Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

SUBCLINICAL HYPERTHYROIDISM

ANTHONY D. TOFT, M.D.

A 67-year-old woman presents with palpitations and is found to be in atrial fibrillation at a rate of 120 beats per minute. The only other finding on physical examination is a goiter, which is known to be long-standing. Echocardiography shows neither valvular disease nor left ventricular systolic dysfunction. The serum thyrotropin concentration is less than 0.05 mU per liter, and the serum total triiodothyronine and free thyroxine concentrations are in the normal range. Should the thyroid dysfunction be treated?

THE CLINICAL PROBLEM

The combination of an undetectable serum thyrotropin concentration, as measured by an assay with a threshold of detection that is 0.1 mU per liter or less, and normal serum triiodothyronine and thyroxine concentrations (usually at the upper end of the normal range) is known as subclinical hyperthyroidism. This condition reflects the fact that before clinical features of thyrotoxicosis are apparent, the thyrotrophs usually respond to minor increments in thyroid hormone concentrations, which remain within the normal range, by switching off the production and secretion of thyrotropin.[1] An absence of symptoms was once part of the definition of subclinical hyperthyroidism, but we now understand that subtle symptoms or signs of thyrotoxicosis may be present. Subclinical hyperthyroidism is classified as endogenous in patients with thyroid hormone production associated with nodular thyroid disease or underlying Graves' disease; it is classified as exogenous in those with undetectable serum thyrotropin concentrations as a result of treatment with levothyroxine. Not all patients with undetectable serum thyrotropin concentrations and normal thyroxine and triiodothyronine concentrations have subclinical hyperthyroidism, and this combination of findings can be associated with various other conditions (Table 1).

Multinodular goiter is usually palpable, if not visible, and may be sufficiently large to cause compressive complications. Imaging with technetium-99m pertechnetate or iodine-123 generally shows "hot" (functioning) nodules and is particularly useful for detecting a single, impalpable, autonomously functioning adenoma. Most patients who present with multinodular goiter have been aware of thyroid enlargement for several years, and they may have undergone partial thyroidectomy. The so-called simple, diffuse goiter observed in patients in their late teens and 20s tends to progress to a more obvious, multinodular goiter at around 40 years of age. As the goiter increases in size and as the autonomous nodules become larger and more numerous, subclinical or overt hyperthyroidism is increasingly present.[2]

Underlying Graves' disease may be present if a patient has a family history of the disorder or has other organ-specific autoimmune diseases, such as type 1 diabetes mellitus, vitiligo, pernicious anemia, myasthenia gravis, or Addison's disease, or if the patient has diffuse goiter, ophthalmopathy, or pretibial myxedema. Thyroid imaging with isotope methods shows an even distribution, and the results in patients with early-stage Graves' disease are likely to be similar to those in normal persons. The presence of thyrotropin-receptor antibodies in serum is diagnostic of Graves' disease, irrespective of the clinical findings, but the antibodies are absent in approximately 5 to 20 percent of patients with hyperthyroid Graves' disease, depending on the assay used,[3] and almost certainly in a greater proportion of those with subclinical hyperthyroidism.

STRATEGIES AND EVIDENCE

The issue of screening for thyroid disease in patients with few or no symptoms was discussed in a recent article in the *Journal*.[4] In view of the relatively high prevalence of unrecognized hypothyroidism in older adults, especially women, an expert panel of the American Thyroid Association has recommended routine screening of adults for thyroid disease by measurement of serum thyrotropin.[5] In hospital practice, thyroid-function testing has become almost routine. Such screening will inevitably identify patients with undetectable serum thyrotropin concentrations but normal thyroxine and triiodothyronine concentrations, although the prevalence of such findings is low. In one study, for example, involving 1210 patients over the age of 60 years who were seen at a single general practice in the United Kingdom and who were not taking

From the Endocrine Clinic, Royal Infirmary of Edinburgh, Lauriston Pl., Edinburgh EH3 9YW, Scotland, where reprint requests should be addressed to Dr. Toft.

