Thyroid Disease in Primary Care

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In this presentation I will discuss presentation, investigation and management of thyroid disease in primary care.

Thyroid Disorders are common. The NZ Health Survey 2006/2007 revealed that 1% of men and 5% of women have a thyroid disorder. The incidence rises with age. After disorders of glucose homeostasis, thyroid dysfunction is amongst the commonest endocrine presentations seen in primary care. Significant overlap can exist between the symptoms of thyroid dysfunction and of other non-thyroid conditions. It is therefore essential to be able to appropriately recognise, investigate and manage thyroid disorders, and to know who to refer to an Endocrinologist.

Normal Thyroid Physiology

Before discussing abnormal thyroid function it is important to understand the mechanisms behind normal thyroid hormone release and its physiological regulation. Thyrotrophin Releasing Hormone (TRH) from the hypothalamus passes via the portal vessels in the pituitary stalk to the anterior pituitary where it stimulates Thyrotrophin (or Thyroid Stimulating Hormone (TSH) synthesis and release. TSH enters the systemic circulation and stimulates the thyroid to synthesise and release tetra-iodothyronine(T4) and tri-iodothyronine (T3), which in turn are used by all cells in the body to regulate metabolic rate with T3 being the active hormone. Only 20% of the circulating T3 is made by the thyroid, the remainder being synthesised by peripheral conversion of T4 to T3 by deiodinase enzymes. The thyroid is the only source of T4 production. Both T4 and T3 are almost entirely protein-bound in the circulation with only the free hormone being available for metabolism by the tissues.

The liver metabolises fT3 and fT4 leading to their clearance. Enzyme inducers such as phenytoin, carbemazepine and barbiturates lead to increased metabolism and more rapid clearance of free thyroid hormones from the circulation.

The Hypothalamus-Pituitary-Thyroid axis is regulated by a classic endocrine negative feedback loop. Both fT3 and fT4 pass through the blood-brain barrier and inhibit synthesis and release of TRH in the hypothalamus and TSH synthesis and release from the pituitary gland. Accordingly, when thyroid disease is suspected on the basis of symptoms, measurement of TSH alone is adequate in most situations to indicate the overall level of thyroid function.

The important exception to this rule that may be encountered in primary care is thyroid hormone replacement in the context of pituitary or hypothalamic disease (ie secondary hypothyroidism) where the TSH level will be inappropriately low and so fT4 must be measured and the replacement thyroxine dose titrated to achieve fT4 in the upper half of the normal range.
Other than in special situations where thyroid disease is more likely (e.g., amiodarone treatment, those with other autoimmune disorders, a family history of thyroid disease, Downs or Turners Syndromes, post-radiotherapy to the neck) routine assessment of thyroid function is not considered to be cost effective.

**Hypothyroidism**

Hypothyroidism is termed Primary when there is failure of production of T3 and T4 from the thyroid gland. The lack of T3/T4 feedback to the hypothalamus and pituitary leads to increased TSH in the context of subnormal fT3 and fT4. By far the commonest cause for hypothyroidism is autoimmune (or Hashimoto’s) thyroiditis, and hence thyroid autoantibodies should be checked. The thyroperoxidase (TPO) autoantibody is positive in most, and other thyroid autoantibodies can also be detected (e.g., against thyroglobulin (Tg)).

The classic symptoms of hypothyroidism are well known and are often present especially with TSH of more than 20 or 30 mU/l but may be mild or absent. Moreover, symptoms are often missed or ignored by affected individuals on account of the insidious nature of the disease.

Treatment of hypothyroidism is relatively straightforward. For most patients a starting dose of 100 mcg thyroxine is appropriate. If there is a known history of ischaemic heart disease or the patient is over 65 yrs old then start with the lower dose of 50mcg to avoid exacerbation of angina or arrhythmia. Repeat TFTs after 6-8 weeks and titrate the dose against TSH, not fT4. Target TSH in thyroid hormone replacement is between 0.5 to 2.0 mU/l.

