Long-Term Outcome of Graves' Disease Patients Treated in a Region with Iodine Deficiency: Relapse Rate Increases in Years with Thionamides

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Background: Graves' disease (GD) is an autoimmune disease affecting the thyroid gland and eyes and is treated with three therapeutic modalities. This prospective study was designed to find out the outcome of patients with GD treated with thionamides, radioactive iodine (RAI) or surgery in an iodine deficient region.

Materials and Methods: Fifty-six nonsmoking patients (mean age 38.9 ± 13.7 years) with GD were enrolled and followed for a mean period of four years. They were analyzed with respect to their treatment options and their outcome.

Results: Remission rate by thionamides was 74.4% in the first year but decreased to 65.1% in the following four years (p=0.0001). Remission rate achieved in the second year did not predict long-term remission with thionamides. Long-term remission rates for RAI and surgery were 100% during about seven years of follow-up. These remission rates for RAI and surgery were reached in the first year and did not reveal a statistically significant change in the following years. Thyroidectomy, both subtotal and total, was carried out without any complication. Graves' ophthalmopathy emergence and progression were not found to be correlated with the preferred therapeutic modality of thyrotoxicosis.

Conclusion: Long-term thionamide therapy offered a relatively low rate of long-term remission in a region with iodine deficiency. Two years of remission achieved by thionamides did not predict long-term remission in patients living in iodine-deficient areas. RAI and thyroidectomy in experienced hands proved to be better therapeutic alternatives that can be carried out safely.

Key words: Graves' disease ■ thionamides ■ radioactive iodine ■ surgery ■ iodine deficiency

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INTRODUCTION

Graves' disease (GD) is an autoimmune disorder in which thyroid-stimulating hormone (TSH) receptor antibodies cause the thyroid gland to synthesize and release thyroid hormones. In case of thyrotoxic GD, there are three treatment modalities, including antithyroid drugs, radioactive iodine (RAI) and thyroidectomy. The choice of an antithyroid drug, thyroidectomy or RAI for the treatment of hyperthyroidism caused by GD is usually dictated by age, the size of the thyroid gland, the severity of hyperthyroidism, local resources, practice and the patient's preference.[1]

Antithyroid drugs are widely used as the initial therapy for hyperthyroidism of GD, but the rate of permanent cure is not satisfactory in iodine-sufficient areas.[2-4] Radioiodine has been recommended as the best option because of its ease, low cost and low rate of serious complications. Thyroidectomy is an immediate and effective form of treatment; however, it may be associated with direct complications such as hypoparathyroidism, laryngeal nerve palsy, bleeding and infections.[5]

Turkey is one of the countries with moderate-to-severe iodine deficiency that legislated mandatory iodination of household salt late in 1999.[6] This study, which was conducted before this period, reflects the results of treatment outcomes of patients with GD living in moderate-to-severe iodine-deficient areas. The aim of this study was to find out the outcome of patients with GD treated with different therapeutic modalities and to analyze the success rate and/or disadvantages of the treatment options in a country with iodine deficiency. In this prospective study, we reviewed the long-term outcomes of 56 patients with GD who were treated and followed for up to eight years during years 1991–2000 and discussed the role of antithyroid medication, radioiodine and surgery with regard to disease remission, complications and Graves' ophthalmopathy progression.

MATERIALS & METHODS

For this prospective study, a population of nonsmoking 56 patients with GD who were being followed in the outpatient clinic of Hacettepe University Faculty of Medicine, Department of General Surgery, Endocrinology and Metabolism from 1991–2000 were enrolled randomly for the study. Those patients with history of smoking and disease affecting orbital structures other than GD, subjects in postpartum, on immunomodulatory drugs or off thionamides prematurely on their own volition, those who received any medication containing iodine or those given iodinated contrast media in the last 12 months and those who didn't participate in the follow-up in the Hacettepe University after their treatment of GD for ≥24 months were excluded due to missing follow-up data.

The diagnosis of GD was based on common clinical and laboratory criteria, including signs and symptoms of hyperthyroidism with elevated total and free thyroxine levels and suppressed TSH levels with rapid and diffuse uptake of radioiodine or technetium 99, and elevated serum thyroid autoantibodies with or without diffuse goiter.

