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Review Article

Thyroid disorders and gastrointestinal and liver dysfunction: A state of the art review

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ABSTRACT

Thyroid disorders commonly impact on the gastrointestinal system and may even present with gastrointestinal symptoms in isolation; for example, metastatic medullary thyroid carcinoma typically presents with diarrhoea. Delays in identifying and treating the underlying thyroid dysfunction may lead to unnecessary investigations and treatment, with ongoing morbidity, and can potentially be life-threatening. Similarly, gastrointestinal diseases can impact on thyroid function tests, and an awareness of the concept and management of non-thyroidal illness is necessary to avoid giving unnecessary thyroid therapies that could potentially exacerbate the underlying gastrointestinal disease. Dual thyroid and gastrointestinal pathologies are also common, with presentations occurring concurrently or sequentially, the latter after a variable time lag that can even extend over decades. Such an association aetiologically relates to the autoimmune background of many thyroid disorders (e.g. Graves' disease and Hashimoto's thyroiditis) and gastrointestinal disorders (e.g. coeliac disease and inflammatory bowel disease); such autoimmune conditions can sometimes occur in the context of autoimmune polyglandular syndrome. Emphasis should also be given to the gastrointestinal side effects of some of the medications used for thyroid disease (e.g. anti-thyroid drugs causing hepatotoxicity) and vice versa (e.g. interferon therapy causing autoimmune thyroid dysfunction). In this review, we discuss disorders of the thyroid-gut axis and identify the evidence base behind the management of such disorders.

1. Introduction

Thyroid disorders are common in the general population. The prevalence of spontaneous hypothyroidism is between 1% and 2% in iodine-replete communities; it is more common in older women and 10 times more common in women than in men [1]; subclinical hypothyroidism, defined as a raised serum thyroid stimulating hormone (TSH) level with normal thyroid hormone levels, affects about 3% of men and 8% of women, respectively. The prevalence of hyperthyroidism in women is between 0.5% and 2% and is 10 times more common in women than in men in iodine-replete communities [1]; subclinical hyperthyroidism, defined as a low serum TSH level and normal thyroid hormone levels in the absence of diseases (hypothalamic, pituitary, or non-thyroidal illness) or medications that inhibit TSH secretion, affects up to 3% of the population. Thyroid dysfunction can present with gastrointestinal (GI) symptomatology or can be associated with and/or exacerbate underlying GI disease. Particular diagnostic difficulty is encountered when thyroid disease presents with isolated GI symptoms. A high index of suspicion is required in such circumstances to identify the underlying culprit thyroid disorder. Conversely, GI disease can be associated with non-thyroidal illness, causing disruption of thyroid function. In this narrative review, we discuss the common and some not so common associations between thyroid disorders and gastrointestinal dysfunction.

2. Methods

We undertook a focussed review of the literature and discussions with colleagues. We carried out a search of the published literature in Medline, PubMed (www.pubmed.gov) and Google Scholar (www.scholar.google.com) with a broad range of combinations of the medical subject headings (MeSH) terms, 'digestive system diseases', 'thyroid diseases', 'hypothyroidism', 'thyrotoxicosis', 'hyperthyroidism', 'thyroiditis', 'autoimmune thyroid disease', 'non-thyroidal illness', 'thyroid function tests', 'medullary thyroid carcinoma', 'liver disease', 'coeliac disease', 'inflammatory bowel disease' and 'interferon', 'obesity', 'bariatric surgery', and 'weight reduction surgery'. Inclusion criteria include 'English language', and articles retrieved from 1960 to February 2015. References of articles included were read to identify any further articles that were missed from the above database searches and personal archived references were also sought. Whenever

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available, we gave preference to meta-analysis, systematic reviews, randomised controlled trials, and prospective epidemiological studies. As appropriate, we included observational, retrospective and non-randomised studies, and case reports.

3. Normal thyroid physiology

Thyroid hormones play critical roles in differentiation, growth, and metabolism and are necessary for the normal function of nearly all tissues, with major effects on oxygen consumption and metabolic rate [2]. Thyrotropin-releasing hormone (TRH) secreted from the hypothalamus regulates TSH production from the thyrotroph cells of the anterior pituitary (Fig. 1). TSH stimulates thyroid hormone production and release from the thyroid gland. Iodine is an essential mineral for normal thyroid hormone synthesis in the thyroid gland which is predominantly in the form of thyroxine (tetraiodothyronine; T4), which can be considered as a pre-hormone. T4 undergoes conversion to the more potent molecule, triiodothyronine (T3), and vice versa, in the peripheral tissues catalysed by a group of enzymes, called iodothyronine deodinases that occur in three isoforms (D1, D2, and D3). Within the circulation, both T4 and T3 are almost entirely bound to plasma proteins, namely, thyroid binding globulin, transthyretin (formerly known as pre-albumin), and albumin. These are all synthesised in the liver and are thought to possess both storage and carrier functions. Only free (unbound) thyroid hormones are metabolically active. It is precisely for this reason that it has become an established practice to measure free T4 and free T3 levels nowadays, as the unbound thyroid hormone levels are overall constant whereas the total T4 and T3 levels are susceptible to variations in the binding protein levels, which can be influenced by a range of conditions such as liver disease, malnutrition, pregnancy, medications, and hereditary conditions. T3 is less strongly bound to carrier proteins and hence has a more rapid onset and offset of action. Thyroid hormones enter cell membranes via active transport proteins. Within the cell, they behave similarly to steroid hormones; they ultimately bind to thyroid hormone response elements in the promoter region of thyroid hormone responsive genes and stimulate, or inhibit, gene transcription and translation [3].

