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REVIEW

The interplay between thyroid and liver: implications for clinical practice

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Abstract

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. Conversely, thyroid hormones affect activities of hepatocytes and hepatic metabolism. 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, mimicking those of liver failure. Liver function tests are frequently abnormal also in hyperthyroidism, due to oxidative stress, cholestasis, or enhanced osteoblastic activity. Antithyroid drug-associated hepatotoxicity is a rare event, likely related mainly to an idiosyncratic mechanism, ranging from a mild hepatocellular damage to liver failure. Propylthiouracil-induced liver damage is usually more severe than that caused by methimazole. On the other hand, thyroid abnormalities can be found in liver diseases, such as chronic hepatitis C, liver cirrhosis, hepatocellular carcinoma, and cholangiocarcinoma. In particular, autoimmune thyroid diseases are frequently found in patients with hepatitis C virus infection. These patients, especially if thyroid autoimmunity preexists, are at risk of hypothyroidism or, less frequently, thyrotoxicosis, during and after treatment with interpheron-alpha alone or in combination with ribavirin, commonly used before the introduction of new antiviral drugs. The present review summarizes both liver abnormalities related to thyroid disorders and their treatment, and thyroid abnormalities related to liver diseases and their treatment.

Keywords Hypothyroidism · Hyperthyroidism · Antithyroid drugs · Chronic hepatitis C · Thyroid autoimmunity

Abbreviations

A	Albumin
AbTg	Anti-thyroglobulin antibodies
AbTPO	Anti-thyroid peroxidase antibodies
AITD	Autoimmune thyroid diseases
ALP	Alkaline phosphatase
ALT	Alanino amino transferase
AST	Aspartate amino transferase
ATDs	Antithyroid drugs
CCA	Cholangiocarcinoma
DAAs	Direct-acting antiviral
DTC	Differentiated thyroid carcinoma
GGT	Gamma glutamyl transferase
GT	Genotype
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IFN	Interferon
LDH	Lactate dehydrogenasis
MMI	Methimazole
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PEG	Polyethylene glycol
PTU	Propylthiouracil

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RAI	Radioiodine
RFA	Radiofrequency ablation
SVR	Sustained virologic response
TACE	Transarterial chemoembolization
TBG	Thyroxine-binding globulin
Tg	Thyroglobulin
TNF-α	Tumor necrosis factor alpha
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone or thyrotropin
TTR	Transthyretin

The liver is usually considered to be a hormone-independent organ, but a complex relationship indeed exists between thyroid gland and liver both in health and disease. This complex interplay is critical for maintaining homeostasis in both sites.

The thyroid secretes two iodine-containing amine hormones derived from the amino acid tyrosine, L-thyroxine (T4) and 3,5,3′-L-tri-iodothyronine (T3). Thyroid hormone metabolism is regulated from the iodothyronine seleno-deiodinase enzyme system including type 1 (D1), type 2 (D2), and type 3 (D3) deiodinases. These enzymes act by activating conversion of the prohormone T4 to T3 (D1, mainly expressed in liver and kidney, and D2, in the pituitary, CNS, and skeletal muscle), inactivating T3, or preventing activation of T4 through conversion to the inactive metabolite, reverseT3 (D3, expressed in the liver, CNS, and skin) [1].

In addition to the role in thyroid hormone activation and inactivation through deiodinase activity, the liver is a first player in thyroid hormone transport and metabolism. In fact, the liver extracts 5–10% of plasma T4 during a single passage, thus influencing T4 plasma levels [1]; in addition, it synthesizes the major thyroid hormone-transport proteins: thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin (A) [2], which provide a rapidly exchangeable pool of circulating thyroid hormone. Liver dysfunction might, therefore, account for a major variation in the bioavailability of thyroid hormones.

On the other hand, thyroid status is essential for normal organ growth, development and activities, through the precise regulation of cellular activities in every human cell, including hepatocytes. In addition to hepatic metabolic activities, thyroid hormones also contribute to bilirubin production and composition, partly because of thyroid involvement in lipid metabolism; furthermore, the Oddi's sphincter expresses thyroid hormone receptors, and thyroxine has a direct prorelaxing effect on the sphincter [3, 4].

Liver abnormalities in thyroid disease

Hypothyroidism

Hypothyroidism is a common condition worldwide, affecting 0.6–12% of woman and 1.3–4% of men, with highest prevalence in the elderly [5, 6].

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. Nevertheless, the relationship between liver and thyroid is often overlooked, and thyroid function is not commonly investigated in patients with liver diseases and vice versa.

Serum liver enzymes are frequently abnormal in hypothyroid patients (Table 1). Hypothyroidism per se may be associated with slightly increased serum alanino amino-transferase (ALT) and gamma glutamyl transferase (GGT) concentrations, which might be due to diminished lipid metabolism and hepatic steatosis reported in hypothyroidism [7]. In addition, an increase in the aspartate

Table 1 Biochemical liver abnormalities that may be found in patients with thyroid dysfunction

		Hypothyroidism		Thyrotoxicosis/hyperthyroidism
Alanine aminotransferase (ALT)	N/high	Diminished lipid metabolism Hepatic steatosis	High	Increased oxygen consumption, with relative hypoxia leading to apotosis and oxidative stress
Aspartate aminotransferase (AST)	High	Hypothyroidism-induced myopathy	High	Increased oxygen consumption, with relative hypoxia leading to apotosis and oxidative stress
Gammaglutamyl transferase (GGT)	N/high	Diminished lipid metabolism Hepatic steatosis	High	Cholestasis
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		

N = normal

amino-transferase (AST) and lactate dehydrogenase (LDH) might be related to hypothyroidism-induced myopathy [8].

