HYPERTHYROIDISM IN AGING

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ABSTRACT

Hyperthyroidism in the elderly is a serious clinical condition that is associated with significant morbidity. It may be difficult to diagnose due to the confounding effects of drugs and acute or chronic illnesses on the interpretation of thyroid function tests. In addition, there is a relative paucity of typical hyperadrenergic symptoms in older patients with hyperthyroidism, who instead may present with unexplained weight loss, neurocognitive changes, or cardiovascular effects. Of particular concern is the elevated risk of atrial fibrillation and cardiovascular complications in this age group. There is increasing evidence that even mild (subclinical) hyperthyroidism in the elderly is associated with these risks. Graves' Disease and toxic multinodular goiter are the most common etiologies of hyperthyroidism in the elderly, although other causes of hyperthyroidism also occur. The use of amiodarone or administration of iodinated contrast agents can also lead to hyperthyroidism, and are commonly prescribed to older patients. Radioiodine or thionamide therapy are typically used to treat hyperthyroidism in older patients. Treatment decisions must be individualized, taking into account projected lifespan, comorbidities, and side effects of therapy.

PREVALENCE OF HYPERTHYROIDISM IN AGING

Hyperthyroidism is a common disorder (1); a population-based survey (2) conducted over 40 years ago revealed a prevalence in the general UK population of around 2.7% in women (10-fold less in men) and of undiagnosed disease in around 0.5% of women. A more recent population-based survey in the United States revealed a prevalence of hyperthyroidism of 1.3%, with no difference between men and women (3). This prevalence decreases to 0.4% if one excludes patients with known thyroid disease and those taking thyroid hormone preparations, indicating that many cases of hyperthyroidism are due to overtreatment with exogenous thyroid hormone.

A number of studies have reported the prevalence of hyperthyroidism specifically in elderly populations. Prevalence rates vary depending on whether patients taking thyroid hormone are included, but most surveys report that approximately 1–3% of subjects over the age of 60-65 years have hyperthyroidism (2-7). If one excludes patients taking thyroid hormone, prevalence rates of hyperthyroidism appear similar in younger and older populations (3).

CLINICAL CONSEQUENCES OF HYPERTHYROIDISM

Classical symptoms and signs of thyrotoxicosis are shown in Table 1 (1). While some or all of these may be present in elderly subjects with thyrotoxicosis, the clinical picture is often different in this age group (8,9). Problems such as weight loss and depression or agitation may predominate - so-called "apathetic" thyrotoxicosis, a condition in which more typical symptoms and signs reflecting sympathetic activation such as tremor and hyperactivity are absent (10-12). Instead, cardiovascular symptoms and signs often predominate in older patients, including atrial fibrillation. Other findings more common in older patients with hyperthyroidism include fatigue, anorexia, weight loss, apathy, agitation, or cognitive

decline (11-14). Particularly in this age group, the diagnosis of thyrotoxicosis should also be considered in the presence of other symptoms and signs considered "non-specific" in nature, such as muscle weakness, persistent vomiting, hypercalcemia, and worsening osteoporosis.

Table 1. Symptoms and Signs in Hyperthyroidism

Symptoms	Signs
1. Weight loss	1.Tremor
2. Sweating/heat intolerance	2. Hyperactivity
3. Nervousness/agitation	3. Proximal myopathy
4. Tiredness	4. Sinus tachycardia
5. Muscle weakness	5. Atrial fibrillation/atrial dysrhythmias
6. Palpitation	6. Systolic hypertension
7. Shortness of breath	7. Goiter
8. Tremor	8. Lid lag/lid retraction
	9. Ophthalmopathy*
	10. Pretibial myxedema*
	11. Thyroid acropachy*
	* specific for Graves' Disease

Cardiovascular Complications

Cardiovascular complications of thyrotoxicosis are especially common in the elderly and may be a cause of significant morbidity and mortality (1,15). A number of studies have reported increased all-cause and cardiovascular mortality, and increased risks of atrial fibrillation, arterial embolism, acute myocardial infarction, heart failure, venous thromboembolism, and stroke in hyperthyroid patients, compared to euthyroid controls (16-20). Risks are higher in older subjects and in untreated or undertreated groups, with a direct association between the duration of suppressed TSH levels and mortality in both untreated and treated patients (19). Risks decrease with treatment, regardless of treatment modality (21,22). All-cause mortality is also increased in treated hypothyroid patients with suppressed TSH levels, highlighting the importance of avoiding overtreatment.

In addition to classical findings of sinus tachycardia and systolic hypertension, it is well recognized that atrial fibrillation complicates thyrotoxicosis in about 15% of cases (23). The incidence of this complication rises with age, so it is observed more frequently in the elderly (24). It has been estimated that atrial fibrillation occurs at least three times more commonly in those with thyrotoxicosis than those without. Development of atrial fibrillation may itself lead to deteriorating cardiac status, especially in the presence of pre-existing heart disease, and it may also be associated with embolic complications, especially cerebral embolism (25). These influences probably contribute significantly to the increased cardiovascular and cerebrovascular mortality described above. Furthermore, the likelihood of spontaneous restoration of sinus rhythm in those with atrial fibrillation complicating thyrotoxicosis lessens with age, probably reflecting the presence of underlying ischemic, hypertensive, or valvular heart disease (26).

