Hypothyroidism and the elderly

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Hypothyroidism is common and increases with age affecting between five and twenty per cent of women and three to eight per cent of men. Thyroid hormone deficiency can result from failure of the thyroid gland itself (primary hypothyroidism) or, far less commonly, inadequate production of Thyroid Stimulating Hormone (TSH), due to pituitary or hypothalamic disease (i.e. secondary or central hypothyroidism). The thyroid gland predominantly secretes thyroxine (T_4) (which is essentially an inactive prohormone), and to a lesser extent triiodothyronine (T_3). T_4 is largely converted in the periphery to triiodothyronine (T_3). T_3 is the active form of thyroid hormone and binds to intracellular thyroid hormone receptors, which in turn act as transcription factors to activate or repress specific genes. As T_3 affects almost all cellular function, the clinical consequence of deficiency affects most organ systems. (See Table 2)

Primary hypothyroidism

Primary hypothyroidism is by far the most common form of hypothyroidism and indicates that the thyroid gland is unable to respond to TSH. This form of hypothyroidism may be clinically obvious with low levels of free T_4 (FT_4) and elevated TSH, or subclinical with FT_4 levels in the lower end of the reference range and a raised TSH. Elderly patients have an increased prevalence of both these forms of primary hypothyroidism, and more commonly have elevated anti-thyroid antibodies.

Like all forms of thyroid disease, primary hypothyroidism is more common in females.

The most common cause is autoimmune with either lymphocytic invasion of the thyroid and progressive destruction of the gland or, less frequently, the presence of anti-TSH receptor blocking antibodies. Positive anti-thyroid peroxidase (TPO or antimicrosomal) antibodies serve only as markers of an autoimmune process, but do not cause the hypothyroidism. As with all autoimmune disorders, there is often a family history of thyroid disease (hypo- or hyper-), or other autoimmune disease.

The other common cause of primary hypothyroidism is iatrogenic – either due to surgical removal of the gland or previous treatment with radioactive iodine (I^{131}). In the elderly, prior treatment with surgery or I^{131} may be so remote as to be easily overlooked, with the patient's symptoms of hypothyroidism mistakenly being attributed to the ageing process.

Common drug causes of primary hypothyroidism include amiodarone, lithium, and even the anti-thyroid drugs carbimazole and propylthiouracil (PTU) (when these are used as part of treatment for primary hyperthyroidism without titrating the doses down according to the resulting levels of thyroid hormone). Patients on these medications should have regular monitoring of their thyroid function, e.g. six monthly for patients on amiodarone, and more frequently for the anti-thyroid drugs.

Secondary hypothyroidism

This is rare and results from pituitary (or less frequently hypothalamic) disorders leading to insufficient production of TSH and consequently low levels of T_4 and T_3 and clinical hypothyroidism. Secondary hypothyroidism is usually diagnosed in patients already known to have pituitary or hypo-

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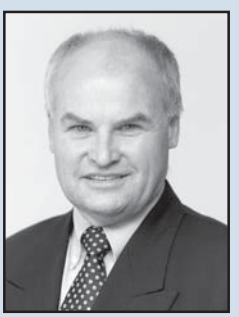

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thalamic disease or in those who have had previously radiotherapy in which the hypothalamus or pituitary was within the treatment field. Although rare, this disorder when undiagnosed is important, as it may be secondary to an underlying pituitary tumour, which can, if undetected, result in visual field defects and blindness. For this reason, if a patient presents with symptoms, e.g. tiredness, weight gain, cold intolerance, and the doctor is checking the thyroid function, both the FT_4 and TSH must be checked, as in patients with secondary hypothyroidism the TSH will often be within the laboratory's reference range with the FT_4 usually below the reference range. In elderly women, if one is considering secondary hypothyroidism, it can be useful to measure LH and FSH (which should normally be raised in a postmenopausal women when not on hormone replacement therapy), as well as checking an 0800h cortisol and prolactin in both genders if pituitary disease is suspected.

