



## Medical Management of Hyperthyroidism

a report by

Ramzi A Ajjan<sup>1</sup> and Anthony P Weetman<sup>2</sup>

1. Academic Unit of Molecular and Vascular Medicine, The LIGHT Laboratories, University of Leeds;

2. The Medical School, University of Sheffield

Hyperthyroidism mainly affects the female population, occurring in around 2% of women and 0.2% of men.<sup>1</sup> The majority of patients with hyperthyroidism have Graves' disease (GD) and, less often, solitary toxic nodule or toxic multinodular goitre. Other causes of hyperthyroidism are relatively rare and are summarised in *Table 1*. Establishing the accurate cause of hyperthyroidism is important as this influences treatment strategy and is usually achieved by a combination of clinical assessment, thyroid function tests – including thyroid autoimmune screening – and radionuclide scans with <sup>123</sup>I, <sup>131</sup>I or <sup>99m</sup>Tc for difficult cases. This review will focus on the medical management of hyperthyroidism with special emphasis on GD.

### Medical Management of Hyperthyroidism

Antithyroid drugs and radioactive iodine (RAI) remain the mainstay of medical treatment for patients with GD or toxic nodular goitre, although surgery still has a place in some cases. Patients with severe symptoms may require additional symptomatic treatment.

### Graves' Disease

#### Antithyroid Drugs

Known as thionamides, this group of drugs includes propylthiouracil, carbimazole and its active metabolite, methimazole. These agents interfere with the action of thyroid peroxidase, thereby inhibiting thyroid hormone production. In addition, they have an immunosuppressive action, which helps in inducing disease remission, although the basis of this effect remains in debate.<sup>2</sup> Propylthiouracil is the only antithyroid agent that inhibits peripheral deiodination, thereby blocking the conversion of thyroxine to the active hormone tri-iodothyronine, although this effect does not seem to be clinically important.<sup>3</sup> Antithyroid drugs are given in two different ways: either as titration or as block and replace regime. In titration therapy, treatment is usually continued for 18–24 months, whereas most use the block and replace regimen for six months, as longer treatment is not associated with higher remission rate.<sup>4</sup> Using either programme, however, the remission rate is disappointingly low as half to two-thirds of patients relapse. Recurrence usually occurs within the first 6–12 months after stopping treatment but may occur years later.<sup>5</sup> Other regimens using low-dose antithyroid drugs in combination with thyroxine or antithyroid drugs alone for 12–18 months, followed by thyroxine treatment, have not shown any difference in relapse rate and therefore these regimes cannot be advocated.<sup>4</sup>

Side effects of antithyroid drugs (summarised in *Table 2*) are marginally higher with the block and replace compared with the titration regime, but advantages of the former are quicker control and less fluctuation of thyroid function, fewer hospital visits and shorter period of treatment. The most serious complication is agranulocytosis and all patients are

advised to report immediately to their physician if they develop a temperature, sore throat or mouth ulcers while on treatment. Switching from one antithyroid agent to another is possible in cases of mild side effects, but agranulocytosis with any of the antithyroid drugs represents a contraindication to the further use of these agents.

Unfortunately, there is no reliable clinical marker that can predict relapse,<sup>6</sup> but patients with severe thyrotoxicosis, a large goitre or extrathyroidal complications are less likely to enter remission.<sup>3</sup> Individuals with high thyroid-stimulating hormone (TSH) receptor antibodies post-treatment are more likely to relapse, but the converse is not true, and therefore antibody measurement has a limited role in planning treatment strategy.<sup>7</sup> Patients who relapse after antithyroid treatment are usually offered RAI treatment or surgery. A minority opt for long-term antithyroid drug therapy, which can effectively control thyroid function with no long-term side effects.<sup>8</sup>

#### Radioactive Iodine

Although this treatment is safe and effective, it is not yet routinely used as first-line therapy for GD in Europe. A significant number of patients are reluctant to undergo this treatment due to unfounded fear of radiation. Some patients are also concerned about permanent hypothyroidism post-RAI necessitating thyroid hormone replacement for life. RAI treatment carries a small risk of aggravating thyroid eye disease, particularly in smokers.<sup>9</sup> This risk of cancer after RAI has been addressed in a number of studies. A comprehensive study by Franklyn and colleagues showed no increase in general cancer rates post-RAI, but a small increase in thyroid and bowel cancer was documented.<sup>10</sup> More recent work in Finland failed



Anthony P Weetman has been the Sir Arthur Hall Professor of Medicine at the University of Sheffield and Consultant Endocrinologist at the Sheffield Teaching Hospitals Foundation Trust since 1991. He is a former Editor of *Clinical Endocrinology* and *Clinical and Experimental Immunology*, and has served as an Associate Editor of *Endocrine Reviews*. He received the Merck Prize of the European Thyroid Association (ETA) in 2002 and is President of the British Thyroid Association (BTA), as well as a member of the Executive Committee of the ETA.