TABLE 1. PATTERNS OF THYROID FUNCTION ASSOCIATED WITH A SUPPRESSED SERUM THYROTROPIN CONCENTRATION AND A THYROID HORMONE CONCENTRATION THAT MAY BE NORMAL.

CONDITION OR FACTOR	TRIIODOTHYRONINE		THYROXINE	
	FREE	TOTAL	FREE	TOTAL
Endogenous subclinical hyperthyroidism (associated with Graves' disease or nodular goiter)*	Upper end of normal range	Upper end of normal range	Upper end of normal range	Upper end of normal range
Exogenous subclinical hyperthyroidism (associated with levothyroxine therapy)	Normal	Normal	Upper end of normal range or elevated	Upper end of normal range or elevated
Nonthyroidal illness	Normal, low, or elevated†	Normal or low	Normal, low, or elevated‡	Normal, low, or elevated§
Drug therapy¶				
Dopamine	Normal	Normal	Normal	Normal
Corticosteroids	Normal	Normal	Normal	Normal
Amiodarone	Normal	Normal	Usually elevated but may be at upper end of normal range	Usually elevated but may be at upper end of normal range
Central hypothyroidism	Normal or low	Normal or low	Low end of normal range or low	Low end of normal range or low

*Subclinical hyperthyroidism may also be noted during the hyperthyroid phase of subacute, silent, or postpartum thyroiditis.

†In patients with nonthyroidal illness, the concentration of free triiodothyronine may be found to be elevated if a particular commercial assay system (Vitros ECi, Ortho Clinical Diagnostics) is used.

‡The value depends on both the severity of the illness and the method of measurement used.

§The value depends on the type and severity of the illness.

¶Thyroid-function test results in patients with nonthyroidal illness may be influenced by concomitant drug therapy.

thyroxine, serum thyrotropin concentrations were undetectable in 16 patients (1.3 percent).[6] During one year of follow-up, thyrotoxicosis developed in only one patient, and serum thyrotropin concentrations returned to normal in two patients. In some patients, the thyrotropin concentration may have been undetectable because of a transient nonthyroidal disorder or because of drug therapy for such a disorder.

The estimated rate of progression from subclinical to overt hyperthyroidism in patients with multinodular goiter is 5 percent each year,[7] and it may be significantly higher with the administration of iodine as a dietary supplement in areas where goiter is endemic, or with the use of the antiarrhythmic drug amiodarone, which contains iodine. Progression to prolonged overt hyperthyroidism in patients with underlying Graves' disease is probably less common, given the relapsing and remitting nature of Graves' disease and the eventual development of hypothyroidism in some patients.

If screening or the investigation of goiter shows that a patient has subclinical hyperthyroidism, should it be treated? Other than regular monitoring, the options for managing subclinical hyperthyroidism are the same as those for managing overt hyperthyroidism: the administration of antithyroid drugs (in patients with Graves' disease only) or iodine-131. Although iodine-131 uptake is likely to be lower in patients with subclinical hyperthyroidism than in those with overt hyperthyroidism, there is no evidence that a dose that is therapeutic in the second group is less effective in the first. Partial thyroidectomy would be indicated for a large multinodular goiter that caused mediastinal compression. One reason to treat subclinical hyperthyroidism is to prevent the development of overt hyperthyroidism. Prevention of atrial fibrillation and prevention of osteoporosis are the other chief potential benefits of treatment, but how good is the evidence of these preventive effects?