In view of these cardiovascular manifestations/complications, the diagnosis of thyrotoxicosis should be suspected in all subjects presenting with atrial fibrillation, worsening heart failure, systolic hypertension, and deteriorating ischemic heart disease. Nonetheless, case-finding studies have shown that thyrotoxicosis accounts for

less than 5% of newly diagnosed cases of atrial fibrillation (23).

Bone Metabolism and Hyperthyroidism

The other significant consequence of thyrotoxicosis is its effect on bone metabolism. Overt hyperthyroidism is associated with increased bone turnover and reduction in bone mineral density (27). Meta-analysis of available data (28) has shown that this influence is especially marked in estrogen deficient postmenopausal women. While antithyroid treatment results in an improvement in bone mineral density, recovery is incomplete so risks of osteoporosis associated with aging, especially in women, are exacerbated (29). Several large-scale epidemiological studies (16,30) have revealed independent associations between a history of thyrotoxicosis and risk of fracture of the femur.

DIAGNOSIS OF HYPERTHYROIDISM

It is essential that a clinical suspicion of thyrotoxicosis is confirmed or refuted by biochemical testing before further investigation or treatment is contemplated (1). The single most important biochemical test is measurement of serum TSH. If the serum TSH concentration is within the normal range, then a diagnosis of thyrotoxicosis is effectively ruled out. Exceptions to this rule are rare TSH-dependent causes of hyperthyroidism, such as TSH-secreting tumors of the pituitary and syndromes of thyroid hormone resistance, although these diagnoses are more typically associated with a modest rise in TSH (with raised serum thyroid hormones, as opposed to the usual pattern of raised TSH in conjunction with low thyroid hormone levels).

Studies of healthy elderly subjects have shown that serum concentrations of thyroxine (T4) and tri-iodothyronine (T3) are unchanged compared with younger age groups (31). Analysis of large U.S. population-based normative data suggest that there is a slight increase in the upper limit of normal TSH levels with aging, but the lower limit of normal TSH levels remains relatively unchanged (32). Therefore, in a healthy older patient, a low or suppressed TSH level suggests hyperthyroidism. On the other hand, "non-thyroidal" illnesses and drug therapies that alter tests of thyroid function are more common with increasing age. These effects typically lead to reduced peripheral conversion of T4 to T3 and reduction in serum T3 concentrations. Serum TSH may be unaffected by illness, although a reduction in TSH is commonly seen, as is a modest elevation in TSH particularly during the recovery phase of illness (33). Therefore, in an acutely or chronically ill older patient, interpretation of a low TSH level must be done with caution, as low serum TSH, especially if below the normal range but nonetheless detectable, often reflects a "non-thyroidal" illness or therapy with a wide variety of drugs (34) (Table 2). A diagnosis of thyrotoxicosis should be confirmed biochemically by measurement of serum free thyroxine (T4) (and in some cases T3 if free T4 is in the high/normal range and T3-toxicosis is therefore suspected).

Table 2. Effect of Drugs on Tests of Thyroid Function

Drug	Serum T4	Serum T3	Serum TSH
Dopamine	↓, →	↓, →	↓
Glucocorticoids	↓, →	↓, →	↓
Estrogens	↑ total T4	↑ total T3	→
Anticonvulsants	↓, →	↓, →	→
Acetylsalicylic acid	↑, →	↑, →	↓ →
Amiodarone	↑	↓	variable
Heparin	↑, →	↑, →	↓, →
Fenclofenac	↓, →	↓, →	→
Anabolic steroids	↓ total T4	↓ total T3	→

In the majority of cases of thyrotoxicosis, a typical biochemical picture of elevated free T4 and T3 with associated undetectable TSH will be observed. In some cases, a biochemical diagnosis of "T3-toxicosis" is evident, characterized by elevation of serum T3 in the absence of a rise in T4. This is typically observed in mild cases of toxic nodular hyperthyroidism and early in the course of Graves' hyperthyroidism. In some instances, the converse is true in that a rise in T3 is absent despite elevation in free T4 and suppression of TSH in a patient thought clinically to have thyrotoxicosis. This lack of rise in T3 may reflect the presence of another "non-thyroidal" illness, evident upon re-testing once the other morbidity is eliminated.

CAUSES OF THYROTOXICOSIS

Graves' Disease and Toxic Nodular Hyperthyroidism

In iodine replete parts of the world, Graves' disease is the most common endogenous cause of thyrotoxicosis. In the elderly, however, toxic nodular hyperthyroidism becomes an important cause (1,35). In all age groups, toxic nodular hyperthyroidism is more common in areas of the world that are relatively iodine deficient (36). The natural history of goiter is of progression from the presence of diffuse thyroid enlargement to development of one or more nodules and eventual autonomous function of one or more of these nodules resulting in thyrotoxicosis. This natural history is typically long so the elderly patient presenting with thyrotoxicosis often describes the presence of a goiter for many years. A relatively rare cause is the presence of a single toxic adenoma - a benign tumor exhibiting autonomous secretion of thyroid hormones. This diagnosis accounts for less than 2% of cases of thyrotoxicosis occurring in the US (36). Biochemically, the development of autonomous function in a nodular goiter is first evidenced by suppression of serum TSH with normal serum concentrations of thyroid hormones ("subclinical" hyperthyroidism - see below), followed by elevation of serum T3 and free T4.

