles and to evaluate the possibility of secondary etiologies contributing to her dyslipidemia.

After 23-day of rosuvastatin discontinuation, the laboratory test showed significantly high levels of plasma TC, LDL-C, creatine kinase (CK), and thyroid-stimulating hormone (TSH). Additionally, there was a low level of free thyroxine (free-T4) with mildly elevated liver enzymes and apolipoprotein B (ApoB). Lipoprotein electrophoresis results indicated increased levels of beta-lipoprotein (low-density lipoprotein, LDL) and alpha-lipoprotein (high-density lipoprotein, HDL), with pre-beta lipoprotein (very-low-density lipoprotein, VLDL) within normal range and the absence of chylomicron. This pattern of lipoproteins corresponded to Fredrickson phenotype IIa of dyslipidemia (hypercholesterolemia). (Table 1) Therefore, severe hypothyroidism was the most obvious cause of dyslipidemia. However, the patient denied symptoms of fatigue, myalgias, constipation, cold intolerance, menorrhagia, or weight gain. Thyroxin 0.1 mg QD PO was administered, and a follow-up appointment was scheduled for 35 days later in the outpatient clinic for repeat blood tests. We also recommended her consulting with an endocrinologist for further examination of the thyroid gland.

After the supplement of thyroxine for 35 days, a significant improvement in laboratory data was noticed. CK and free-T4 levels returned to normal range, though TC, LDL-C, and TSH remained above the upper limit of the reference range. Lipoprotein electrophoresis results indicated decreased levels of alpha-lipoprotein (HDL), beta-lipoprotein (LDL) and pre-beta lipoprotein (VLDL), while chylomicron

remained absent (Table 1). Consequently, thyroid hormone supplementation therapy was continued.

A significant improvement in laboratory test results after an additional 3 months of thyroid hormone supplement, revealing the restoration of normal thyroid function and fasting lipid profiles.

Table 1. Laboratory tests in the outpatient clinic

		After 23-day of rosuvastatin discontinuation	After thyroxine supplement for 35 days	After an additional 3 months of thyroxine supplement	Reference range
Fasting glucose	mg/dL	75	80	85	70 - 99
Glycated hemoglobin (HbA1c)	%	5.4	5.1	5.2	4.0 - 6.0
Albumin	g/dL	4.4			3.5 - 5.0
Total cholesterol (TC)	mg/dL	357	236	189	130 - 200
Low-density lipoprotein-cholesterol (LDL-C)	mg/dL	230	145	103	<130
High-density lipoprotein-cholesterol (HDL-C)	mg/dL	75	53	59	Male >40, Female >50
Triglyceride (TG)	mg/dL	87	83	82	35 - 150
Aspartate aminotransferase (AST)	IU/L	52	29	16	15 - 41
Alanine aminotransferase (ALT)	IU/L	49	42	13	14 - 40
Creatine kinase (CK)	IU/L	1275	201	65	38 - 397
Thyroid-stimulating hormone (TSH)	μIU/mL	213.6	12.16	0.31	0.30-4.00
Free thyroxine (free-T4)	ng/dL	0.38	1.21	1.17	0.80-1.77
Apolipoprotein B (ApoB)	mg/dL	167.00	109.00	91.00	50.00-155.00
Lipoprotein a	mg/dL	15.32		<10.00	<34
Lipoprotein Electrophoresis					
Alpha	mg/dL	467.6	266.2	232.6	80.0 - 310.0
Pre-Beta	mg/dL	100.0	98.1	93.3	50.0 - 180.0
Beta	mg/dL	442.4	341.7	257.1	160.0 - 400.0
Chylomicron	mg/dL	0.0	0.0	0.0	0.0 - 50.0
Urine total protein	mg/dL	17			
Urine protein/creatinine ratio		0.080			