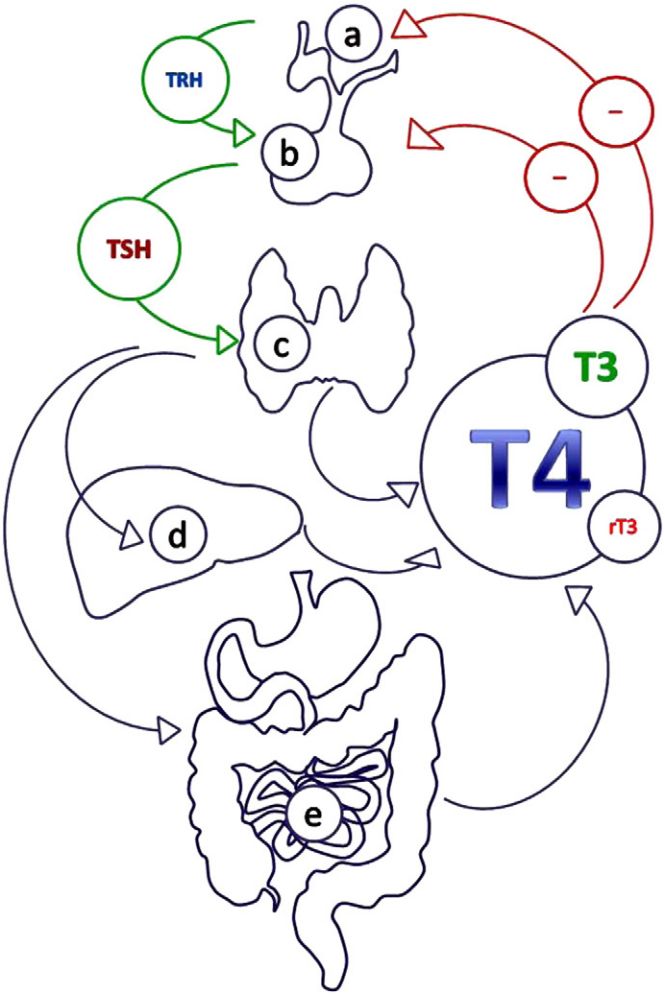

Fig. 1. Summary of thyroid hormone regulation and peripheral action. *Central regulation*: Thyrotropin-releasing hormone (TRH), a modified tripeptide produced by the parvocellular region of paraventricular nuclei of hypothalamus (a), stimulates production and release of thyroid stimulating hormone (TSH). TSH is a glycoprotein secreted by thyrotrophs of the anterior pituitary (b); it consists of an α-subunit (that shares homology with human chorionic gonadotrophin, luteinising hormone and follicle stimulating hormone) and a β-subunit. TSH stimulates secretion and release of the thyroid hormones tetraiodothyronine (T4) and triiodothyronine (T3), produced by follicular cells in the thyroid gland (c). T4 can be considered as a pre-hormone, whereas T3 is more metabolically active. Circulating thyroid hormones induce feedback inhibition of TRH and TSH synthesis and secretion. Neurotransmitters are also important modulators of TSH synthesis and secretion. *Thyroid hormone transport*: Thyroid hormones are poorly soluble in water and hence bind reversibly to plasma proteins; they are bound in order of reducing affinity to thyroid binding globulin, transthyretin and albumin. All three of these proteins are synthesised in the liver (d) and hepatic failure can cause reduction in the levels of these proteins and, consequently, the total T4 and T3 levels. The affinity of thyroid binding globulin for T3 is about 20-fold lower than for T4, and this explains its rapid onset and offset of action. The bound hormones serve as a thyroid hormone reservoir, whereas the free thyroid hormones are available at the tissue level for intracellular transport and feedback regulation and control of metabolism. In the steady state, it is the rate of T3 and T4 metabolism that is the rate-limiting step in the exit of hormones from the plasma (and not the dissociation rate from plasma proteins). Thyroid hormone transport across cell membranes occurs via an active transport mechanism. Thyroid hormones bind to thyroid receptors intracellularly and form a heterodimer with retinoid X receptor; this whole complex binds to the thyroid hormone response element in DNA in order to increase (or decrease) transcription and translation. T3 has a 15-fold greater affinity than T4 for thyroid receptors. *Peripheral thyroid hormone metabolism*: About 80% of the total amount of thyroid hormones secreted by the thyroid gland is in the form of T4 and only 20% as T3. Nearly 80% of T3 is derived peripherally by enzymatic removal of a single 5′ iodine atom from the outer ring of the T4 molecule. Both T4 and T3 are inactivated by inner ring deiodination. The deiodinase enzymes occur in three isoforms. D1 is a plasma membrane protein mainly present in the liver, kidney, and thyroid and is involved in T4 to T3 activation, but also in the degradation of the inactive thyroid hormone, reverse triiodothyronine (rT3). D2 is an intracellular protein found mainly in the central nervous system, pituitary, and brown adipose tissue; it induces T4 to T3 activation intracellularly and is a source of plasma T3. D3 is a plasma membrane protein found in the central nervous system, placenta, and liver and is involved in thyroid hormone inactivation, e.g. conversion of T4 to rT3. All three isoforms contain the rare amino acid selenocysteine in the active catalytic centre. *Thyroid hormone excretion*: Thyroid hormone breakdown involves the conjugation of the phenolic hydroxyl group with sulphate or glucuronic acid. Glucuronidated T4 and T3 are excreted in the bile, acting as intermediates in the enterohepatic cycle and faecal excretion of thyroid hormones, but may be partially reabsorbed after deglucuronidation in the intestine (e). Sulfation accelerates the deiodination of different iodothyronines by D1 and initiates the irreversible degradation of the thyroid hormones.

4. Hyperthyroidism and the gut

Hyperthyroidism is commonly associated with weight loss despite an increased appetite, presumably due to increased energy expenditure in relation to an increased metabolic rate (Table 1). Occasionally, weight gain is seen, especially in younger patients with milder hyperthyroidism. In the elderly, the disease may masquerade itself as anorexia and weight loss.

4.1. Upper gastrointestinal dysfunction

Hyperthyroidism can be associated with a goitre, which in turn can mechanically compress the oesophagus and cause dysphagia [4]. Alternatively, dysphagia can also occur due to altered neurohormonal regulation or myopathy [5]. Treatment of the underlying hyperthyroidism is usually sufficient to reverse the dysphagia [5,6]. Hyperthyroidism can also have a variety of adverse effects on the stomach. Graves' disease may be associated with atrophic gastritis in the context of pernicious anaemia, given the autoimmune aetiology of these conditions. Severe

Table 1
Gastrointestinal features of thyroid disease.

	Hyperthyroidism	Hypothyroidism
Upper gut	• Dysphagia • Atrophic gastritis • Recurrent vomiting • Recurrence of *Helicobacter pylori* following eradication therapy	• Dysphagia • Dyspepsia • Achlorhydria • Gastrointestinal bleeding
Lower gut	• Diarrhoea (including steatorrhoea) • Lactose intolerance	• Constipation • Small intestinal bacterial overgrowth • Features of irritable bowel syndrome • Megacolon • Ileus • Colonic pseudo-obstruction
Liver	• Deranged liver function and hepatitis • Fulminant hepatitis (rare)	• Deranged liver function and hepatitis • Gallstones • Non-alcoholic fatty liver disease • Increased risk of hepatocellular carcinoma
Other	• Weight loss • (Weight gain in about 10%)	• Weight gain • Anaemia

vomiting associated with epigastric pain that had 'no clear cause' and was refractory to all anti-emetics has been described in association with hyperthyroidism; it resolved once therapy with thioamides was commenced [7]. The proposed mechanism is either a direct effect of thyroid hormones on gut motility or, alternatively, via a central stimulatory effect on the chemoreceptor trigger zone [8].

4.1.1. Hyperemesis gravidarum

The combination of biochemical thyrotoxicosis and persistent vomiting is also common in the context of *hyperemesis gravidarum*, often occurring in the first trimester of pregnancy [9]. This self-limiting disorder, termed *transient gestational hyperthyroidism*, results from stimulation of TSH receptors by high levels of human chorionic gonadotrophin (hCG) produced by the placenta. This effect is due to the α-subunit homology between hCG and TSH. High thyroid hormone levels cause feedback inhibition and suppression of TSH giving a biochemical picture of thyrotoxicosis. Anti-thyroid drug therapy is usually not indicated because the symptoms subside spontaneously with progression of pregnancy, with normalisation of T4 levels by 14–20 weeks of gestation [10].

4.2. Intestinal dysfunction

Intestinal dysfunction due to hyperthyroidism is widely recognised. Up to a quarter of patients with thyrotoxicosis suffer from mild to moderate diarrhoea; increased frequency of defecation and, rarely, steatorrhoea has been described. Hyperthyroidism is thought to cause diarrhoea via intestinal hypermotility reducing transit time in the small and large bowel and/or secretory diarrhoea and/or by enhancing beta-adrenergic activity [11]. The diarrhoea and the reduced transit time along the alimentary canal resolve with treatment of the underlying hyperthyroidism [12].

4.3. Hepatic dysfunction

The liver is the GI organ that is most affected by functional thyroid disease. Indeed, a bidirectional relationship exists between the liver and the thyroid in health and disease. The physiology of thyroid hormone metabolism is dependent on adequate liver function; in the circulation, thyroid hormones are mostly bound to thyroid binding proteins which are synthesised in the liver. It is only the free (unbound) thyroid hormones that can enter the cells and exert their action. Also, as aforementioned, T4 needs to be converted to T3 in peripheral organs and tissues; this is achieved via the selenoprotein deiodinase enzymes D1 and D2 which are abundant in, but not limited to, the liver. Conversely, thyroid hormones are necessary for normal hepatic function and hepatobiliary metabolism.