In many cases, the cause of thyrotoxicosis is obvious from the clinical picture (1,35). The diagnosis of Graves' disease may be evident by the presence of diffuse goiter and ophthalmopathy, whereas toxic nodular hyperthyroidism is characterized by the presence of a nodular goiter on examination of the neck. It should be noted, however, that the thyroid might be impalpable in about 30% of cases of Graves' disease or toxic nodular hyperthyroidism. If the cause of thyrotoxicosis is not obvious, further investigation may be warranted. The presence of thyroid autoantibodies (to thyroid peroxidase - TPO and/or thyroglobulin) is suggestive (but not diagnostic of) Graves' disease; TSH receptor antibodies are more specific for the diagnosis. Such antibodies are positive in 90% of Graves' Disease cases, and are usually negative in cases of toxic nodular hyperthyroidism. If TSH receptor antibodies are positive in the presence of a nodular goiter, both conditions may co-exist. Radioisotope scanning, using technetium-99m or iodine-123, typically shows a diffuse pattern of uptake in Graves' disease, in contrast to the presence of multiple "hot" nodules with surrounding thyroid tissue not demonstrating any uptake in cases of toxic nodular hyperthyroidism (figure 1). Occasionally, a single "hot" nodule, with absent uptake elsewhere in the thyroid is observed. This finding suggests the presence of a toxic nodular adenoma.

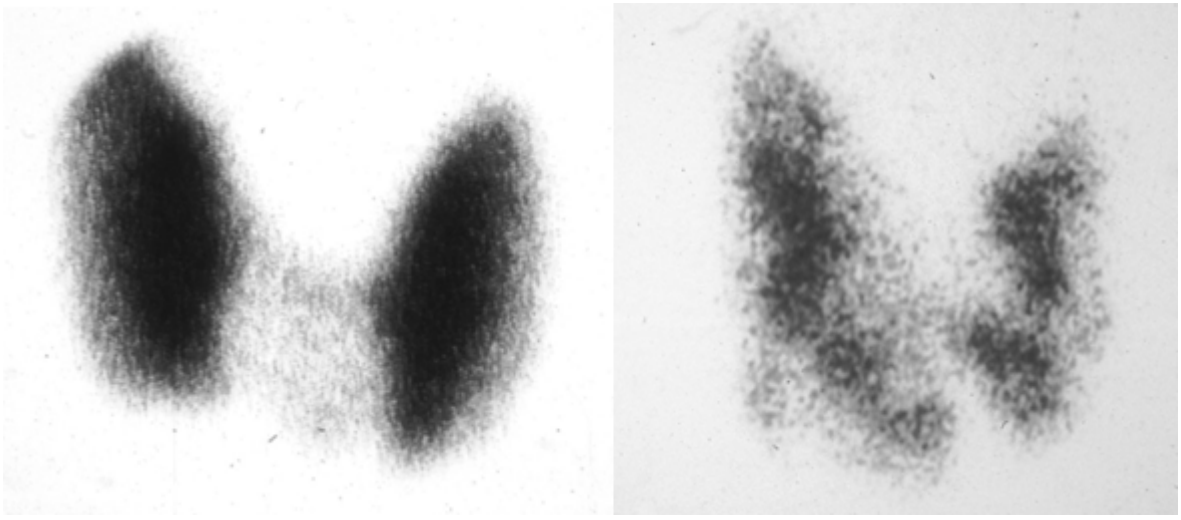

Figure 1. Radionuclide imaging of the thyroid illustrating hot nodules in toxic nodular hyperthyroidism (right) which contrasts with a diffuse uptake in Graves' Disease (left)

Other Causes of Thyrotoxicosis

Although Graves' disease and toxic nodular goiter are by far the most common causes of endogenous thyrotoxicosis in older patients, it is important to consider other diagnoses. As in other age groups, the elderly patient may develop transient thyroid hormone excess secondary to a temporary thyroiditis, i.e., destruction of the thyroid with release of pre-formed thyroid hormones (35). Sub-acute thyroiditis should be suspected if the patient complains of sore throat or neck tenderness, typically associated with symptoms of a viral illness or an upper respiratory tract infection. The diagnosis is confirmed by the finding of a raised erythrocyte sedimentation rate (ESR) and absent or very low uptake of iodine-123. This is an important diagnosis to make since antithyroid treatment with antithyroid drugs or radioiodine is inappropriate, because it is ineffective and because the condition resolves spontaneously (usually after a self-limiting period of hypothyroidism). Silent thyroiditis has a similar clinical course as subacute thyroiditis, but the gland is not tender and there is no increase in ESR. Both subacute and silent thyroiditis can occur in older patients, although the peak age range for these two conditions is among younger patients (37).

Iodine-induced thyroiditis should be considered in patients with a history of iodine ingestion (e.g., in the form of sea weed preparations or over the counter iodine containing compounds, such as expectorants) or after administration of iodine containing radiographic contrast agents (35). The diagnosis can be confirmed by the finding of low iodine uptake. This condition also remits spontaneously and radioiodine therapy is contraindicated. This diagnosis is more common in older patients, who are more likely to receive iodinated contrast agents and to have underlying multinodular goiters that predispose them to iodine-induced thyrotoxicosis.