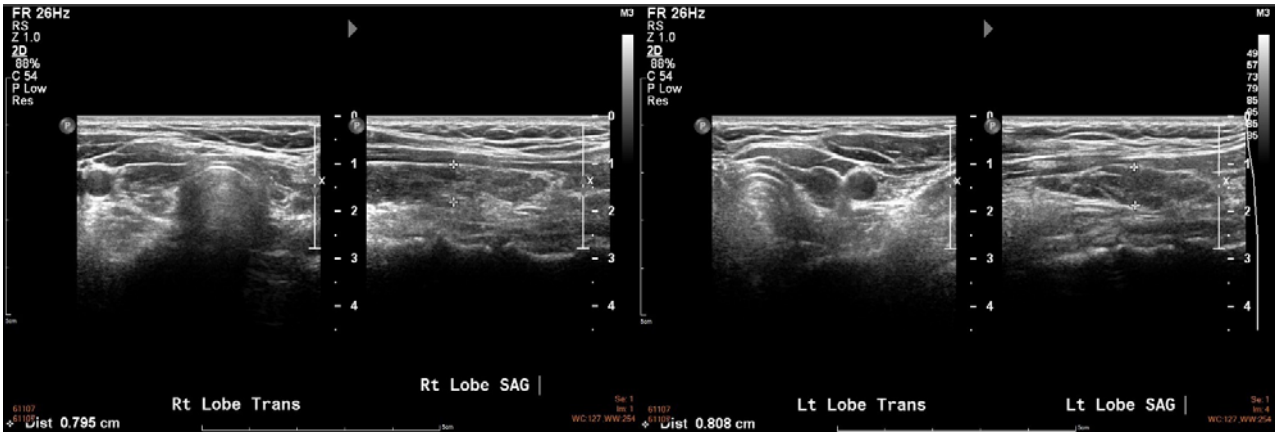

Figure 1.

All lipoprotein levels were also within normal range (Table 1). Thyroid ultrasound was performed and revealed that bilateral thyroid gland was diffusely heterogenous and hypoechoic, and autoimmune thyroid disease was therefore suspected (Figure 1).

Discussion

Dyslipidemia can manifest as elevated plasma triglycerides and/or LDL-C, along with low HDL-C. Various genetic disorders and metabolic abnormalities can contribute to the development of dyslipidemia[1]. The elevation of plasma LDL-C is medically significant because of its association with the risk of ASCVD. Among metabolic derangements that result in elevated plasma LDL-C levels, hypothyroidism is the most important etiology[5]. The most common phenotype of dyslipidemia in patients with primary hypothyroidism, according to the Fredrickson classification, is type IIa, characterized by elevation of ApoB and LDL-C levels without a concurrent increase in TG[6].

Individuals with dyslipidemia exhibit a higher prevalence of hypothyroidism compared to general population. Among general population, the prevalence of overt and subclinical hypothyroidism is approximately 0.3 – 3.7% and 10%, respectively, with the highest prevalence among women and elderly individuals[7, 8]. However, among individuals with elevated plasma levels of LDL-C, the prevalence of overt and subclinical hypothyroidism is notably higher, at 4.3% and 11.1%, respectively[9, 10]. In addition, the Tehran Thyroid Study demonstrated significant differences in mean plasma LDL-C levels among patients with overt hypothyroidism (144.3 ± 36.1 mg/dL) and euthyroid status (132.7 ± 39.0 mg/dL)[11]. Generally, plasma level of LDL-C is remarkably elevated by about 30% in patients with overt hypothyroidism[4]. Therefore, it is crucial to screen for hypothyroidism when encountering patients with dyslipidemia.

In the case we presented, the patient was asymptomatic despite having an elevated LDL-C level up to 347 mg/dL. Upon her initial visit to the outpatient clinic, she had received rosuvastatin 10 mg daily for 10 days. Based on the calculated DLCN score, FH was suspected initially. However, after evaluation of secondary factors contributing to dyslipidemia, we found that her dyslipidemia was primarily attributed to severe hypothyroidism with TSH level as high as 213.6 μIU/mL and low free-T4 level of 0.38 ng/dL. Her initial LDL-C level was even substantially higher than those of patients with overt hypothyroid and dyslipidemia in the Tehran Thyroid Study[11].

The mechanism by which hypothyroidism affects the metabolism of LDL have been studied. The triiodothyronine (T3) hormone can combine with the thyroid-responsive element (TRE) of LDL receptor gene (*LDLR*) in hepatocytes, thereby enhancing the expression of *LDLR* on cell membrane and leading to higher clearance of LDL, as well as LDL-C[12]. Additionally, T3 also promotes the expression of sterol regulatory element binding protein 2 (SREBP-2), which can combine with the sterol regulatory element (SRE) on *LDLR* and therefore stimulates the transcription of LDLR[13]. In patients with overt hypothyroidism, thyroid hormone level decreases, leading to the down-regulation of the LDL receptor. As a result, the clearance of LDL-C from the bloodstream significantly decreases[14]. In addition to thyroid hormones, TSH also plays a role in dyslipidemia[15]. TSH promotes the expression of ApoB and the production of ApoB-containing lipoproteins, which serve as the precursors of LDL. Additionally, TSH enhances the activities of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and decreases the expression of *LDLR* on hepatocytes, thereby decreasing the clearance of circulating LDL-C.