Hepatic disease can cause deranged thyroid function tests (see Section 9 *Non-thyroidal illness and the gut*). On the other hand, liver dysfunction is common in thyroid disease. For instance, alkaline phosphatase is raised in the majority of thyrotoxic patients (64–70%) and may have a hepatic or skeletal origin [13,14]. Alanine and aspartate aminotransferases may be raised in 37% and 27%, respectively; they arise from relative hypoxia in the hepatic perivenular regions [15]. Bilirubin and γ-glutamyl transferase elevations are uncommon (5% and 17%, respectively) [15]. Hepatitis is self-limiting as a general rule, but fulminant hepatitis has previously been described, precipitated by congestive cardiac failure and arrhythmia [16]. Non-specific histological hepatic changes are usually evident with thyrotoxicosis, with some patients showing progressive liver damage with centrizonal necrosis and perivenular fibrosis [15,17]; additional intrahepatic cholestasis has also been described. Liver disease is reversible in the vast majority of cases seen nowadays [15,17], which makes prompt recognition and treatment of thyrotoxicosis paramount.

Of note, propylthiouracil used in the treatment of hyperthyroidism can itself cause an often transient derangement of liver function tests (LFTs) in up to 30% of patients [18]. That is one of the reasons why propylthiouracil has fallen out of favour in the management of hyperthyroidism nowadays (hepatotoxicicty is much rarer with carbimazole and methimazole). However, the estimated incidence of propylthiouracil-induced severe hepatitis is less than 0.1% [17]. Nevertheless, it is advisable to check LFTs at baseline and periodically thereafter whenever propylthiouracil is used.

5. Hypothyroidism and the gut

Modest weight gain, in spite of reduced appetite, can occur in hypothyroidism due to reduced metabolism and accumulation of fluid rich in glycosaminoglycans (*myxoedema*) (Table 1). Hypothyroidism can be associated with anaemia. Hypothyroidism-induced menorrhagia in women can lead to microcytic, iron deficiency anaemia. On the other hand, macrocytic anaemia can occur when autoimmune hypothyroidism is associated with pernicious anaemia, which causes vitamin B12 deficiency and marrow megaloblastosis.

5.1. Upper gastrointestinal dysfunction

Oropharyngeal dysphagia has been described in people with hypothyroidism, as well as oesophagitis and hiatus hernia with more distal oesophageal involvement [11]. Hashimoto's thyroiditis is associated with a goitre, which can also cause dysphagia. One study reported mean oesophageal transit and gastric emptying times were significantly prolonged in people with hypothyroidism compared to healthy controls; all hypothyroid participants reported minor dyspeptic symptoms [19]. This study did not identify any significant link between reduced gastric emptying and gastric mucosal pathology. The authors did advocate checking thyroid function tests in patients presenting with dyspepsia. Such delayed gastric emptying has been shown to resolve with treatment of the underlying hypothyroidism [20].

5.2. Intestinal dysfunction

Constipation is the most commonly seen intestinal effect of hypothyroidism. Small intestinal bacterial overgrowth has also been described. In one study, when patients with a previous history of overt hypothyroidism (but who were rendered euthyroid with levothyroxine therapy) were tested with a hydrogen glucose breath test, 54% were found to be positive versus 5% in controls [21]. Abdominal discomfort, bloating, and flatulence were significantly associated with the presence of bacterial overgrowth and were significantly improved following antibiotic therapy [21]. Reduced GI motility may be implicated as it can

reduce the ability of the small bowel to prevent stasis and overgrowth of luminal bacteria [21]. It would therefore seem reasonable to test for small intestinal bacterial overgrowth in patients who have persisting gastrointestinal symptomatology despite resolution of their hypothyroidism. Hypothyroidism should be considered in the differential diagnosis of irritable bowel syndrome, gastrointestinal bleeding, megacolon, ileus, and colonic pseudo-obstruction [22–26].

5.3. Hepatic metabolism

Hypothyroidism commonly reduces hepatic metabolism and induces hepatic dysfunction. Symptoms such as fatigue, muscle cramps, and myalgias can be manifestations of both conditions and can cause diagnostic uncertainty. Deranged LFTs are seen in about half of patients with hypothyroidism (albeit often mildly deranged) despite normal hepatic histology [11], and thyroid function tests should be considered in all patients with deranged LFTs. Microscopically, reduced hepatic oxygen consumption and gluconeogenesis are observed [27,28]. Hypothyroidism causes reduced gallbladder motility, reduced bilirubin excretion, and hypercholesterolaemia, and hence increases the risk of gallstones [29]. Hypothyroidism is also twice as common in non-alcoholic fatty liver disease (NAFLD) compared to other causes of chronic liver disease (15% versus 7%, respectively) [30]. Following levothyroxine replacement in a patient with hypothyroidism and NAFLD, normalisation of LFTs has been reported with a much improved lipid profile and a drastic reduction in liver fat as measured by magnetic resonance spectroscopy [31]. Hepatic histological changes in NAFLD can mimic those of hypothyroidism [31], and as such hypothyroidism should be considered in the differential diagnosis of NAFLD with or without an associated metabolic syndrome picture. An association of hypothyroidism with primary biliary cirrhosis is also well established (see Section 6.3). Finally, hypothyroidism (but not hyperthyroidism) has been shown to confer a significantly increased risk of hepatocellular carcinoma in a case-control study, even after adjustment for other known risk factors [32].

5.4. Myxoedema and the gut

Hypothyroidism is reported to cause ascites in up to 4% of cases [33], although the exact incidence may be currently lower given the earlier identification and treatment of hypothyroidism. Myxoedema ascites is a rare cause of ascites (<1%), has more of an exudative fluid on aspiration (raised total protein >3.5 g/dL), and although it is universally reversible with treatment of the underlying hypothyroidism, there is often a significant time lag from presentation to diagnosis [33]. The likely mechanism of action involves hypothyroidism-induced increased protein extravasation and/or hyaluronic acid accumulation in the omentum, and hence a hygroscopic effect [33].

6. Thyroid autoimmunity and the gut

Autoimmune thyroid disease (AITD) can be associated with autoimmune disorders of the digestive system such as pernicious anaemia (discussed earlier, Section 5), coeliac disease, inflammatory bowel disease, and primary biliary cirrhosis.

6.1. Coeliac disease

The prevalence of coeliac disease in Western populations is about 1% [34]. In a prospective study, 3% of patients with AITD were identified as having coeliac disease with anti-endomysial antibody positivity and histological confirmation; all of these patients exhibited reduced bone mineral density, three had iron deficiency, and only one admitted to gastrointestinal symptoms [35]. Other studies have reported prevalence rates of coeliac disease of 2–5% among people with AITD [36]. One study reported a coeliac disease prevalence of 5% (versus 1% in controls) in people with Graves' disease [37]. Similarly, the prevalence among people with Hashimoto's disease was estimated at 4% [37]. Whilst screening for coeliac disease in AITD patients has been suggested [35], the difficulty is that the majority of these patients are asymptomatic or minimally symptomatic, which may hinder acceptance of a life-long gluten-free diet. However, it is worth noting that coeliac disease confers a slightly increased risk of malignancy and mortality [38], which could be reduced with a gluten-free diet. Also, a gluten-free diet has been reported to aid AITD with either levothyroxine dose reduction or amelioration of hypothyroidism [39]. Indeed, coeliac disease as well as other malabsorptive and maldigestive conditions is the commonest cause of treatment-refractory hypothyroidism (after non-concordance and incorrect administration are excluded) [40].