Table 1. Causes of hypothyroidism in the elderly

Common	Uncommon
Autoimmune	**Transient Hypothyroidism**
Autoimmune thyroiditis (Hashimotos)	Primary adrenal insufficiency
(Anti-TSH receptor blocking antibodies)	After prolonged thyroxine therapy leading to TSH suppression in a euthyroid patient
Iatrogenic	Sick euthyroid syndrome
Thyroidectomy	Post iodine exposure
I^{131} treatment	
Drug-Induced	**Iodine-associated**
Amiodarone Lithium	Iodine-deficiency Iodine-induced
Antithyroid drugs – carbimazole, PTU	
Interferon	
Interleukin-2	
Transient Hypothyroidism	**Infiltrative disease (Rare)**
Recovery from subacute or silent thyroiditis	Reidel's thyroiditis Haemochromatosis
Early post-I^{131} treatment	Amyloidosis Scleroderma
	Secondary (central)
	Pituitary or hypothalamic disease

Clinical features of hypothyroidism

The symptoms of hypothyroidism vary according to the severity of the hypothyroidism, however the rapidity of development of the hypothyroid state is an important factor, with a gradual onset (as is often the case in the older patient) being less obvious to the patient and their physician than abrupt loss of thyroid hormone, e.g. following a thyroidectomy. In addition, in the elderly, as the classical symptoms and signs (Table 2) may not be so obvious, a high degree of clinical suspicion is necessary. Elderly hypothyroid patients may have less weight gain, cold intolerance and muscle cramps, and the hypothyroidism can be easily overlooked in these patients who also have a higher prevalence of other chronic illnesses, use of medications and cognitive change than their younger counterparts.

In the aged, psychiatric symptoms may dominate, with most texts on psychogeriatrics listing hypothyroidism as a cause for depression, delirium and dementia, although hypothyroidism is an uncommon cause of these conditions and thyroxine replacement does not always relieve these conditions.

The effects on the cardiovascular system can be a major problem and include bradycardia, hypertension, hyperlipidaemia, ischaemic heart disease, and pericardial effusions. Sleep apnoea due to myopathy and extracellular fluid accumulation can be caused by, or aggravated by, hypothyroidism, particularly in the elderly.

The anaemia of hypothyroidism is classically macrocytic, however in the elderly this is not always the case and there can be associated deficiencies in iron, B_{12} or folate.

Diagnosis

In asymptomatic individuals TSH can be used as a screening test, but if the TSH is abnormal it should be repeated along with a measure of FT_4. In primary hypothyroidism the TSH is elevated and the FT_4 level may be either low if there is overt disease or low normal if subclinical disease is present. Patients with symptoms suggestive of thyroid disease, (particularly the elderly), should have both the FT_4 and TSH measured to avoid missing secondary (central) hypothyroidism. In secondary hypothyroidism the TSH level may be low, normal, or mildly elevated accompanied by a low FT_4 level. Routine measurement of Free T_3 is not usually helpful in the diagnosis of hypothyroidism (but may be useful in diagnosis and monitoring of hyperthyroidism).

Treatment

The mainstay of treatment for hypothyroidism is synthetic levothyroxine sodium (thyroxine). Thyroxine is typically given once daily on an empty stomach away from other medications.

The average full replacement dose is 1.6mcg/kg of lean body weight but requirements will be lower in mild hypothyroidism. In the elderly the dose requirement may also be lower and it is important to gently titrate up the thyroxine dose in this age group. Thyroxine has a half-life of approximately one week in young individuals but the half-life increases to approximately nine days by the 7th decade of life.[1] Levels should be checked when there is a steady state (after four to six half-lives) therefore approximately four to six weeks after initiation of therapy or after dose changes. There is no convincing evidence for a benefit of routine triodothyronine (T_3) treatment in hypothyroidism, either alone or in combination with thyroxine.

In the elderly, and for patients with ischaemic heart disease, initiating thyroid hormone replacement and increasing the dose needs to be cautious as angina and congestive cardiac failure may be exacerbated. A thyroxine starting dose as low as 25 micrograms on alternate days may be necessary when commencing treatment in this setting with small dose increments every one to two months. Starting with low doses offers the opportunity to withdraw the medication more promptly if angina increases. Hypothyroid patients with symptomatic ischaemic heart disease should be managed by an endocrinologist in collaboration with a cardiologist as these patients sometimes need coronary intervention such as coronary angiography and angioplasty or stenting and occasionally even coronary artery surgery, before the hypothyroidism can safely be treated.

In patients with secondary hypothyroidism (and combined primary thyroid and adrenal failure) the cortisol status needs to be assessed urgently, prior to starting thyroxine as thyroid replacement alone can precipitate cortisol deficiency. Patients with secondary hypothyroidism should be discussed with an endocrinologist to ascertain the cause and an appropriate management plan.

