Thelma's thyroid

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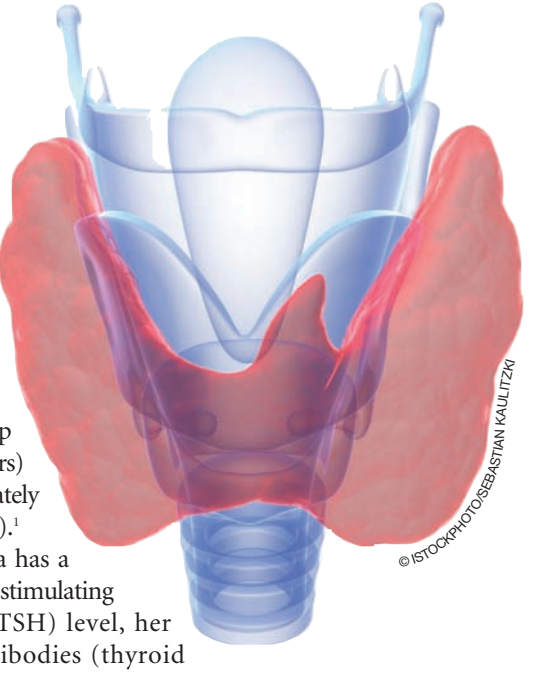
The case of a 71-year-old woman with suspected hypothyroidism is used to review the prevalence, risk factors, diagnosis and management of the condition.



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Hypothyroidism is one of several common and often unrecognised conditions in women aged over 65 years. This article reviews why it is important to identify patients with this condition and also discusses the management of affected patients.

Case scenario

Thelma is 71 years old and is worried that her thyroid might be 'underactive' after reading a weekly medical column in a magazine. Thelma has most of the symptoms listed: she feels tired, she has been putting on weight, she is constipated, her skin and hair are dry and she is losing her hearing.

Suspected hypothyroidism

Is Thelma likely to be hypothyroid and if so, what biochemical tests would be best?

Even though Thelma's symptoms are typical of hypothyroidism, they could be attributable to age. Nonetheless, it is quite possible that she has hypothyroidism. The risk of hypothyroidism in her age group (65 to 75 years) is approximately 12% (Figure).[1]

If Thelma has a high thyroid stimulating hormone (TSH) level, her thyroid antibodies (thyroid peroxidase [TPO] antibodies) levels should be measured, particularly if she were predisposed to autoimmune thyroid disease. A high titre would indicate that she is at increased risk of becoming hypothyroid in the future and so a TSH test every year or second year would be valuable.

Would a thyroid ultrasound or radionuclide scan be useful?

A thyroid ultrasound is useful to guide a fine needle aspiration of a lump and sometimes to assess a goitre. The major risk of an enlarged thyroid is that it can compromise structures at the thoracic inlet (e.g. the trachea). This can be difficult to assess clinically. Examination may suggest retrosternal extension of the lower edge of the thyroid on palpation or confirm retrosternal

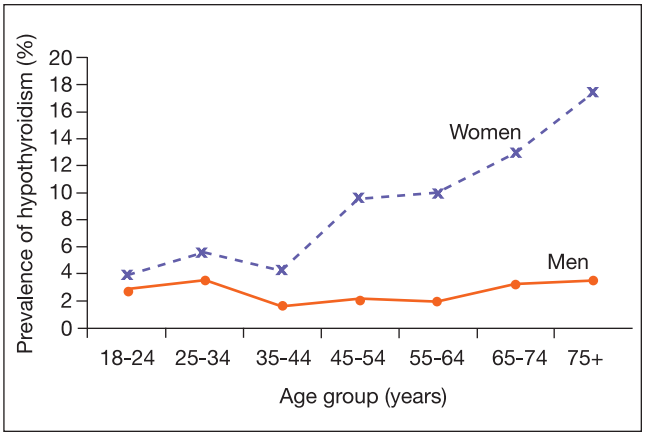

Figure. Hypothyroidism is much more prevalent in older women than in older men.[1]

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Autoimmune polyendocrine syndromes affecting organs

Type I syndrome	Type II syndrome*
Hypoparathyroidism	Hypophysitis
Hypothyroidism	Hypothyroidism
Pernicious anaemia	Myasthenia gravis
Addison's disease	Pernicious anaemia
Type 1 diabetes	Coeliac disease
Male hypogonadism	Addison's disease
Candidiasis	Type 1 diabetes
	Vitiligo

PHOTOLIBRARY

* Type II syndrome is much more common than type I syndrome.

resonance. Venous flow is unlikely to be compromised if there is no neck vein distension when the arms are raised above the head. This manoeuvre narrows the inlet and may reveal subclinical obstruction (Pemberton's sign).

