Co-Morbid Hypothyroidism and Liver Dysfunction: A Review

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ABSTRACT: The liver and thyroid hormones interact at multiple levels to maintain homoeostasis. The liver requires large adequate amounts of thyroid hormones to execute its metabolic functions optimally, and deficiency of thyroid hormones may lead to liver dysfunction. Hypothyroidism has been associated with abnormal lipid metabolism, non-alcoholic fatty liver disease (NAFLD), hypothyroidism-induced myopathy, hypothyroidism-associated gallstones and occasionally, interferon-induced thyroid dysfunction. NAFLD remain an important association with hypothyroidism and further studies are needed that specifically compare the natural course of NAFLD secondary to hypothyroidism and primary NAFLD. Hepatic dysfunction associated with hypothyroidism is usually reverted by normalizing thyroid status. Large scale studies geared towards finding new and effective therapies, especially for NAFLD are needed. The clinician must be aware that there exists overlapping symptomatology between liver dysfunction and severe hypothyroidism which may make delay the diagnosis and treatment of hypothyroidism; this requires a high index of suspicion.

KEYWORDS: Hypothyroidism, thyroid dysfunction, liver dysfunction, hepatic dysfunction

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Introduction

The activities of nearly all cells in the body are affected by thyroid hormones. Their normal physiology result in increased basal metabolic rate, affect neural maturation, and regulate growth of long bones with the help of growth hormone. Thyroid hormones also increase the body's sensitivity to catecholamines.[1] They regulate protein, fat, carbohydrate, and vitamin metabolism. The synthesis of thyroid hormones are under the influence of many physiological and pathological stimuli.[1]

Hypothyroidism, a deficiency of thyroid hormones results in many non-specific manifestations such as dry skin, coarse facial features, fatigue, loss of energy, cold intolerance, menstrual abnormalities, bradycardia weight gain, pericardial effusion amongst others.

A population-based study in the United States (US) reported hypothyroidism prevalence of 3.7%, where hypothyroidism was defined as TSH levels exceeding 4.5 mIU/.[2] Hypothyroidism is more prevalent in elderly populations, with 2% to 20% of older age groups having some form of hypothyroidism. In the NHANES 1999-2002, it was found out that among individuals aged 12 to 49 years, the odds of having hypothyroidism were 5 times greater in persons aged 80 years and above.[2] The Framingham study also found the prevalence of hypothyroidism (defined as TSH $>$ 10 mIU/L) to be 5.9% and 2.4% of women and men older than 60 years respectively.[3] Worldwide, and in less-developed countries, iodine deficiency remains the most common cause, however, autoimmune thyroid disease (Hashimoto disease) is the most common cause of hypothyroidism in areas of adequate iodine intake.

At multiple levels, the liver and thyroid hormones, thyroxine (T4) and 3,5,3[1] triiodothyronine (T3) interact to maintain homoeostasis. These 2 biologically active thyroid hormones, T4 and T3 are synthesized in the thyroid gland, but in addition T3 is synthesized in other tissues.[4,5] Most of T3 (80%) is formed in extrathyroidal tissue (commonly the liver and kidney and rapidly) by 5[1]-deiodination of T4. It degraded at a rate of approximately 75% per day through deiodination.[4,5] All of T4 is produced in the thyroid gland at about 80 to 100mcg per day, with a daily degradation rate of 10%. Out of the approximately 80% of T4 that is deiodinated, 40% form T3 and 40% reverse T3 (rT3). The remaining 20% is form tetraiodothyroacetic acid (tetrac) in the liver after undergoing conjugation with glucoronide and sulphate, deaminated and finally decarboxylation.[4,5]

Majority (99%) of thyroid hormones (T4 and T3) in serum are protein-bound to thyroxine-binding globulin (TBG), transthyretin, albumin, and lipoproteins. These ensures that serum free thyroid hormones are in a dynamic equilibrium within narrow limits that ensures immediate and continuous availability to tissues. The biological activity of thyroid hormones are determined by the serum free T4 and T3 concentrations.[4,5]

Adequate amounts of thyroid hormones are needed for the optimal metabolic functioning of the liver. The levels of ligandin, an anion-binding protein is regulated by thyroid hormones, which in turn affect the enzymatic activity of glucuronyltransferase in maintaining the metabolism of bilirubin.[6]

Methodology

The Review focussed on literature search in English language using MEDLINE via Ovid and EMBASE databases from the