A significant role of hypothyroidism in non-alcoholic fatty liver disease (NAFLD), the commonest liver disease and leading cause of cryptogenic cirrhosis worldwide, has been recently postulated by several studies. 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 [9]. This is supported by a recent large prospective cohort study, the Rotterdam Study, showing that in the general population even subclinical hypothyroidism is associated with an increased risk of developing NAFLD and fibrosis [10]. As illustrated in Fig. 1, several mechanisms might contribute: (1) hypothyroidism is associated 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 involves the sequestration and degradation of lipidic droplets within hepatic lysosomes [11], eventually resulting in decreased triglyceride clearance and increased hepatic accumulation of triglycerides [12]; (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 [13], thereby contributing to hepatic inflammation and fibrosis via a direct effect or indirectly through an increase in oxygen free radicals [14].

Based on the multiple pathogenic mechanisms outlined above, hypothyroidism-related NAFLD might be a distinct and potentially curable disease [15]. Although results obtained in animal models are promising, potential clinical applications in humans of thyroid hormones, thyroid hormone metabolites (such as 3,5-diiodothyronine-T2 or 3,5,3′ triiodothyroacetic acid-TRIAC) or analogs/mimetics need to be further investigated [16]. The association between thyroid autoimmunity and NAFLD has been investigated, but with inconclusive or conflicting results [10, 17].

Another common hepatic disease in which thyroid hypofunction may act as an etiopathogenic factor is gallstone disease. Gallstone disease is very common, with a prevalence of 10–15% in the general population [18]. Cholesterol gallstones result from precipitation of cholesterol crystals from supersaturated bile. Hypothyroidism may favor gallstone formation through three different mechanisms: (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 [19, 20]. In men, but not in women, an independent association has been reported between high serum TSH levels and cholelithiasis (OR 3.77; $p < 0.05$) [19]. Several studies found a significant association between common bile duct stones found at endoscopic retrograde cholangiopancreatography and either previously diagnosed clinical hypothyroidism [21] or undiagnosed subclinical hypothyroidism [22, 23], in particular in the elderly and in women. Thus, it is advisable that all patients (especially women) > 60 years of age with common bile duct stones be screened for thyroid dysfunction.

Finally, it is important to recall that some clinical features of hypothyroidism [24] may mimic those seen in hepatic dysfunction (Fig. 2). 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 [25].

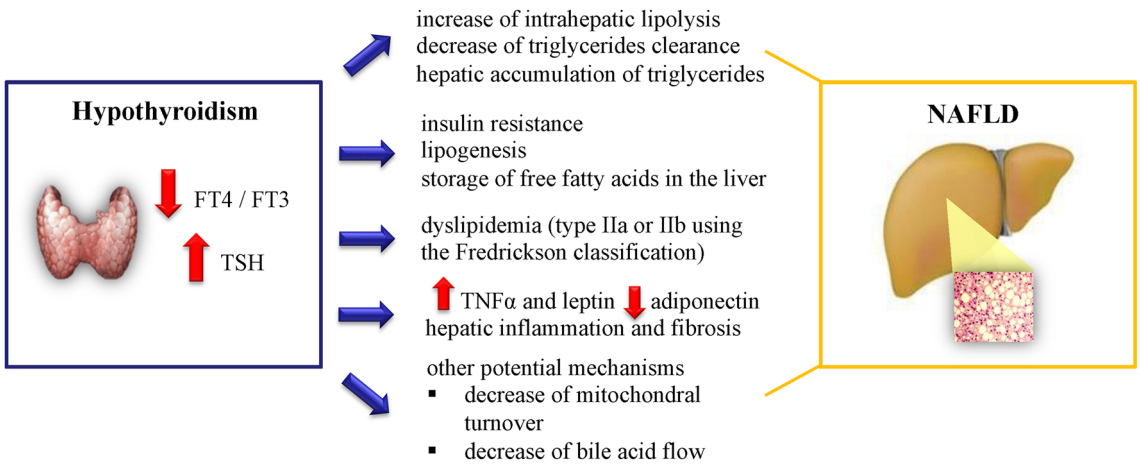

Fig. 1 Possible pathogenic mechanisms underpinning hypothyroidism-related non-alcoholic fatty liver disease

