The Diagnosis and Management of Hyperthyroidism in Korea: Consensus Report of the Korean Thyroid Association

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Hyperthyroidism is one of the causes of thyrotoxicosis and the most common cause of hyperthyroidism in Korea is Graves disease. The diagnosis and treatment of Graves disease are different according to geographical area. Recently, the American Thyroid Association and the American Association of Clinical Endocrinologists suggested new management guidelines for hyperthyroidism. However, these guidelines are different from clinical practice in Korea and are difficult to apply. Therefore, the Korean Thyroid Association (KTA) conducted a survey of KTA members regarding the diagnosis and treatment of hyperthyroidism, and reported the consensus on the management of hyperthyroidism. In this review, we summarized the KTA report on the contemporary practice patterns in the diagnosis and management of hyperthyroidism, and compared this report with guidelines from other countries.

Keywords: Consensus; Diagnosis; Graves disease; Hyperthyroidism; Management

INTRODUCTION

Thyrotoxicosis, which is defined as all clinical statuses resulting from thyroid hormone excess in peripheral blood and tissues, is divided into two major categories by etiology: the presence or absence of accompanying hyperthyroidism. The most common cause of thyrotoxicosis in Korea is Graves disease (82.7%), followed by subacute thyroiditis (13.3%), painless thyroiditis (3.5%), and toxic adenoma (0.5%) [1]. Familial or sporadic nonautoimmune hyperthyroidism due to the germ-line mutation in the thyroid stimulating hormone (TSH) receptor is a rare cause of thyrotoxicosis and should be differentiated from Graves disease [2].

Graves disease is an autoimmune disorder in which TSH receptor antibodies stimulate the thyroid gland and result in hyperthyroidism, diffuse goiter, ophthalmopathy, and dermatopathy. The treatment of Graves disease includes antithyroid medication, ¹³¹I therapy, and thyroidectomy. Numerous medical and nonmedical factors, including patient compliance, age, size of goiter, symptom severity, patient socioeconomic status, experience and preference of physicians and surgeons, and availability of medical facilities for ¹³¹I therapy, affect the choice of
treatment modality. In addition, the most preferred treatment differs from country to country according to the medical insurance system, medical expenses, and patients reluctance to be exposed to radioactive material or surgery.

Recently, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) published new management guidelines for hyperthyroidism [3]. However, these guidelines are quite different from clinical practice in Korea and are difficult to apply. Therefore, the Korean Thyroid Association (KTA) conducted a survey of KTA members regarding the diagnosis and treatment of hyperthyroidism, and subsequently reported the consensus on the management of hyperthyroidism [4]. In this review, we summarized the KTA consensus report on the management of hyperthyroidism and compared it with guidelines from other countries.

**DIAGNOSIS OF HYPERTHYROIDISM IN KOREA**

When hyperthyroidism is strongly suspected, the KTA guidelines suggest measurement of both serum TSH and free thyroxine (T4) levels at the time of the initial evaluation [4]. The total triiodothyronine (T3) measurement is helpful for the diagnosis of T3-toxicosis. If serum TSH is normal and free T4 is elevated, TSH-producing pituitary adenoma and thyroid hormone resistance should be considered. Euthyroid hyperthyroxinemia is mostly due to thyroid hormone-binding protein disorders that cause elevated total T4 and normal TSH concentrations in the absence of hyperthyroidism [5]. A pituitary lesion on magnetic resonance imaging and a high serum level of TSH α-subunit support the diagnosis of a TSH-producing pituitary adenoma [6]. A family history and positive result of genetic testing for mutations in the T3-receptor gene support a diagnosis of thyroid hormone resistance [7].

The severity of thyrotoxic symptoms is inversely correlated with age [8]; therefore, cardiac evaluation, including electrocardiogram, echocardiogram, Holter monitor, or the myocardiac perfusion test, may be required for the diagnosis and treatment of ischemic heart disease, congestive heart failure, or atrial arrhythmias in older patients [9].

