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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].

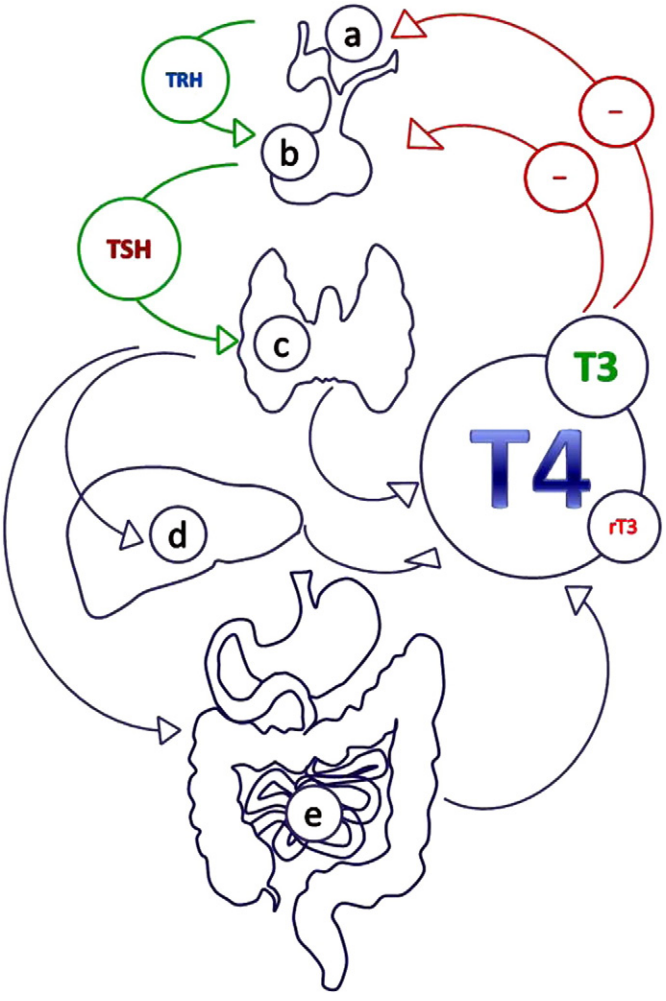

Fig. 1. Summary of thyroid hormone regulation and peripheral action. *Central regulation*: Thyrotropin-releasing hormone (TRH), a modified tripeptide produced by the parvocellular region of paraventricular nuclei of hypothalamus (a), stimulates production and release of thyroid stimulating hormone (TSH). 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