Atrial Fibrillation

The best evidence that subclinical hyperthyroidism is a risk factor for the development of atrial fibrillation comes from the Framingham Study.[8] A cohort of 2007 persons 60 years of age or older was followed for 10 years, and the development of atrial fibrillation was analyzed in relation to the initial concentration of serum thyrotropin. Among the 61 subjects with a thyrotropin concentration of less than 0.1 mU per liter and a normal serum thyroxine concentration at the outset, atrial fibrillation developed in 13, of whom an unspecified number were taking thyroxine. The relative risk of atrial fibrillation in this group of 61 subjects was 3.1 as compared with those who had a nor-

mal serum thyrotropin concentration (0.4 to 5.0 mU per liter); the risk was similar when the patients who were taking thyroxine were excluded from the analysis. A low but detectable serum thyrotropin concentration (0.1 to 0.4 mU per liter) was not associated with an increased risk of atrial fibrillation.

Assuming that antithyroid therapy would reduce the risk of dysrhythmia to that in the general population, 4.2 cases of subclinical hyperthyroidism would need to be treated to prevent 1 case of atrial fibrillation over a period of 10 years.[9] There is only limited evidence that established atrial fibrillation in patients with subclinical hyperthyroidism reverts spontaneously or after cardioversion once the serum thyrotropin concentration has been normalized with antithyroid therapy.[10]

Thyrotoxic atrial fibrillation is commonly considered a risk factor for systemic embolism, but the reported risk has ranged from negligible to 40 percent — extremes that do not reflect clinical experience. Even a risk of 10 percent probably represents an overestimate, since it is based on data obtained at a time when accurate tests of thyroid function were not widely available[11] and when an early diagnosis of hyperthyroidism was less likely than it is now. However, the available data suggest that among patients with atrial fibrillation that is unrelated to rheumatic heart disease, those with thyrotoxicosis have a higher rate of embolism than do patients without the condition. The risk of systemic embolism in patients with atrial fibrillation complicating subclinical hyperthyroidism is not known.

Osteoporosis

Frank hyperthyroidism is a recognized risk factor for osteoporosis, but the effects of subclinical hyperthyroidism on bone mineral density are less well defined. The increased bone turnover that is characteristic of Graves' disease persists during treatment with antithyroid drugs if serum thyrotropin concentrations remain suppressed, despite normal concentrations of thyroid hormones.[12] In two cross-sectional studies of patients with subclinical hyperthyroidism due to multinodular goiter, there was statistically and clinically significantly lower bone mineral density at the femoral neck and radius than in age-matched controls.[13,14] Whether these changes are associated with an increased rate of fracture is not known. More impressive are the reports that postmenopausal women with subclinical hyperthyroidism due to multinodular goiter have a 2 percent loss of bone mineral density each year, which can be reversed by treatment that restores serum thyrotropin concentrations to the normal range.[15,16]

A large meta-analysis of patients with exogenous subclinical hyperthyroidism showed that bone loss was greater among postmenopausal women with this condition than among those without it.[17] However, the validity of these results is questionable, since the study also found increased bone loss in premenopausal women who were receiving levothyroxine replacement therapy and who had normal serum thyrotropin concentrations. Furthermore, the increased risk of fracture reported in older women taking thyroid hormones disappears when those with a history of hyperthyroidism are excluded.[18] The evidence that exogenous subclinical hyperthyroidism is a risk factor for osteoporosis is therefore inconclusive.[19,20]

Other Considerations

Other abnormalities have been linked to both endogenous and exogenous subclinical hyperthyroidism. There is evidence that patients with subclinical hyperthyroidism due to multinodular goiter have increased left ventricular mass, increased systolic function, and impaired diastolic function, but the clinical significance of these observations is not known.[21] Impairment of the quality of life, as assessed with the use of a questionnaire, was also reported in these patients.[21] Whether normalization of the serum thyrotropin concentration improves these measures is uncertain. An increased risk of dementia and Alzheimer's disease was recently reported among patients with endogenous subclinical hyperthyroidism who were 55 years of age or older, particularly if antibodies against thyroid peroxidase were present[22]; this finding requires confirmation.