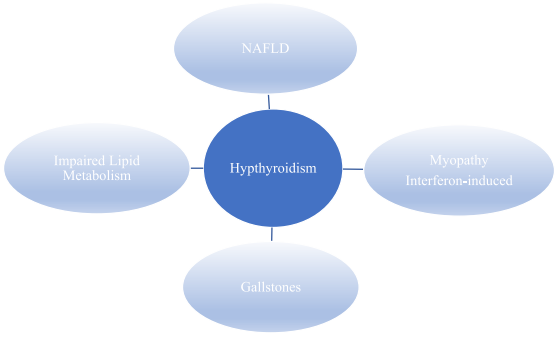

Figure 1. Causes of hypothyroidism-associated liver disease.[7,8]
Abbreviations: NAFLD, non-alcoholic fatty liver disease.

period January 1990 to August 2023. Six random and relevant literature published before 1990 were included. Key search terms included hypothyroidism, thyroid dysfunction, liver dysfunction, liver enzymes, hepatic steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic dysfunction-associated steatotic liver disease, and metabolic dysfunction-associated steatohepatitis.

Causes of liver dysfunction associated with hypothyroidism

Liver dysfunction associated with hypothyroidism may be due to diseases related to the thyroid gland, or infrequently, thyroid hormone use.[7] The liver dysfunction is believed to be as a result of impaired lipid metabolism, non-alcoholic fatty liver disease (NAFLD), hypothyroidism-induced myopathy, hypothyroidism-associated gallstones, thyroid hormone use, and occasionally, interferon-induced thyroid dysfuntion (Figure 1).[7,8] The pattern of liver dysfunction associated with hypothyroidism are varied.[7] Hypothyroidism may be associated with slightly increased serum gamma glutamyl transferase (GGT) and alanine amino-transferase (ALT), a finding which is thought to be due to reduced metabolism of lipids and hepatic steatosis associated with hypothyroidism.[9] Also hypothyroidism-induced myopathy may be associated with increased serum levels of aspartate amino-transferase (AST) and lactate dehydrogenase (LDH) independently of liver dysfunction,[10] whilst obstructive jaundice may be caused by hypothyroidism-associated gallstones.[11]

Non-alcoholic fatty liver disease (NAFLD) and fatty infiltration of the liver

Non-alcoholic fatty liver disease (NAFLD) is associated with hepatic steatosis confirmed by imaging or histology in the absence of secondary causes of fat accumulation in the liver, such as heavy alcohol consumption and the long-term use of a steatogenic medications.[12] NAFLD, as a spectrum of diseases, histologically may include non-alcoholic fatty liver (NAFL) or steatotic liver, non-alcoholic steatohepatitis (NASH), bridging fibrosis, and cirrhosis. The terms NAFLD and NASH have recently been replaced with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) respectively, to reflect its strong association with metabolic syndrome such as obesity, type 2 diabetes, impaired glucose tolerance hypertension, and dyslipidaemia.[13] The global prevalence of NAFLD in a metanalyses was 24%, with subcontinental prevalence of 32% in Middle East, 31% in South America, 23% in Europe, 27% in Asia, 14% in Africa and 24% in USA.[14] Apart from liver-related morbidity described earlier, NAFLD maybe associated with extrahepatic conditions such as cardiovascular diseases, chronic kidney diseases and other endocrine conditions such as type 2 diabetes, insulin resistance and metabolic syndrome, and thyroid dysfunction.[14-19] Increasingly, untreated hypothyroidism is being recognized as an independent risk factor for NAFLD with a reported prevalence of 15.2 to 36.3% among patients with NAFLD.[20] The prevalence of NAFLD seems to be inversely related to FT4 levels in a dose-dependent manner,[21] which was supported by the findings of a large prospective cohort study that found that even with subclinical hypothyroidism, there is an increased risk of developing NAFLD and fibrosis.[22]