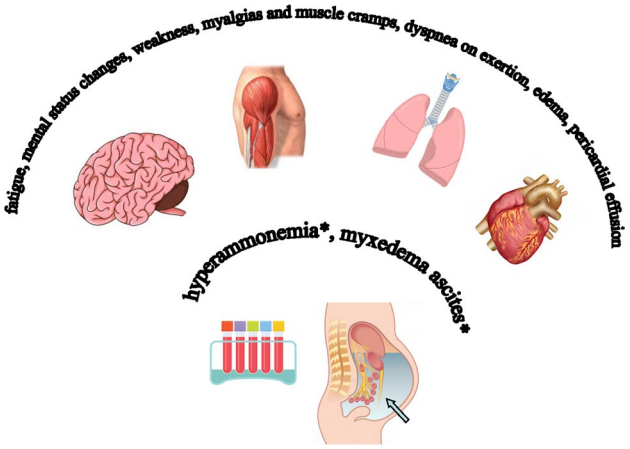

Fig. 2 Clinical features shared by overt hypothyroidism and hepatic failure

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 elucidated. In a murine model, hypothyroidism seemed to increase urea synthesis enhancing proteolysis and affecting urea metabolism [26]. Other co-factor might be 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 [26]. Most cases of hypothyroidism-related hyperammonemia have been described in patients who also had underlying liver failure. A case of hyperammonemic coma during severe hypothyroidism due to thyroid hormone replacement therapy withdrawal was described, which was reverted after restoration of euthyroidism [27]. Myxedema ascites is rarely seen in severe hypothyroid patients, and it is an even more uncommon cause of ascites [28]. In this case, the underpinning mechanisms seem to be the altered capillary permeability [29] and the decreased lymphatic drainage [30]. Restoration of euthyroidism by thyroid hormone replacement therapy always leads to resolution of ascites in a relatively short period of time, even if diagnosis is late. Thus, once routine evaluation has ruled out the most common causes of ascites, such as liver cirrhosis, peritoneal malignancies, sepsis, congestive heart failure and pancreatic diseases, clinicians should check serum thyroid hormone levels to exclude hypothyroidism. Hypothyroidism may also mimic hepatic encephalopathy in patients with hepatitis C virus (HCV)-related cirrhosis [25, 31]. Accordingly, it has been proposed that thyroid function should be assessed in patients with well-compensated liver cirrhosis, normal liver synthetic function, and apparent hepatic encephalopathy that is refractory to lactulose treatment: the lack of effect of lactulose might be related to gastrointestinal hypomotility associated with hypothyroidism [25, 31].

Thyrotoxicosis and hyperthyroidism

Thyrotoxicosis is a condition due to an excess of circulating thyroid hormones of any cause. Hyperthyroidism represents the excess of endogenous thyroid hormone and has an overall prevalence of 2% in women and 0.3% in men [32]. Thyroid hormone excess has an important impact on virtually all organs and systems [33]. Graves' disease is the most common cause of hyperthyroidism in iodine-sufficient areas, particularly in young and middle-aged persons, while toxic goiter (uninodular or multinodular) is more frequent in the elderly [34]. The liver is known to be an important target of thyroid hormone excess since one of the first studies published in the Lancet in 1874, which described a fatal case of a patient with exophtalmic goiter, heart disease, and jaundice [35]. Many subsequent case reports and series highlighted the relationship between thyroid hormone excess and liver damage [10, 36, 37].

Liver function tests are frequently abnormal in patients with newly diagnosed thyrotoxicosis/hyperthyroidism (Table 1), with a prevalence ranging between 15 and 76% [36, 38]. Age, but not gender, is a predisposing factor [39]. Most studies failed to find a direct relationship between liver and thyroid biochemical tests [36, 38–40], but the basic mechanism leading to liver abnormalities in thyrotoxic patients seems to be the increased oxygen consumption consequent to the enhanced metabolic rate. This results in a relative hypoxia in the perivenular region, leading in turn to apoptosis and oxidative stress [41–43].

Serum alkaline phosphatase (ALP) elevation is the most frequent abnormality in hyperthyroidism, being observed in the 64% of thyrotoxic patients [44]. This increase depends both on the liver and the bone isoforms, due to the enhanced osteoblastic activity, but could also be secondary to hormone-induced cholestasis. Other common biochemical abnormalities involve an increase in AST in 27% of patients, ALT in 37% of patients [45], GGT in up to 62% of patients [46], and total bilirubin [36, 38]. Indeed, thyroid hormone excess has been linked to an increased rate of cholestasis, suggested by the concomitant increase of ALP, GGT and bilirubin elevation and the histological evidence of centrilobular intrahepatocytic cholestasis [47]. An experimental human model has shown that hyperthyroidism causes cholesterol gallstone formation secondary to the overexpression of hepatic lithogenic nuclear receptor genes, such as Lxrα and Rxr [48].

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 [36]; electron microscopy may show hyperplasia of the smooth endoplasmic reticulum, reduced cytoplasmic glycogen, and an increase in mitochondria size and number [48, 49]. If hyperthyroidism is severe, hepatic damage may be worse, leading to centrizonal necrosis and perivenular fibrosis [48].