Patients receiving long-term suppressive therapy with levothyroxine have been reported to have diminished cardiac reserve and exertional capacity.[23] However, similar abnormalities were abolished by reducing the dose of levothyroxine to a level that was still associated with subclinical hyperthyroidism.[24] Short-term studies of small numbers of patients with exogenous subclinical hyperthyroidism have found changes in target-organ function — e.g., an increase in the nocturnal heart rate and an altered ratio of diurnal urinary sodium excretion to nocturnal excretion. These changes are similar to but less marked than those in overt hyperthyroidism[25] but may not be sustained in the long term.[26]

AREAS OF UNCERTAINTY

The natural history of subclinical hyperthyroidism remains unclear. Furthermore, the evidence that endogenous or exogenous subclinical hyperthyroidism is a risk factor for osteoporosis and atrial fibrillation is not definitive. However, it would be surprising if the complications of overt hyperthyroidism were not seen, albeit at a reduced frequency, in a condition that is effectively the mildest form of thyrotoxicosis; such complications are more likely to occur in patients with multinodular goiter, since the biochemical abnormality is persistent and the age of affected persons puts them at increased risk for bone loss or ischemic or structural heart disease.

The issue is further complicated by confusion over the meaning of subclinical hyperthyroidism, which is sometimes used to describe elevated serum thyroxine

concentrations in patients who are taking thyroxine as replacement therapy. The inclusion of patients with wide ranges of thyroid-function test results and ratios of thyroxine to triiodothyronine may explain, at least in part, the disparate results of studies of target-organ function.

GUIDELINES

In its 1995 consensus statement on the treatment of patients with hyperthyroidism and hypothyroidism, the American Thyroid Association does not mention subclinical hyperthyroidism.[27] However, the association does state that in patients taking levothyroxine as replacement therapy, the dose should be adjusted to achieve clinical euthyroidism, with normal serum concentrations of both thyroxine and thyrotropin.[28] In statements issued in 1996 and 1998, respectively, the Royal College of Physicians of London[29] and the American College of Physicians[9] concluded that there is no agreement about the benefits of detecting and treating endogenous subclinical hyperthyroidism or about whether it causes excess morbidity. The statement of the American College of Physicians was based on a meta-analysis of available data. In contrast, the American Association of Clinical Endocrinologists[30] concluded that subclinical hyperthyroidism associated with goiter requires treatment in most cases.

RECOMMENDATIONS

In the absence of clinical signs of thyroid disease, and even after additional investigations such as isotope uptake and imaging and measurement of the thyrotropin-receptor antibody concentration, it may be difficult to decide whether the pattern seen on thyroid-function tests is a consequence of nonthyroidal illness and concomitant medication, underlying autonomous thyroid function, or the initial phase of thyroiditis. In such circumstances, thyroid-function tests should be repeated after eight weeks; a normal or elevated serum thyrotropin concentration at this time suggests recovery from nonthyroidal illness or the hypothyroid phase of thyroiditis. If the initial pattern persists, the choice should be made between a trial of antithyroid drugs and close clinical follow-up.

Exogenous Subclinical Hyperthyroidism

The dose of thyroxine should normally be reduced in patients with exogenous subclinical hyperthyroidism, excluding those with prior thyroid cancer, in whom thyrotropin suppression may be desired. The dose can usually be reduced abruptly to a more appropriate level. For example, in a symptomatic patient who has a markedly elevated serum free thyroxine concentration and a triiodothyronine concentration at the high end of the normal range while taking 250 μg of levothyroxine daily, it would be appropriate to reduce the dose to 150 μg daily and to retest thyroid function at a follow-up visit. The thyrotropin concentration may remain suppressed for six to eight weeks or more in patients with previous overreplacement of levothyroxine.

