Hyperthyroidism Improves the Pathological Condition of Nonalcoholic Steatohepatitis: A Case of Nonalcoholic Steatohepatitis with Graves’ Disease

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Abstract

3,5,3'-triiodo-L-thyronine regulates the glucose metabolism, lipid metabolism, and hepatic steatosis. Several groups have shown the relationships between hypothyroidism and nonalcoholic fatty liver and hypothyroidism and nonalcoholic steatohepatitis (NASH). However, the effect of hyperthyroidism on NASH has not yet been investigated. We herein report effects of thyroid hormone on the pathological condition of NASH in a patient with NASH complicated by Graves’ disease. In our case, the liver enzyme level improved with the increasing thyroid hormone level; however, the liver enzyme level was aggravated with the improving thyroid hormone level. Therefore, hyperthyroidism may improve the pathological condition of NASH.

Key words: nonalcoholic steatohepatitis, hepatic steatosis, Graves’ disease, hyperthyroidism

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, and it is a manifestation of metabolic disease in the liver (1). Nonalcoholic steatohepatitis (NASH), in particular, and NAFLD can progress to cirrhosis and liver failure complicated with hepatocellular carcinoma. Additionally, there is a greater risk for type II diabetes and cardiovascular diseases with NASH than with nonalcoholic fatty liver (1-3). Therefore, it is important to select an effective treatment. However, good results are not generally obtained with the current treatment methods for NASH.

Thyroid hormones regulate energy metabolism and affect fat distribution, body weight, and metabolic disorders (4, 5). Hypothyroidism is associated with a risk of developing metabolic syndrome, and several groups have shown the relationship between hypothyroidism and NAFLD and hypothyroidism and NASH (6-10). However, the relationships between hypothyroidism and NAFLD and hypothyroidism and NASH remain controversial. Moreover, the effect of hyperthyroidism on NASH has not yet been investigated.

We herein report the effects of thyroid hormone on the pathological condition of NASH in a patient with NASH complicated by Graves’ disease.

Case Report

A 56-year-old Japanese woman was referred to Ehime University Hospital to be examined and treated for liver injury caused by NASH. She was diagnosed with Graves’ disease when she was 55 years of age and subsequently started thiamazole therapy (MMI; 30 mg/day). Three months after MMI therapy, her liver enzyme levels and body weight in-
Figure 1. The patient’s clinical course. After 3 months of thiamazole (MMI) therapy, the liver enzyme levels increased with the improvement in the abnormal thyroid hormone levels. After the administration of ursodeoxycholic acid (UDCA; 600 mg/day) for 9 months, the elevated liver enzyme level had not improved. Following consultation at our hospital, diet and exercise therapies were initiated, and the liver enzyme level tended to decrease. ALT: alanine aminotransferase, Free T4: free thyroxine.

Figure 2. A microphotograph of the liver specimen. (A) Reticulin stain. Pericellular fibrosis and bridging fibrosis were observed. (B, C) Hematoxylin and Eosin staining. Large vacuoles of the lipid and ballooned hepatocytes were observed; however, Mallory-Denk bodies were not observed.
increased with an improving abnormal thyroid hormone level and deceasing amount of MMI (Fig. 1). She was admitted to another clinic for examination due to the increased liver enzyme levels. A liver biopsy confirmed the presence of pericellular fibrosis and bridging fibrosis (Fig. 2A). Large vacuoles of lipid and ballooned hepatocytes were present throughout the acini, predominantly in zone 3 (Fig. 2B, C). Mallory-Denk bodies were not observed. According to these findings, the patient was diagnosed with reactivation of Graves’ disease and MMI therapy (15 mg/day) was resumed. As the elevated thyroid hormone level improved, her liver enzyme level and body weight increased (Fig. 3). Liver ultrasonography showed irregular internal echogenicity and steatosis. We reinstituted the diet and exercise therapies, which subsequently controlled her body weight and liver enzyme level (Fig. 3).