After routine clinical and endocrinological evaluation, patients with thyrotoxicosis were treated with long-term thionamide therapy for about 18 months (n=43; 17.4 ± 2.9 months). Those with recurrent GD or in whom rapid surgical decompression is essential due to large gland disease and those patients not willing to be given long-term medical therapy were treated with RAI or surgery after maintenance of euthyroidism with short-term thionamide therapy. RAI was chosen as the primary therapy for those who did not prefer a long-term medical therapy (n=5) and for whom toxic hepatitis occurred due to thionamides (n=2). It was chosen as the second-line therapy after failure of maintenance of euthyroidism after long-term treatment with thionamides (n=12). Surgery was the primary treatment option for those with tracheal compression symptoms (n=3) and those with infiltrative ophthalmopathy (n=3), and it was the secondary option for those with failure of the medical treatment for hyperthyroidism (n=3).

Patients were analyzed with respect to their age; sex; duration of disease; presence of disease complications such as arrythmia, hepatitis or ophthalmopathy; treatment options and their outcome during ≥12 months of follow-up after completion of the programmed treatment protocol. Thyrotoxic hepatitis was defined by at least 2–3 times the increment of liver enzymes due to thyrotoxicosis before the institution of the thionamide treatment and normalization of the enzymes with achievement of euthyroidism. Patients given antithyroid drug were also analyzed with regard to the time needed to achieve euthyroidism and supplementation of L-thyroxine to suppress TSH. These patients received enough dose of the drug to achieve euthyroidism in the short term, and L-thyroxine was added soon afterward to prevent iatrogenic hypothyroidism in accordance with the block-and-replace regimen. Medical treatment was continued for about 18 months to achieve long-term remission. Achievement of euthyroidism or hypothyroidism for a minimum of 12 months after completion of the programmed treatment protocol was considered remission. Duration of disease was estimated from the first diagnosis of the symptoms related to disease.

After clinical evaluation of Graves' ophthalmopathy and globe positions by Hertel exophthalmometer, magnetic resonance imaging (MRI) of the orbit of the patients was performed at the first visit (n=46) and after ≥12 months of follow-up to analyze the progress of the disease in the orbit (n=23).

All patients gave informed consent to participate in the study in accordance with the Helsinski declaration.

Serum-free T_3, T_4 and TSH were measured using Microparticle Enzyme Immunoassay (MEIA) (AxSYM System, Abbott). Antimicrosomal and antithyroglobulin antibodies were measured using ELISA (Immulite, Bio-DPC Diagnostics Products Corp., Los Angeles, CA).

Orbital MRI

MR imaging was performed with a 0.5 T superconducting system with use of a 13-cm-diameter

Table 1. Comparison of primary treatment protocols

	Medical Therapy (n=43)	Radioactive Iodine (n=7)	Surgery (n=6)
Duration of follow-up (years)	4.3 ± 2.3	6.4 ± 2.6	3.3 ± 1.8
Remission rate	28/43 (65.1%)	7/7 (100%)	6/6 (100%)
Duration of remission (months)	21.1 ± 17.9	66.9 ± 42.1	26.0 ± 4.9
Complications			
Toxic hepatitis	2/43 (4.7%)	–	–
Ophthalmopathy aggravation (number of patients)	1	1	0
Postoperative laryngeal nerve palsy	–	–	0
Postoperative hypoparathyroidism	–	–	0

circular surface coil (Gyroscan NT; Philips, Eindhoven, the Netherlands). MRI study consisted of spin-echo T1-weighted and turbo-spin-echo T2-weighted and Short T1 Inversion Recovery images.

Statistical Analysis

Differences between patient groups were assessed for statistical significance using the Student's t test, Pearson Correlation and the Chi-square where appropriate. All results were expressed as means ± SD unless otherwise indicated. Statistical analysis was conducted using the SPSS for Windows® software package, release 10.0. Statistical significance was considered when a p value was ≤0.05.

RESULTS

Fifty-six patients with active GD (20 males, 36 females; age range 19–78 years, mean age 39.4 ± 13.7 years) were enrolled for the study. Comparison of the groups with regard to the primary treatment protocols and outcome are given in Table 1.

