A Review of Thyroid dysfunction and Cirrhosis

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Abstract

Liver cirrhosis is one of the most common diseases affecting Egyptian population and viral hepatitis is the most common etiological factor causing hepatic cirrhosis. Among the hepatitis viruses, hepatitis C virus appears to be a common cause of liver cirrhosis. Cirrhosis affects 2.8 million people and was the cause of death in 1.3 million in 2015. Clinically, cirrhosis may be compensated or decompensated, depending upon the absence or presence of the complications of cirrhosis. Patients with decompensated cirrhosis usually present to different medical wards with moderate to severe ascites, variceal bleeding, hepatic encephalopathy, hepatorenal or hepatopulmonary syndrome or with hepatocellular carcinoma. Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically, it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures. Approximately 60% of patients with cirrhosis will develop ascites within 10 years after diagnosis of this disease. Refractory ascites, which develops in 5% - 10% of all patients with cirrhotic ascites, has a high mortality rate. A complex relationship exists between thyroid and liver in health and disease. Liver plays an essential physiological role in thyroid hormone activation and inactivation, transport, and metabolism. Alternately, activities of hepatocytes and hepatic metabolism are affected by thyroid hormones. Serum liver enzyme abnormalities observed in hypothyroidism may be related to impaired lipid metabolism, hepatic steatosis or hypothyroidism-induced myopathy. Severe hypothyroidism may have biochemical and clinical features such as hyperammonemia and ascites, impersonating those of liver failure. Liver function tests are frequently abnormal also in hyperthyroidism, because of oxidative stress, cholestasis, or enhanced osteoblastic activity.

Key Words: Thyroid dysfunction, Cirrhosis

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Introduction

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically, it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures ***(1)***.

This distortion results in increased resistance to portal blood flow and hence, in portal hypertension and hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for esophageal varices and hepatocellular carcinoma ***(2)***.

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Alcoholic liver disease and hepatitis C are the most common causes in the Western world, while hepatitis B is more common in most parts of Asia and sub-Saharan Africa. After the identification of the hepatitis C virus in 1989 and nonalcoholic steatohepatitis (NASH) in obese and diabetic subjects, the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is rarely made ***(2)*.**

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion ***(3)*.**

This process leads to pronounced hepatic microvascular changes, characterized by sinusoidal remodeling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarization of hepatic sinusoids), formation of intra hepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction. ***(4)*.**

A complex relationship exists between thyroid and liver in health and disease. Liver plays an essential physiological role in thyroid hormone activation and inactivation, transport, and metabolism. Alternately, activities of hepatocytes and hepatic metabolism are affected by thyroid hormones. Serum liver enzyme abnormalities observed in hypothyroidism may be related to impaired lipid metabolism, hepatic steatosis or hypothyroidism-induced myopathy. Severe hypothyroidism may have biochemical and clinical features such as hyperammonemia and ascites, impersonating those of liver failure. Liver function tests are frequently abnormal also in hyperthyroidism, because of oxidative stress, cholestasis, or enhanced osteoblastic activity ***(5)*.**

A. Liver abnormalities in thyroid disease:

- **Hypothyroidism:**

Since thyroid hormones have a role in cell metabolism of the whole body, it is not surprising that liver may also be affected by hypothyroidism. The relationship among liver and thyroid is not completely understood, and thyroid function is not commonly investigated in patients with liver diseases and vice versa ***(5)*.**

Serum liver enzymes are frequently abnormal in hypothyroid patients. Hypothyroidism may be related with slightly increased serum alanine amino-transferase (ALT) and gamma glutamyl transferase (GGT) concentrations, which might be due to diminished lipid metabolism and hepatic steatosis occurred in hypothyroidism. In addition, an increase in the aspartate amino-transferase (AST) and lactate dehydrogenase (LDH) might be related to hypothyroidism-induced myopathy.***(6).***

Table 1. Biochemical liver abnormalities that may be found in patients with thyroid dysfunction ***(5)*.**

	Hypothyroidism		**Thyrotoxicosis/ hyperthyroidism**	
Alanine aminotransferase (ALT)	Normal/high	Diminished lipid metabolism	High	Increased oxygen consumption, with relative hypoxia leading to apotosis and oxidative stress
		Hepatic steatosis		
Aspartate aminotransferase (AST)	High	Hypothyroidism-induced myopathy	High	Increased oxygen consumption, with relative hypoxia leading to apotosis and oxidative stress
Gammaglutamyl transferase (GGT)	Normal/high	Diminished lipid metabolism	High	Cholestasis
		Hepatic steatosis		
Alkaline phosohatase (ALP)		–	High	Enhanced osteoblastic activity
				Cholestasis
				(if high levels of GGT and bilirubin coexist)
Bilirubin		–	High	Cholestasis
Lactate dehydrogenase (LDH)	High	Hypothyroidism-induced myopathy		