For the determination of etiology, the KTA report remarked on the usefulness of an anti-TSH receptor antibody (TRAb) assay for the diagnosis of Graves disease [4]. A second-generation thyrotropin-binding inhibitor immunoglobulin assay, which utilizes human recombinant TSH receptors, showed a specificity of 99% and a sensitivity of 95% for the diagnosis of Graves disease [10]. The ATA/AACE guidelines strongly recommend radioactive iodine uptake test when the clinical presentation of thyrotoxicosis is not diagnostic of Graves disease, and also suggest adding a thyroid scan in the presence of thyroid nodularity [3]. In contrast, only 37% (50/137) of KTA members responded that they perform a thyroid uptake test and 61% (83/137) use a thyroid scan for the diagnosis of hyperthyroidism. Furthermore, most of KTA members (92%, 70/76) use 99mTcO4 rather than 123I or 131I for a thyroid uptake test or thyroid scan. A TRAb assay is used by 94.5% (129/137) of KTA members for the diagnosis of Graves disease. These results show that a TRAb assay is mainly used for the determination of etiology in thyrotoxicosis, and this trend is also shown in Europe and Japan. On the other hand, the ATA/AACE guidelines suggest a TRAb assay and the ratio of total T3 to total T4 as an alternative method of diagnosing Graves disease when a thyroid scan and uptake are unavailable or contraindicated [3,11]. Color Doppler ultrasonography is used by only 16.8% (23/137) of KTA members to diagnose hyperthyroidism, whereas Doppler flow is generally used in Europe and Japan [12].

**TREATMENT OF HYPERTHYROIDISM DUE TO GRAVES DISEASE IN KOREA**

For the symptomatic management of thyrotoxicosis, the KTA report recommends β-adrenergic blockade [4]. Once it has been established that a patient has hyperthyroidism caused by Graves disease, the initial treatment options are an antithyroid drug (ATD), 131I therapy (radioactive iodine), and thyroidectomy. In the United States, radioactive iodine has been the most preferred therapy, whereas there has been a greater physician preference for ATDs in Europe and Japan [13]. In the KTA survey, 97.1% (133/137) of KTA members reported choosing ATDs and remaining 2.9% (4/137) chose radioactive iodine for the initial treatment. The ATA/AACE guidelines recommend that the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and cost [3]. The long-term quality of life after initial treatment for Graves disease was not different among the three treatment options [14]. The KTA report suggests suitable indications and contraindications for each treatment option.

**Antithyroid drugs**

Although ATDs have been employed for six decades [15] and
are very effective in controlling hyperthyroidism, these medi-
cations do not cure Graves disease. Their major effect is to
reduce thyroid hormone synthesis and maintain a euthyroid
state while awaiting spontaneous remission. The KTA report
recommends methimazole or carbimazole for patients who
choose ATD therapy for Graves disease, except during the
first trimester of pregnancy, in the treatment of thyroid storm,
and in patients with minor reactions to methimazole or car-
binazole who refuse radioactive iodine therapy or surgery
[4]. In practice, methimazole was chosen as an initial ATD by
85.5% (112/131) of KTA members. Propranolol (85.5% (112/131)
and carbimazole were chosen by 9.9% (13/131) and 4.3% (6/131)
of KTA members, respectively. The KTA report advi-

Radioactive iodine

131I has been used to treat hyperthyroidism for six decades. This
therapy is well tolerated with rare complications, except for
those related to ophthalmopathy. The KTA report recommends
that the use of methimazole or β blockades before and after 131I
treatment may be considered in patients with severe thyrotoxi-
cosis [4]. The ATA/AACE guidelines remark that if given as
pretreatment, methimazole should be discontinued 3 to 5 days
before the administration of radioactive iodine, restarted 3 to 7
days later, and generally tapered over 4 to 6 weeks as thyroid
function normalizes [3]. In the KTA survey, ATDs were used
before and after 131I treatment by 56% and 43% of KTA mem-
bers, respectively.

Although the ATA/AACE guidelines do not recommend a
special diet before 131I therapy, excessive iodine intake should be
avoided for at least 7 days before treatment. Because daily intake
of iodine is more than 500 µg in Korea, the need for a special
diet before 131I treatment should be validated in future studies.

Administering a fixed 131I activity or calculating the activity
based on the size of the thyroid and its ability to trap iodine
showed no difference in controlling hyperthyroidism by ren-
dering the patient hypothyroid [16]. The KTA report recom-
mends sufficient radiation (10 to 15 mCi) in a single dose [4].
A pregnancy test should be obtained within 48 hours prior to
treatment in any female with childbearing potential [4].

After radioactive iodine therapy for Graves disease, a fol-
low-up thyroid function test should be performed within the
first 1 to 2 months. If the patient remains thyrotoxic, biochemi-
cal monitoring should be continued at 4 to 6 week intervals [4].
The KTA report recommends retreatment with 131I when hyper-
thyroidism persists after 6 months following 131I therapy, or if
there is minimal response 3 months after therapy [4].