Although most patients feel well when thyroid function is normalized, a minority of patients have a sense of well-being only when taking a suppressive dose of levothyroxine.[31] In the absence of apparent complications of excess thyroid hormone, which would clearly warrant a dose reduction (Table 2), I would consider a slightly supratherapeutic dose acceptable as long as the serum triiodothyronine concentration remained well within the normal range.[29]

Endogenous Subclinical Hyperthyroidism

In many patients with endogenous subclinical hyperthyroidism who do not have nodular thyroid disease or complications of excess thyroid hormone, treatment is unnecessary, but thyroid-function tests should be performed every six months, with the recognition that the serum triiodothyronine concentration may become elevated before the serum thyroxine concentration does. In patients with questionable symptoms, such as fatigue, I would use the empirical approach of a six-month trial with an antithyroid drug at a low dose, such as methimazole at a daily dose of 5 to 10 mg initially, and if this approach was effective, I would consider ablative therapy with iodine-131. To treat a woman who wanted to become pregnant, propylthiouracil at a dose of 50 mg twice a day would be more appropriate, because aplasia cutis congenita, a rare scalp defect, has been linked to the use of methimazole during pregnancy. The management of hyperthyroidism during pregnancy is beyond the scope of this review, but it would require extremely close monitoring and use of the lowest possible dose of propylthiouracil.[32] In older patients with atrial fibrillation or osteoporosis that could have been caused or exacerbated by the mild excess of thyroid hormone, ablative therapy with iodine-131 is the best initial option.

Treatment of patients with subclinical hyperthyroidism due to nodular thyroid disease is more routinely justified, given the expected progression to overt hyperthyroidism. The patient described in the vignette has both goiter and atrial fibrillation, two findings that warrant therapy. In the case of atrial fibrillation, I would first administer an antithyroid drug such as

TABLE 2. INDICATIONS FOR REDUCING THE DOSE OF THYROXINE IN PATIENTS WITH EXOGENOUS SUBCLINICAL HYPERTHYROIDISM.

New atrial fibrillation, angina, or cardiac failure
Accelerated loss of bone density
Oligomenorrhea, amenorrhea, or infertility
Nonspecific symptoms such as tiredness, hyperdefecation, and palpitations
Borderline high serum triiodothyronine concentration

methimazole in order to restore the serum thyrotropin concentration to a normal value as quickly as possible. I would also administer warfarin because of the risk of systemic embolism, even though there are no data from controlled studies of anticoagulant therapy in patients with thyrotoxic atrial fibrillation. Careful monitoring of the dose is essential, since patients with overt hyperthyroidism and, presumably to a lesser degree, those with subclinical hyperthyroidism are more sensitive than euthyroid patients to the anticoagulant effects of warfarin. If sinus rhythm is not restored within four months after the normalization of the serum thyrotropin concentration, cardioversion should be performed.[33] The definitive treatment would be an ablative dose of iodine-131. In the case described, and in similar cases, this approach is warranted for several reasons: the potential contribution of subclinical hyperthyroidism to the development of osteoporosis, the low incidence of hypothyroidism after iodine-131 therapy in patients with multinodular goiter (6 percent at one year at my institution, as compared with 75 percent in patients with Graves' disease), the possibility of loss to follow-up and the attendant worsening of symptoms if treatment is withheld in favor of continued observation, and the likely cosmetic benefit of up to a 50 percent reduction in the size of the goiter at one to two years.[34,35]