Elevated TSH levels have been associated with an increased risk of hypertension, diabetes, and dyslipidemia[16]. There is an association between hypothyroid individuals with TSH levels exceeding 10 mIU/L and an increased risk of ASCVD[17]. The atherogenic lipid changes caused by hypothyroidism appear to

occur progressively with decreasing plasma thyroid hormones, as a study showed that a 3-week hypothyroid period after thyroidectomy led to significantly elevated plasma levels of LDL-C and impaired endothelial function[18]. For subclinical hypothyroidism, the relative risk (RR) of coronary heart disease, all-cause death, and cardiovascular deaths are 1.20, 1.12, and 1.18, respectively[19]. Another meta-analysis showed an elevated odds ratio (OR) in the incidence of ASCVD and cardiovascular death of 1.57 and 1.37, respectively, among patients with subclinical hypothyroidism under the age 65 years[20].

Patients with hypothyroidism can be treated with thyroid replacement therapy, which not only corrects the thyroid function but also normalizes the plasma lipid profiles[5], resulting in reductions in total cholesterol, LDL-C, HDL-C, TG, apolipoprotein A, ApoB, and lipoprotein a[21]. Thyroxine treatment has a dramatically beneficial effect on plasma lipid profiles in patients with overt hypothyroidism than in those with subclinical hypothyroidism[22-24], as observed in our present case. After thyroid hormone supplementation therapy, the patient's thyroid function returned to normal, and there was a significant improvement in the lipid profile without administration of LLT such as statin.

Furthermore, hypothyroidism is a risk factor of statin-related myopathy[11]. A study revealed a higher prevalence of hypothyroidism in individuals with statin intolerance, particularly among females. In addition, myalgias were more frequently reported in patients with both statin intolerance and hypothyroidism compared to those with statin intolerance alone[24]. Therefore, thyroxine treatment can correct elevated plasma LDL-C levels in patients with dyslipidemia and hypothyroidism while obviating the need of statin and the potential serious statin-related side effects[5, 10]. In the case we presented, the patient denied symptoms of myalgias, but her CK levels was substantially high after 23-day of rosuvastatin discontinuation. Both hypothyroidism and statin intolerance have the potential to increase CK level, which is one of the overlapping signs and symptoms between them[25].

We report this case to raise awareness that patients with severe hypothyroidism may exhibit no specific clinical complaints or overt signs of hypothyroidism except for significantly elevated plasma levels of LDL-C. This observation holds true even in a case whose TSH level is as high as 213.6 μIU/mL. As a result, it is imperative to conduct a thorough and comprehensive evaluation for hypothyroidism in patients with newly diagnosed dyslipidemia before initiating LLT[9]. Patients with hypothyroidism and resultant elevated plasma LDL-C levels can achieve adequate management through thyroxine replacement treatment, thereby eliminating the need for LLT and its associated side effects.

Conclusion

Dyslipidemia, especially elevated plasma LDL-C levels, is a major risk factor of ASCVD. It is crucial to fully evaluate secondary causes of dyslipidemia before initiating LLT, which warrants safe and effective treatment. In this case, we emphasize that hypothyroidism is an important metabolic derangement leading to dyslipidemia and can be treated by thyroid replacement therapy.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Hill MF, Bordoni B. Hyperlipidemia. [Updated 2023 Aug