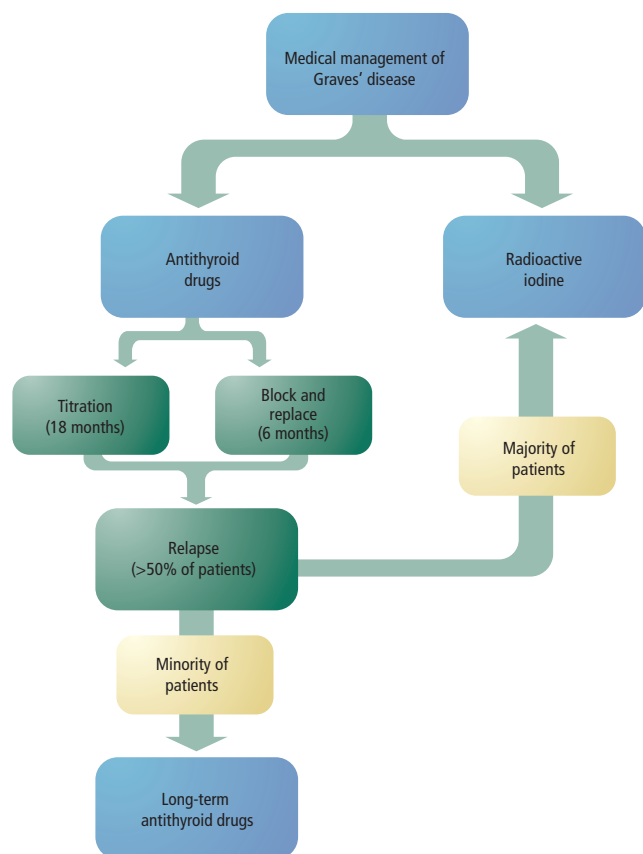


Ramzi A Ajjan is a Senior Lecturer/Consultant in Diabetes and Endocrinology at the University of Leeds. He has been awarded a Department of Health Clinician Scientist Award for five years to investigate the role of genes and environment in modulating blood clot structure, which may offer new treatment strategies for individuals at risk of cardiovascular disease. He is a member of the British and European Endocrine Societies, British Thyroid Foundation, Diabetes UK and the European Association for the Study of Diabetes (EASD). Dr Ajjan completed his postgraduate studies at the University of Sheffield, focusing on thyroid autoimmunity, after obtaining his medical degree from Aleppo University, Syria.



# Thyroid Disorders

**Figure 1. Medical Management of Graves' Disease**



First-line treatment for Graves' disease in Europe is antithyroid drugs, although radioactive iodine can be considered initially after discussion with the patient. Antithyroid drugs are given for 6–18 months either as block and replace or titration regime. More than 50% of patients relapse after antithyroid drug treatment and most are subsequently treated with radioactive iodine.

to show an increase in thyroid cancer after RAI but found a significant increase in stomach, kidney and breast cancers.<sup>11</sup> However, the absolute risk was quite small and mainly found in older patients with nodular disease and therefore the increased cancer incidence in this study could not be conclusively attributed to RAI treatment. An increase in cardiovascular risk after RAI treatment has also been suggested.<sup>12–14</sup> However, Metso and colleagues found that hypothyroidism post-RAI offered protection from cardiovascular disease, suggesting that hyperthyroidism *per se* rather than RAI treatment is responsible for the increased cardiovascular events in these patients.

Complex calculations to administer 'the optimal dose' of RAI are unnecessary and a fixed-dose approach is preferred as it simplifies treatment and has a similar success rate with no increase in side effects.<sup>15</sup> The failure rate of RAI treatment is less than 20%; therefore, this form of therapy should be considered initially and discussed with GD patients. Antithyroid drugs should not be given immediately before or after RAI as this may increase treatment failure rate.<sup>16</sup> Furthermore, the use of carbimazole or methimazole prior to RAI is preferred over the use of propylthiouracil, which is associated with higher RAI treatment failure, although this effect is perhaps smaller than previously thought.<sup>16</sup> Immediate side effects of RAI are rare and include transient nausea and pain over the thyroid gland 1–3 days after administration.<sup>17</sup> Thyroid storm may occur rarely after RAI, particularly in those with large goitres and severe hyperthyroidism.<sup>18</sup> *Figure 1* summarises the medical management of GD.