Hepatic involvement in overt thyrotoxicosis/hyperthyroidism is usually self-limited, but there are a few case reports of thyrotoxic patients with fulminant hepatic failure [50, 51], especially in patients with coexisting heart failure [52, 53], in particular, right-sided heart failure can result in congestive hepatopathy. In most patients, mild abnormalities in liver enzymes and bilirubin levels are observed, but clinical features may include deep jaundice, coagulopathy, hepatomegaly, and even ascites due to sinusoidal congestion and exudation of protein-rich fluid into the space of Disse [54]. However, in the event of thyroid storm, an extreme and life-threatening form of thyrotoxicosis characterized by severe signs and symptoms (fever, hypotension, tachycardia, tremor, nausea and vomiting), liver dysfunction [55] and jaundice are frequent, and liver failure [53, 56, 57] may occur. A case report of severe neonatal hyperthyroidism due to maternal Graves' disease, causing liver failure, but promptly responsive to carbimazole, has recently been reported [58].

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 [59]. A case report has described a patient with Graves'disease, heart failure, jaundice, and positive autoimmune markers for autoimmune colangiopathy [60].

Treatment in case of liver dysfunction secondary to thyrotoxicosis should be based on the prompt restoration of euthyroidism, which usually reverts liver function abnormalities.

Thyroid cancer

Liver metastases from differentiated thyroid carcinoma (DTC) are rare, with a reported prevalence of 0.5–1% [61, 62], and apparently do not correlate with the histological type of DTC [63]. In a cohort of 242 patients with papillary thyroid carcinoma, four had liver metastases that were detected after a mean of 16 years [64]. In the largest series of 11 cases, mean age was 56 years and 8 patients had multiple liver metastases, often coexisting with lung, bone and brain metastases; survival in this study ranged from 1 to 60 months after diagnosis of the metastatic spread [65]. Liver masses can be detected by ultrasound, CT, SPECT/CT, and frequently they do not uptake radioiodine; functional metastases are rare [63, 65, 66]. Surgical resection of liver lesions has been reported to offer the best chance to prolonge survival [67]. Radiofrequency ablation (RFA) may have a role and should be considered an option if surgery is not feasible or not effective [68].

Liver metastases of anaplastic carcinoma, a rare and highly aggressive undifferentiated thyroid tumor, are quite uncommon [69, 70] since in this case distant metastases more commonly involve lung, bone, and brain. In general, however, the rapidly unfavorable outcome depends on the locoregional recurrence and massive disease in the central compartment of the neck.

Liver abnormalities due to thyroid disease treatment

Thyroid hormone medication

Levothyroxine (LT4) is the treatment of choice for hypothyroidism and a safe medication if the dose is appropriate [71]. In overtreated patients (iatrogenic thyrotoxicosis), among other manifestations, liver abnormalities may occur similar to those observed in endogenous hyperthyroidism. Anecdotally, immunoallergic hepatitis or hypersensitivity reactions to levothyroxine associated with liver enzyme increase and mild jaundice have been observed [72]. Ohmori et al. reported the case of a hypothyroid patient, in whom liver dysfunction occurring during replacement treatment (associated with detection of serum antibodies to T4) improved after switching from LT4 to triiodothyronine [73]. Interestingly, these LT4-associated liver abnormalities were in Japanese patients, suggesting a possible genetically determined predisposition to idiosyncratic hypersensitivity reactions.

Antithyroid drugs

Antithyroid drugs (ATDs), propylthiouracil (PTU), methimazole (MMI), and its prodrug, carbimazole, are the first-line treatment for Graves' hyperthyroidism [74]. They mainly act by inhibiting synthesis of thyroid hormones and, in the case of PTU, deiodination of T4 to the active hormone, T3.

The overall incidence of ATD-associated hepatotoxicity is estimated to be less than 0.5%, although the exact figures are unknown [75, 76]. The risk of severe liver injury appears to be more frequent using PTU, especially in children [77]. Therefore, MMI currently is the preferred ATD [74], except for particular conditions, such as in the first trimester of pregnancy because of the higher risk of malformations associated with MMI [78], and in thyroid storm because of PTU peculiar effect of the inhibition of peripheral T4–T3 conversion [79].

PTU has been used since the 1940s, and over the years, hepatic side effects have been described, until in 2010 FDA issued a black box warning on the drug insert. About 1 in

10,000 adult patients and 1 in 20,000 children patients prescribed with PTU develops hepatotoxicity [80]. The mechanism underpinning PTU-associated hepatotoxicity is unsettled, although it might be an autoimmune or idiosyncratic reaction to cause liver injury [80, 81]. There is a wide variation in the dose and duration of therapy in patients who developed hepatotoxicity during PTU treatment; indeed, this adverse event seems to be dose independent, but toxicity occurs more frequently within 3 months after the initiation of treatment [75]. The most common findings are a moderate increase in serum AST and ALT (hepatocellular toxic pattern), and bilirubin [82], mild symptoms, such as nausea, vomiting and malaise. In most cases, these abnormalities remit spontaneously [76], but sometimes a persistent mild alteration of liver function parameters for weeks may progress to hepatic failure and overt jaundice. In addition, a few studies have reported PTU-associated acute autoimmune hepatitis, leading to liver failure [83–85]. Indeed, PTU is the third medication most strongly linked to liver transplant, and mortality from PTU-induced hepatotoxicity is around 25% [86]. Recent European guidelines [87] and consensus by experts from Italian Endocrine and Gynecologic Scientific Societies [88] recommend to limit the use of PTU only to first trimester of pregnancy [87, 88] and as a second-line ATD treatment, if MMI caused toxic reactions, and just as a short-term treatment, while waiting for radioiodine therapy or thyroid surgery [87]; PTU should also be avoided in children [87]. Taking into account these observations, if PTU is selected, it seems appropriate to obtain baseline blood count and liver function tests, and repeat them promptly if signs and/or symptoms of hepatic involvement develop. When liver function tests in a symptomatic patient are over two- or threefold above the upper normal limit, PTU therapy should be immediately discontinued, and, if tests do not promptly normalize, the patient should be referred to a hepatologist [34].