Conversely, AITD was present in 21% of people with coeliac disease; the majority of these patients had AITD with euthyroidism [35]. This figure varies between 6% and 20% on review of the various studies [36], with some of the difference being accounted for by whether euthyroid AITD was included or not. It is currently unclear whether the introduction of a gluten-free diet will have any impact on the natural history of AITD, given that thyroid antibodies were observed to either disappear or persist with a gluten-free diet [41]. It has previously been suggested that thyroid function assessment in coeliac disease is probably less justified [35]; however, we would suggest that because thyroid function tests are easy to perform and inexpensive, it is worth obtaining baseline thyroid function tests in these patients at presentation and whenever they are unwell with symptomatology consistent with thyroid disease. Recent guidelines from the British Society of Gastroenterology recommend routine annual testing for TSH and thyroid hormones in patients with coeliac disease [42].

The association between coeliac disease and thyroid autoimmunity has been challenged in an Italian prospective survey of 545 paediatric and adolescent patients with coeliac disease established on a gluten-free diet [43]. This study found no statistical difference in rates of thyroid autoimmunity among patients with coeliac disease compared to healthy controls, although thyroid autoimmunity was common in both groups (10% vs. 8%, respectively). The authors advised against routine thyroid screening of this patient population. However, it is worth noting that thyroid hormones were tested only when thyroid autoimmunity was identified and hence we do not know with absolute certainty the thyroid status of the full study cohort. In a much larger study of the Swedish national registry data, not only was there a clear association between coeliac disease and thyroid disease in children, but this association was stronger than that seen in adults, and persisted regardless of the temporal sequence between the two conditions [44].

Hypotheses proposed to explain the link between coeliac disease and AITD include the presence of a common genetic pathway with HLA-DQ2 and DQ8, with the former being commoner in patients suffering from both conditions; the same holds true for the gene encoding CTLA-4 (cytotoxic T-lymphocyte associated antigen-4), a T cell surface molecule involved in T cell proliferation [44].

6.2. Inflammatory bowel disease

Thyroid disease has also been linked to inflammatory bowel disease, with disordered autoimmunity hypothesised as the underlying cause. Thyroid disease has been reported in 10% of patients with inflammatory bowel disease compared to 2% in healthy controls; this was despite no significant difference in the mean free T3, free T4, and TSH levels [45]. There was no statistical difference in the prevalence of thyroid disease between patients with ulcerative colitis or Crohn's disease [45]. However, not all studies are in agreement with this association; in a large population-based study that included 8,072 patients with inflammatory bowel disease, the prevalence of thyroid disease was similar to that of controls [46]. On balance, it is likely that inflammatory bowel disease increases the risk of thyroid disease. Current inflammatory bowel disease treatment guidelines have overlooked screening/monitoring of thyroid

function [47,48]. Given that thyroid disease can worsen the symptomatology of inflammatory bowel disease, we suggest a low threshold for performing thyroid function tests in this patient group. Treatment-refractory colitis in the context of inflammatory bowel disease and hyperthyroidism has been described; remission was achieved once anti-thyroid medications were commenced [49]. These findings are consistent with another study that reported doubling of the risk of thyroid disease in patients with inflammatory bowel disease compared with healthy western populations [50].

6.3. *Primary biliary cirrhosis*

Primary biliary cirrhosis is frequently associated with autoimmune diseases, including thyroid disease. Its prevalence among patients with hypothyroidism is 5–20% [51,52], whereas the prevalence of anti-thyroid antibodies among patients with primary biliary cirrhosis is about 20% [52]. One study examined the prevalence of thyroid dysfunction in primary biliary cirrhosis compared with primary sclerosing cholangitis and NAFLD [53]. The prevalence of thyroid dysfunction in primary biliary cirrhosis was 13%, which was similar to that seen in primary sclerosing cholangitis (11%), but (non-significantly) less than in NAFLD (25%) [53]. The incidence of thyroid dysfunction in primary biliary cirrhosis was 2.9 patients per 100 person-years, which was similar to the other two conditions [53]. In conclusion, thyroid disease possibly confers a mildly increased susceptibility to primary biliary cirrhosis, but thyroid disease seems to be no commoner in primary biliary cirrhosis compared to other (non-autoimmune) liver conditions.

7. Medullary thyroid cancer and the gut

Medullary thyroid cancer is a calcitonin-producing tumour of the parafollicular C-cells of the thyroid. The mean age at presentation is 38 years [54], and it can occur spontaneously or be hereditary as part of familial medullary thyroid cancer, multiple endocrine neoplasia type 2 or type 3 (formerly known as type 2B). The mode of presentation among sporadic cases was that of a thyroid mass, local symptoms (such as dysphagia, breathlessness, or hoarseness) or systemic symptoms (such as diarrhoea, flushing, and/or bone pain) in 74%, 16%, and 10%, respectively; all patients with systemic symptoms had metastatic disease [54]. The corresponding percentages for hereditary medullary thyroid cancer were 48%, 4%, and 7%, respectively; 48% of this cohort were asymptomatic and were diagnosed via biochemical or genetic screening [54]. Older series have reported higher prevalence of diarrhoea (28–39%) [55,56], which probably reflects the altered natural history of the disease nowadays with earlier diagnosis and genetic testing of asymptomatic carriers. The presence of diarrhoea was indeed associated with risk of recurrent or persistent disease [54]. Other investigators also reported that diarrhoea is commoner in advanced (metastatic) disease; in about two thirds of patients, it preceded the diagnosis of medullary thyroid cancer by a median duration of 1 year and it usually resolved on curative surgical treatment of the cancer; diarrhoea resurgence can signify disease recurrence [56].

The pathophysiology of diarrhoea in medullary thyroid cancer is not fully understood. It is thought to be hypersecretory and/or due to gastrointestinal hypermotility [57]. It was studied using scintigraphic investigations; the overall handling of water and ions in the small bowel was normal with normal gastric emptying, which makes calcitonin an unlikely culprit for the diarrhoea, albeit calcitonin is known to stimulate small intestinal mucosal secretion [58]. There was, however, marked reduction in the transit time of colonic contents [58]. Prostaglandins E2 and F2α, serotonin, and substance P are raised in patients with medullary thyroid cancer [59,60] and have been postulated as being involved in the pathogenesis of the cancer-associated diarrhoea [58]. Currently, it is thought that the cause of the diarrhoea may vary from one individual to another; prostaglandins, serotonin, and calcitonin do remain the likely culprits though [61]. The European Thyroid Association guidelines recommend that initial therapy should include antimotility agents (such as loperamide) and that surgery and hepatic (chemo-) embolisation should be employed in selected cases, with the use of tyrosine kinase inhibitors (vandetanib and cabozantinib) in more advanced and progressive disease [57].

8. The thyroid and interferon therapies

Interferons are a class of cytokines that possess antiviral and anti-tumour activity; they work mainly by augmenting the T-lymphocyte Th1 immune response. Synthetic interferon is used for the treatment of viral infections, such as the hepatitis C virus (HCV). Whilst HCV infection *per se* is not associated with thyroid dysfunction [62], in one study of patients receiving interferon therapy for 12 months, 39% developed thyroid antibody (TAb) positivity and 5% developed thyroid dysfunction; all patients with thyroid dysfunction were TAb positive [63]. On a few occasions, TAb positivity emerged following discontinuation of underlying interferon therapy. In other studies, the presence of TAb positivity and thyroid dysfunction ranged from 1% to 40% and 3% to 9%, respectively [64–68]; disease resolution was reported in most, but not all, cases on interferon discontinuation. One large review reported 6% incidence of thyroid dysfunction among 1800 patients treated with interferon, with two thirds due to hypothyroidism and the remaining third due to hyperthyroidism [69].