Hypothyroidisms have a significant role in development of non-alcoholic fatty liver disease (NAFLD). NAFLD is the commonest liver disease and leading cause of cryptogenic cirrhosis around the world. The prevalence of NAFLD seems to be inversely related to FT4 levels; accordingly, decreased serum FT4 concentrations increase the risk of NAFLD in a dose-dependent manner ***(7)***. 6976

Several mechanisms might contribute in development of NAFLD in patients with hypothyroidism ***(8)*:**

(1) hypothyroidism is related with dyslipidemia and higher body mass index, which are in turn bound to an increased NAFLD risk

(2) thyroid hormone induces intrahepatic lipolysis through lipophagy, which includes the sequestration and degradation of lipid droplets within hepatic lysosomes, eventually resulting in decreased triglyceride clearance and increased hepatic accumulation of triglycerides

(3) hypothyroidism-related insulin resistance may induce lipogenesis, thus promoting storage of free fatty acids in the liver

(4) hypothyroidism increases adipocytokines, such as TNFα

and leptin, and decreases adiponectin, thereby contributing to hepatic inflammation and fibrosis via a direct effect or indirectly through an increase in oxygen free radicals

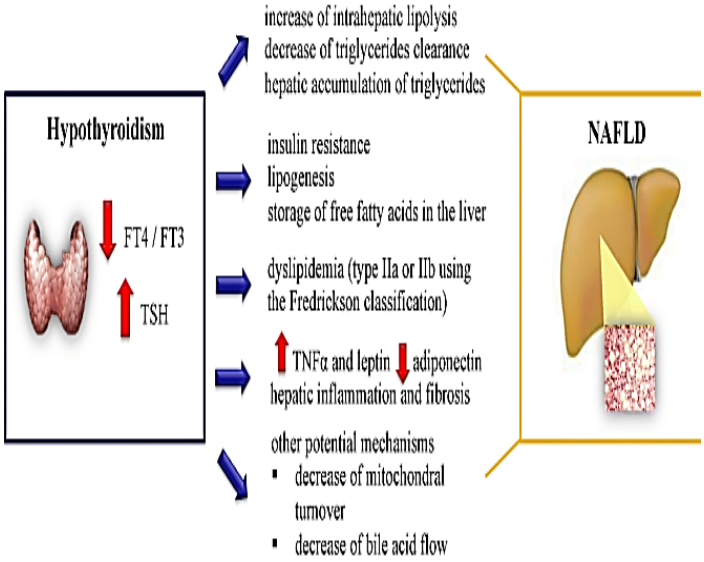

Figure 1: Possible pathogenic mechanisms underpinning hypothyroidism-related non-alcoholic fatty liver disease ***(5)*.**

Thyroid hypofunction may be a cause for gallbladder stone disease. Gallbladder stone disease is very common, with a prevalence of 10 - 15% in the general population. Cholesterol gallstones result from precipitation of cholesterol crystals from supersaturated bile. Hypothyroidism may favor gallstone formation through three different mechanisms ***(9)***:

(1) a decrease in bilirubin excretion rate due to the decreased activity of bilirubin UDP-glucuronyltransferase, thereby impairing hepatic bilirubin metabolism.

(2) hypercholesterolemia, characterized by higher concentrations of both total cholesterol and LDL cholesterol.

(3) hypotonia of the gallbladder causing delayed emptying of the biliary tract**.**

Finally, some clinical features of hypothyroidism may impersonate those seen in hepatic dysfunction. Fatigue, mental status changes, weakness, myalgias, and muscle cramps, dyspnea on exertion, edema, and pericardial effusion are observed both in hypothyroidism, especially in severe forms, and hepatic failure. In particular, two unusual manifestations of hypothyroidism might make the correct diagnosis more difficult: hyperammonemia and myxedema ascites ***(10).***

Hyperammonemia has been rarely reported in patients with severe hypothyroidism, particularly if chronic liver disease is concomitant. The exact mechanism whereby hyperammonemia occurs in severe hypothyroidism has not been fully understood. In a murine model, hypothyroidism seemed to increase urea synthesis enhancing proteolysis and affecting urea metabolism. Other co-factor may be the cause of the decreased intestinal motility due to hypothyroidism, which might favor bacterial production and absorption of ammonia, and the decreased glutamine synthetase activity, which might reduce glutamine utilization by the urea cycle in the liver ***(11)*.**

- **Thyrotoxicosis and hyperthyroidism:**

The liver is known to be an important target of thyroid hormone excess. Liver function tests are frequently abnormal in patients with newly diagnosed thyrotoxicosis/hyperthyroidism, with a prevalence ranging between 15 and 76% ***(12)*.**

In most cases, hyperthyroidism causes only minor changes in liver function and histology. At light microscopy common findings are non-specific: mild lobular inflammatory infiltrate, nuclear irregularities, and Kupffer cell hyperplasia; electron microscopy may show hyperplasia of the smooth endoplasmic reticulum, reduced cytoplasmic glycogen, and an increase in mitochondria size and number. If hyperthyroidism is severe, hepatic damage may be worse, leading to centrizonal necrosis and perivenular fibrosis ***(5)*.**