MMI-induced hepatotoxicity is a very rare adverse event, with less than 30 cases reported in the literature [89]. Clinical picture, which potentially ranges from toxic hepatitis with elevation of hepatic enzymes to acute hepatic failure, is usually mild, and occur mostly in people older than 40 years [90]. As far as we know from the literature and FDA notes, no death from MMI-related hepatotoxicity has ever been reported, and we found a single case report of carbimazole treatment in combination with propranolol inducing acute hepatic failure requiring liver transplant [91]. The latent period between first drug exposure and the development of hepatotoxicity appears to be shorter than PTU-related hepatotoxicity (mean of 17 days, ranging from 2 days to 6 months) [92]. The exact mechanism of MMI-induced liver damage has not been fully clarified, but, as for PTU, hypersensitivity seems to be the most plausible explanation. MMI/carbimazole seems to be associated in a dose-dependent manner with an increased risk of hepatotoxicity, but not with an increased risk of cholestasis or acute liver failure [93]. However, histopathological features often have an intrahepatic cholestatic pattern, with expanded portal tracts, inflammatory cells infiltration, proliferating cholangioles and bile plugs [94–96]. In the event of signs and/or symptoms suggestive of hepatotoxicity, it is recommended that liver function tests be assessed and, if liver injury is confirmed, MMI be discontinued. In case of cholestatic damage, ursodeoxycholic acid might be administered; only few cases treated with steroids have been reported in the literature [97].

Some similarities exist between MMI- and PTU-induced hepatotoxicity. In both cases, this feared adverse event is rare and likely mainly related to an idiosyncratic mechanism; no specific factors (gender, type of thyrotoxicosis/hyperthyroidism, presence or absence of liver tests abnormalities before antithyroid drug treatment) predict the risk of hepatotoxicity in an individual patient. On the other hand, some differences exist. The time from first drug exposure to the development of hepatotoxicity is usually longer with PTU than with MMI, hepatotoxicity is dose independent for PTU, and PTU-induced liver damage is usually more severe.

Finally, it should be underscored that, as discussed before, baseline hepatic function test abnormalities may be related to hyperthyroidism per se and, therefore, do not necessarily contraindicate the use of ATDs.

Radioiodine treatment

Radioiodine (RAI) is widely used for the definitive treatment of hyperthyroidism due to Graves'disease or uninodular/multinodular toxic goiter, as well as for the management of remnant or metastatic thyroid tissue after total thyroidectomy for DTC [34, 74, 98]. RAI has been linked to liver toxicity in a few cases. In one case series, hepatic dysfunction occurred after RAI treatment for Graves' disease [99]. However, it should be noted that this adverse effect occurred in the presence of thyrotoxicosis, which is quite common in the immediate post-RAI period, particularly if the patient is not pretreated with ATDs. Thus, the observed abnormalities of liver function tests were more likely related to uncontrolled thyrotoxicosis than to RAI treatment. In this respect, in addition to MMI pretreatment, ATDs might be given again after RAI administration for a short course, especially in the elderly and fragile patients. Another case regards a patient who underwent high-dose (100 mCi) RAI ablative treatment after total thyroidectomy for papillary thyroid carcinoma [100]. Two weeks after ablative therapy, a marked increase in liver enzyme concentrations occurred, abdominal ultrasonography showed prominent periportal interstitial echogenicity, and liver biopsy showed moderate lobular inflammation and a mild portal inflammation without fibrosis [100]. A similar clinical case of a patient presented

with typical cholestatic damage after RAI remnant ablation post-total thyroidectomy was successfully treated by steroids [101]. An increased hepatic iodine uptake, due to the absence of thyroid gland, might explain liver damage in these cases [102]. It should be emphasized that this low risk of hepatotoxicity is even more unlikely nowadays since lower doses of RAI are usually employed to ablate athyreotic DTC patients [98].

Thyroid abnormalities in liver diseases

Chronic hepatitis C

According to the World Health Organization, approximately 71 million people worldwide (1% of population) have active hepatitis C virus (HCV) infection, which is a global health problem [103]. 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 [104] (Table 2). 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 [105]. In particular, Hashimoto's thyroiditis is the most common thyroid disorder reported in these patients [106]. In most studies, approximately 10–15% of the patients had positive thyroid antibodies before starting interferon (IFN) treatment [107]. Some years ago, a large Italian population-based study investigated the prevalence of autoimmune thyroid diseases in 630 consecutive patients with chronic hepatitis C, not on IFN treatment [107]. Compared to control groups, including subjects from an iodine-deficient area, subjects living in an area of iodine sufficiency, and patients with chronic hepatitis B, patients with chronic hepatitis C were more likely to have positive tests for anti-thyroid peroxidase antibodies (21%), anti-thyroglobulin antibodies (17%), and hypothyroidism (13%) [107]. A recent meta-analysis of twelve studies published by Shen et al. [106] involving 1,735 HCV-infected IFN-alpha-naïve subjects and 1868 non-HCV-infected subjects found that chronic HCV infection, compared to controls, was associated with a nearly twofold increase in the prevalence of anti-thyroid antibodies and just over threefold higher prevalence of hypothyroidism. Thus, pretreatment thyroid screening is recommended for all HCV patients, regardless of the drug chosen.