Interferon-induced hypothyroidism can be subclinical or overt; it often occurs in the presence of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) positivity, and in two thirds of cases, it follows thyroiditis [70]. Thyroiditis is diagnosed by the presence of thyrotoxicosis and the absence of TSH receptor antibodies, reduced tracer uptake on a radioiodine scan and (often) diffusely reduced echogenicity and vascularity on thyroid ultrasonography; it usually occurs early post-interferon therapy, its duration varies from weeks to months, can have subclinical course, and can ultimately lead to transient, or (occasionally) permanent, hypothyroidism [65]. Graves' disease is less common than thyroiditis and can be diagnosed in the presence of TSH receptor antibody positivity [71,72], with supporting evidence from radioiodine scan (normal or increased uptake) and thyroid ultrasound (may have increased vascularity); it can occasionally emerge after thyroiditis or hypothyroidism [65]. Female gender, interferon dose, and treatment duration were identified as predisposing factors for thyroid toxicity.

The exact mechanism by which interferon therapy affects the thyroid remains unclear. Activation of the immune system with aberrant expression of major histocompatibility antigens in the thyroid, direct inhibitory effect on thyroid function, and genetic predisposition to AITD have been proposed [65,73]. Interferon possibly unmasks thyroid dysfunction causing hyperthyroidism in those with pre-existing subclinical AITD, whereas, in those with no pre-existing AITD, it may have a more direct toxic effect with resultant thyroiditis [74]; both actions are similar to amiodarone-induced thyrotoxicosis.

8.1. *Management of interferon-induced thyroid dysfunction*

It is recommended that thyroid function tests, TgAb and TPOAb should be measured at baseline and every 8–12 weeks during interferon therapy (Fig. 2), with earlier measurement if any symptomatology appears that could be suggestive of thyroid dysfunction [70]. If hypothyroidism is identified, it should be treated with levothyroxine and interferon therapy can continue [65]. For thyroiditis, beta-blockers, and occasionally glucocorticoids, can be used for symptom control and interferon can usually be continued (unless prominent symptomatology exists) [65]. Mild Graves' disease can be managed with thioamides and continuation of interferon, whereas severe disease would require definitive treatment with radioiodine therapy or thyroidectomy; interferon can be discontinued whilst the definitive therapy is given and the patient is rendered euthyroid (invariably with levothyroxine

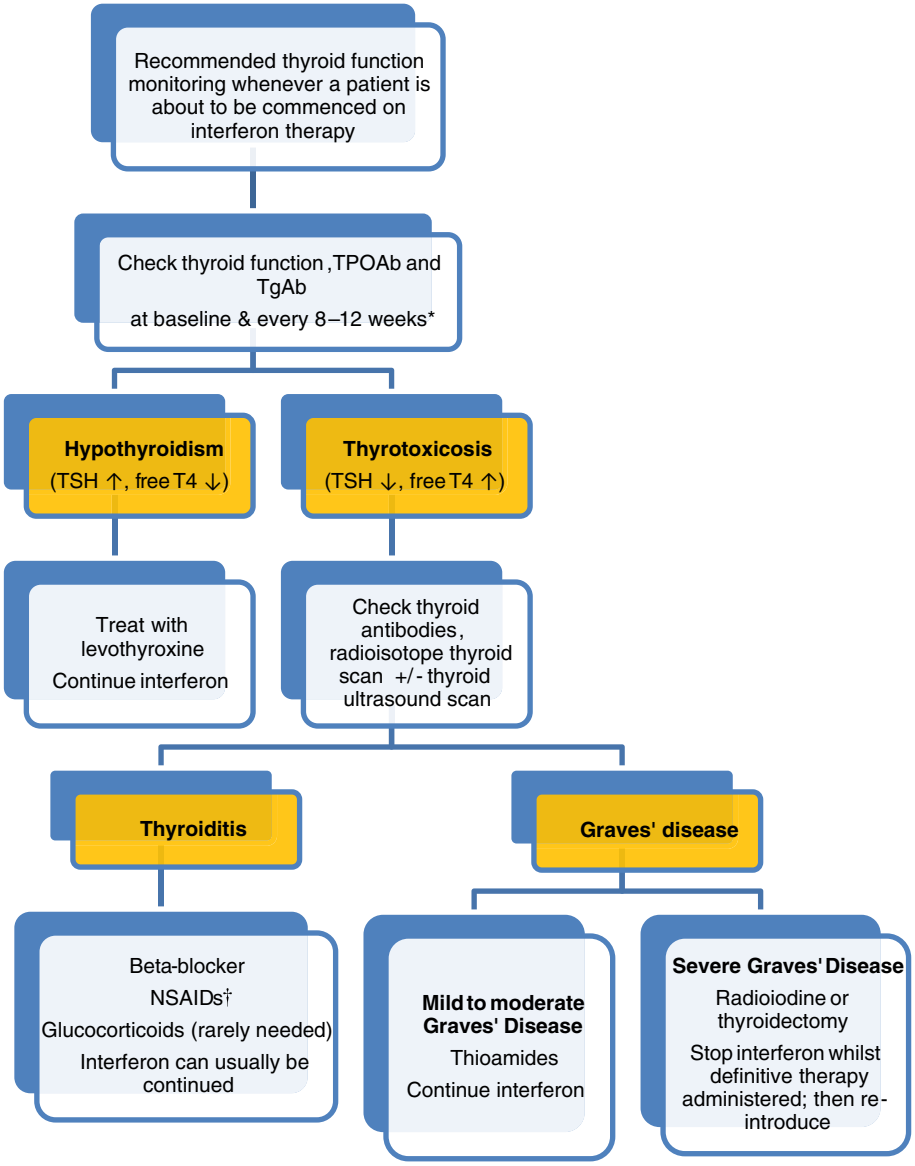

Fig. 2. Management of interferon-induced thyroid dysfunction. *It is advisable to check thyroid function more urgently whenever any signs and symptoms are identified that could be consistent with thyroid disease. †Non-steroidal anti-inflammatory drugs (NSAIDs) may be required when a patient experiences thyroiditis pain; their use should be limited to a few days or weeks and concurrent use of proton pump inhibitor therapy should be considered. Abbreviations: TFTs: thyroid function tests, TPOAb: thyroid peroxidase Antibodies; TgAb: thyroglobulin antibodies; NSAIDs: non-steroidal anti-inflammatory drugs.

supplements) and then can be shortly re-introduced [65]. We would suggest that all patients with thyroid dysfunction whilst on interferon therapy should be followed up by an endocrinologist.

9. Non-thyroidal illness and the gut

Non-thyroidal illness, sometimes also known as *sick euthyroid syndrome*, refers to thyroid dysfunction secondary to extra-thyroidal illness; examples include, but are not limited to, septicaemia, any acute inflammatory condition, trauma, surgery, and severe disease requiring intensive care input. Reduced free T3 is the commonest finding; TSH is also commonly reduced although it can be raised in the recovery phase; free T4 can be reduced, normal, or even raised. Free T4 and TSH are often affected with more severe illness [75]. The traditional explanation for this observation related to deiodinase dysfunction. General illness is thought to increase hepatic and renal D3 (that mainly deactivates thyroid hormones) and reduce hepatic and skeletal D2 (converts free T4 to the more metabolically active free T3). However, a more up-to-date explanation for the non-thyroidal illness phenomenon is that there is a central hypothyroidism defect due to a change in the set point of the hypothalamic–pituitary–thyroid axis [75], given that the usual negative feedback mechanism that would have normally caused a rise in TRH and TSH in the face of suppressed free T3 does not exist. TRH inhibition in this situation may relate to relative malnutrition and/or release of cytokines and/or an increased free T4 observed in some patients [75].

It is currently unclear whether or not pharmacotherapy is of any benefit in non-thyroidal illness [76,77]. On balance, most experts in the field recommend close observation with periodic monitoring of thyroid function tests, but no drug therapies. This, however, implies that a correct diagnosis of non-thyroidal illness has been established. Given that, in our experience, the non-specialist may be more inclined to misdiagnose non-thyroidal illness as primary thyroid disease and vice versa, we would advocate referral to an endocrinologist in such scenarios.