In seven of 43 patients (16.2%), thyrotoxic hepatitis was diagnosed, which resolved spontaneously after establishment of euthyroidism.

Medical treatment with thionamides was the first option in 43 patients. Propylthiouracil (mean 400 ± 150 mg/day) was chosen as the thionamide for all the patients. Among these, 32 (74.4%) patients maintained euthyroidism during ≥12 months of being off the drug. Mean duration of follow-up was 4.3 ± 2.3 years. Among the patients treated with thionamides, 16.3% of them achieved euthyroidism in the first three months of therapy and were given L-thyroxine. In 40.7% of them, euthyroidism was reached after nine months of treatment. Achievement of euthyroidism in the first three months of medical therapy did not reveal any correlation with regard to duration of remission and relapse frequency of the disease. Twelve patients could not maintain euthyroidism in the following months after cessation of thionamides and were treated with RAI. Thyroidectomy was chosen as the second-line therapy for the remaining three thyrotoxic patients because of patient's preference (n=2) and coexistence of ophthalmopathy (n=1). Remission frequency of the patients are given in Table 2. In the following year after cessation of the thionamide, about 74.4% of the patients maintained euthyroidism. This rate decreased to 69.8% in the second year and 65.1% after four years. These decreasing remission rates during the first two and four years revealed statistical significance (p=0.0001 and p=0.0001, respectively).

Mean RAI dose was 8.1 ± 3.7 mCi (range 4.0–15.0 mCi). In three patients, a second dose of RAI was needed to achieve remission. About 36.8% (n=7) who were given RAI as the primary or secondary treatment developed hypothyroidism and the rest (n=12) maintained euthyroidism during a mean follow-up duration of six years (minimum two, maximum 10 years). Achievement of remission was seen 7.0 ± 2.5 months after the last RAI given.

Subtotal thyroidectomy (remnant <6 g) was performed in four, and total thyroidectomy was performed in five of the patients. All cases achieved remission of GD immediately after surgery. Two of them remained euthyroid and the rest (n=7) hypothyroid. None of the patients experienced acute and chronic complications of thyroidectomy, including hypoparathyroidism, bleeding or hoarseness.

Forty-six patients were evaluated radiologically for the presence of Graves' ophthalmopathy. There were 24 patients with Graves' ophthalmopathy, among which 13 of them (28.3%) revealed normal orbital physical examination findings. Among the patients with Graves' ophthalmopathy, one of them refused to take control orbital MRI in the following year. Of those patients who have been evaluated for the progress of ophthalmopathy during ≥12 months of follow-up (n=23), two of them (8.7%) demonstrated disease progress in the orbit, eight of them (34.8%) demonstrated regression of the findings in the orbit and 13 of them (56.5%) had no change. Ophthalmopathy progress or regression was not found to be correlated with the treatment option for thyrotoxicosis.

DISCUSSION

Optimal therapy of GD is controversial. When given for 12–18 months, thionamides are shown to reduce serum concentrations of TSH receptor antibodies and thus result in remission in up to 60% of patients in iodine sufficient areas.[8-14] This percentage was similar (65.1%) for our patients living in iodine-deficient areas. Turkey is one of the iodine-deficient

Table 2. Remission rates in years after treatment

	Thionamide therapy	RAI	Thyroidectomy
Remission rate in the first year	32/43 (74.4%)	7/7 (100%)	6/6 (100%)
Remission rate in the second year	30/43 (69.8%)	7/7 (100%)	6/6 (100%)
Remission rate after four years	28/43 (65.1%)	7/7 (100%)	1/1 (100%)
p	0.0001	NS	NS