The definitive imaging investigation to confirm a retrosternal goitre is a CT scan of the thoracic inlet (without contrast, as the iodine content may alter thyroid function). This will give a clear picture of the thyroid and its effects on adjacent structures.

A radionuclide scan is useful in hyperthyroidism because it can define the cause of high thyroid hormone levels and thereby guide appropriate management. However, their use in other situations may trigger a series of unnecessary and uncomfortable investigations. For example, although a radionuclide scan might show that a thyroid nodule was 'cold' and therefore more likely to be malignant, the appropriate investigation in a patient with a thyroid nodule would be a fine needle aspiration because any nodule may be malignant; the scan only delays the appropriate next step.

It would be confusing to use a radionuclide scan to diagnose hypothyroidism because the scan uptake can be decreased (indicating extensive thyroid destruction), normal or increased.

How should Thelma's TSH of 6 mU/L be interpreted?

The TSH level is a sensitive indicator of primary hypothyroidism but may be falsely positive (normal range is 0.3 to 3 mU/L).

'Sick euthyroid syndrome' is characterised by abnormal thyroid function tests occurring with nonthyroidal illness in the absence of hypothalamic–pituitary and thyroid gland dysfunction. The phases of the sick euthyroid syndrome are initially a low free thyroxine (T4) level with a relatively low TSH level, since illness resets the hypothalamic–pituitary axis to control free T4 at a lower level than usual. On recovery, the hypothalamic–pituitary axis resets again to control free T4 at the normal level. The free T4 level that was physiological during sickness is now regarded as low, and triggers a surge in TSH to increase thyroid hormone release and restore levels to normal. Finally, the hypothalamic–pituitary–thyroid system settles down with normal free T4 and TSH levels.[2]

Testing during the recovery phase will identify low free T4 and high TSH levels that may lead to a misdiagnosis of long-term hypothyroidism. Hence laboratories often suggest repeat testing several weeks later when any recovery phase will be over.

Assuming the abnormality is confirmed, Thelma's TSH in the single digits (below 10 mU/L) is unlikely to be associated with symptoms that improve with thyroxine supplementation. Nonetheless, supplements may be considered, particularly if there is a high titre of TPO antibodies (suggesting that progression of hypothyroidism will be relatively rapid), dyslipidaemia is present or a rise in TSH occurs. High TSH values are also associated with an increased risk of cardiovascular events and death. Despite the lack of robust evidence for the use of thyroid supplements in 'subclinical hypothyroidism', supplements are still recommended.

What is the prevalence of hypothyroidism in women?

The prevalence of hypothyroidism in women and men is similar up to the age of 45 years and progressively dissimilar thereafter. There is an increase in hypothyroidism in early adult life, a decline to a trough at age 35 to 44 years and thereafter a rapid increase in prevalence in women and a very much lesser increase in men (see Figure).[1]

What are the major risk factors for older women becoming hypothyroid?

The most common risk factors for women of Thelma's age becoming hypothyroid are a family history of autoimmune thyroid disease (hyper- or hypothyroidism) and a personal history of hyperthyroidism. The presence of other autoimmune disease and amiodarone therapy are other major risk factors.

Autoimmune thyroid disease is hereditary and mainly affects the female side. Previous autoimmune hyperthyroidism predisposes to later hypothyroidism, partly because destructive antibodies are often present as well as stimulatory ones and partly because destructive therapy (surgery or radioactive iodine) reduces the absolute amount of thyroid tissue. Similarly, destructive therapy for a toxic multinodular goitre may cause hypothyroidism later in life. Hypothyroidism is also likely later in life in a person with Graves' disease, and it is

important to stress this and the need for regular lifelong testing of thyroid function when such a person is being treated.

Autoimmune thyroid disease is part of an autoimmune cluster, including coeliac disease, type 1 diabetes, pernicious anaemia and Addison's disease (the autoimmune polyendocrine syndrome type II).[3] The full cluster of autoimmune polyendocrine syndromes affecting organs is shown in the box on page 60. Different components of the cluster may affect different family members and one member may have several autoimmune conditions.

Autoimmune thyroid disease is also associated with other nonendocrine autoimmune diseases, such as rheumatoid arthritis and Sjögren's syndrome. There should be a low threshold for considering thyroid disease in these populations.