Pathophysiology. Several mechanisms have been proposed to mediate the relationship of NAFLD and hypothyroidism (Figure 2). Some metabolic conditions have been associated with NAFLD such as insulin resistance, obesity and dyslipidaemia.[23,24] Obesity and insulin resistence appear to be important, and associated with hypothyroidism compard with general population.[25] Whilst insulin resistance accelerate liver damage,[26] obesity underpins the relationships between NAFLD and hypothyroidism in rat models.[27] Again, overt hypothyroidism can accelerate fatty infiltration of the liver, a situation which increases the risk of NAFLD.[28] Lipid metabolism in the liver is regulated by thyroid hormones through the thyroid hormone receptor (TSR) β leading to decrease in cholesterol and triglyceride levels.[29-31] Therefore, low thyroid hormones in hypothyroidism lead to dyslipidaemia: high cholesterol levels, low-density lipoproteins (LDL) and triglyceride due to the delivery of hepatic fatty acids but with a reduced level of high-density lipoprotein (HDL).[32] The dyslipidaemia resulting from hypothyroidism appear to play a role in the development of NAFLD.[28,33] In addition, derivatives of thyroid hormones metabolism such as 3,5-Diiodo-l-thyronine (T2) has shown in vitro lipid-lowering potential by causing reduction the excess fat in cultured hepatocytes[34,35]; a deficiency of these derivatives in hypothyroidism may lead to reduction in lipid levels. Another mechanism that TSH impact on liver function is through its direct effect on hepatocytes mediated through TSH receptor,[36-38] which heighten hepatic gluconeogenesis, decrease bile acid synthesis, promote hyperlipidaemia from the inhibition of phosphorylation of HMG-CoA reductase,[37-39] with the

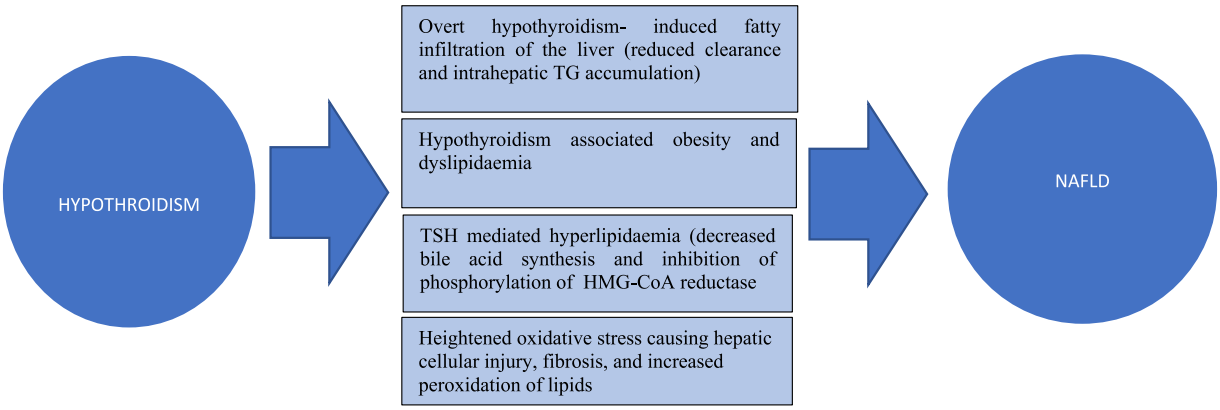

Figure 2. Proposed mechanisms of hypothyroidism associated NAFLD.[23,24,26,27,29-31,37-39,43]
Abbreviations: HMG-CoA, hydroxymethylglutaryl-coenzyme A; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride.

resultant effect of promoting NAFLD. Finally, patients with hypothyroidism have increased oxidative stress and its markers (increased tumour necrosis factor (TNF)α and leptin with reduced adiponectin) which is a well-known mechanism for the development of NAFLD.[40,41] The heightened oxidative stress and its markers cause cellular injury and insulin resistance through reduction in beta-oxidation of fatty acids and increased peroxidation of lipids.[40,42]

Some studies that have explored the interrelationships between NAFLD and thyroid function tests with varied conclusions.[8,44,45] A metanalysis by He et al[8] showed that individuals with subclinical and overt hypothyroidism were at a significantly higher risk for NAFLD compared to euthyroid subjects. This was true in the whole-group and sub-group analyses. Another systematic review and meta-analysis by Jaruvongvanich et al however showed that NAFLD is not associated with thyroid hormone levels and hypothyroidism.[45] In a systematic review of 26 studies and over 61 000 participants, regardless of age, being euthyroid or hypothyroid, patients with NAFLD/NASH had significantly higher TSH levels than controls.[44] Such differences remained even among participants with normal TSH, and with the progression of NAFLD, TSH further increased. However, they found out that results were inconsistent among the subgroup meta- analyses of subclinical and overt hypothyroidism, possible because of the smaller numbers involved. No consistent findings were also made between NAFLD on one hand and total T3 and total T4. They conclude that TSH level may be an important risk factor for the development and progression of NAFLD, independent of thyroid hormones.[44]