RAI: radioactive iodine; NS: nonsignificant

countries that legislated mandatory iodination of household salt in July 1999.[6] Although this study was conducted before iodine supplementation, we found unexpectedly a similar rate of long-term remission by thionamides with those encountered in iodine-sufficient areas. It is known that inadequate duration of treatment or dosing of the thionamide drug may affect the outcome of treatment.[15] In the present study, thionamide drugs were given for about 18 months. Achievement of euthyroidism in the first three months of medical therapy did not reveal any correlation with regard to duration of remission and relapse frequency of the disease. In the present study, which was conducted in an iodine-deficient area, mean duration of disease follow-up for those patients given thionamides was about four years with a range of 2–7 years. Long duration of disease follow-up may have increased the chance of diagnosis of recurrence and thus may have decreased the success of treatment in our patients. In accordance with this, we found a relatively high treatment success with thionamides in the first year, which decreased progressively and significantly in the following years to 65.1%. Most of the studies presented before have estimated the remission rate after a shorter period of follow-up thus may have overestimated the success of thionamides in the long term.[13-17] The present study showed clearly that remission rate decreased, thus relapse rate increased progressively as the follow-up period lengthened even in a region with iodine deficiency.

Although about 17% of the patients given RAI needed a second dose to achieve remission, all patients given RAI could achieve remission. It is known that with an ideal intermediate radiation dose, the number of hyper- as well as hypothyroid patients should be low, leaving the highest percentage of cases euthyroid.[2,18] In the present study, permanent hypothyroidism was encountered in about one-third of the patients who received RAI. Euthyroidism was maintained in about two-thirds of patients given RAI during an average six years of follow-up. Although we could find no exact statistical relationship between RAI dose and the appearance of hypo- or euthyroidism, maintenance of euthyroidism in the long term in about 65% of patients needs to be paid attention. Hence, achievement of euthyroidism should be targeted in the subgroup of Graves' patients living in iodine-deficient areas.

The method of treatment of hyperthyroidism is known to influence the course of eye changes in GD. Radioiodine treatment for GD is followed by changes in thyroid autoimmunity and may aggravate pre-existing infiltrative ophthalmopathy, compared with antithyroid drugs or surgery.[1,4,18-23] In the present study, orbital pathology was not affected by the type of treatment of the thyrotoxicosis. Acute changes in extraoccular muscles during the thyrotoxic state were found to be reversible in the short-term irrespective of the antithyroid treatment modality. In this regard, we found RAI treatment safe even in those with documented ophthalmopathy.

Surgical therapy of GD is particularly preferred when rapid control of hyperthyroidism is essential, in large-gland disease, hyperthyroidism with infiltrative endocrine ophthalmopathy, in children and in women of child-bearing age.[24-26] In the present study, thyroidectomy resulted in remission rate with no acute and chronic complications of the procedure. Approximately one out of 10 of our patients with GD underwent thyroidectomy after medical treatment failure. This incidence rate is expected to increase after sufficient iodination in Turkey, because increment of the iodine pool in the thyroid gland is expected to decrease the remission rates further by thionamides and RAI.[15,27] After a median follow-up period of about seven years after thyroidectomy, euthyroidism was maintained in two patients who had subtotal thyroidectomy, and no recurrent hyperthyroidism was diagnosed. Hypothyroidism developed in seven patients immediately after surgery. Surgical treatment for GD can be a total thyroidectomy or a "near-total" thyroidectomy to reduce disease relapse and have a major efficacy in the ophthalmopathy because of its theoretical advantage of complete autoantigen removal.[26,28,29] Until 2000, subtotal thyroidectomy has been advocated as the standard surgical management of GD by some surgeons in our center because of the possibility of avoiding thyroxine therapy as well as the assumed lower risk of complications compared to total thyroidectomy. Given that subtotal thyroidectomy provides an unpredictable outcome and that the risk of permanent complications is no better, total thyroidectomy has become increasingly the more preferred technique for the surgical management of GD by the surgeons.[28-34]

In conclusion, this study has unmasked the unexpected poor success rate of treatment of GD with thionamides even in a region with moderate-to-severe iodine deficiency. Remission achieved in the first two years of thionamide treatment does not predict long-term success with these drugs. Treatment with RAI or total thyroidectomy offered better remission rates. Also, remission rate achieved in the first year by RAI or surgery was found to be predictive of long-term remission. Presence of endocrine ophthalmopathy does not stand as a drawback for RAI treatment. In experienced hands, thyroidectomy is a good therapeutic alternative that can be carried out with insignificant rate of morbidity and mortality offering an immediate remission of disease with no functional insult except for permanent hypothyroidism.

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