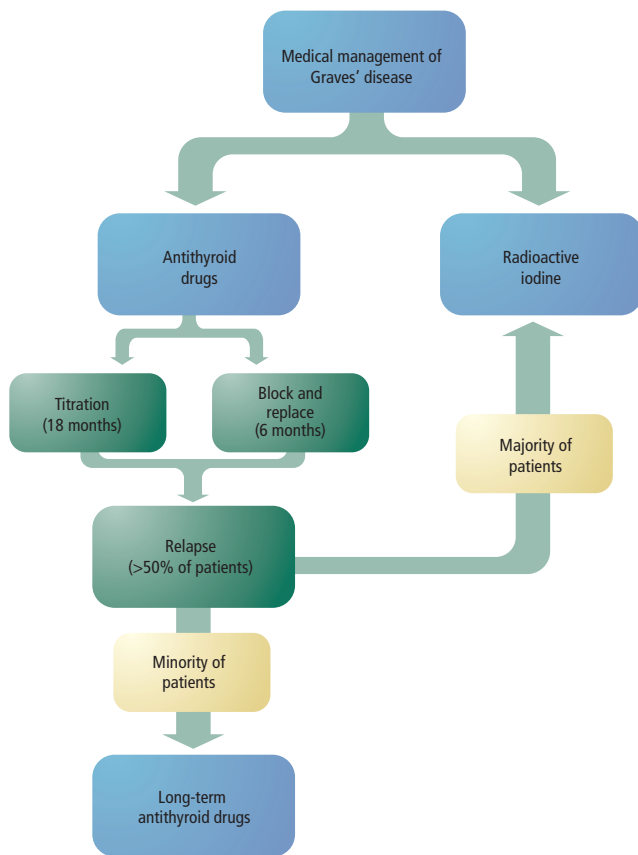
### Symptomatic Treatment

In a minority of patients with severe symptoms, non-selective  $\beta$ -adrenergic blocking agents can be used, which provide partial relief from symptoms such as palpitations, tremors and anxiety without affecting thyroid hormone levels.<sup>19</sup> These agents can also be used by individuals intolerant to antithyroid drugs, while considering other forms of therapy including RAI or surgery.

**Table 1: Causes, Aetiology and Diagnosis of Hyperthyroidism**

| Cause of Hyperthyroidism                    | Frequency and Aetiology   | Diagnosis  |
|---|---|--|
| Graves' disease                             | 80%, thyroid-stimulating antibodies                               | Clinical examination (especially for ophthalmopathy)<br>Thyroid autoantibodies<br>Thyroid uptake scan in difficult cases |
| Toxic nodule or toxic multinodular goitre   | 15%, activating mutations in TSH receptor and Gs $\alpha$ protein | Clinical examination<br>Thyroid uptake scan  |
| Thyroiditis                                 | 2–4%, autoimmune-, viral- or drug-related (amiodarone)            | Clinical examination<br>Thyroid uptake scan<br>Erythrocyte sedimentation rate (ESR)                                      |
| TSH-secreting tumour                        | <1%   | Raised TSH and thyroid hormones<br>Pituitary imaging<br>$\alpha$ subunit assay   |
| Exogenous thyroid hormone administration    | Variable, excess ingestion of thyroid hormones                    | Clinical assessment  |
| Hyperemesis, gravidarum and choriocarcinoma | Rare, raised human chorionic gonadotropin (hCG)                   | Clinical assessment<br>Absence of thyroid autoimmunity<br>Known pregnancy<br>Imaging of the pelvis                       |
| Struma ovarii                               | Rare, ectopic ovarian thyroid tissue                              | Clinical assessment<br>Thyroid/pelvic uptake scan<br>Imaging of the pelvis   |
| Thyroid-hormone resistance                  | Rare, pituitary resistance to thyroid hormones                    | Clinical assessment<br>Family history<br>Must be differentiated from TSH-secreting pituitary adenoma                     |

**Figure 1. Medical Management of Graves' Disease**



First-line treatment for Graves' disease in Europe is antithyroid drugs, although radioactive iodine can be considered initially after discussion with the patient. Antithyroid drugs are given for 6–18 months either as block and replace or titration regime. More than 50% of patients relapse after antithyroid drug treatment and most are subsequently treated with radioactive iodine.

to show an increase in thyroid cancer after RAI but found a significant increase in stomach, kidney and breast cancers.<sup>11</sup> However, the absolute risk was quite small and mainly found in older patients with nodular disease and therefore the increased cancer incidence in this study could not be conclusively attributed to RAI treatment. An increase in cardiovascular risk after RAI treatment has also been suggested.<sup>12–14</sup> However, Metso and colleagues found that hypothyroidism post-RAI offered protection from cardiovascular disease, suggesting that hyperthyroidism *per se* rather than RAI treatment is responsible for the increased cardiovascular events in these patients.