Surgery

Thyroidectomy is rarely chosen for treatment of Graves dis-
ease in Korea. The KTA report recommends near-total or total
thyroidectomy as the procedure of choice [4]. The optimal
preparation for thyroidectomy, the monitoring and treatment
strategy for the possible complications, and postoperative
management, including T4 replacement, are described in the
KTA report [4].

CONCLUSIONS

The KTA consensus report was based on the ATA/AACE
guidelines, and therefore, the recommendations are similar.
However, the KTA consensus report was also based on a survey of KTA members and is therefore more suitable for clinical practice in Korea. In addition, the recommendations in the KTA consensus report are limited to the treatment of Graves disease, because other causes of hyperthyroidism are relatively rare and the treatment of those diseases does not differ according to geographical area. Considering the differences in the clinical practice patterns in the diagnosis and treatment of hyperthyroidism in Korea compared with other countries, further studies investigating the characteristics and optimal treatment of hyperthyroidism in Korean patients and the consequential revision of the KTA report are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Cho BY. Clinical thyroidology. 3rd ed. Seoul: Korea Medical Book Publisher; 2010.
2. Gozu HI, Lublinghoff J, Bircan R, Paschke R. Genetics and phenomics of inherited and sporadic non-autoimmune hyperthyroidism. Mol Cell Endocrinol 2010;322:125-34.
3. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Lauberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011;21:593-646.
4. Yi KH, Moon JH, Kim IJ, Bom HS, Lee J, Chung WY, Chung JH, Shong YK. The diagnosis and management of hyperthyroidism consensus: report of the Korean Thyroid Association. J Korean Thyroid Assoc 2013;6:1-11.
5. Rajatanavin R, Liberman C, Lawrence GD, DArcangues CM, Young RA, Emerson CH. Euthyroid hyperthyroxinemia and thyroxine-binding prealbumin excess in islet cell carcinoma. J Clin Endocrinol Metab 1985;61:17-21.
6. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, Stevensaert A, Beckers A. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol 2003;148:433-42.
7. Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E, Weintraub BD. Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. Ann Intern Med 1995;123:572-83.
8. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 2010;95:2715-26.
9. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007;116:1725-35.
10. Pedersen IB, Knudsen N, Perrild H, Ovesen L, Lauberg P. TSH-receptor antibody measurement for differentiation of hyperthyroidism into Graves’ disease and multinodular toxic goitre: a comparison of two competitive binding assays. Clin Endocrinol (Oxf) 2001;55:381-90.
11. Shigemasa C, Abe K, Taniguchi S, Mitani Y, Ueda Y, Aodashi T, Urabe K, Tanaka T, Yoshida A, Mashiba H. Lower serum free thyroxine (T4) levels in painless thyroiditis compared with Graves’ disease despite similar serum total T4 levels. J Clin Endocrinol Metab 1987;65:359-63.
12. Bogazzi F, Vitti P. Could improved ultrasound and power Doppler replace thyroidal radiiodine uptake to assess thyroid disease? Nat Clin Pract Endocrinol Metab 2008;4:70-1.
13. Wartofsky L, Gliñor D, Solomom B, Nagataki S, Lagasse R, Nagayama Y, Izumi M. Differences and similarities in the diagnosis and treatment of Graves’ disease in Europe, Japan, and the United States. Thyroid 1991;1:129-35.
14. Abraham-Nordling M, Torring O, Hamberger B, Lundell G, Tallstedt L, Calissendorff J, Wallin G. Graves’ disease: a long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. Thyroid 2005;15:1279-86.
15. Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.
16. Klein I, Becker DV, Levey GS. Treatment of hyperthyroid disease. Ann Intern Med 1994;121:281-8.
17. Mazza E, Carlini M, Flecchia D, Blatto A, Zuccarini O, Gamba S, Beninati S, Messina M. Long-term follow-up of patients with hyperthyroidism due to Graves’ disease treated with methimazole: comparison of usual treatment schedule with drug discontinuation vs continuous treatment with low methimazole doses: a retrospective study. J Endocrinol Invest 2008;31:866-72.
18. The Japan Thyroid Association. Guideline for the treatment of Graves’ disease with antithyroid drug in Japan.
19. Abraham P, Avenell A, Park CM, Watson WA, Bevan JS. A systematic review of drug therapy for Graves’ hyperthyroidism. Eur J Endocrinol 2005;153:489-98.