10. The thyroid and obesity

Clear associations between thyroid function and obesity have been observed in the euthyroid general population, with higher TSH correlated to weight gain [78–80]. In addition, morbid obesity has been associated with higher TSH concentrations [81,82]. The relationship with free thyroid hormones is less clear. Furthermore, studies into the effect of weight loss on thyroid function in people with morbid obesity have given inconsistent results [81,83–87]. It has been reported that moderate weight loss results in a decrease in T3 with minimal changes in other thyroid hormone homeostasis parameters, suggesting that a decrease in peripheral conversion of T4 to T3 is at least in part responsible for the observed changes in thyroid hormone homeostasis [88].

10.1. The thyroid and bariatric surgery

Studies in bariatric surgery patients have reported improvement in thyroid hormone levels following gastric bypass surgery in obese people with subclinical or overt hypothyroidism [87]. Studies involving gastric banding or gastric bypass in euthyroid people have reported significant increase in free T4 concentrations but no change in TSH with weight loss [78,89]. A recent small study of sleeve gastrectomy in euthyroid obese patients has reported reduction in TSH with no change in free T4 levels [90]. Another study demonstrated that obesity was associated with higher TSH, T3, and reverse T3 levels and normal free T4 levels when compared with lean controls, and that both calorie restriction and gastric bypass surgery induced a decline in serum TSH levels and a rise in reverse T3 and free T4 levels [91].

It has been reported that biliopancreatic diversion is associated with an increased prevalence of subclinical or even frank hypothyroidism through several integrated mechanisms including iodine malabsorption and increased free T3 losses through changes in the entero-hepatic circulation [92].

Reduced drug absorption of levothyroxine may occur post-bariatric surgery [93], necessitating individual dose-adjustment and therapeutic monitoring. This effect may vary depending on the type of bariatric surgery. One study has reported that gastric bypass does not diminish levothyroxine absorption [94]. A small study has reported that the pharmacokinetic parameters of levothyroxine absorption are improved following sleeve gastrectomy and biliopancreatic diversion types of bariatric procedures but unchanged after gastric bypass [95].

In summary, different types of bariatric surgery can influence thyroid function variably. Whilst weight loss generally improves thyroid function, severely malabsorptive procedures may decrease the bioavailability of endogenous and/or exogenous thyroid hormones.

11. Conclusion

As evidenced by the above assessment of the evidence, there is a bidirectional relationship between the thyroid gland and the gastrointestinal tract, both in health and disease. Hyperthyroidism and hypothyroidism can impact on all the different gastrointestinal organs and functions, whereas autoimmune thyroid disease can be associated with coeliac or, occasionally, inflammatory bowel disease. Medullary thyroid carcinoma, of all thyroid cancers, is of particular note as it presents to the non-endocrinologist with diarrhoea. Medications used for the treatment of primary gastrointestinal disorders, such as interferon, can be associated with thyroid dysfunction; likewise, thyroid therapies can cause GI adverse effects (e.g. propylthiouracil-induced hepatitis) and the absorption of thyroid medications (levothyroxine) can be influenced by gastrointestinal disorders. We conclude that it is important to recognise that the thyroid and the gut do not function in isolation, but rather, have an intricate relationship both in health and disease.

Learning Points

- The thyroid and the gut are closely intertwined in both health and disease.
- We recommend checking thyroid function in the following settings: unclear aetiology, suspected functional or treatment-refractory gastrointestinal disease, and also whenever new or unexplained symptoms arise in the context of an autoimmune gastrointestinal disease. For coeliac disease in particular, check thyroid function at baseline and annually thereafter.
- There should be a low threshold for checking thyroid function in hepatitis and hepatic failure, especially when there is no apparent cause.
- Always consider non-thyroidal illness whilst interpreting thyroid function tests in the context of acute hepatic and gastrointestinal disease and in all severely ill patients.
- Medullary thyroid carcinoma is a rare neuroendocrine tumour that should be considered in the differential diagnosis of chronic diarrhoea.

Conflict of interest

The authors state that they have no conflicts of interest.

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References

[1] Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull 2011;99:39–51. http://dx.doi.org/10.1093/bmb/ldr030.
[2] Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev 2001;81:1097–142.
[3] Salvatore D, Davies T, Schlumberger M-J, Hay I, Larsen P. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronemberg HM, editors. Williams Textb. Endocrinol, 12th ed., Philadelphia: Saunders Elsevier; 2011.
[4] Anders HJ. Compression syndromes caused by substernal goitres. Postgrad Med J 1998;74:327–9. http://dx.doi.org/10.1136/pgmj.74.872.327.
[5] Chiu W-Y, Yang C-C, Huang I-C, Huang T-S. Dysphagia as a manifestation of thyrotoxicosis: report of three cases and literature review. Dysphagia 2004;19:120–4.
[6] Branski D, Levy J, Globus M, Aviad I, Keren A, Chowers I. Dysphagia as a primary manifestation of hyperthyroidism. J Clin Gastroenterol 1984;6:437–40.
[7] Hoogendoorn EH, Cools BM. Hyperthyroidism as a cause of persistent vomiting. Neth J Med 2004;62:293–6.
[8] Sellin JH, Vassilopoulou-Sellin R. The gastrointestinal tract and liver in thyrotoxicosis. Warn. Ingbar's Thyroid; 2000 622–6.
[9] Verberg MFG, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update 2006;13:207-207. http://dx.doi.org/10.1093/humupd/dml050.
[10] Patil-Sisodia K, Mestman JH. Graves hyperthyroidism and pregnancy: a clinical update. Endocr Pract n.d.;16:118–29. doi:10.4158/EP09233.RA.
[11] Daher R, Yazbeck T, Jaoude JB, Abboud B. Consequences of dysthyroidism on the digestive tract and viscera. World J Gastroenterol 2009;15:2834–8.
[12] Papa A, Cammarota G, Tursi A, Certo M, Montalto M, Capelli G, et al. Effects of propylthiouracil on intestinal transit time and symptoms in hyperthyroid patients. Hepatogastroenterology 1997;44:426–9.
[13] Doran GR. Serum enzyme disturbances in thyrotoxicosis and myxoedema. J R Soc Med 1978;71:189–94.
[14] Huang MJ, Li KL, Wei JS, Wu SS, Fan KD, Liaw YF. Sequential liver and bone biochemical changes in hyperthyroidism: prospective controlled follow-up study. Am J Gastroenterol 1994;89:1071–6.
[15] Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM 2002;95:559–69.
[16] Choudhary AM, Roberts I. Thyroid storm presenting with liver failure. J Clin Gastroenterol 1999;29:318–21.
[17] Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. J Gastroenterol Hepatol 10:344–50.
[18] Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: what have we learned? J Clin Endocrinol Metab 1997;82:1727–33. http://dx.doi.org/10.1210/jcem.82.6.4011.
[19] Yaylali O, Kirac S, Yilmaz M, Akin F, Yuksel D, Demirkan N, et al. Does hypothyroidism affect gastrointestinal motility? Gastroenterol Res Pract 2009;2009:529802. http://dx.doi.org/10.1155/2009/529802.
[20] Holdsworth CD, Besser GM. Influence of gastric emptying-rate and of insulin response on oral glucose tolerance in thyroid disease. Lancet 1968;2:700–2.

[21] Lauritano EC, Bilotta AL, Gabrielli M, Scarpellini E, Lupascu A, Laginestra A, et al. Association between hypothyroidism and small intestinal bacterial overgrowth. J Clin Endocrinol Metab 2007;92:4180–4. http://dx.doi.org/10.1210/jc.2007-0606.

[22] Bassotti G, Pagliacci MC, Nicoletti I, Pelli MA, Morelli A. Intestinal pseudoobstruction secondary to hypothyroidism. Importance of small bowel manometry. J Clin Gastroenterol 1992;14:56–8.