Complex calculations to administer 'the optimal dose' of RAI are unnecessary and a fixed-dose approach is preferred as it simplifies treatment and has a similar success rate with no increase in side effects.<sup>15</sup> The failure rate of RAI treatment is less than 20%; therefore, this form of therapy should be considered initially and discussed with GD patients. Antithyroid drugs should not be given immediately before or after RAI as this may increase treatment failure rate.<sup>16</sup> Furthermore, the use of carbimazole or methimazole prior to RAI is preferred over the use of propylthiouracil, which is associated with higher RAI treatment failure, although this effect is perhaps smaller than previously thought.<sup>16</sup> Immediate side effects of RAI are rare and include transient nausea and pain over the thyroid gland 1–3 days after administration.<sup>17</sup> Thyroid storm may occur rarely after RAI, particularly in those with large goitres and severe hyperthyroidism.<sup>18</sup> Figure 1 summarises the medical management of GD.

### Symptomatic Treatment

In a minority of patients with severe symptoms, non-selective  $\beta$ -adrenergic blocking agents can be used, which provide partial relief from symptoms such as palpitations, tremors and anxiety without affecting thyroid hormone levels.<sup>19</sup> These agents can also be used by individuals intolerant to antithyroid drugs, while considering other forms of therapy including RAI or surgery.

**Table 1: Causes, Aetiology and Diagnosis of Hyperthyroidism**

| Cause of Hyperthyroidism                    | Frequency and Aetiology   | Diagnosis  |
|---|---|--|
| Graves' disease                             | 80%, thyroid-stimulating antibodies                               | Clinical examination (especially for ophthalmopathy)<br>Thyroid autoantibodies<br>Thyroid uptake scan in difficult cases |
| Toxic nodule or toxic multinodular goitre   | 15%, activating mutations in TSH receptor and Gs $\alpha$ protein | Clinical examination<br>Thyroid uptake scan  |
| Thyroiditis                                 | 2–4%, autoimmune-, viral- or drug-related (amiodarone)            | Clinical examination<br>Thyroid uptake scan<br>Erythrocyte sedimentation rate (ESR)                                      |
| TSH-secreting tumour                        | <1%   | Raised TSH and thyroid hormones<br>Pituitary imaging<br>$\alpha$ subunit assay   |
| Exogenous thyroid hormone administration    | Variable, excess ingestion of thyroid hormones                    | Clinical assessment  |
| Hyperemesis, gravidarum and choriocarcinoma | Rare, raised human chorionic gonadotropin (hCG)                   | Clinical assessment<br>Absence of thyroid autoimmunity<br>Known pregnancy<br>Imaging of the pelvis                       |
| Struma ovarii                               | Rare, ectopic ovarian thyroid tissue                              | Clinical assessment<br>Thyroid/pelvic uptake scan<br>Imaging of the pelvis   |
| Thyroid-hormone resistance                  | Rare, pituitary resistance to thyroid hormones                    | Clinical assessment<br>Family history<br>Must be differentiated from TSH-secreting pituitary adenoma                     |

subclinical hyperthyroidism. The prevalence of this condition varies according to the cut-off of TSH used as well as to the iodine intake of the population studied and ranges from 0.6 to 16%.<sup>38–40</sup> The underlying aetiology is the same as for patients with full-blown hyperthyroidism and therefore the majority will have GD or toxic goitre, the latter being particularly common in the elderly and in iodine-deficient areas.<sup>40</sup>

Untreated subclinical hyperthyroidism predisposes to osteoporosis and is also associated with cardiovascular complications, including atrial fibrillation and left ventricular hypertrophy.<sup>40,41</sup> Although the term subclinical hyperthyroidism suggests asymptomatic disease, individuals with this condition may experience thyrotoxic symptoms, which can affect their quality of life.<sup>42,43</sup> Only a limited number of studies have investigated the effects of treating this condition on the prevention of osteoporosis and cardiovascular complications, and therefore conclusive evidence for a beneficial effect of treatment is still lacking. Guidelines drawn up by an expert panel recommend treatment for older individuals and those with risk factors acknowledging that treatment in these individuals is based on 'fair evidence' only.<sup>44</sup> Also, the decision to treat may be influenced by the degree of TSH suppression<sup>41</sup> as the risk of complications in subjects with no history of heart disease or osteoporosis and partial TSH suppression (TSH >0.1) is probably small (see *Figure 2*).