Curiously, although autoimmune thyroid diseases are in the general population far more frequent in women, conflicting results emerge from the published studies, because some studies reported a higher prevalence of thyroid diseases in female HCV patients compared to male patients [108], whereas other studies failed to show any gender difference [109]. No increase in the prevalence of thyroid disorders with increasing age in HCV patients has been observed, irrespective of gender [110].

Regarding the pathogenesis of HCV-related thyroid dysfunction, it has recently been shown that HCV can directly affect in vitro a human thyroid cell line (ML1), which presents the membrane expression of the important HCV receptor CD81 [111]. On the other hand, development of autoimmune thyroid disease might be mediated by stimulation of the immune system by HCV, rather than by HCV infection itself. In particular, breaking of tolerance to self-antigens would trigger autoreactivity [112, 113]. Moreover, infection of the lymphatic cells, viral proteins, chromosomal aberrations, cytokines (such as IL-8), or microRNA molecules have been postulated to play a role in the association between HCV infection and thyroid diseases [113].

A potential oncogenic role of HCV through the direct infection of thyroid cells has been postulated to explain the relationship between HCV infection and the risk of papillary thyroid cancer [112]. Based on available studies, recently summarized in a systematic review and meta-analysis by Wang et al. [114], an association seems to exist between

Table 2 Biochemical thyroid abnormalities that may be found in patients with liver diseases

	Chronic hepatitis C	Liver cirrhosis	Hepatocellular carcinoma
Total T3 (TT3)		Low	
FreeT3 (FT3)	Low	Low	N/low
Reverse T3 (rT3)		High	
Thyrotropin (TSH)	High	N/high*	High
FreeT4	Low	Low	N/low
Thyroxin-binding protein (TBG)	N/high	High	High
Anti-thyroid peroxidase antibodies (TPOAb)	+	±	
Anti-thyroglobulin antibodies (TgAb)	+	±	

N = normal; *an increase in serum TSH can occur in the presence of thyroid autoimmunity

HCV infection and thyroid cancer risk, but further studies are needed to confirm or deny this hypothesis.

Liver cirrhosis

Prevalence of serum thyroid hormone abnormalities in patients with liver cirrhosis ranges from 13 to 61% [115] (Table 2). The most common finding is a decrease in serum total T3 and free T3, an increase in reverseT3, in the presence of normal serum TSH levels [116]. Serum T3 concentration is negatively correlated with the Child–Turcotte–Pugh score, a measure of severity of liver dysfunction [116, 117], indicating a direct relationship between severity of liver dysfunction and changes in circulating thyroid hormones. Indeed, cirrhotic patients with hepatic encephalopathy have serum FT3 levels significantly lower than cirrhotic patients without encephalopathy [117], suggesting that serum FT3 concentrations is a prognostic marker in these patients. Several pathogenic mechanisms underpin 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 [117, 118]. 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 [118]. On the other hand, although the prevalence of thyroid autoimmunity is not significantly increased in patients with liver cirrhosis [118], an increase in serum TSH concentrations has also been reported in cirrhotic patients [119, 120], suggesting primary hypothyroidism. Hyperthyroidism has been also reported in patients with cirrhosis, although less frequently than hypothyroidism [121]. Based on these observations, it is reasonable to suggest that thyroid function tests should be regularly checked in patients with liver cirrhosis and prompt treatment initiated in case of overt or subclinical hypothyroidism (elevated TSH and normal-to-low FT4 and FT3), whereas it is not indicated to treat isolated low FT3.

Finally, it is important to recall that liver cirrhosis is a cause of malabsorption, thus hypothyroid patients with severe cirrhosis may require higher doses of levothyroxine. In this context, a switch to newer levothyroxine formulations, such as liquid ampoules or softgel capsules, may be considered to obtain a better thyroid function control.