### Discussion

As the prevalence of NASH increases, more clinicians need to know how to treat patients with NASH. Lifestyle interventions, such as diet and exercise therapies, are considered to be the first-line treatment for NASH because weight loss is an important factor for improving the liver enzyme levels, steatosis, and necroinflammation in the liver (12). However, it is difficult for patients with NASH to maintain motivation for diet and exercise therapies, and many patients fail to achieve their target weight loss (12, 13). Thus, the majority of patients are treated with pharmacological therapy. However, pharmacological therapy for NASH is insufficient (12, 14), and the expected effect is not often obtained. Therefore, new evidence on the effects of these new pharmacological approaches is needed.

Thyroid hormone stimulates the expression of uncoupling proteins in the mitochondria of fat and skeletal muscle, modulates adrenergic receptor numbers by enhancing the responsiveness of catecholamines, and controls metabolic and energy homeostasis (15, 16). Previous epidemic studies have examined the relationship between hypothyroidism and NAFLD, including NASH, and several studies have shown that hypothyroidism is a risk factor for NAFLD and NASH (6-10). However, the relationships between hyperthyroidism and NASH have not yet been examined. In the present patient with NASH complicated by Graves’ disease, her liver enzyme levels and body weight were both improved after the onset of Graves’ disease, and her thyroid hormone level was elevated. However, although her liver enzyme levels and body weight worsened after starting treatment for Graves’ disease, her thyroid hormone level improved. Interestingly, the body weight and serum tranaminase level appeared to have an inverse correlation with the serum thyroid hormone level in this patient. Reasons why the free T4 levels are not always consistent with the ALT levels over the patient’s clinical course are associated with the status of NASH. At the onset of Graves’ disease, the patient was already considered to be suffering from NASH with an elevated ALT level. After the diagnosis of NASH, the patient started diet therapy and exercise and substantially reduced her body weight. At the time of relapse, her body weight

### Table 1. Laboratory Data at Referral Visit.

| Test                        | Reference range |
|-----------------------------|-----------------|
| White blood cells (μL)      | 5,000 (3,900-9,800) |
| Hemoglobin (g/dL)           | 14 (13.5-17.6)  |
| Platelets (×10^3/μL)        | 14.3 (13.6-14.9) |
| Prothrombin time (%)        | 87.3 (80-120)   |
| Total bilirubin (mg/dL)     | 1.0 (0.1-1.1)   |
| Aspartate aminotransferase (IU/L) | 101 (9-37) |
| Alanine aminotransferase (IU/L) | 134 (3-49) |
| Alkaline phosphatase (IU/L) | 355 (104-338)  |
| γ-glutamyl transpeptidase (IU/L) | 88 (6-71)  |
| Albumin (g/dL)              | 4.6 (3.9-4.9)   |
| Uric acid (mg/dL)           | 4.7 (2.7-5.8)   |
| Blood urea nitrogen (mg/dL) | 7 (7-21)        |
| Creatinine (mg/dL)          | 0.57 (0.5-1.2)  |
| C-reactive protein (mg/dL)  | 0.16 ≤0.3       |
| Total cholesterol (mg/dL)   | 209 (113-233)   |
| Triglycerides (mg/dL)       | 86 (66-213)     |
| High-density lipoprotein cholesterol (mg/dL) | 47 (45-55) |
| Fasting plasma glucose (mg/dL) | 96 (70-110)  |
| Hemoglobin A1c (%)          | 5.4 (4.6-6.2)   |
| Thyroid stimulating hormone (μIU/mL) | 0.953 (0.5-5)  |
| Free thyroxine (ng/dL)      | 1.09 (0.9-1.7)  |
| Free 3,5,3’-triiodo-L-thyronine (pg/mL) | 2.96 (2.3-4) |
| Ferritin (ng/mL)            | 328 (27-211)    |
| Type IV collagen (ng/mL)    | 7.8 (6-8)       |
| Hyaluronic acid (ng/mL)     | 89 (60-50)      |
| Antinuclear antibody        | -               |
| Antimitochondrial antibody  | <5 index        |
| Hepatitis B surface antigen | -               |
| Antibody against hepatitis C virus | -    |
| Immunoglobulin G (mg/dL)    | 1,424 (870-1,700) |
| Immunoglobulin M (mg/dL)    | 94 (46-260)     |