Hyperthyroidism due to autoimmune thyroid disease, particularly Graves' disease, could also be associated with autoimmune hepatobiliary diseases, such as primary biliary cirrhosis and autoimmune hepatitis. A case report has described a patient with Graves' disease, heart failure, jaundice, and positive autoimmune markers for autoimmune cholangitis ***(13)*.**

B. Liver abnormalities due to thyroid disease treatment:

Levothyroxine (LT4) is the treatment of choice for hypothyroidism and a safe medication if the dose is appropriate. In overtreated patients (iatrogenic thyrotoxicosis), among other manifestations, liver abnormalities may occur similar to those observed in endogenous hyperthyroidism. Immuno-allergic hepatitis or hypersensitivity reactions to levothyroxine associated with liver enzyme increase and mild jaundice have been observed ***(14)*.**

Interestingly, these LT4-associated liver abnormalities were in Japanese patients, suggesting a possible genetically determined predisposition to idiosyncratic hypersensitivity reactions ***(5)***.

C. Thyroid abnormalities in liver diseases:

- **Chronic hepatitis C**

In addition to hepatic complications, chronic HCV infection may have several extrahepatic consequences, including endocrine and metabolic diseases, in particular type 2 diabetes mellitus and thyroid dysfunction. Autoimmune thyroid disorders (AITD), not infrequently associated with thyroid dysfunction, can be detected in a significant proportion of chronically HCV-infected patients, before antiviral drug treatment ***(15)***.

In particular, Hashimoto's thyroiditis is the most common thyroid disorder reported in these patients. In most studies, approximately 10 -15% of the patients had positive thyroid antibodies before starting interferon (IFN) treatment ***(16)***.

- **Liver cirrhosis**

The most common finding is a decrease in serum total T3 and free T3, an increase in reverseT3, in the presence of normal or high serum TSH levels. Serum T3 concentration is negatively correlated with the Child – Turcotte - Pugh score, indicating a direct relationship between severity of liver dysfunction and changes in circulating thyroid hormones. Cirrhotic patients with hepatic encephalopathy have serum FT3 levels significantly lower than cirrhotic patients without encephalopathy, suggesting that serum FT3 concentrations are a prognostic marker in these patients. Several pathogenic mechanisms explain these thyroid function changes, including: (1) abnormalities in serum concentrations of thyroid hormone-binding proteins. (2) inhibition of type 1 deiodinase, that causes decreased conversion of T4 to T3, as well as preserved activity of type 2 deiodinase, causing increased T4 conversion into rT3. (3) impaired hepatic clearance of reverse T3. Compared to healthy controls, patients with cirrhosis have significantly lower levels of both FT3 and FT4 ***(17)***.

The decrease in serum FT3 and FT4 levels in association with normal TSH values may be consistent with relative and functional central hypothyroidism, as observed in non-thyroidal illness. On the other hand, although the prevalence of thyroid autoimmunity is not significantly increased in patients with liver cirrhosis, an increase in serum TSH concentrations has also been reported in cirrhotic patients, suggesting primary hypothyroidism. Hyperthyroidism has been also reported in patients with cirrhosis, although less frequently than hypothyroidism ***(18)***.

- **Hepatocellular carcinoma and cholangiocarcinoma**

Although mechanisms whereby hypothyroidism can favor the occurrence of HCC development are unclear. Risk of HCC may be increased in patients with NASH who have hyperlipidemia, decreased fatty acid oxidation, insulin resistance, and lipid peroxidation, all conditions often found in hypothyroidism ***(19)***.

Patients with HCC of unknown etiology seem to have a significantly higher probability of being hypothyroid compared to patients with HCV infection-related HCC and controls. However, little is known about the underlying mechanisms linking thyroid hormones to HCC development ***(20)***.

Some human hepatocellular carcinomas (HCCs) may produce thyroxine-binding globulin (TBG), which can significantly decrease in serum after resection of the tumor. HCC is a possible, although rare, cause of thyroid metastases. Therefore, the list of cancers which potentially metastasizing to the thyroid (as kidney, lung, breast and gastrointestinal tract cancers, rarely nasopharyngeal carcinoma, choriocarcinoma, osteosarcoma, leiomyosarcoma, liposarcoma, melanoma, and neuroendocrine tumors) should also include HCC. When it happens, HCC metastasizes to thyroid either synchronously with the diagnosis of primary tumor or years after its cure ***(21)***.

All patients with a history of cancer, even remote, should be evaluated for possible metastasis when a new thyroid lesion is discovered, particularly if ultrasound reveals a thyroid nodule with suspicious features. Cholangiocarcinoma (CCA) is a malignancy of the biliary duct system that may originate in the liver or extrahepatic bile ducts, which terminate at the ampulla of Vater. Similar to HCC, CCA is a very rare cause of metastasis to the thyroid ***(22)***

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