A 2-step hypothesis is widely believed as the mechanism for the development of NAFLD. The intracytoplasmic accumulation of lipids (step-1) triggers cytotoxic events and inflammatory responses within the liver cells (step-2). Since the liver is the central organ involved in triglyceride metabolism, abnormal hepatocyte accumulation enhances fatty liver formation. A positive correlation has been shown between triglyceride concentration and TSH levels,[46,47] a relationship that persists even when TSH levels are within the normal range.[48] Putatively, the mechanism for the TSH-induced triglyceride accumulation and hepatic steatosis, is by TSH binding to TSH-receptor which then triggers hepatic SREBP-1c activity via the cAMP/PKA/PPARa pathway associated with decreased AMPK, which further increases the expression of genes associated with lipogenesis.[49]

Treatment. Potential treatment of NAFLD associated with hypothyroidism appear to be gaining more insights.[7] The cholesterolaemia induced by hypothyroidism, which is thought to promote NAFLD,[50] has been found to normalise rapidly with treatment with thyroid hormone.[51] The observation is believed to be due to the reduction the levels of TSH following the administration of thyroxine, which plays a critical role in the development and progression of NAFLD, independent of thyroid hormones. Again, in vivo studies have shown that 3,5-Diiodo-l-thyronine (T2), a derivative of thyroid hormone, can cause the reduction in lipid accumulation by stimulating the of lipid oxidation pathways.[52,53] These findings hold promise for the use of thyroid hormone or its derivatives for managing NAFLD in the future.[53,54] We believe that large placebo-controlled trials are needed for further investigate and establish whether treatment of hypothyroidism will lead to the improvement in hepatic disease progression in patients with NAFLD/NASH.

Hypothyroidism-associated gallstones

The prevalence of gall stones diseases in the general population is about 10% to 15%,[55] with hypothyroidism frequently encountered as an causative factor. The frequency of the disease tends to increase with age with about 25% of women above 60% years being affected.[56,57] The disease is largely asymptomatic with only between 10% and 20% showing symptoms after 5 to 20 years after diagnosis.[58,59] High TSH levels has been associated with almost a 4-fold increase gallstone formation in men,[11]

whilst both overt and subclinical hypothyroidism have been associated with common bile ducts stones retrieved at endoscopic retrograde cholangiopancreatography procedures particularly among the elderly and in women.[60,61]

The mechanism suggested for the formation of gallstones associated with hypothyroidism include a decrease in bilirubin excretion because of reduced activity of bilirubin UDP-glucuronyltransferase,[11] as well as an increase in membrane cholesterol-phospholipid ratio and diminished membrane fluidity.[62] Secondly, hypothyroidism is associated with hyperlipidaemia (increases total cholesterol and LDL-c); thirdly, there is delayed emptying of bile due to hypotonia of the gallbladder.[11,63] These 3 mechanisms favour the formation of cholesterol stones precipitated from supersaturated bile. The reduced bile flow and gallstone formation may also lead to obstructive jaundice.[57]

Liver dysfunction associated with thyroid hormone replacement

Liver dysfunction may occur in during the treatment of hypothyroidism with Levothyroxine (LT4). Allergic and hypersensitivity reactions, although, extremely rare, may also occur with the use of LT4 leading to elevations in liver enzymes and mild jaundice.[64] This phenomenon appears to have a genetic predisposition and idiosyncratic in nature, and may reverse when therapy is switched from LT4 to triiodothyronine.[65] Iatrogenic thyrotoxicosis resulting from the over treatment of hypothyroidism may cause liver dysfunction similar to the manifestations of intrinsic hyperthyroidism.[66]

Interferon-induced thyroid dysfunction

Interferon-induced thyroid dysfunction is a common complication occurring among patients receiving interferon alpha (IFNα) for the treatment of chronic hepatitis C infection.[43,67] Approximately 10% and 30% develop clinical thyroiditis and subclinical autoimmune thyroiditis respectively.[67] Generally, interferon-induced thyroiditis (IIT) clinically, may manifest as autoimmune IIT in the form of Graves; disease, Hashimoto's thyroiditis and even thyroid antibody development. It may also manifest as non-autoimmune IIT in the form of destructive thyroiditis or non-autoimmune hypothyroidism. Putatively, both immune effects and direct thyroid toxic effects of IFNα as well as genetic causes play a role in the development of interferon-induced thyroid dysfunction.[67] Direct effects of hepatitis C virus infection is thought to also play a role. A baseline TSH and thyroid autoantibodies is recommended before that start of IFNα for the treatment of hepatitis C infection, with a 2 to 3 monthly TSH monitoring. Treatment interferon-induced thyroid dysfunction depends on the clinical presentation.[67] Non-autoimmune IIT manifesting as hypothyroidism is usually transient and resolves spontaneously upon completion of IFNα therapy.[67,68]