RAI is frequently the first-line therapy for these patients, particularly as

toxic goitre is a common underlying aetiology, but antithyroid drugs can also be used. Future studies are needed to clarify the role of treating subclinical hyperthyroidism on prevention of osteoporosis and cardiovascular complications, particularly in younger patients and in those with marginal TSH suppression.

## Conclusion

The mainstay of medical treatment for GD remains antithyroid drugs and RAI. The former is used as first-line therapy in Europe and results in disease remission in around 40% of patients. RAI is used in most GD patients who relapse after antithyroid drugs, but can also be considered as initial treatment, particularly in patients who find the high relapse rate after antithyroid drug treatment unacceptable. RAI should be considered as first-line treatment in subjects with a toxic nodule or toxic multinodular goitre, as antithyroid drug treatment does not induce remission in these cases. Although RAI has been used in children with no apparent long-term side effects, this form of treatment is best avoided in pre-pubertal children until more evidence of long-term safety becomes available. Treatment of individuals with subclinical hyperthyroidism should be considered in the older age group and in those at high risk of osteoporosis or cardiac disease. ■

## Acknowledgement

RA Ajan is funded by a Department of Health Clinician Scientist Award.

- Ajan RA, Weetman AP, Autoimmune thyroid disease and autoimmune polyglandular syndrome. In: Austin KF, Frank MM, Canton HI, et al., (eds), *Samter's Immunological Diseases*, Wolters Kluwer Company, 2001:605–26.
- Laurberg P, Remission of Graves' disease during anti-thyroid drug therapy, Time to reconsider the mechanism?, *Eur J Endocrinol*, 2006;155(6):783–6.
- Cooper DS, Antithyroid drugs, *N Engl J Med*, 2005;352(9):905–17.
- Abraham P, Avenell A, Park CM, et al., A systematic review of drug therapy for Graves' hyperthyroidism, *Eur J Endocrinol*, 2005;153(4):489–98.
- Hedley AJ, Young RE, Jones SJ, et al., Antithyroid drugs in the treatment of hyperthyroidism of Graves' disease: long-term follow-up of 434 patients, Scottish Automated Follow-Up Register Group, *Clin Endocrinol (Oxf)*, 1989;31(2):209–18.
- Benker G, Reinwein D, Kahaly G, et al., Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study, the European Multicentre Trial Group of the Treatment of Hyperthyroidism with Antithyroid Drugs, *Clin Endocrinol (Oxf)*, 1998;49(4):451–7.
- Schott M, Morgenthaler NG, Fritzen R, et al., Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease, *Horm Metab Res*, 2004;36(2):92–6.
- Azizi F, Ataie L, Hedayati M, et al., Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine, *Eur J Endocrinol*, 2005;152(5):695–701.
- Bartalena L, Marcocci C, Tanda ML, et al., Cigarette smoking and treatment outcomes in Graves ophthalmopathy, *Ann Intern Med*, 1998;129(8):632–35.
- Franklyn JA, Maisonneuve P, Sheppard M, et al., Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study, *Lancet*, 1999;353(9170):2111–15.
- Metso S, Auvinen A, Huhtala H, et al., Increased cancer incidence after radioiodine treatment for hyperthyroidism, *Cancer*, 2007;109(10):1972–9.
- Franklyn JA, Maisonneuve P, Sheppard MC, et al., Mortality after the treatment of hyperthyroidism with radioactive iodine, *N Engl J Med*, 1998;338(11):712–18.
- Nyirenda MJ, Clark DN, Finlayson AR, et al., Thyroid disease and increased cardiovascular risk, *Thyroid*, 2005;15(7):718–24.
- Metso S, Jaatinen P, Huhtala H, et al., Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism, *J Clin Endocrinol Metab*, 2007. Published online.
- Leslie WD, Ward L, Salamon EA, et al., A randomized comparison of radioiodine doses in Graves' hyperthyroidism, *J Clin Endocrinol Metab*, 2003;88(3):978–83.