Subclinical hypothyroidism refers to the situation where the TSH is elevated but fT4 and fT3 remain in the normal range. Most affected individuals will have positive thyroid antibodies. This reflects the underlying autoimmune aetiology. Because progression to overt hypothyroidism with elevated TSH and low fT4 and fT3 is almost inevitable subclinical hypothyroidism should be treated. Generally, replacement with L-thyroxine is recommended when TSH is 10 mU/l or greater on 2 consecutive tests taken 2 months apart. Rarely thyroxine can be started when TSH is <10 mU/l if there are marked hypothyroid symptoms.

There are a number of studies that have shown no objective benefit when combination T3/T4 therapy is used to replace thyroid hormones in hypothyroidism.

Before synthetic L-thyroxine was available, dessicated animal thyroid was used to treat hypothyroidism. This contains T3 and T4, plus numerous metabolites and peptides from the animal. The relative quantities of T3 and T4 do not reflect normal human physiology and can lead to potentially harmful levels of T3. Additionally, there is often marked inter-batch variability in the proportions of each hormone which can result in over or under treatment. Although often perceived by the public as “natural” and hence preferred, there is no
advantage in using such products (eg Whole Thyroid) and so they are not recommended for use.

**Thyrotoxicosis**
The term thyrotoxicosis refers to the clinical, physiological and biochemical findings that result when the body is exposed to excess thyroid hormone. The commonest causes for thyrotoxicosis are Graves Disease or autoimmune thyrotoxicosis (Hashitoxicosis), toxic nodule (either solitary or multiple as in multinodular goiter) and thyroiditis (de Quervain’s, post-partum or associated with Amiodarone use)). Over treatment with exogenous thyroid hormones will also result in thyrotoxicosis and should be avoided. The symptoms and clinical signs are well recognized but can be more difficult to spot in mild cases. In the case of Graves disease there may be symptoms and signs of Graves Ophthalmopathy and/or pretibial myxoedema due to cross reactivity of the TSI with antigens in the orbit and lower leg skin respectively.

When thyrotoxicosis is confirmed the thyroid autoantibodies (TPO +/-TgAb) should be checked. It is also helpful to specifically request the Thyroid Stimulating Immunoglobulin (TSI) which is specific for Graves Thyrotoxicosis and if detected secures the diagnosis. There is usually no need to request a thyroid ultrasound, and although often helpful a thyroid scintiscan and uptake scan are best reserved for specialist use.

First line therapy for most is Carbimazole in the dose range of 5- 40 mg daily. Higher doses can be used if thyrotoxicosis is especially aggressive. Doses over 20mg should be divided (morning and evening). All patients should be counselled regarding the rare but important bone marrow suppression that occurs in 1 in 1000 individuals. The drug should be stopped immediately and a full blood count checked the same day if unexplained fever, sore throat and mouth ulcers develop. If cell counts are normal then the Carbimazole can be restarted.

Carbimazole is contraindicated in the first trimester of pregnancy and in the peri-conceptual period due to teratogenicity concerns (causes aplasia cutis). In this situation Propylthiouracil should be used instead (Special Authority from any practitioner). 50mg PTU is equivalent to 5mg Carbimazole. In pregnancy PTU is switched back to Carbimazole after the first trimester because organogenesis is completed and the risk of hepatic failure due to PTU is greater than risk of harm from Carbimazole.

In most cases a new diagnosis of Thyrotoxicosis (regardless of cause) should be referred to an Endocrinologist for accurate diagnosis and formulation of a management plan that may include 12-18 months titrated Carbimazole, thyroidectomy or radioiodine treatment.