Hepatocellular carcinoma and cholangiocarcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the ninth leading cause of cancer deaths in the United States [122]. Independently of its etiology, cirrhosis is the most important risk factor for the development of HCC. Hypothyroidism may be a possible additional risk factor for HCC [123, 124]. A case–control study of 420 newly diagnosed HCC patients showed that long-term hypothyroidism (more than 3-year duration) was associated with a significantly increased risk (from 2.1- to 2.9-fold) of liver cancer, particularly in women, independently of other well-known risk factors, such as HCV infection and diabetes [123]. Although mechanisms whereby hypothyroidism can favor the occurrence of HCC development are unclear, susceptibility to HCC might be enhanced by NASH, in turn favored by hyperlipidemia, decreased fatty acid oxidation, insulin resistance, and lipid peroxidation, all conditions often found in hypothyroidism [123]. 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 [124]. However, little is known about the underpinning mechanisms linking thyroid hormones to HCC development [125]. HCC may produce TBG, which can significantly decrease in serum after resection of the tumor [126]. HCC is a possible, although rare, cause of thyroid metastases. Therefore, the list of cancers potentially metastasizing to the thyroid (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 [127–129]. Anecdotally HCC can initially present as a thyroid mass [130]. In this case report, the radiological picture suggested a malignant thyroid tumor and metastasis from HCC was suspected on the basis of core needle thyroid biopsy. Subsequent abdominal CT scan showed an advanced HCC [130]. We agree with the recommendation that all patients with a history of cancer, even remote, should be evaluated for possible metastasis when a new thyroid lesion is discovered [131], 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. To date, we found only two cases reported in the literature, which refer to a 55-year-old man presenting with palpable masses on the left thyroid and lateral neck [132], and a 58-year-old man with severe hypothyroidism probably due to destruction of thyroid tissue by cancer cells [133].

Thyroid abnormalities due to liver disease treatment

Chronic hepatitis C

Treatment of HCV infection has undergone a profound evolution in the last 30 years. In 1991, the first IFN-alpha was approved for the treatment of hepatitis C, but the rates of sustained virologic response (SVR) were only between 9% for genotype (GT) 1 and 30% for GT2 and GT3. The addition of ribavirin to IFN-alpha from 1998 improved the response rate to 29% of SVR for GT1 and 62% for GT2 and GT3 [134]. In 2001, further progress in clinical outcomes was allowed by linking the IFN molecule to polyethylene glycol (PEG-IFN), which increased favourable outcomes to 41–51% SVR for GT1 and 70–82% for GT2 and GT3 [135, 136]. More recently, direct-acting antiviral (DAAs), in particular second-wave DAAs, ensure SVR rates above 90%, as well as reduced toxicity and treatment duration. Therefore, the recent European Association for the Study of the Liver guidelines recommend IFN-free, ribavirin-free, DAA-based regimens as first-choice treatment in HCV-infected patients without cirrhosis or with compensated (Child–Pugh A) cirrhosis because of their virological efficacy, ease of use, safety, and tolerability [137]. Up to the recent introduction of the new antivirals, the endocrinologists had to deal with the adverse effects on the thyroid due to the use of IFN-alpha alone or in combination with ribavirin. Nowadays, the most common situation in clinical practice is the long-term follow-up of patients treated with interferon alone or in combination with ribavirin, with permanent thyroid disease, in most cases hypothyroidism under LT4 replacement therapy. No information is available on short-term or long-term effects of the DAAs on thyroid function and/or autoimmunity [138]. Indeed, today only a Pakistani paper investigated the prevalence of thyroid disorders in DAA drug-treated patients compared to IFN-treated patients, concluding that the latter were more likely to develop thyroid dysfunction, especially hypothyroidism, whose prevalence was higher in IFN-treated (around 30%) than DDA-treated patients (around 20%) [139]. However, obvious limitations of the study design (small sample size, thyroid assessment limited to serum TSH, and absence of long-term follow-up) do not allow to draw conclusive remarks.

IFN-alpha has been associated with the occurrence of thyroid disorders, resulting from a disregulation of the immune system, a direct effect on thyroid cells involving hormonogenesis, secretion and metabolism of thyroid hormones, as well as expression of major histocompatibility antigens on thyroid cells [140, 141]. Thyroid abnormalities could occur both during and after the treatment period, with a widely variable prevalence ranging from 1 to 35% [142]. The spectrum of thyroid abnormalities includes hypothyroidism (overt or subclinical), which is more frequent (2.4–19%), especially in patients with preexisting thyroid autoimmunity, and hyperthyroidism (0.9–3%), presenting either as destructive thyrotoxicosis or Graves' disease (overt or subclinical) [141–144]. Different dietary iodine intake in the populations studied affects the pattern of thyroid diseases; in general, higher iodine intake is associated with a higher risk of hypothyroidism, whereas lower iodine intake is more frequently associated with hyperthyroidism [145]. Most studies showed that the strongest risk factor for the occurrence of thyroid dysfunction is the presence of thyroid autoantibodies prior to IFN-alpha therapy. Patients with positive autoantibodies at the initiation of treatment had up to 80% probability of developing thyroid dysfunction during or after IFN-alpha therapy [142, 144, 146]; detection of TPOAb before therapy was associated with a 3.5- to 3.9-fold greater chance of becoming hypothyroid during IFN-alpha treatment [147, 148]. For these reasons, according to the recommendations of both the British Society of Gastroenterology and the American Gastroenterological Association [149, 150], assessment of thyroid autoimmunity before IFN-alpha therapy is mandatory, to identify patients who are at high risk of developing thyroid diseases. With regard to gender, several [119, 151, 152], but not all studies [148, 153, 154] found that women are more prone to become hypothyroid. Data regarding the outcome of thyroid dysfunction after antiviral treatment withdrawal are controversial. Complete normalization as well as partial reversal of thyroid dysfunction after IFN withdrawal have been reported [144, 155, 156]. During a median follow-up period of more than 2 years, about 60% of the patients showed permanent thyroid dysfunction [146].