Finally, it should be noted that exogenous thyrotoxicosis due to excessive doses of thyroid hormone in the treatment of hypothyroidism is quite common. One study indicated that over 40% of older subjects taking thyroid hormone had low TSH levels, indicating excess thyroid hormone doses (38). A second study reported that iatrogenic thyrotoxicosis accounted for about 50% of low TSH events in a large cohort of subjects, with the highest rates in older women (39). A third study reported that thyroid hormone use increased 1.8-fold in the UK from 2001-2009, with decreasing TSH thresholds for initiating treatment. Of concern, 90% of treated subjects remained on L-T4 for > 5 years, and 16% had low or suppressed TSH levels, indicating excessive doses (40). A fourth study reported that thyroid hormone use doubled in the U.S. from 1997-2016, from 4% to 8%, while expenditures for thyroid hormone tripled. Thyroid hormone use was higher in women, older

individuals, and non-Hispanic whites (41). These reports clearly indicate that thyroid hormone is being over-prescribed, with high risks of overtreatment and potential clinical consequences, particularly in older subjects who may have underlying cardiac issues or osteoporosis.

Amiodarone Induced Thyrotoxicosis

The diagnosis of thyroid dysfunction should be considered in an elderly patient prescribed the antiarrhythmic agent amiodarone. This drug is widely used in the older age group for control of dysrhythmias, particularly those associated with poor left ventricular function. Amiodarone is an iodine-containing compound that affects the results of tests of thyroid function, even in those who are euthyroid (35,42). Typically, amiodarone, through its effect on peripheral conversion of T4 to T3, results in modest reduction in serum concentrations of T3 (often to below the normal range) and modest elevation in serum T4 (often to above the normal range). TSH is typically slightly elevated early after commencement of treatment and normalizes later in euthyroid patients. Therefore, beginning 2-3 months after amiodarone is started, the serum TSH level is an accurate indication of thyroid function.

Although amiodarone results in overt thyroid dysfunction in 5-10% of cases, it is important not to over-interpret mildly abnormal results of tests of thyroid function. Thyrotoxicosis should only be diagnosed in the presence of significant elevation of free T4, together with elevation in serum T3 and suppression of TSH; sometimes serum T3 is at the upper range of normal rather than elevated, probably because of associated "non-thyroidal" illness in this age group, together with the block of T4 to T3 conversion seen with amiodarone.

TREATMENT OF THYROTOXICOSIS

Antithyroid Drugs

The thionamides – methimazole (or its precursor drug carbimazole) and propylthiouracil - represent the mainstay of drug treatment of thyrotoxicosis (1,35). These drugs inhibit the oxidation and organification of iodide and hence block the synthesis of T4 and T3 early in their biosynthetic pathway. They represent the most effective and rapid means of reducing circulating thyroid hormone concentrations. They can be used in several ways: short-term in preparation of the patient for definitive treatment with radioiodine or surgery, medium term in the hope of inducing remission in cases of thyrotoxicosis due to Graves' disease, or long-term for control of clinical and biochemical thyroid hormone excess.

In many elderly patients, thionamides are used short-term in the preparation for curative treatment. A typical starting dose of methimazole is 20-30 mg per day as a single daily dose. In contrast, propylthiouracil is typically given in divided doses, the equivalent to methimazole 20 mg being 200mg. Doses higher than this are rarely required, since high doses have not been shown to be more effective in terms of restoration of euthyroidism in prospective studies (43,44). Since compliance is better and side effects are less frequent, methimazole or carbimazole are considered the drugs of choice, in preference to propylthiouracil (35). Serum free T4 should be checked 4-6 weeks after beginning therapy and the thionamide dose adjusted accordingly. It is usually possible to render the patient euthyroid (or near euthyroid) after 2-3 months, so they can proceed to curative therapy.

Drug side effects are relatively uncommon, but it is essential that all subjects (in whichever age group) be warned (preferably in writing) of the potential risk of agranulocytosis so that they present urgently for a full blood count if they develop a fever or sore throat. Agranulocytosis often, but not always, occurs in the first few weeks after beginning thionamide therapy and is probably more common in those taking higher doses (35). The latter observation represents a relative contraindication to doses of methimazole/carbimazole of greater than 20-30 mg per day; doses higher than this are rarely necessary in the elderly.

Other serious side effects can occur, notably antineutrophil cytoplasmic antibody-associated-vasculitis (typically associated with prescription of

propylthiouracil), hepatitis, or pancreatitis (35,44), although these are rare. These serious complications, together with agranulocytosis, represent absolute contraindications to further use of thionamides. Less serious side effects such as pruritic rash are more common and can usually be managed conservatively, although sometimes a change in drug therapy from one thionamide to another is required (ATA guidelines).

ANTITHYROID DRUGS AND GRAVES' DISEASE

In general, remission rates following thionamide therapy in Graves' hyperthyroidism are less than 50%, nonetheless, there is some evidence that the remission rate in Graves' may be higher in the elderly age group, probably reflecting the presence of milder disease. If the objective is to achieve remission or "cure" of thyrotoxicosis secondary to Graves' disease, then thionamide treatment should be prescribed for a course of not less than 12 or 18 months, since shorter courses are associated with a lower rate of remission (35). Drug doses should be titrated according to serum concentrations of free T4 (serum TSH may remain suppressed for months); the majority of subjects will require a methimazole maintenance dose of 5-10 mg daily once normal fT4 levels are achieved (propylthiouracil 50-100mg daily in divided doses). Larger dose requirements are suggestive of poor compliance. Poor prognostic features for achieving long-term remission (35) (established in younger age groups) include male sex, the presence of a large goiter and biochemically severe disease at diagnosis. Most relapses of Graves' thyrotoxicosis occur 3-6 months after thionamide withdrawal.