Subclinical thyrotoxicosis describes the situation where fT3 and fT4 are within the normal range but TSH is suppressed in the absence of any symptoms or clinical signs of an overactive thyroid. Remembering the negative feedback loop discussed earlier, the TSH tells us that the circulating fT3 and fT4 levels are inappropriately high. Over time this is toxic to bones (leading to reduced
bone density and osteoporotic fracture) and to the heart (leading to AF and with it, increased stroke risk). In the Framingham cohort over 60 yrs of age the 10 year AF risk in those was 28% when TSH was <0.1 mU/l, whereas the risk was only 11% when TSH was between 0.1 and 0.4 mU/l. There are no large, randomised long term studies to help guide practice in this area, but most Endocrinologists would favour treatment for peri- and postmenopausal women (bone density risk), those with concomitant hypertension (AF risk) and those over age 60.

**Thyroiditis**

Inflammation of the thyroid can lead to transient thyrotoxicosis followed by hypothyroidism before normal thyroid function is restored. The normal thyroid stores sufficient hormone for around 6-8 weeks of normal thyroid function. Inflammation leads to a loss of integrity of the storage reservoir and thus can cause a large unregulated surge of thyroid hormone to be released into the circulation leading to thyrotoxicosis. As the thyroid cells regenerate and repair, the focus is on restoration of the reservoir before normal regulated thyroid hormone release can resume and thus a hypothyroid phase is often observed. In most cases euthyroidism returns with no need for intervention.

de Quervain’s (Subacute) Thyroiditis can be caused either directly or indirectly by viral infection (e.g. Mumps virus, adenovirus, coxsackie virus, influenza virus) and more cases tend to be observed in the spring. TPO antibody is often transiently detectable. Often coryzal or flu-like symptoms precede thyrotoxicosis, and although the characteristic feature is thyroid pain that can occur with or without fever cases without pain are seen. Typical examination findings would be of an exquisitely tender enlarged tender thyroid.

The ESR is often raised and thyroglobulin levels also increased, reflecting thyroid cell damage. Treatment is with NSAIDS +/- steroid (e.g. prednisone 20-40mg daily for 1-4 weeks, reducing dose if >10 days). Resist the temptation to treat the hypothyroid phase as this can prolong recovery since TSH, which is suppressed by thyroxine, is required for regeneration of damaged thyroid cells. Most cases will resolve within 2-3 months.

Postpartum thyroiditis develops in 5-10 % of women within a year of delivery or miscarriage and reflects immune system changes during pregnancy and a transient upregulation of thyroid autoimmunity. 30% present with thyrotoxicosis manifest as fatigue within 4 months of delivery, 40% present with hypothyroidism within 6 months of delivery and 25% have thyrotoxicosis followed by hypothyroidism. 80% recover spontaneously within 6-12 months. Care should be taken to treat hypothyroidism when there is potential for further pregnancy (to prevent subsequent congenital hypothyroidism). Treatment of thyrotoxicosis is advised if symptoms are marked, and Carbimazole is safe for use in breast-feeding.

**Thyroid Nodules, Euthyroid Goitre and Cancer**

Thyroid nodules are common, and become increasingly more likely with age. They are more common (up to 4x) in females. 1 in 10 will have a discrete thyroid nodule identified on palpation by experienced hands, whereas 30-50%
will have a thyroid nodule demonstrable on ultrasound. The vast majority (~95%) of thyroid nodules are benign.

Concern is raised when the nodule is enlarging, when there is a family history of thyroid cancer, when there is associated hoarseness or dysphagia or when there has been radiation exposure (especially in childhood). Thyroid cancer is rare and accounts for <1% of all cancer and <0.5% of all cancer deaths. Long-term (20 year) survival from early stage (stage I or II) differentiated thyroid cancer is in excess of 95%.

Euthyroid goitre is often familial and can be associated with iodine deficiency. Although in most cases the concern is principally cosmetic, large goitre can lead to symptoms of hoarseness, dysphagia, airway compression or thoracic outlet obstruction. In such cases consideration should be given to surgical thyroidectomy or use of radioiodine (which would be expected to reduce goitre volume by up to 50% at 1 year).