[23] Batke M, Cappell MS. Adynamic ileus and acute colonic pseudo-obstruction. Med Clin North Am 2008;92:649–70. http://dx.doi.org/10.1016/j.mcna.2008.01.002 [ix].

[24] Maser C, Toset A, Roman S. Gastrointestinal manifestations of endocrine disease. World J Gastroenterol 2006;12:3174–9.

[25] Fukunaga K. Refractory gastrointestinal bleeding treated with thyroid hormone replacement. J Clin Gastroenterol 2001;33:145–7.

[26] Bacharach T, Evans JR. Enlargement of the colon secondary to hypothyroidism. Ann Intern Med 1957;47:121. http://dx.doi.org/10.7326/0003-4819-47-1-121.

[27] Comte B, Vidal H, Laville M, Riou JP. Influence of thyroid hormones on gluconeogenesis from glycerol in rat hepatocytes: a dose-response study. Metabolism 1990;39:259–63.

[28] Liverini G, Iossa S, Barletta A. Relationship between resting metabolism and hepatic metabolism: effect of hypothyroidism and 24 hours fasting. Horm Res 1992;38:154–9.

[29] Mansourian AR. A review of literatures on the adverse effects of thyroid abnormalities and liver disorders: an overview on liver dysfunction and hypothyroidism. Pak J Biol Sci 2013;16:1641–52.

[30] Liangpunsakul S, Chalasani N. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? J Clin Gastroenterol 2003;37:340–3.

[31] Gardner CJ, Richardson P, Wong C, Polavarapu N, Kemp GJ, Cuthbertson DJ. Hypothyroidism in a patient with non-alcoholic fatty liver disease. BMJ 2011;342:c7199. http://dx.doi.org/10.1136/bmj.c7199.

[32] Hassan MM, Kaseb A, Li D, Patt YZ, Vauthey J-N, Thomas MB, et al. Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. Hepatology 2009;49:1563–70. http://dx.doi.org/10.1002/hep.22793.

[33] Ji J-S, Chae H-S, Cho Y-S, Kim H-K, Kim S-S, Kim C-W, et al. Myxedema ascites: case report and literature review. J Korean Med Sci 2006;21:761–4.

[34] West J, Logan RFA, Hill PG, Lloyd A, Lewis S, Hubbard R, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003;52:960–5.

[35] Sategna-Guidetti C, Bruno M, Mazza E, Carlino A, Predebon S, Tagliabue M, et al. Autoimmune thyroid diseases and coeliac disease. Eur J Gastroenterol Hepatol 1998;10:927–31.

[36] Ch'ng CL, Jones MK, Kingham JGC. Celiac disease and autoimmune thyroid disease. Clin Med Res 2007;5:184–92. http://dx.doi.org/10.3121/cmr.2007.738.

[37] Cuoco L, Certo M, Jorizzo RA, De Vitis I, Tursi A, Papa A, et al. Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders. Ital J Gastroenterol Hepatol 1999;31:283–7.

[38] West J, Logan RFA, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. BMJ 2004;329:716–9. http://dx.doi.org/10.1136/bmj.38169.486701.7C.

[39] Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, et al. Prevalence of coeliac disease in patients with thyroid autoimmunity. Horm Res 1999;51:124–7 [doi:23344].

[40] Ramadhan A, Tamilia M. Treatment-refractory hypothyroidism. CMAJ 2012;184:205–9. http://dx.doi.org/10.1503/cmaj.110994.

[41] Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol 1997;136:315–8.

[42] Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014;63:1210–28. http://dx.doi.org/10.1136/gutjnl-2013-306578.

[43] Diamanti A, Ferretti F, Guglielmi R, Panetta F, Colistro F, Cappa M, et al. Thyroid autoimmunity in children with coeliac disease: a prospective survey. Arch Dis Child 2011;96:1038–41. http://dx.doi.org/10.1136/archdischild-2011-300595.

[44] Elfström P, Montgomery SM, Kämpe O, Ekbom A, Ludvigsson JF. Risk of thyroid disease in individuals with celiac disease. J Clin Endocrinol Metab 2008;93:3915–21. http://dx.doi.org/10.1210/jc.2008-0798.

[45] Yakut M. Thyroid disorders in patients with inflammatory bowel diseases. Int J Clin Med 2011;02:89–92. http://dx.doi.org/10.4236/ijcm.2011.22018.

[46] Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005;129:827–36. http://dx.doi.org/10.1053/j.gastro.2005.06.021.

[47] Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53(Suppl. 5):V1–V16. http://dx.doi.org/10.1136/gut.2004.043372.

[48] Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. Am J Gastroenterol 2009;104:465–83. http://dx.doi.org/10.1038/ajg.2008.168 [quiz 464, 484].

[49] Modebe O. Autoimmune thyroid disease with ulcerative colitis. Postgrad Med J 1986;62:475–6.

[50] Cesarini M, Angelucci E, Rivera M, Pica R, Paoluzi P, Vernia P, et al. Thyroid disorders and inflammatory bowel diseases: retrospective evaluation of 909 patients from an Italian Referral Center. Inflamm Bowel Dis 2010;16:186–7. http://dx.doi.org/10.1002/ibd.20964.

[51] Valera MJM, Smok SG, Poniachik TJ, Oksenberg RD, Silva PG, Ferrario BM, et al. Primary biliary cirrhosis: a thirteen years experience. Rev Med Chil 2006;134:469–74. http://dx.doi.org/10.4067/S0034-98872006000400010.

[52] Elta GH, Sepersky RA, Goldberg MJ, Connors CM, Miller KB, Kaplan MM. Increased incidence of hypothyroidism in primary biliary cirrhosis. Dig Dis Sci 1983;28:971–5.

[53] Silveira MG, Mendes FD, Diehl NN, Enders FT, Lindor KD. Thyroid dysfunction in primary biliary cirrhosis, primary sclerosing cholangitis and non-alcoholic fatty liver disease. Liver Int 2009;29:1094–100. http://dx.doi.org/10.1111/j.1478-3231.2009.02003.x.

[54] Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer 2000;88:1139–48.

[55] Williams ED. Diarrhoea and thyroid carcinoma. Proc R Soc Med 1966;59:602–3.

[56] Steinfeld CM, Moertel CG, Woolner LB. Diarrhea and medullary carcinoma of the thyroid. Cancer 1973;31:1237–9. http://dx.doi.org/10.1002/1097-0142(197305)31:5<1237::AID-CNCR2820310530>3.0.CO;2-K.

[57] Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JWA. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. Eur Thyroid J 2012;1:5–14. http://dx.doi.org/10.1159/000336977.

[58] Rambaud JC, Jian R, Flourié B, Hautefeuille M, Salmeron M, Thuillier F, et al. Pathophysiological study of diarrhoea in a patient with medullary thyroid carcinoma. Evidence against a secretory mechanism and for the role of shortened colonic transit time. Gut 1988;29:537–43.

[59] Skrabanek P, Cannon D, Dempsey J, Kirrane J, Neligan M, Powell D. Substance P in medullary carcinoma of the thyroid. Experientia 1979;35:1259–60.

[60] Williams ED, Karim SM, Sandler M. Prostaglandin secretion by medullary carcinoma of the thyroid. A possible cause of the associated idarrhoea. Lancet 1968;1:22–3. http://dx.doi.org/10.1016/S0140-6736(68)90010-X.

[61] Ebert EC. The thyroid and the gut. J Clin Gastroenterol 2010;44:402–6. http://dx.doi.org/10.1097/MCG.0b013e3181d6bc3e.

[62] Loviselli A, Oppo A, Velluzzi F, Atzeni F, Mastinu GL, Farci P, et al. Independent expression of serological markers of thyroid autoimmunity and hepatitis virus C infection in the general population: results of a community-based study in northwestern Sardinia. J Endocrinol Invest 2014;22:660–5. http://dx.doi.org/10.1007/BF03343626.