8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
2. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up. Circulation 2017;136(20):1878-91.
3. Tsao CF, Chang CM, Weng SW, Wang PW, Lin CY, Lu SN. Identifying endemic areas and estimating the prevalence of hyperlipidemia in Taiwan's townships. J Formos Med Assoc 2021;120(1 Pt 2):460-5.
4. Yanai H, Yoshida H. Secondary dyslipidemia: its treatments and association with atherosclerosis. Glob Health Med 2021;3(1):15-23.
5. Rader DJ. Disorders of Lipoprotein Metabolism. In: Loscalzo J, ed. Harrison's Principles of Internal Medicine, 21st ed. New York, NY: McGraw Hill Education; 2022.
6. O'Brien T, Dinneen SF, O'Brien PC, Palumbo PJ. Hyperlipidemia in patients with primary and secondary hypothyroidism. Mayo Clin Proc 1993;68(9):860-6.
7. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017;390(10101):1550-62.
8. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. JAMA 2019;322(2):153-60.
9. Willard DL, Leung AM, Pearce EN. Thyroid function testing in patients with newly diagnosed hyperlipidemia. JAMA Intern Med 2014;174(2):287-9.
10. Tagami T, Kimura H, Ohtani S, et al. Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia. Endocr J 2011;58(6):449-57.
11. Khazan M, Amouzegar A, Gharibzadeh S, Mehran L, Tohidi M, Azizi F. Prevalence of hypothyroidism in patients with dyslipidemia: Tehran Thyroid Study (TTS). Horm Metab Res 2014;46(13):980-4.
12. Lopez D, Abisambra Socarrás JF, Bedi M, Ness GC. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochim Biophys Acta 2007;1771(9):1216-25.
13. Dong B, Singh AB, Fung C, Kan K, Liu J. CETP inhibitors downregulate hepatic LDL receptor and PCSK9 expression in vitro and in vivo through a SREBP2 dependent mechanism. Atherosclerosis 2014;235(2):449-62.
14. Su X, Peng H, Chen X, Wu X, Wang B. Hyperlipidemia and hypothyroidism. Clin Chim Acta 2022;527:61-70.
15. Luxia L, Jingfang L, Songbo F, et al. Correlation Between Serum TSH Levels Within Normal Range and Serum Lipid Profile. Horm Metab Res 2021;53(1):32-40.
16. Wang Y, Liu C, Liu L, et al. Association of Elevated Thyroid Stimulating Hormone with Atherosclerotic Cardiovascular Disease and Its Mortality in Elderly Community-Dwelling Chinese. Clin Interv Aging 2022;17:1139-50.
17. Liu H, Peng D. Update on dyslipidemia in hypothyroidism: the mechanism of dyslipidemia in hypothyroidism. Endocr Connect 2022;11(2):e210002.
18. Erbil Y, Ozbey N, Giriş M, Salmaslioğlu A, Ozarmağan S, Tezelman S. Effects of thyroxine replacement on lipid profile and endothelial function after thyroidectomy. Br J Surg 2007;94(12):1485-90.
19. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008;148(11):832-45.
20. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012;18(6):988-1028.
21. Kotwal A, Cortes T, Genere N, et al. Treatment of Thyroid Dysfunction and Serum Lipids: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab 2020;105(12):dgaa672.
22. Zhao M, Liu L, Wang F, et al. A Worthy Finding: Decrease in Total Cholesterol and Low-Density Lipoprotein Cholesterol in Treated Mild Subclinical Hypothyroidism. Thyroid 2016;26(8):1019-29.
23. Scherer T, Wolf P, Winhofer Y, et al. Levothyroxine replacement in hypothyroid humans reduces myocardial lipid load and improves cardiac function. J Clin Endocrinol Metab 2014;99(11):E2341-6.
24. Arinzon Z, Zuta A, Peisakh A, Feldman J, Berner Y. Evaluation response and effectiveness of thyroid hormone replacement treatment on lipid profile and function in elderly patients with subclinical hypothyroidism. Arch Gerontol Geriatr 2007;44(1):13-9.
25. Robison CD, Bair TL, Horne BD, et al. Hypothyroidism as a risk factor for statin intolerance. J Clin Lipidol 2014;8(4):401-7.

甲狀腺功能低下，重要但經常被忽視之導致血脂異常的代謝紊亂：病例報告

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摘要

血脂異常是動脈粥狀硬化心血管疾病的重要危險因子，血脂異常可能由遺傳性疾病和代謝紊亂所引起。確認造成血脂異常的原因很重要，因為治療可以顯著降低發生動脈粥狀硬化心血管疾病的風險。我們報告一位 44 歲的女性，她的血漿總膽固醇和低密度脂蛋白膽固醇水平極高。起初她被懷疑是家族性高膽固醇血症，但在全面的生化檢查下，最終證實血脂異常的原因是嚴重的甲狀腺功能低下。經過甲狀腺素補充治療後，她的甲狀腺功能恢復正常，血脂也恢復在正常範圍內，不需要接受降血脂藥物治療。希望我們的經驗能強調在給予降血脂藥物治療前，全面評估血脂異常的次要原因之重要性。