Ribavirin is a nucleoside analogue with immunomodulatory effects, which may cause thyroid disease via an autoimmune mechanism, acting alone or synergistically with IFN-alpha [157]. Thyroid dysfunction during IFN-alpha + ribavirin combination therapy was reported to occur in 4.7–27.8% of patients [144, 158–160]. The prevalence is higher in patients treated with combination therapy (12.1%) than in those treated with IFN-alpha alone (6.6%) [143]. Thyroid dysfunction, in particular hypothyroidism, which is more common than hyperthyroidism, is more frequent in women than in men [144, 158–161]. Routine screening for thyroid disease was recommended in all patients with HCV infection before and during treatment with interferon in combination with ribavirin [161], especially in those with a family history of thyroid disorders [160]. Antiviral therapy can usually be continued despite the development of subclinical or overt thyroid disease, but a reduction of the dose has been suggested [144, 162]. In any case, patients treated with

IFN-alpha alone or in combination with ribavirin therapy should be informed about the risks of thyroid dysfunction and the possible need for its long-term treatment [160]. In any case, periodical assessment of thyroid function after completion of therapy is advisable.

A few years after the introduction of IFN-alpha, pegylated interferon (PEG-IFN), was approved and used as the first choice for patients infected with virus of GT1 or for non-responding patients infected with virus of GT2 and 3. PEG-IFN is characterized by the addition of a polyethylene glycol (PEG) moiety to the regular IFN molecule, which results in a longer half-life and increased therapeutic efficacy; moreover, it can be conveniently given on a weekly basis rather than thrice weekly, resulting in improved compliance. Regarding the effects on the thyroid gland, a meta-analysis by Tran and coworkers [163] failed to show any difference between PEG-IFN and regular IFN in terms of thyroid dysfunction. This finding is not surprising, because pegylation of IFN-a-2b involves the addition of a 12-KDa polyethylene glycol molecule, which is not expected to have any effect on the thyroid gland.

Hepatocellular carcinoma

Current options in systemic therapy of HCC include receptor tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). Sorafenib, an orally active multi-targeted TKI with antiangiogenic, apoptotic, and antiproliferative activity, approved in 2007 for the treatment of HCC, is still the first-line standard of care for many patients with locally advanced form [164]. In the last years, occurrence of sorafenib-induced thyroiditis was reported, in few cases leading to temporary thyrotoxicosis, followed by overt or subclinical hypothyroidism [165, 166]. An increase in serum TSH or FT4 concentrations, as well as a decrease in T3/rT3 ratio and T3/T4 × 100 ratio were observed; in vitro experiments suggest a possible role of sorafenib-induced inhibition of T3 transport into the cell by monocarboxylate transporter (MCT) 8 or MCT 10 [166]. In the warning label both hypo- and hyperthyroidism are referred as uncommon (0.1–1% of treated patients) side effects. Since the prevalence seems to be small, we cannot suggest a wide thyroid screening in patients taking Sorafenib for HCC, but we recommend measuring TSH and free thyroid hormones if symptoms of hypo- or hyperthyroidism occur or are suspected. As far as immunotherapy, the monoclonal antibodies directed against programmed cell death protein 1 (PD1), nivolumab, and pembrolizumab were approved by the FDA in 2017 and 2018, respectively, for the second-line treatment of advanced HCC [164]. Among endocrine and metabolic adverse effects that may occur in patients treated with anti-PD1, thyroid disorders are the most common and include painless thyroiditis, Hashimoto's thyroiditis, primary hypothyroidism, and thyrotoxicosis due to a transient destructive or, less commonly, to Graves' disease [167]. Thyroid function abnormalities are more frequent in women and usually occur within few months from starting treatment [168]. In general, the prevalence of thyroid disorders in nivolumab-treated patients reaches 4.5% for hypothyroidism and hyperthyroidism, and 6% for Hashimoto's thyroiditis [169], but there is a notable variability depending on the type of treated cancer. Few data are available in the literature regarding the treatment of HCC; however, on the basis of knowledge in other cancer, close clinical monitoring and thyroid function assessment (FT4, FT3, and TSH) is recommended at every cycle for the first 3 months, then every second cycle [169]. Pre-existing autoimmune thyroiditis is not an absolute contraindication to immunotherapy and newly diagnosed thyroid dysfunction requires conventional management, in most patients without the need to stop immunotherapy.

Conclusions

A complex interplay exists between the thyroid and the liver. On the one hand, thyroid dysfunction (both hypo- and hyperthyroidism) can cause liver function test abnormalities, usually reverted by normalizing thyroid status. Likewise, treatment of thyroid dysfunction, particularly antithyroid drug treatment of hyperthyroidism, may cause, although rarely, liver dysfunction. On the other hand, liver disorders may cause thyroid function abnormalities that may or may not need to be treated. Therefore, a close interaction between endocrinologists and gastroenterologists is recommended for a proper and correct assessment of these patients.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any study with human participants or animals performed by any of the authors.

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