[63] Mäki M, Kallonen K, Lähdeaho M-L, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. Acta Paediatr 1988;77:408–12. http://dx.doi.org/10.1111/j.1651-2227.1988.tb10668.x.

[64] Imagawa A, Itoh N, Hanafusa T, Oda Y, Waguri M, Miyagawa J, et al. Autoimmune endocrine disease induced by recombinant interferon-alpha therapy for chronic active type C hepatitis. J Clin Endocrinol Metab 1995;80:922–6. http://dx.doi.org/10.1210/jcem.80.3.7883851.

[65] Carella C, Mazziotti G, Morisco F, Manganella G, Rotondi M, Tuccillo C, et al. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. J Clin Endocrinol Metab 2001;86:1925–9. http://dx.doi.org/10.1210/jcem.86.5.7459.

[66] Preziati D, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 1995;132:587–93.

[67] Watanabe U, Hashimoto E, Hisamitsu T, Obata H, Hayashi N. The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. Am J Gastroenterol 1994;89:399–403.

[68] Marazuela M, García-Buey L, González-Fernández B, García-Monzón C, Arranz A, Borque MJ, et al. Thyroid autoimmune disorders in patients with chronic hepatitis C before and during interferon-alpha therapy. Clin Endocrinol (Oxf) 1996;44:635–42.

[69] Koh LK, Greenspan FS, Yeo PP. Interferon-alpha induced thyroid dysfunction: three clinical presentations and a review of the literature. Thyroid 1997;7:891–6.

[70] Carella C, Mazziotti G, Amato G, Braverman LE, Roti E. Clinical review 169: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. J Clin Endocrinol Metab 2004;89:3656–61. http://dx.doi.org/10.1210/jc.2004-0627.

[71] Matthews DC, Syed AA. The role of TSH receptor antibodies in the management of Graves' disease. Eur J Intern Med 2011;22:213–6. http://dx.doi.org/10.1016/j.ejim.2011.02.006.

[72] Barbesino G, Tomer Y. Clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab 2013;98:2247–55. http://dx.doi.org/10.1210/jc.2012-4309.

[73] Floreani A, Chiaramonte M, Greggio NA, Fabris P, De Lazzari F, Naccarato R, et al. Organ-specific autoimmunity and genetic predisposition in interferon-treated HCV-related chronic hepatitis patients. Ital J Gastroenterol Hepatol 1998;30:71–6.

[74] Oppenheim Y, Ban Y, Tomer Y. Interferon induced autoimmune thyroid disease (AITD): a model for human autoimmunity. Autoimmun Rev 2004;3:388–93. http://dx.doi.org/10.1016/j.autrev.2004.03.003.

[75] Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol 2010;205:1–13. http://dx.doi.org/10.1677/JOE-09-0412.

[76] Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 2014;24:1456–65. http://dx.doi.org/10.1089/thy.2014.0201.

[77] Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diab Endocrinol 2015. http://dx.doi.org/10.1016/S2213-8587(15)00225-9.

[78] MacCuish A, Razvi S, Syed AA. Effect of weight loss after gastric bypass surgery on thyroid function in euthyroid people with morbid obesity. Clin Obes 2012;2:25–8. http://dx.doi.org/10.1111/j.1758-8111.2012.00036.x.

[79] Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 2005;90:4019–24.

[80] Svare A, Nilsen TI, Bjoro T, Asvold BO, Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol 2011;74:769–75. http://dx.doi.org/10.1111/j.1365-2265.2011.04009.x.

[81] Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid volume and function in obese women. Clin Endocrinol 2003;59:258–62. http://dx.doi.org/10.1046/j.1365-2265.2003.01836.x.

[82] Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, et al. Thyroid function in humans with morbid obesity. Thyroid 2006;16:73–8. http://dx.doi.org/10.1089/thy.2006.16.73.
[83] Papavramidis ST, Zisiadis AC, Karamouzis MN, Kessissoglou II II, Antoniadou HA, Aidonopoulos AP. Alterations in thyroid hormones and thyrotropin (TSH) in morbidly obese patients before and after vertical gastroplasty. Obes Surg 1995;5: 298–301. http://dx.doi.org/10.1381/096089295765557674.
[84] Buscemi S, Verga S, Maneri R, Blunda G, Galluzzo A. Influences of obesity and weight loss on thyroid hormones. A 3-3.5-year follow-up study on obese subjects with surgical bilio-pancreatic by-pass. J Endocrinol Invest 1997;20:276–81.
[85] Yashkov YI, Vinnitsky LI, Poroykova MV, Vorobyova NT. Some hormonal changes before and after vertical banded gastroplasty for severe obesity. Obes Surg 2000; 10:48–53. http://dx.doi.org/10.1381/09608920060674111.
[86] Moulin de Moraes CM, Mancini MC, de Melo ME, Figueiredo DA, Villares SM, Rascovski A, et al. Prevalence of subclinical hypothyroidism in a morbidly obese population and improvement after weight loss induced by Roux-en-Y gastric bypass. Obes Surg 2005;15:1287–91. http://dx.doi.org/10.1381/096089205774512537.
[87] Chikunguwo S, Brethauer S, Nirujogi V, Pitt T, Udomsawaengsup S, Chand B, et al. Influence of obesity and surgical weight loss on thyroid hormone levels. Surg Obes Relat Dis 2007;3:631–6. http://dx.doi.org/10.1016/j.soard.2007.07.011 [S1550-7289(07)00576-X [pii]].
[88] Agnihothri RV, Courville AB, Linderman JD, Smith S, Brychta R, Remaley A, et al. Moderate weight loss is sufficient to affect thyroid hormone homeostasis and inhibit its peripheral conversion. Thyroid 2014;24:19–26. http://dx.doi.org/10.1089/thy.2013.0055.
[89] Dall'Asta C, Paganelli M, Morabito A, Vedani P, Barbieri M, Paolisso G, et al. Weight loss through gastric banding: effects on TSH and thyroid hormones in obese subjects with normal thyroid function. Obesity (Silver Spring) 2010;18:854–7.
[90] Abu-Ghanem Y, Inbar R, Tyomkin V, Kent I, Berkovich L, Ghinea R, et al. Effect of sleeve gastrectomy on thyroid hormone levels. Obes Surg 2014. http://dx.doi.org/10.1007/s11695-014-1415-7.
[91] Lips MA, Pijl H, van Klinken JB, de Groot GH, Janssen IM, Van Ramshorst B, et al. Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. Eur J Endocrinol 2013;169:339–47. http://dx.doi.org/10.1530/eje-13-0339.
[92] Gniuli D, Leccesi L, Guidone C, Iaconelli A, Chiellini C, Manto A, et al. Thyroid function and insulin sensitivity before and after bilio-pancreatic diversion. Obes Surg 2010; 20:61–8. http://dx.doi.org/10.1007/s11695-009-0005-6.
[93] Padwal R, Brocks D, Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. Obes Rev 2010;11:41–50. http://dx.doi.org/10.1111/j.1467-789X.2009.00614.x.
[94] Rubio IG, Galrao AL, Santo MA, Zanini AC, Medeiros-Neto G. Levothyroxine absorption in morbidly obese patients before and after Roux-En-Y gastric bypass (RYGB) surgery. Obes Surg 2012;22:253–8. http://dx.doi.org/10.1007/s11695-011-0452-8.
[95] Gkotsina M, Michalaki M, Mamali I, Markantes G, Sakellaropoulos GC, Kalfarentzos F, et al. Improved levothyroxine pharmacokinetics after bariatric surgery. Thyroid 2013;23:414–9. http://dx.doi.org/10.1089/thy.2011.0526.