If thyroid nodule or goitre is discovered or suspected then thyroid ultrasound should be performed to further characterise the gland. For nodules ≥ 1cm diameter or more consideration should be given to performing ultrasound-guided FNA, especially if there are suspicious features (microcalcification, hypoechoic, poorly-defined lesions) or cervical lymphadenopathy. There are no ultrasonographic features that are pathognomonic for thyroid cancer although the presence of lymphadenopathy is highly suggestive of malignancy.

An Endocrinologist can often perform thyroid ultrasound and FNA.

Other Considerations
In severe systemic illness deranged TFTs are often observed. The typical pattern of low TSH, fT4 and fT3 is termed sick euthyroid and requires no specific therapy. These changes will resolve over the course of 4-6 weeks following resolution of illness. Even in critical care (ICU setting) replacement of thyroid hormones (either T3 or T4) has no influence on outcome or survival.

Around 40% of Amiodarone by mass is iodine, which is an integral component of T3 and T4. Moreover, the size and shape of the molecule resembles that of thyroid hormone metabolites hence the ability of Amiodarone to disrupt thyroid function. The elimination half-life of Amiodarone is in excess of 50 days, therefore the effects can either emerge or persist long after the drug has been withdrawn. Around one half of all those treated with Amiodarone will have some abnormality of thyroid function, with 2% developing thyrotoxicosis and 13% developing overt hypothyroidism (via the Wolff-Chaikoff effect). Amiodarone induced hypothyroidism is more common in the iodine replete, and AIT more common in areas of endemic iodine deficiency (i.e. New Zealand). TFTs should be checked 6 monthly in Amiodarone-treated individuals.

Two forms of Amiodarone-induced thyrotoxicosis (AIT) are recognised: Type 1 AIT is due to the iodine component leading to increased hormone synthesis
and release (Jod-Basedow phenomenon), whereas Type 2 AIT is due to a
direct toxic effect of the drug (causing a thyroiditis). A mixed picture often
exists, making accurate diagnosis and therapy a challenge. First line therapy
for AIT should include initiation of Carbimazole and referral to an
Endocrinologist. Type 1 AIT responds well to Carbimazole and Type 2 AIT
responds with Prednisone. Whenever possible consideration should be given
to discontinuation of the Amiodarone (in consultation with the Cardiologist).

Lithium can disrupt thyroid function. Although mostly it causes hypothyroidism
lithium treatment can also lead to thyrotoxicosis. Such cases should be
toferred to the Endocrinologist.

Thyroid disorders are often discovered during pregnancy, and pregnancy can
exacerbate a pre-existing thyroid disorder due to both the physiological
changes of pregnancy, and also the changes that occur in immune system
function in the setting of pregnancy. Outcomes for both mother and baby are
negatively affected by both untreated thyrotoxicosis and hypothyroidism.

Suppressed TSH and mildly increased fT4 and fT3 are common in the first
trimester due to stimulation by hCG, a phenomenon much more marked in
hyperemesis gravidarum. Until 10-12 weeks gestation the foetus is unable to
synthesize any thyroid hormones and so relies entirely on the mother for T3
and T4. During this vital period of organogenesis a lack of T3 and T4 can lead
to neurodevelopmental delay (or Cretinism). For this reason it is important to
ensure euthyroidism before conception in mothers with a history of thyroid
disease. Peri-conceptual and first trimester Carbimazole exposure can cause
aplasia cutis and so PTU is preferred in this setting.

Replacement thyroid hormone requirement generally increases progressively
throughout pregnancy and so TFTs should be checked at each trimester and
the dose increased accordingly. If a thyroid disorder occurs during pregnancy
then a referral should be made either to an Endocrinologist or Maternal
Medicine Specialist.

In summary, thyroid disease is a common presentation in Primary Care. For
most cases hypothyroidism can mostly be managed in the Primary Care
setting, whereas thyrotoxicosis should usually be referred to the
Endocrinologist. Consider thyroiditis if there is neck pain. Thyroid cancers are
rare, and prognosis is good if they are discovered early: any concerning
nodule or mass should be investigated by ultrasound and/or FNA. In the event
of uncertainty cases can be discussed with your local Endocrinologist.