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Case Report

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Hypothyroidism and Non-Alcoholic Fatty Liver Disease

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Abstract

Data supporting an association between primary hypothyroidism and non-alcoholic fatty liver disease (NAFLD) is lacking. Thyroid hormones are totally involved in the regulation of body weight, lipid metabolism, and insulin resistance. Therefore, thyroid hormones may have a role in the pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH). The results of studies investigating the association between NAFLD and thyroid dysfunction have been inconsistent; many have provided data supporting the association, while a few others have refuted it. This report presents the case of a 56-year-old obese Hispanic man who was diagnosed with liver cirrhosis secondary to NAFLD and presented 3 months later with severe hypothyroidism.

Keywords: Liver cirrhosis; Non-alcoholic fatty liver disease; Hypothyroidism

Introduction

Non-alcoholic fatty liver disease (NAFLD) is hepatic steatosis with no identifiable secondary causes of hepatic fat accumulation, such as significant alcohol consumption or long-term use of a steatogenic medication. NAFLD is considered a hepatic feature of metabolic syndrome, and its clinical presentation ranges from asymptomatic to full-blown liver cirrhosis [1]. Despite the close relationship between thyroid dysfunction and metabolic syndrome [1], evidence supporting the association between hypothyroidism and NAFLD is still weak, and the pathophysiology underlying this association remains unclear. Several studies have investigated the association between NAFLD and thyroid dysfunction; however, their results have been inconsistent [2-4]. In this report, we present a case of severe hypothyroidism in a patient with liver cirrhosis secondary to NAFLD.

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Case Report

A 56-year-old obese man with a history of liver cirrhosis secondary to NAFLD presented with altered mental status. He was intubated in the emergency department and admitted to the intensive care unit (ICU). He has no history of alcohol abuse, blood transfusion, or recreational drug use. Vital signs were normal, with body mass index (BMI) of 36. Physical exam showed thickened and dry skin, goiter and bilateral non-pitting edema. Labs showed ammonia level 0.139 mmol/L (0.011 - 0.032 mmol/L), white blood cells (WBCs) $2.5 \times 10^3/\mu L$, hemoglobin (HGB) 10.4 g/dL, platelets (PLTs) $173 \times 10^3/\mu L$, mean corpuscular volume (MCV) 100 fL, total bilirubin 0.91 mg/dL, alkaline phosphatase 96 units/L, aspartate aminotransferase (AST) 33 units/L and alanine aminotransferase (ALT) 18 units/L. Electrocardiogram and arterial blood gases were unremarkable. Thyroid-stimulating hormone (TSH) was 380 mU/L and free thyroxine (T4) 0.18 ng/dL. Chest X-ray showed cardiomegaly and normal lungs. The patient was diagnosed with severe hypothyroidism and was initially managed with intravenous levothyroxine and then oral liothyronine. He was also co-managed for hepatic encephalopathy. Afterwards, he had an uneventful hospital course; mental status had improved and was extubated on day 3.

Three months prior to this admission, the patient presented with dyspnea and progressive abdominal distension. Albumin level was 2.3 g/dL, total bilirubin 1.37 mg/dL, alkaline phosphatase 114 units/L, AST 60 units/L, ALT 28 units/L, prothrombin time (PT) 13.5 s, international normalized ratio (INR) 1.24 (high), partial thromboplastin time (PTT) 33.6 s, WBC $2.3 \times 10^3/\mu L$, red blood cell (RBC) $2.35 \times 10^6/\mu L$, HGB 9.0 g/dL, hematocrit (HCT) 26%, MCV 104 fL, and PLT $146 \times 10^3/\mu L$. Abdominal computed tomography (CT) scan showed shrunken and nodular cirrhotic liver, enlarged spleen, para-esophageal varices and large ascites suggesting liver cirrhosis and portal hypertension. Workup at that time was negative for hepatitis B surface antigen, hepatitis C antibody, alpha-1 antitrypsin, ceruloplasmin, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCAs), anti-mitochondrial antibody and analysis for hereditary hemochromatosis (HH) mutations. Therefore, the diagnosis of liver cirrhosis secondary to NAFLD was established.

Discussion

During the patient's first admission, he presented with abdominal distension and features of decompensated liver disease. Laboratory workup revealed impaired synthetic and metabolic hepatic function, and there was radiological evidence of liver cirrhosis in an abdominal CT scan. The patient denied alcohol use, and other potential etiologies of liver cirrhosis were ruled out with negative testing of hepatitis and autoimmune panels, Wilson's disease, and hereditary hemochromatosis. Given his elevated BMI, nonalcoholic steatohepatitis (NASH) was assumed to be the underlying etiology of liver cirrhosis. Since the focus was the liver cirrhosis, the treating team did not pursue a thyroid function test during this admission.

On the patient's second admission, non-pitting edema (myxedema), goiter, and thickened skin were noted, findings that were probably missed during the first admission. Non-pitting edema and thickened skin result from infiltration of the skin with glycosaminoglycan and associated water retention, which take a long time to manifest in a hypothyroidism patient [1]. Therefore, we believe the patient has had undiagnosed thyroid disease for a prolonged period.