Although standard recommendations for treating Graves' disease with thionamides include a 12-18 month course of therapy, recent studies suggest that long term thionamide therapy is safe and efficacious (46,47). This option may be particularly useful in older patients with limited life expectancies, since it leads to more rapid attainment of euthyroidism and lower rates of hypothyroidism than radioactive iodine or surgery (48). Updated guidelines for treating hyperthyroidism now include the option for long-term thionamide therapy (35).

ANTITHYROID DRUGS AND TOXIC NODULAR HYPERTHYROIDISM

Time-limited courses of thionamides virtually never result in remission or cure of thyrotoxicosis secondary to toxic nodular goiter, although some spontaneous fluctuation in the severity of the disease is seen. Thionamides may thus be used short-term (as above) to induce euthyroidism prior to definitive treatment, but a time-limited course should not be prescribed in the hope of inducing cure. Recent studies show that long-term thionamide therapy is safe and efficacious in toxic nodular hyperthyroidism (47,49). Once biochemical control has been achieved, biochemical monitoring every 3-6 months is desirable.

BETA-ADRENERGIC BLOCKING AGENTS AND OTHER DRUGS AS ADJUNCTIVE THERAPIES

Beta adrenergic blockers are useful adjuncts to thionamides in the management of thyrotoxicosis. In cases of thyroiditis or mild cases of hyperthyroidism proceeding to radioiodine, they may be the only additional treatment required. Beta adrenergic blockers act promptly to reduce symptoms and signs of tremor and to improve tachycardia and associated palpitations (35). Such agents should be used cautiously in elderly subjects with heart failure (although a beneficial effect often results because of amelioration of some of the cardiovascular effects of thyroid hormone excess) and in those with asthma or chronic obstructive pulmonary disease. Propranolol has been widely used in thyrotoxic subjects but requires multiple daily dosing; longer acting beta adrenergic blockers such as atenolol (50-100mg daily) may therefore be preferred.

Other adjunctive therapies include salicylates for relief of local pain and tenderness in cases of subacute thyroiditis; occasionally glucocorticoids such as prednisolone are required short-term.

Anticoagulation with coumarin derivatives such as warfarin should be considered in elderly subjects with thyrotoxicosis complicated by atrial fibrillation. This is driven by evidence for embolic complications. There

have been no controlled trials of the use of anticoagulants in thyrotoxic atrial fibrillation, but overwhelming evidence of their efficacy in other settings argues in favor of their use in this situation (50), unless contraindications exist. Therapy to restore sinus rhythm should be considered but not until the patient has been rendered euthyroid. This therapy may comprise pharmacological cardioversion (with agents such as sotalol) or electrical cardioversion. Restoration of sinus rhythm is more likely in those whose atrial fibrillation is of short duration and in those without underlying heart disease (23), although rates of restoration of sinus rhythm may be relatively low, even with cardiologic intervention (24).

Radioiodine Therapy

Radioiodine (I-131) is a reasonable therapy in elderly hyperthyroid subjects, as it can be administered by mouth in the outpatient setting and is associated with few side effects. Some patients notice sore throat or neck tenderness (reflecting a radiation thyroiditis), but this is usually mild and transient. Its long-term efficacy is well established (35). Reports of potential risks of secondary cancers following radioactive iodine therapy for hyperthyroidism have been inconsistent, but long-term risks appear modest, and are likely to be of less importance in older subjects (51-53). There are few, if any, contraindications to radioiodine therapy apart from inability to comply with local radiation protection regulations. Such compliance may be difficult to achieve in hospital or nursing home residents, those with urinary incontinence, and those with significant mental impairment. In such cases, long-term thionamide therapy is often the best practical option (see above).

A relative contraindication to the use of radioiodine in cases of Graves' thyrotoxicosis is the presence of moderate or severe ophthalmopathy. There is a slightly increased risk of development or worsening of pre-existing thyroid eye disease in those treated with radioiodine compared with thionamides or surgery (35). Problematic eye disease is more likely in those with pre-existing ophthalmopathy, in smokers (smoking is an independent risk factor for development of ophthalmopathy in Graves' disease), and those with severe biochemical disease. In view of evidence (35) that a course of glucocorticoid abolishes any increase in risk of ophthalmopathy in those receiving radioiodine, many experts prescribe a short course of prednisone/prednisolone at the time of therapy. Typical doses of prednisone are 0.4-0.5 mg/kg/day starting 1-3 days following I-131 therapy and continued for one month, with gradual tapering over the next two months. However, recent data suggest that a lower dose of prednisone of 0.2 mg/kg/day for 6 weeks may be equally efficacious (54).

In those with severe clinical and biochemical thyrotoxicosis it is desirable to restore euthyroidism before proceeding to radioiodine therapy. This is because of the theoretical risk of inducing "thyroid storm" due to thyroid destruction and release of pre-formed thyroid hormones following radioiodine administration, together with the need to stop thionamide therapy temporarily at the time of treatment. In mild cases (judged both clinically and biochemically), such pre-treatment with thionamides may be unnecessary and radioiodine may be given as initial therapy or after short-term preparation with beta-adrenergic blockers.