Table 2. Features of hypothyroidism

Symptoms	Signs
Fatigue	Hypokinesia and slowed speech
Cold intolerance	Bradycardia
Muscle weakness and/or discomfort	Delayed relaxation of deep tendon reflexes
Weight gain	Carotenaemia
Memory impairment	Coarse dry skin
Constipation	Puffy face
Exertional shortness of breath	Loss of eyebrows
Dry skin and hair	Periorbital oedema
Hoarse voice	Macroglossia
Oedema	Pleural/pericardial effusions
Hearing impairment	Ascites
Depression	Galactorrhoea
Arthralgia	Features of carpal tunnel syndrome
Paraesthesia	Obstructive sleep apnoea
Other – hypercholesterolaemia, anaemia (macrocytic or normochromic normocytic), hyponatraemia, elevated creatine kinase levels, hyperprolactinaemia, decreased clearance of some drugs e.g. warfarin, opiates.	

Monitoring therapy

In primary hypothyroidism the thyroxine dose should be titrated to normalise the TSH level. If there has been long-standing severe primary hypothyroidism thyrotroph hyperplasia may have occurred so the TSH may take three to six months to respond to the treatment-induced increase in free thyroid hormone levels.

In secondary hypothyroidism (due to pituitary or hypothalamic disease) the TSH level is not useful for monitoring adequacy of replacement and instead the FT_4 level should be maintained in the reference range.

General

Thyroid hormone levels should only be checked four to six weeks after initiation of treatment or after a dose change to ensure a steady state has been reached. The absorption of thyroxine may be reduced by other medications such as iron and antacids (Table 3). The most common cause of difficulty in achieving biochemical euthyroidism in patients who are prescribed an adequate replacement dose is poor compliance. In the elderly it may be important to consider other strategies to improve adherence to taking the medication such as prescribing in blister packs, or involving other members of the family or whanau in supervision. Patients who forget a dose can take it as a 'catch up' dose when they remember, even if it means taking two days' tablets at once. If poor compliance is not an issue, malabsorption needs to be considered and the patient should be advised to take the tablets separately from food and other medications. Once a patient is euthyroid on a stable dose, measurement of the TSH is adequate once or twice per year. Progressive thyroid destruction may cause a requirement for an increase in dosage. For a patient that only needs a small increase in dose this can often easily be achieved by adding 50–100mcg once or twice per week, e.g. 50 micrograms Monday to Saturday, 100 micrograms Sunday.

Sick euthyroid syndrome

In very unwell, hospitalised patients almost any pattern of thyroid function can be seen. Commonly there may be mildly low levels of free thyroid hormone levels with a low or inappropriately normal TSH level. As the patient recovers the TSH level may become elevated temporarily before it normalises (but usually it will be less than 20mU/L).[2] These patients are euthyroid despite the abnormal thyroid tests. In patients who have recently recovered from severe illness the thyroid function tests should be rechecked before thyroid hormone replacement is started.

Subclinical hypothyroidism

In subclinical hypothyroidism the TSH is elevated and free thyroid hormone levels are normal. Like overt hypothyroidism this condition is more common in the elderly.

Thyroid antimicrosomal antibodies should be measured in patients with subclinical hypothyroidism as the presence of positive antibodies signifies an increased risk of developing overt hypothyroidism (4.3% per year versus 2.1% per year for antibody negative patients). Treatment of subclinical hypothyroidism is controversial.[3,4] There is general consensus that thyroxine treatment should be started if the TSH is >10mU/L whether or not the patient is symptomatic. Asymptomatic patients with TSH <10mU/L and negative thyroid antibodies should be monitored, e.g. three to six monthly initially or sooner if symptoms develop. For asymptomatic patients with a TSH of 4.5–10mU/L and positive thyroid antibodies treatment can be considered depending on patient preference. Likewise for a 'symptomatic' patient, regardless of antibody status, with a TSH of 4.5–10mU/L, treatment can be discussed but the patient must be aware that this may make no difference to the symptoms (i.e. fatigue is common and any improvement with thyroxine therapy may be a placebo effect). If treatment is offered to patients with subclinical hypothyroidism, care must be taken not to over-replace, and a low dose of thyroxine, e.g. 25–50mcg/day should be started with the aim to normalise the TSH, again checking levels after four to six weeks. In elderly patients with subclinical hypothyroidism, in which ischaemic heart disease is suspected or known about, it is probably wise just to keep a watching brief.