Overlapping clinical presentation of hypothyroidism and liver dysfunction

Some clinical features of hypothyroidism, especially in severe forms are also shared by liver dysfunction, and this must be emphasised. These include but not limited to altered mental state, fatigue, myalgias, weakness, exertional dyspnoea, peripheral oedema, and pericardial effusion. Clinicians ought to be aware that hypothyroidism-associated ascites and hyperammonaemia, may mimic and make the diagnosis of similar conditions in liver dysfunction difficult.[69] The exact mechanism for hyperammonaemia found in severe hypothyroidism is not clear. It is suggested that bacterial overgrowth and increased absorption of ammonia, spurred on by reduced intestinal motility in hypothyroidism coupled with reduced glutamine synthetase activity might reduce glutamine utilisation in the urea cycle.[70] Animal studies have also shown that hypothyroidism may lead to impaired urea metabolism from increases in urea synthesis which enhances protein breakdown.[70] Severe forms of hyperammonaemia associated with hypothyroidism which tend to occur in the presence underlying liver disease, can be reversed with thyroid hormone replacement.[71] The uncommon myxoedema ascites is thought to be due to decreased lymphatic drainage[72] and altered capillary permeability.[73] Interestingly, thyroid hormone replacement and restoration of euthyroidism frequently lead to the resolution of the ascites within a few months with no residual damage. Due to the uncommon nature of myxoedema ascites, clinicians must rule out more common causes of ascites such as cirrhosis of the liver, gastrointestinal and pelvic malignancies, congestive heart failure and sepsis before excluding hypothyroidism as a cause. Clinicians must be aware that in compensated liver cirrhosis due to hepatitis C virus, hypothyroidism may present apparently as hepatic encephalopathy.[69,74] In such a situation, liver function tests would be normal, and the encephalopathy will be unresponsive to lactulose use. The non-response to lactulose is thought to be due to reduced intestinal motility associated with hypothyroidism.[69,74]

Limitations

Some articles that were outside the scope of the search period for this review, articles in non-English databases and those not covered by the search terms may have been inadvertently excluded. These potential limitations were minimised by purposely including some relevant articles outside the search period and broadening the search terms as much as possible. There is also a potential bias in the selection and interpretation relevant publications.

Conclusions

The liver and thyroid hormones interact at multiple levels to maintain homoeostasis. The liver requires large adequate amounts of thyroid hormones to execute its metabolic functions optimally, and deficiency of thyroid hormones may lead to liver dysfunction. There are overlapping symptomatology between liver dysfunction and severe hypothyroidism which may make

delay the diagnosis and treatment of hypothyroidism. NAFLD remain an important association with hypothyroidism and further studies are needed that specifically compare the natural course of NAFLD secondary to hypothyroidism and primary NAFLD. Hepatic dysfunction associated with hypothyroidism is usually reverted by normalizing thyroid status.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

List of Abbreviations

ALT	Alanine amino-transferase
AMPK	AMP-activated protein kinase
AST	Aspartate amino-transferase
cAMP	*Cyclic* adenosine monophosphate
HDL	High- density lipoprotein
HMG-CoA	β-Hydroxy β-methylglutaryl-Coenzyme A
LDH	Lactate dehydrogenase
LDLc	Low-density lipoproteins cholesterol
LT4	Thyroxine
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PKA	*protein kinase* A
PPARa	*Peroxisome proliferator-activated receptor alpha*
US	Unites States of America
T2	3,5-Diiodo-l-thyronine
T3	3,5,3[1] triiodothyronine
T4	Thyroxine
rT3	Reverse T3
SREBP	Sterol regulatory element binding proteins
TBG	Thyroxine-binding globulin
THR	Thyroid hormone receptor
TNF	Tumour necrosis factor
TSH	Thyroid stimulating hormone

Consent for Publication

Not applicable.

Author Contributions

Ernest Yorke: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Writing – original draft; Writing – review & editing.

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Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

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