RADIOIOIDINE DOSING

Many studies have attempted to define optimal radioiodine doses in the hope of inducing euthyroidism and avoiding iatrogenic hypothyroidism in hyperthyroid patients (35). Studies have examined attempts to titrate doses of radioiodine according to factors such as thyroid size (judged clinically or by imaging), isotope uptake, or isotope turnover in the thyroid. Older literature suggested that cases of toxic nodular hyperthyroidism require larger doses of radioiodine to induce euthyroidism than cases of Graves' disease. It is clear, however, that measures of thyroid size or isotope uptake/turnover generally do not allow effective "dose titration". Furthermore, the dose of radioiodine required to cure toxic nodular hyperthyroidism is not different from that required in Graves' disease in the majority of cases (55). In some subjects with large goiter, higher initial doses or multiple treatments are required.

Many large thyroid centers thus avoid attempts at radioiodine "dose titration" and administer empirical doses. Such an approach avoids the necessity for extra hospital visits to document isotope uptake into the gland or the need for other imaging. The dose of radioiodine administered varies between centers, and is determined in part by radiation protection restrictions that vary considerably around the world. Typically, a dose of radioiodine is chosen which can be administered in the outpatient setting and which results in cure of thyrotoxicosis in the majority after a single dose, while not inducing hypothyroidism in all. In iodine-replete parts of the world such as the US and UK, a standard dose of radioiodine is 10-15 mCi or 400-600 MBq. In a UK series (56) a dose of this size resulted in cure of thyrotoxicosis in more than two thirds, at a cost of early hypothyroidism in 50%. Some centers administer larger doses to those with large goiter or to men, in view of evidence of relative radioresistance in these groups. There is also evidence that use of thionamides, especially propylthiouracil, before and/or after radioiodine treatment also induces relative radioresistance and hence the need for repeat dosing or a larger initial dose (35). It has been suggested that large doses should be administered routinely to elderly subjects, particularly those with cardiovascular disease or complications, to be certain of rapid restoration of euthyroidism. This view is reinforced by evidence that effective cure as indicated by the development of hypothyroidism requiring thyroxine replacement therapy is associated with a lessening of vascular mortality (compared with those not rendered hypothyroid) (17) and more likely conversion to sinus rhythm in those with AF associated with hyperthyroidism (24).

FOLLOW-UP AFTER RADIOIODINE THERAPY

Thionamide therapy should be withdrawn 3-7 days before radioiodine (to allow iodine uptake into the thyroid) and should be restarted after a similar period post-treatment if the elderly subject has severe disease, incomplete biochemical control, significant complications (e.g., atrial fibrillation), or has return of symptoms in the short period of thionamide withdrawal before radioiodine therapy. After therapy, clinical and biochemical assessment should be carried out every 4-6 weeks for the first few months so that thionamide doses may be adjusted (according to free T4) and hypothyroidism identified. A transient rise in serum TSH may be seen in the first few months after radioiodine and does not necessarily indicate permanent hypothyroidism, but more marked biochemical or symptomatic hypothyroidism usually indicates the need for life-long T4 therapy. Persistence of biochemical hyperthyroidism 6 months after radioiodine therapy usually indicates the need for re-dosing. Unless small empirical doses are administered, the vast majority of patients with either toxic nodular hyperthyroidism or Graves' disease are rendered euthyroid (off all treatment) or hypothyroid (on T4) with one, two or (uncommonly) three doses (56,57). Occasional cases of apparent resistance to radioiodine treatment are seen.

Long-term, patients treated with radioiodine require biochemical follow-up for detection of hypothyroidism. Such follow-up is essential since the incidence of hypothyroidism is significant even many years after radioiodine and eventually up to 90% of those treated in this way become hypothyroid (35). Hypothyroidism rates may be slightly lower in those with toxic nodular hyperthyroidism (56) because of relative sparing of normal thyroid tissue through concentration of isotope in "hot" autonomous nodules.

Surgical Treatment of Thyrotoxicosis

Surgical treatment of thyrotoxicosis is a viable option in selected patients, and if experienced thyroid surgeons are available (35). However, there is a higher risk of complications of anesthetic and surgery in elderly subjects, which limits its utility in this population.

If surgery is contemplated, it is essential that clinical and biochemical euthyroidism are restored beforehand. This requires therapy with thionamides, ideally for 2-3 months prior to surgery, sometimes in conjunction with pre-operative preparation with beta-adrenergic blockers or Lugol's iodine (35). Thorough preparation is essential in order to avoid thyroid storm post-operatively, as well as other significant complications of thyroid hormone excess, especially cardiovascular complications.

There is on-going debate regarding the most appropriate surgical approach for treatment of thyrotoxicosis. Many large centers advocate total thyroidectomy for Graves' hyperthyroidism, since partial thyroidectomy is associated with significant rates of short - and long-term recurrence (35), while in expert hands surgical complication rates should be similar. Such complications include bleeding into the neck, hypoparathyroidism, and damage to recurrent laryngeal nerves. Hypothyroidism is inevitable after total thyroidectomy (the patient leaves the hospital on T4 therapy) but is also common after partial thyroidectomy. Life-long follow-up (as with cases treated with radioiodine) is essential for detection of hypothyroidism (and recurrence of hyperthyroidism) after partial thyroidectomy.

