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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 germline 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 dermopathy. The treatment of Graves disease includes antithyroid medication, ^{131}I 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 ^{131}I therapy, affect the choice of

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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 ^{99m}TcO4 rather than ^{123}I or ^{131}I 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), ^{131}I 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 medications 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 carbimazole 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. Prophylthiouracil (PTU) and carbimazole were chosen by 9.9% (13/131) and 4.3% (6/131) of KTA members, respectively. The KTA report advises higher doses of ATDs at the start of medication (methimazole, 10 to 20 mg daily; PTU, 50 to 150 mg three times daily) to restore euthyroidism, and the titration to a maintenance level (methimazole, 5 to 10 mg daily; PTU, 50 mg two or three times daily) [4]. The KTA report strongly emphasizes notifying all patients of the side effects of ATDs and proper management for the side effects, including agranulocytosis and hepatotoxicity [4]. Monitoring strategies for patients using ATDs are also suggested.

If serum TSH, free T4, and T3 levels have been maintained within normal ranges for 1 year after discontinuation of ATD therapy, remission can be considered. The remission rate varies between geographical areas. In the United States, the remission rate is approximately 20% to 30% after 12 to 18 months of medication [16], whereas a long-term European study showed a 50% to 60% remission rate after 5 to 6 years of ATD treatment [17]. In Japan, maintenance of a minimal dose of ATDs (methimazole, 2.5 mg daily) longer than 6 months after the normalization of TSH is recommended for a higher remission rate [18]. However, a meta-analysis showed that the maintenance of ATDs longer than 18 months did not improve the remission rate in adults [19]. ATDs are discontinued after the normalization of both serum TSH and TRAb by 60% to 70% of KTA members. About 30% of respondents answered that they use ATDs for a fixed duration, most frequently for 12 to 24 months. In case of the recurrence after ATD treatment, 46.9% (60/128) of KTA members chose ATDs again for the treatment of Graves disease; while radioactive iodine and thyroidectomy were chosen by 48.4% (62/128) and 4.7% (6/128) of KTA members, respectively. In Korea, ATDs are the most preferred modality for retreatment as well as initial treatment, and the treatment duration of ATDs is longer compared with other countries.

Radioactive iodine

^{131}I 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 ^{131}I treatment may be considered in patients with severe thyrotoxicosis [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 ^{131}I treatment by 56% and 43% of KTA members, respectively.

Although the ATA/AACE guidelines do not recommend a special diet before ^{131}I 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 ^{131}I 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 rendering the patient hypothyroid [16]. The KTA report recommends 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 follow-up thyroid function test should be performed within the first 1 to 2 months. If the patient remains thyrotoxic, biochemical monitoring should be continued at 4 to 6 week intervals [4]. The KTA report recommends retreatment with ^{131}I when hyperthyroidism persists after 6 months following ^{131}I therapy, or if there is minimal response 3 months after therapy [4].

Surgery

Thyroidectomy is rarely chosen for treatment of Graves disease 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.

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