Amiodarone can cause almost any thyroid function abnormality and conflicting thyroid investigation results. The most common abnormality is hypothyroidism relating to the high iodine load resulting from amiodarone therapy; patients taking amiodarone should have their thyroid function monitored as this problem can present some time after starting the drug. Other medications that cause hypothyroidism do so less commonly (Table). If these medications are being taken by a patient, the threshold for thyroid function testing should be lowered.

Management

As mentioned earlier, the use of thyroxine supplements is recommended in patients with subclinical hypothyroidism, the category into which Thelma falls, despite the lack of robust evidence for their use.

How should Thelma's thyroxine supplements be started?

Thyroxine can be titrated to keep the TSH level in the normal range, starting with low doses (e.g. 25 or 50 µg/day) and increasing doses as indicated by the TSH values six to eight weeks later. (The half-life of thyroxine is one week and it is suggested a period of six to eight half-lives is allowed to achieve steady state levels of thyroxine.) This can be tedious and time-consuming, and the alternative is to 'guestimate' the total replacement dose, prescribe this and recheck the TSH level after four to six weeks to ensure the 'guestimate' is correct. Usually this achieves adequate replacement initially or after one dosage adjustment. The 'guestimate' total replacement dose is usually between 100 and 200 µg/day, depending on the size of the patient; in Thelma's case it would be 100 µg/day.

In a patient taking T4, the free T4 value that is reported by some laboratories along with the TSH value may be in the upper part of the reference range or even slightly higher. This is because the patient is taking only T4, whereas the thyroid produces triiodothyronine (T3) as well as T4; the high free T4 levels are compensating for the low free triiodothyronine (T3) levels.

Table. Medications affecting thyroxine hormone levels

Medications affecting thyroxine absorption

- Metals: calcium, iron, strontium, zinc, aluminium hydroxide
- Resins: cholestyramine, colestipol

Medications affecting the hypothalamic–pituitary–thyroid axis

- Cardiovascular: amiodarone, high-dose frusemide
- Neurological: dopamine, phenytoin
- Anti-inflammatory: glucocorticoids
- Others: lithium, iodine (including radiographic contrast)

T3 (as liothyronine, the L-isomer of triiodothyronine) is rarely used for thyroid hormone replacement. However, it is listed on the PBS (Authority required) for use in those patients who have intolerance or resistance to thyroxine.

How should thyroxine be stored?

Warm temperatures and humidity reduce the activity of thyroxine supplements. To reduce heat exposure, thyroxine tablets should be stored in the fridge, although a limited supply for day-to-day use can be kept at ambient temperature. Thyroxine tablets are now supplied in blister packs and so humidity no longer causes a problem.

Which medications can affect thyroxine supplements?

Common medications that may have important interactions with thyroxine supplements are listed in the Table. There are two general forms of interaction: interference with thyroxine absorption and interference with the hypothalamic–pituitary–thyroid axis.

The most likely problem to occur happens with co-administration of thyroxine with calcium or iron supplements, as calcium and iron reduce thyroxine absorption and thereby cause the TSH level to rise. It is important to exclude this cause of decreased effectiveness of thyroxine because an increased dose of thyroxine puts the patient at risk of over-replacement if the iron or calcium supplement is later stopped. Patients taking thyroxine should be advised to check with their doctor before taking any additional prescription or nonprescription medications (including health foods and vitamin supplements).

How often should Thelma's thyroid function be monitored?

Regular monitoring of Thelma's thyroid function is advised (e.g. annually if the results have been stable), as medication

continued

Pregnancy and hypothyroidism

Case scenario

Thelma's grand-daughter, Susan (aged 23 years), plans to fall pregnant in the next year. Susan's mother recently became hypothyroid and Thelma is worried that Susan might be too. She asks you if Susan should have her thyroid checked.

Should Susan have her thyroid function tested?

Susan should have both her thyroid function and her TPO antibodies levels checked. If she is euthyroid now but has high levels of TPO antibodies, she may develop hypothyroidism during pregnancy, as pregnancy increases thyroxine requirements. Her thyroid may be adequate to maintain euthyroidism before pregnancy but not be able to meet later increased requirements during her pregnancy.

Susan should be reminded of the need for iodine supplements before and during pregnancy. Iodine deficiency occurs in several areas in Australia as little iodine is consumed in the usual Australian diet. The recommended dietary intake of iodine for pregnant women is 220 µg/day. Pregnancy supplements generally contain iodine as well as folic acid and other recommended nutrients.