Table 3. Factors influencing thyroxine requirements[1]

Decreased thyroxine absorption
Antacids
Iron supplements
Calcium supplements
Cholestyramine
Food
Sucralfate
Raloxifene
Malabsorption secondary to small bowel disease or resection
Altered thyroxine metabolism leading to increased dosage requirement
Rifampicin
Phenytoin
Carbamazepine
Amiodarone
Oestrogens
Altered bioavailability secondary to change in thyroxine preparation
Altered thyroxine metabolism leading to decreased dose requirement
Increased age
Androgens
Loss of lean body mass
Altered bioavailability secondary to change in thyroxine preparation

Screening for hypothyroidism

Screening asymptomatic patients for primary hypothyroidism is controversial. A recent consensus statement recommended against routine population-based screening although many expert panels have endorsed screening, particularly for older women, using routine TSH measurement.[3,4] Routine screening of all elderly patients will increase the number of patients identified with subclinical hypothyroidism. As discussed above, the treatment of this is controversial and until there is more evidence a better approach may be aggressive case finding, i.e. having a high index of suspicion for thyroid disease (Table 2) and screening, using TSH, of asymptomatic patients at particularly high risk. This would include patients on medications known to cause hypothyroidism, e.g. amiodarone and lithium, patients with a history of thyroid disease (especially previously radioactive iodine therapy and thyroid surgery), previous head and neck irradiation, and patients with other autoimmune disease, e.g. type 1 diabetes and pernicious anaemia. Remember that if a patient has symptoms or signs suggestive of hypothyroidism it is no longer considered screening and so a TSH and

FT_4 should be measured so as not to miss secondary hypothyroidism.

Does my patient really have primary hypothyroidism?

Occasionally patients turn up who are taking thyroxine but are suspected not to have thyroid disease. If there is uncertainty about the diagnosis, tracking down old letters and laboratory results may be helpful to see if there has been previous raised TSH values or positive thyroid antibodies. If there is no evidence to support the diagnosis and significant doubt about the diagnosis is present then consideration could be given for a closely supervised trial off thyroxine, at a time suitable to the patient (since patients with primary hypothyroidism will generally feel awful off replacement). As the half-life of thyroxine is approximately one week, 50% of the dose will be gone after one week, and 75% will be gone after two weeks, 87.5% after three weeks etc., so weekly monitoring of thyroid function will show a progressive increase in the TSH level if the patient has primary hypothyroidism and confirm the diagnosis. The TSH will not rise appropriately in patients with secondary hypothyroidism and these patients should already be under the care of an endocrinologist.

What about iodine?

The recommended daily intake for iodine is 150mcg/day. Lower levels of iodine intake may increase the rate of goitre and potentially hyperthyroidism (secondary to autonomous nodule function). Low iodine levels usually do not lead to hypothyroidism unless severe. Excess iodine intake may cause hypothyroidism (which is usually transient) through suppression of thyroid hormone biosynthesis (Wolff-Chaikoff effect). A thyroid that is already abnormal because of autoimmune disease may be more susceptible to the effect of excess iodine and develop overt hypothyroidism, which may be permanent. As high iodine intake is a risk factor for both hypo- and hyper-thyroidism, excess 'thyroid health products' in the form of kelp and other iodine-rich over-the-counter medications should be discouraged.

Key Points

- Thyroid dysfunction is common in the elderly
- Symptoms and signs may be more subtle than at a younger age
- Treatment is with thyroxine. Routine use of trioodothyronine (T_3) is not recommended
- In the elderly and those with known or suspected ischaemic heart disease, thyroid hormone replacement should be started cautiously and increased slowly in collaboration with an endocrinologist or cardiologist
- Monitor therapy after a treatment change no sooner than six weeks to ensure that a new steady state has been reached.
- Treatment of subclinical hypothyroidism is controversial when the TSH is <10mU/L but these patients must have regular thyroid function tests every six to 12 months.

References

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4. Surks MI, Ortiz E, Daniels GH, Sawin CT et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and treatment. JAMA 2004; 291: 228–238.

Useful resources

Patient information sheet: American thyroid association http://www.thyroid.org/patients/brochures/Hypo_brochure.pdf