- Walter MA, Briel M, Christ-Crain M, et al., Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials, *BMJ*, 2007;334(7592):514.
- Becker DV, Hurley JR, Complications of radioiodine treatment of hyperthyroidism, *Semin Nucl Med*, 1971;1(4):442–60.
- McDermott MT, Kidd GS, Dodson LE, Jr, Hofeldt FD, Radioiodine-induced thyroid storm, case report and literature review, *Am J Med*, 1983;75(2):353–9.
- Cooper DS, Hyperthyroidism, *Lancet*, 2003;362(9382):459–68.
- Bocchetta A, Loviselli A, Lithium treatment and thyroid abnormalities, *Clin Pract Epidemiol Ment Health* 2006;2:23.
- Nayak B, Burman K, Thyrotoxicosis and thyroid storm, *Endocrinol Metab Clin North Am*, 2006;35(4):663–86, vii.
- Soldin OP, Braverman LE, Lamm SH, Perchlorate clinical pharmacology and human health: a review, *Ther Drug Monit*, 2001;23(4):316–31.
- Basaria S, Cooper DS, Amiodarone and the thyroid, *Am J Med*, 2005;118(7):706–14.
- Erbil Y, Ozluk Y, Giris M, et al., Effect of Lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease, *J Clin Endocrinol Metab*, 2007;92(6):2182–9.
- Glinore D, Management of hypo- and hyperthyroidism during pregnancy, *Growth Horm IGF Res*, 2003;13(Suppl A):S45–S54.
- Mestman JH, Hyperthyroidism in pregnancy, *Best Pract Res Clin Endocrinol Metab*, 2004;18(2):267–88.
- Lazarus JH, Thyroid disorders associated with pregnancy: etiology, diagnosis, and management, *Treat Endocrinol*, 2005;4(1):31–41.
- Mandel SJ, Cooper DS, The use of antithyroid drugs in pregnancy and lactation, *J Clin Endocrinol Metab*, 2001;86(6):2354–9.
- Burrow GN, Thyroid function and hyperfunction during gestation, *Endocr Rev*, 1993;14(2):194–202.
- Glaser NS, Styne DM, Predictors of early remission of hyperthyroidism in children, *J Clin Endocrinol Metab*, 1997;82(6):1719–26.
- Lazar L, Kalter-Leibovici O, Pertzalan A, et al., Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients, *J Clin Endocrinol Metab*, 2000;85(10):3678–82.
- Rivkees SA, Sklar C, Freemark M, Clinical review 99: The management of Graves' disease in children, with special emphasis on radioiodine treatment, *J Clin Endocrinol Metab*, 1998;83(11):3767–76.
- Rivkees SA, Dinauer C, An optimal treatment for pediatric Graves' disease is radioiodine, *J Clin Endocrinol Metab*, 2007;92(3):797–800.
- Hermida JS, Jarry G, Tchong E, et al., Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis, *Am J Med*, 2004;116(5):345–8.
- Dickstein G, Shechner C, Adawi F, et al., Lithium treatment in amiodarone-induced thyrotoxicosis, *Am J Med*, 1997;102(5):454–8.
- Aghini-Lombardi F, Mariotti S, Fosella PV, et al., Treatment of amiodarone iodine-induced thyrotoxicosis with plasmapheresis and methimazole, *J Endocrinol Invest*, 1993;16(10):823–6.
- Hamoir E, Meurisse M, Defechereux T, et al., Surgical management of amiodarone-associated thyrotoxicosis: too risky or too effective?, *World J Surg*, 1998;22(6):537–42.
- Hollowell JG, Staehling NW, Flanders WD, et al., Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III), *J Clin Endocrinol Metab*, 2002;87(2):489–99.
- Laurberg P, Pedersen KM, Hreidarsson A, et al., Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark, *J Clin Endocrinol Metab*, 1998;83(3):765–9.
- Biondi B, Palmieri EA, Klain M, et al., Subclinical hyperthyroidism: clinical features and treatment options, *Eur J Endocrinol*, 2005;152(1):1–9.
- Cooper DS, Approach to the patient with subclinical hyperthyroidism, *J Clin Endocrinol Metab*, 2007;92(1):3–9.
- 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(12):4701–5.
- Sgarbi JA, Villaca FG, Garbeline B, et al., The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities, *J Clin Endocrinol Metab*, 2003;88(4):1672–7.
- Surks MI, Ortiz E, Daniels GH, et al., Subclinical thyroid disease: scientific review and guidelines for diagnosis and management, *JAMA*, 2004;291(2):228–38.