While the exact pathophysiology behind the association between NAFLD and hypothyroidism is not well-known, several mechanisms have been suggested in the literature. On one hand, NAFLD pathogenesis involves disturbances in lipid metabolism that lead to excessive accumulation of triglycerides within hepatocytes [4], and eventually, the formation of fatty liver. Additionally, NAFLD is often accompanied by features of metabolic syndrome, particularly abdominal obesity and type 2 diabetes mellitus [1, 5]. Therefore, it can be seen as a hepatic manifestation of metabolic syndrome. On the other hand, hypothyroidism mediates hyperlipidemia, obesity, and insulin resistance, all of which are components of metabolic syndrome [1]. Additionally, hypothyroidism is prevalent in patients with type 2 diabetes mellitus [5]. Therefore, similar metabolic abnormalities in hypothyroidism and NAFLD suggest a possible association between the two conditions.

Leptin is an adipocytokine that has roles in the regulation of energy homeostasis, glucose and lipid metabolism. It is proposed to be responsible for this association, as its levels are increased in both hypothyroidism and NAFLD patients [6]. While its increase was associated with the severity of NAFLD, leptin is anti-steatotic during the initial stages of NAFLD and is pro-inflammatory and pro-fibrotic during disease progression. Increased levels of leptin in hypothyroidism patients increase collagen production and insulin resistance in the liver [7]. Insulin resistance fosters hepatic *de novo* lipogenesis (DNL) and impairs suppression of lipolysis in adipose tissue; both can lead to the accumulation of fatty acids (FAs) in the liver [8].

Fibroblast growth factor-21 (FGF-21) has been suggested to have a role in the association between NAFLD and hypothyroidism. It induces glucose uptake in mouse and human adipocytes and can improve glucose homeostasis after being administered to obese mice [9]. Increased serum levels of FGF-21 in NAFLD patients have been described in several human studies, indicating a relative FGF-21 resistance in these patients [10-12]. One recent study has shown that administration of triiodothyronine (T3) to mice can induce specific dose-dependent hepatic expression of FGF-21 [13]. These findings together indicate an FGF-21 pathway in NAFLD patients, although the precise mechanism remains unclear. Increased plasma levels of FGF-21 in patients with hypothyroidism have also been observed in a recent study by Lee et al [14].

One theory of NAFLD pathophysiology is based on hepatic damage through mitochondrial dysfunction, oxidative stress and reactive oxygen species (ROS) production. Free fatty acids (FFAs) undergo β-oxidation in the mitochondria under physiological conditions. Excessive accumulation of FFA in the hepatocytes leads to FFA oxidation within the mitochondria, leading to overproduction of ROS [7]. ROS then activates the lipid peroxidation pathway and then hepatocytes that induces inflammation and fibrosis [7]. It has been reported that thyroid dysfunction alters cardiolipin and mitochondrial respiration, leading to mitochondrial dysfunction in skeletal muscle [15]. Moreover, oxidative stress markers, including ROS and lipid peroxidation markers, have been observed in patients with hypothyroidism [16].

Several studies have explored the association between hypothyroidism and NAFLD. Mantovani et al in a meta-analysis of 15 observational studies concluded that hypothyroidism is significantly associated with NAFLD [2]. The same study found that hypothyroidism was associated with a 42% increased risk of imaging-defined or biopsy-proven NAFLD independent of age, sex, BMI, and other common metabolic risk factors. Moreover, Guo et al, in a larger meta-analysis involving 61,548 participants, reported that elevated TSH levels were significantly associated with a higher risk of NAFLD regardless of age and euthyroid status [3].

On the other hand, Jaruvongvanich et al conducted a meta-analysis of 14 studies involving 7,191 NAFLD patients that concluded not only that there was no significant association between NAFLD and hypothyroidism but also that patients with NAFLD had no significant difference in thyroid hormone levels (i.e. free T3, free T4, and TSH) compared to non-NAFLD controls [4]. Compared to Mantovani et al and Guo et al, Jaruvongvanich et al did not include studies on adolescents [17, 18] or cross-sectional or longitudinal studies published on adults from 2016 to 2018 [19-21].

Conclusions

Although an association has been proposed, a causal relationship between NAFLD and primary hypothyroidism has not yet been established in the literature. Large clinical prospective studies are warranted to confirm the clinical association and support the underlying mechanisms of between hypothyroidism and NAFLD.

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None to declare.

Conflict of Interest

The authors have no conflict of interest to disclose.

Informed Consent

Verbal informed consent was obtained from the patient for anonymized information to be published in this article.

Author Contributions

RH and BK contributed to the acquisition and interpretation of the data, drafting and critically revising the manuscript, approving the final publishable version of the manuscript, and agreeing to be accountable for all aspects of the work. AT and JK contributed to the acquisition of the data, drafting the manuscript, approving the publishable version of the manuscript, and agreeing to be accountable for all aspects of the work. NE, SP and FM are all contributed to drafting the manuscript, approving the final publishable version of the manuscript, and agreeing to be accountable for all aspects of the work.

Data Availability

The authors declare that data supporting the findings of this manuscript are available within the article. Also, any inquiries regarding supporting data availability of this article should be directed to the corresponding author Randa Hazam.

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