REFERENCES

1. Snyder PJ, Utiger RD. Inhibition of thyrotropin response to thyrotropin-releasing hormone by small quantities of thyroid hormones. J Clin Invest 1972;51:2077-84.
2. Berghout A, Wiersinga WM, Smits NJ, Touber JL. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. Am J Med 1990;89:602-8.
3. Costagliola S, Morgenthaler NG, Hoermann R, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab 1999;84:90-7.
4. Cooper DS. Subclinical hypothyroidism. N Engl J Med 2001;345:260-5.
5. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000; 160:1573-5.
6. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf) 1991;34:77-83.
7. Wiersinga WM. Subclinical hypothyroidism and hyperthyroidism. I. Prevalence and clinical relevance. Neth J Med 1995;46:197-204.
8. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older patients. N Engl J Med 1994;331:1249-52.
9. Helfand M, Redfern CC. Screening for thyroid disease: an update. Ann Intern Med 1998;129:144-58. [Erratum, Ann Intern Med 1999;130:246.]
10. Forfar JC, Feek CM, Miller HC, Toft AD. Atrial fibrillation and isolated suppression of the pituitary-thyroid axis: response to specific antithyroid therapy. Int J Cardiol 1981;1:43-8.
11. Staffurth JS, Gibberd MC, Fui SNG. Arterial embolism in thyrotoxicosis with atrial fibrillation. Br Med J 1977;2:688-90.
12. Kumeda Y, Inaba M, Tahara H, et al. Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism. J Clin Endocrinol Metab 2000;85:4157-61.
13. Mudde AH, Reijnders FJL, Kruseman AC. Peripheral bone density in women with untreated multinodular goitre. Clin Endocrinol (Oxf) 1992; 37:35-9.
14. Földes J, Tarjan G, Szathmari M, Varga F, Krasznai I, Horvath CS. Bone mineral density in patients with endogenous subclinical hyperthyroidism: is this thyroid status a risk factor for osteoporosis? Clin Endocrinol (Oxf) 1993;39:521-7.
15. Mudde AH, Houben AJHM, Nieuwenhuijzen Kruseman AC. Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. Clin Endocrinol (Oxf) 1994;41:421-4.
16. Faber J, Jensen IW, Petersen L, Nygaard B, Hegedus L, Siersbaek-Nielsen K. Normalization of serum thyrotrophin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. Clin Endocrinol (Oxf) 1998;48:285-90.
17. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. J Clin Endocrinol Metab 1996;81:4278-89.
18. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. N Engl J Med 1995;332:767-73.
19. Toft AD. Thyroxine therapy. N Engl J Med 1994;331:174-80. [Erratum, N Engl J Med 1994;331:1035.]
20. Franklyn JA, Betteridge J, Daykin J, et al. Long-term thyroxine treatment and bone mineral density. Lancet 1992;340:9-13.
21. Biondi B, Palmieri EA, Fazio S, et al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab 2000;85:4701-5.
22. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism and the risk of dementia: the Rotterdam Study. Clin Endocrinol (Oxf) 2000;53:733-7.
23. Biondi B, Fazio S, Cuocolo A, et al. Impaired cardiac reserve and exercise capacity in patients receiving long-term thyrotropin suppressive therapy with levothyroxine. J Clin Endocrinol Metab 1996;81:4224-8.
24. Mercuro G, Panzuto MG, Bina A, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. J Clin Endocrinol Metab 2000;85:159-64.
25. Bell GM, Todd WTA, Forfar JC, et al. End-organ responses to thyroxine therapy in subclinical hypothyroidism. Clin Endocrinol (Oxf) 1985; 22:83-9.
26. Nyström E, Lundberg P-A, Petersen K, Bengtsson C, Lindstedt G. Evidence for a slow tissue adaptation to circulating thyroxine in patients with chronic L-thyroxine treatment. Clin Endocrinol (Oxf) 1989;31:143-50.
27. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995;273:808-12.
28. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA 1990;263:1529-32.
29. Vanderpump MP, Ahlquist JA, Franklyn JA, Clayton RN. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. BMJ 1996;313:539-44.
30. American Association of Clinical Endocrinologists releases clinical guidelines for thyroid disease. Am Fam Physician 1995;51:679-80.
31. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf) 1988;28: 325-33.
32. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55.
33. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of atrial fibrillation in the post-thyrotoxic state. Am J Med 1982;72: 903-6.
34. Hegedus L, Hansen BM, Knudsen N, Hansen JM. Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. BMJ 1988;297:661-2.
35. Le Moli R, Wesche MFT, Tiel-Van Buul MMC, Wiersinga WM. Determinants of longterm outcome of radioiodine therapy of sporadic nontoxic goitre. Clin Endocrinol (Oxf) 1999;50:783-9.