Cases of toxic nodular hyperthyroidism may be treated by thyroid lobectomy or excision of a single hot nodule. Such an approach has the theoretical advantage of avoidance of hypothyroidism, as well as improvement in cosmetic appearance in those with large goiter. It should be noted, however, that reduction in nodule/goiter size is also evident after radioiodine therapy, albeit after several months. Surgery may be considered appropriate if toxic nodular goiter is associated with obstructive symptoms or if there is concern about the presence of co-existent malignancy in the goiter/nodules.

Treatment of Amiodarone-Induced Thyrotoxicosis (AIT)

This condition is difficult to treat and a cause of significant morbidity/mortality in patients with underlying cardiac disease (35,58). AIT can be diagnosed many months after amiodarone has been discontinued, since it persists in the body for long periods of time. AIT can be a life-threatening diagnosis, since it worsens arrhythmias and cardiac function in patients who already have compromised cardiovascular systems.

There are two types of AIT. Type 1 AIT occurs in patients with pre-existing thyroid abnormalities such as nontoxic multinodular goiters or subclinical Graves' Disease. This type is thought to be due to iodine overload, since amiodarone is 37% iodine by weight. Type 2 AIT is a destructive thyroiditis that causes thyrotoxicosis by the release of pre-formed thyroid hormone, which can be prolonged. Some experts report that these two types can be distinguished by measurement of serum interleukin-6 (raised in destructive thyroiditis) or by ultrasonographic definition of thyroid vascularity (35,58). These tests are not, however, routinely available, and it is increasingly recognized that these varieties may co-exist.

In general, thionamide therapy should be considered first line treatment of Type 1 AIT. High dose glucocorticoids are considered first-line therapy for Type 2 AIT, although they can have significant side effects in elderly patients. In practice, it can be difficult to distinguish Type 1 from Type 2 AIT, and in severe acute cases, both thionamides and prednisone are sometimes started simultaneously. Type 2 AIT responds more quickly to glucocorticoids than Type 1 AIT responds to methimazole, so a rapid response to therapy is an indirect indicator of Type 2 AIT. Perchlorate may be a helpful adjunct therapy, although it is not commercially available in the U.S.

Withdrawal of amiodarone is often not possible because of the serious nature of underlying dysrhythmias leading to amiodarone treatment, although it should be carefully considered. In any case, the long half-life of the drug (around 50 days) determines that any effect of amiodarone withdrawal is slow. Because of the iodine content of the drug, radioiodine therapy is ineffective because the radioisotope is not taken up into the thyroid. Radioiodine treatment is typically not feasible until at least 6 months after amiodarone withdrawal. Several groups have described surgical treatment of AIT, with a recent report suggesting that patients treated with thyroidectomy had lower 5-year cardiovascular and 10-year all-cause mortality, compared to medically treated AIT patients (59). Restoration of euthyroidism with thionamides is preferable pre-operatively if possible.

SUBCLINICAL HYPERTHYROIDISM

"Subclinical" hyperthyroidism is a biochemical diagnosis characterized by a low serum TSH with normal serum thyroid hormone concentrations. Many of the subjects included in the studies quoted at the beginning of this chapter had subclinical, rather than overt, hyperthyroidism, as subclinical hyperthyroidism is more common than overt disease. There is significant variation in the reported prevalence of subclinical hyperthyroidism in the elderly, with typically quoted prevalence of 0.8 – 2% (35). As with overt hyperthyroidism, prevalence rates are lower if one excludes subjects taking thyroid hormone preparations. The prevalence of endogenous subclinical hyperthyroidism in a population depends on age, gender and iodine intake (3,60,61).

The most common cause of suppression of TSH in the general population is exogenous thyroid hormone therapy, typically levothyroxine (LT4). Population surveys (62) have shown that approximately one quarter of those prescribed LT4 long-term display reduction in TSH suggestive of mild over-treatment; (this is deliberate in the relatively small number of patients with a history of thyroid cancer). Since LT4 is prescribed to many patients over 60 years old, this medication is a common cause of subclinical hyperthyroidism. In fact, a recent study showed that over 40% of patients over the age of 64 years treated with levothyroxine had low TSH levels, indicating overtreatment (38).

In patients not receiving exogenous thyroid hormone therapy, the differential diagnoses of a low or undetectable TSH includes nonthyroidal illness and medications (see above). Once these have been excluded, nodular goiter is the next most common cause of low serum TSH in this age group. In subjects with a nodular goiter, either detectable clinically or evident on isotope imaging, suppression of serum TSH represents the earliest biochemical marker of thyroid autonomy and onset of hyperthyroidism. Other causes of endogenous subclinical hyperthyroidism in the elderly include Graves' Disease, subacute thyroiditis, and silent thyroiditis, as in younger patients, although these are less common.

The natural history of endogenous subclinical hyperthyroidism is variable, and depends on the underlying cause. Most patients have stable subclinical hyperthyroidism over years, but a sizable minority either progress to overt hyperthyroidism or normalize their thyroid function (35). A low but detectable TSH probably has less pathophysiological significance than a completely suppressed TSH, in terms of clinical consequences as well as progression rates. In addition, endogenous subclinical hyperthyroidism, for example secondary to nodular goiter, is probably of greater significance than exogenous (due to levothyroxine therapy) since the former is associated with higher serum T3 concentrations.