Her laboratory tests indicated a suppressed TSH level, elevated free thyroid hormone levels, elevated anti-thyroid stimulating hormone receptor levels, and an alanine aminotransferase level of 26 IU/L (Table 2). Thyroid ultrasonography showed a diffuse goiter. According to these findings, we diagnosed the patient with reactivation of Graves’ disease and MMI therapy (15 mg/day) was resumed. As the elevated thyroid hormone level improved, her liver enzyme level and body weight increased (Fig. 3). Liver ultrasonography showed irregular internal echogenicity and steatosis. We reinstituted the diet and exercise therapies, which subsequently controlled her body weight and liver enzyme level (Fig. 3).
Table 2. Laboratory Data at Revisit.

| Test                        | Reference range   |
|-----------------------------|-------------------|
| White blood cells (/μL)     | 4,700 (3,900–9,800) |
| Hemoglobin (g/dL)           | 13.3 (13.5–17.6)  |
| Platelets ×10^3/μL          | 12.4 (13.1–36.9)  |
| Prothrombin time (%)        | 92 (80–120)       |
| Total bilirubin (mg/dL)     | 0.6 (0.1–1.1)     |
| Aspartate aminotransferase (IU/L) | 25 (9–37)       |
| Alanine aminotransferase (IU/L) | 26 (3–49)       |
| Alkaline phosphatase (IU/L) | 446 (104–338)    |
| γ-glutamyl transpeptidase (IU/L) | 37 (6–71)       |
| Uric acid (mg/dL)           | 5.5 (2.7–5.8)     |
| Blood urea nitrogen (mg/dL) | 8 (7–21)          |
| Creatinine (mg/dL)          | 0.4 (0.5–1.2)     |
| C-reactive protein (mg/dL)  | 0.1 ≤0.3          |
| Total cholesterol (mg/dL)   | 152 (113–233)     |
| Triglycerides (mg/dL)       | 163 (66–213)      |
| High-density lipoprotein cholesterol (mg/dL) | 53 (45–55)       |
| Plasma glucose (mg/dL)      | 104               |
| Hemoglobin A1c (%)          | 5.4 (4.6–6.2)     |
| Thyroid stimulating hormone (μU/mL) | <0.006 (0.5–5) |
| Free thyroxine (ng/dL)      | 2.29 (0.9–1.7)    |
| Free 3,5,3′-triiodo-L-thyronine (pg/mL) | 7.73 (2.3–4)     |
| Thyroid stimulating hormone receptor antibody (IU/L) | 6.1 (0–2)         |
| Thyroglobulin (ng/mL)       | 49.3 (0–32.7)     |
| Anti-thyroglobulin antibody (IU/mL) | 240.6 (0–27.9)   |
| Anti-thyroid peroxidase antibody (IU/mL) | 10.7 (0–15.9)    |

was lower than that at the onset of Graves’ disease due to hyperthyroidism and her diet and exercise therapy, thus the status of NASH at relapse was milder than that at the onset. For these reasons, the levels of free T4 in our case were not always consistent with the ALT levels. However, thyrotoxicosis and MMI can induce liver injury (17–19). In general, thyrotoxicosis-induced liver injury improves after thyrotoxicosis is removed by proper treatment for hyperthyroidism. MMI-induced liver injury usually occurs within the first few weeks of drug introduction and improves after dose reduc-
tion or withdrawal. In the present case, liver injury developed 3 months after the introduction of MMI therapy and was sustained even after the improvement of hyperthyroidism. Therefore, our case fit neither thyrotoxicosis- nor MMI-induced liver injury. Thyroid hormones control metabolic and energy homeostasis by thermogenesis, lipolysis, cholesterol metabolism, and several other metabolic pathways, and influence body weight (15, 16). Additionally, thyroid hormone receptor agonists can directly reduce hepatic steatosis by increasing hepatic fatty acid oxidation and the mitochondrial respiration rates (20-23). Therefore, we speculate that hyperthyroidism reduced the patient’s body weight and fat deposition in the liver via a direct effect. Moreover, in a large population-based cross-sectional study, Ittermann et al. reported that low free T4 concentrations were associated with hepatic steatosis (9). In addition, a thyroid hormone receptor β-selective agonist, which exhibits a similar effect as thyroid hormone without heart rhythm disturbance, has recently been used in clinical trials as a treatment candidate for dyslipidemia and fatty liver (20). These findings suggest that stimulation of thyroid hormone receptor might be a potential therapy in patients with NASH by controlling body weight and liver fat deposition.