What problems can untreated hypothyroidism cause for Susan?

The potential problems for Susan are very significant. If she were hypothyroid (symptomatic or not), her chances of falling pregnant could be reduced and the risk of serious intra- and postpartum problems (including anaemia, pre-eclamptic toxaemia, placental abruption and postpartum haemorrhage) increased.

What problems could Susan's hypothyroidism cause for her baby?

Similarly, the potential problems for Susan's baby are significant, in particular spontaneous miscarriage, miscarriage or stillbirth associated with placental abruption, premature delivery forced by pre-eclampsia and abnormal development of the brain reducing future intelligence. Thyroid function should be monitored carefully during pregnancy to ensure that euthyroidism is maintained and that the dose of any necessary thyroxine is adequate to meet the increased demands.

There is a strong argument in favour of thyroid function testing in women planning a pregnancy if they are at increased risk of thyroid disease.

Assuming Susan is euthyroid, what postpartum thyroid problems is she at increased risk of?

Postpartum thyroiditis is more common in women who have a family or past history of one of the autoimmune diseases in the cluster. This form of thyroiditis is usually painless, unlike the form not related to pregnancy in which pain can occur in the neck, radiate to the jaw or ear and be associated with an influenza-like illness and increased markers of inflammation.

Postpartum thyroiditis usually causes transient hyperthyroidism (thyroidal damage releases stored thyroxine), followed by transient hypothyroidism and then a return to euthyroidism over one to three months. If Susan did develop this, it would be important to check her TPO antibodies again. If these were present, it would be highly likely that she would become hypothyroid later in life. She should then have thyroid function checks at three months' postpartum and, if euthyroid, six months after that and then yearly for the rest of her life.

Just as other autoimmune diseases (such as rheumatoid arthritis) may occur postpartum, Graves' disease may also present once the immunomodulating effects of pregnancy are over.

If Susan had required thyroxine supplements, her requirements postpartum would return to normal and the higher dose required for pregnancy would then be excessive, causing symptoms and signs of hyperthyroidism.

interactions can occur, thyroid destruction may continue and thyroxine requirements may decrease with age. If the TSH value is below the reference range, consider reconfirming the result after decreasing the dose of thyroxine. Thyroxine is available in Australia as 50, 75, 100 and 200 µg tablets only and small dosage changes may be most easily achieved by alternate day dosing (e.g. to achieve a dosage of 125 µg/day, take a 100 µg tablet one day and a 100 µg tablet plus a 50 µg tablet the next day).

The most common problem is patient adherence, either with the dosing schedule or with medication interactions.

Patient resources

Useful information for patients with thyroid conditions and their families and friends can be found at the websites below:

- Thyroid Australia – http://www.thyroid.org.au
- The Australian Thyroid Foundation http://www.thyroidfoundation.com.au

Summary

- It is important to recognise hypothyroidism in older women because the symptoms may be nonspecific but hypothyroidism can have serious adverse effects.

- The prevalence of hypothyroidism increases in both sexes in early adult life, declines to a trough at age 35 to 44 years and then increases rapidly with age in women and to a much lesser extent in men.
- The four major risk factors associated with adult hypothyroidism are a personal history of hyperthyroidism, a family history of autoimmune thyroid disease, other autoimmune disease and amiodarone therapy.
- Hyperthyroidism predisposes to later hypothyroidism because of destructive autoantibodies (e.g. Graves' disease) and/or destructive therapy (Graves' disease and toxic multinodular goitre).
- Autoimmune thyroid disease is part of a familial autoimmune cluster, with pernicious anaemia, atrophic gastritis, coeliac disease and type 1 diabetes being the most common other components.
- Amiodarone can cause a range of thyroid disorders and abnormal thyroid function tests, especially hypothyroidism.
- In women of child-bearing age, hypothyroidism can decrease fertility, cause antenatal and postnatal problems and miscarriage, and affect fetal brain development (see the box on page 62). Monitoring thyroid function and actively treating any abnormalities are important parts of pre, intra and postnatal care in women with or at high risk of thyroid disease.
- Thyroxine replacement therapy should be started at low dosage and be titrated slowly to normalise TSH levels.
- Medications interfering with thyroxine absorption and/or metabolism include particularly amiodarone, dopamine, phenytoin and glucocorticoids. If indicated, a Home Medications Review can confirm patient adherence, simplify the medication schedule and identify potential drug interactions. MT

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COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.