There is little evidence to suggest that subclinical hyperthyroidism is associated with significant symptoms (63), but there is a growing body of evidence that low serum TSH is associated with adverse effects, particularly on heart, bone, and brain, and possibly increased all-cause and cardiovascular mortality.

An important study of the Framingham population of the US (64) first revealed a 3-fold increased incidence of atrial fibrillation in subjects aged over 60 with serum TSH of less than 0.1 mU/L, compared with those with normal serum TSH. The likelihood of developing atrial fibrillation was also increased, but less markedly, in those with low but detectable TSH. The group in this survey with low TSH was heterogeneous and included some subjects taking exogenous T4 therapy. Similar findings have been reported in larger population-based studies since this initial observation (35).

Recent studies have also reported that subclinical hyperthyroidism is associated with increased mortality and cardiovascular events in subjects 65 years and older (19,21,65). A meta-analysis of individual-level data from 52,674 participants pooled from 10 cohort studies concluded that subclinical hyperthyroidism confers a 24% increased risk of

overall mortality and 29% increased risk of cardiovascular mortality (66). Some of these studies, including the meta-analysis, have also examined non-fatal cardiovascular events in subclinical hyperthyroidism, with similar increased risks (66-69). Data indicate that subclinical hyperthyroid subjects appear to be at particular risk for the development of heart failure (66,70,71), especially older subjects and those with lower TSH levels.

Adverse effects of subclinical hyperthyroidism on bone may occur. A recent meta-analysis of 6 prospective cohorts (5,458 subjects, median age 72 years, 5% with subclinical hyperthyroidism) reported that older subjects with subclinical hyperthyroidism had increased annual rates of bone loss at the femoral neck, especially if the TSH was less than 0.1 mU/L (72). A second meta-analysis of 13 prospective cohorts (70,298 subjects, median age 64 years, median follow-up 12 years, 3% with subclinical hyperthyroidism) reported that subjects with subclinical hyperthyroidism had increased rates of hip fracture, clinical spine fracture, non-spine fracture, and any fracture (73). Risks were greatest if the TSH was less than 0.1 mU/L. There is also evidence for improvement in bone metabolism or BMD after treatment of endogenous subclinical hyperthyroidism (74). Finally, in hypothyroid subjects who were started on LT4 and followed for a mean of 7 years, the number of 6-month periods with low TSH levels increased the risk of hip and major osteoporotic fractures in post-menopausal women, but not in men (75). This further illustrates the importance of avoiding overtreatment in hypothyroidism.

Mood and cognitive function have also been examined in older subjects with subclinical hyperthyroidism (76). A meta-analysis of 11 studies (16,805 subjects, mean age over 70 years, median follow-up 3.5 years) reported an increased risk of dementia in subclinical hyperthyroid subjects (77). A more recent prospective cohort study (2,558 subjects ages 70-79 years, median follow-up 9 years) reported an increased risk of dementia if the TSH was suppressed, but not if the TSH was low but detectable (78). Reports on associations between subclinical hyperthyroidism and rates of depression or anxiety have been variable, with some studies indicating no association in older subjects (35,79), while others report increased rates of depressive symptoms in subclinical hyperthyroidism (80).

Concerns about effects of mild thyroid hormone excess upon heart and bone, and more recently on cognitive function, have led to a trend towards treatment of this condition. In those taking exogenous thyroid hormone, management is relatively straightforward, namely reduction in prescribed dose and re-checking of serum TSH 6-8 weeks later. For those not taking T4, many experts administer either antithyroid drugs or radioiodine to those with persistent subclinical hyperthyroidism, especially in subjects with atrial fibrillation or other underlying cardiac disease. Prospective trials confirming benefit of such therapy have yet to be performed, but analysis of large datasets indicate that prolonged periods of undertreatment confer increased risks (19,21). Based on this, consensus guidelines recommend that older subjects and those with AF or other vascular risk factors should be treated (35).

SCREENING FOR HYPERTHYROIDISM IN ELDERLY SUBJECTS

Several factors should be considered before a decision is made to institute either population or targeted screening for thyroid disorders in groups such as the elderly. Firstly, screening programs should be instituted only for those conditions in which the benefits of screening outweigh the costs. Whether benefits outweigh the costs depends on accurate quantification of these issues, then a judgment as to whether the costs of screening are justified. Although it is clear that hyperthyroidism is common, there are no data that demonstrate that identified subjects benefit from being diagnosed; it is not sufficient to demonstrate only that such subjects exist. Such benefits and costs should ideally be based upon the results of a randomized controlled trial in an appropriate sample of the relevant population. In considering costs, those incurred by those who do not themselves gain from the screening program should be considered. If, for example, the screening process uses a test such as serum TSH

with occasional positives, then some patients may be exposed to investigations which are unnecessary, with accompanying risk and potential morbidity.

While overt and subclinical hyperthyroidism are common in older subjects, and while there is evidence for adverse consequences of these diagnoses, the evidence that treatment in a screened population improves morbidity/mortality, and that the risks of such treatment outweigh the costs, is currently inconclusive. There should, nonetheless, be a high index of suspicion for hyperthyroidism in this age group and a low threshold for biochemical testing, especially in those with a previous personal or family history of thyroid disease or those with conditions such as atrial fibrillation that may reflect hyperthyroidism. Care must also be taken to recognize the atypical presentations of hyperthyroidism that occur in this age group, including unexplained weight loss and psychiatric symptoms.

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