In conclusion, our case showed that the patient’s liver enzyme levels and body weight improved with increasing thyroid hormone levels; however, the liver enzyme level and body weight were aggravated with the improvement of the thyroid hormone level. Therefore, hyperthyroidism may improve the pathological condition of NASH. When conventional therapy is not effective in patients with NASH, then stimulation with thyroid hormone receptor might be an additional treatment option for patients with treatment-resistant disease.

The authors state that they have no Conflict of Interest (COI).

References
1. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 129: 113-121, 2005.
2. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 346: 1221-1231, 2002.
3. Fargion S, Porzio M, Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. World J Gastroenterol 20: 13306-13324, 2014.
4. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity. Thyroid 16: 73-78, 2006.
5. Raftopoulos Y, Gagné DJ, Papasavas P, et al. Improvement of hypothyroidism after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg 14: 509-513, 2004.
6. Chung GE, Kim D, Kim W, et al. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol 57: 150-156, 2012.
7. Carulli L, Ballestri S, Lonardo A, et al. Is nonalcoholic steatohepatitis associated with a high-though-normal thyroid stimulating hormone level and lower cholesterol levels? Intern Emerg Med 8: 297-305, 2013.
8. Mazo DF, Lima VM, Stefano JT, Rabelo F, Faintuch J, Oliveira CP. Gluco-lipidic indices in treated hypothyroidism associated with nonalcoholic fatty liver disease. Arq Gastroenterol 48: 186-189, 2011.
9. Ittermann T, Haring R, Wallaschofski H, et al. Inverse association between serum free thyroxine levels and hepatic steatosis: results from the Study of Health in Pomerania. Thyroid 22: 568-574, 2012.
10. Eshraghian A, Dabbaghmanesh MH, Eshraghian H, Fattahi MR, Omrani GR. Nonalcoholic fatty liver disease in a cluster of Iranian population: thyroid status and metabolic risk factors. Arch Iran Med 16: 584-589, 2013.
11. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 94: 2467-2474, 1999.
12. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 52: 79-104, 2010.
13. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. Hepatology 49: 306-317, 2009.
14. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 385: 956-965, 2015.
15. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism 54: 1524-1528, 2005.
16. Muller R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev 94: 355-382, 2014.
17. Thompson P Jr, Strum D, Boehm T, Wartofsky L. Abnormalities of liver function tests in tyrotoxicosis. Mil Med 143: 548-551, 1978.
18. Nakamura H, Nob JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves’ disease. J Clin Endocrinol Metab 92: 2157-2162, 2007.
19. Heidari R, Niknahad H, Jamshidzadeh A, Abdoli N. Factors affecting drug-induced liver injury: antithyroid drugs as instances. Clin Mol Hepatol 20: 237-248, 2014.
20. Senese R, Lasala P, Leanza C, de Lange P. New avenues for regulation of lipid metabolism by thyroid hormones and analogs. Front Physiol 5: 475, 2014.
21. Vatner DF, Weismann D, Beddow SA, et al. Thyroid hormone receptor-β agonists prevent hepatic steatosis in fat-fed rats but impair insulin sensitivity via discrete pathways. Am J Physiol Endocrinol Metab 305: E89-E100, 2013.
22. Perra A, Simbula G, Simbula M, et al. Thyroid hormone receptor-β agonists prevent hepatic steatosis in fat-fed rats but impair insulin sensitivity via discrete pathways. Am J Physiol Endocrinol Metab 305: E89-E100, 2013.
23. Cable EE, Finn PD, Stebbins JW, et al. Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. Hepatology 49: 407-417, 2009.

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