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Radioiodine Treatment of Hyperthyroidism

Prognostic Factors Affecting Outcome

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Objective: To assess the effectiveness of radioactive iodine (RAI) treatment in patients with hyperthyroidism and to evaluate prognostic factors affecting outcome.

Research Design and Methods: Our cohort comprised 115 consecutive patients with hyperthyroidism treated with RAI at the Endocrinology Clinic at the Farabi Hospital, Trabzon, between 1994 and 2002. Data were retrieved from the endocrinology clinic database. Patients were categorized into three diagnostic groups: Graves' disease (GD), toxic multinodular (TMN) hyperthyroidism, and toxic adenoma. Our policy, over the period of the study, was to offer a single fixed first dose (10 mCi) ^{131}I to all patients with toxic nodular goiter (TNG) for the first time and to all patients with relapsed GD.

Results: There was no significant difference in the cure rate betweeen GD and TNG, but Graves' patients had a significantly higher incidence of hypothyroidism ($p < 0.001$). In contrast, incidence of euthyroidism was significantly increased in TNG than those of the patients with GD ($p < 0.05$). The incidences of hyperthyroidism, euthyroidism, cure rate, and persistent hyperthyroidism did not vary significantly between females and males. Age at onset of hyperthyroidsim at diagnosis was not associated with outcome of RAI therapy. The incidence of hypothyroidism in patients who had nonpalpable goiter was higher than those in patients who had medium or large goiter ($p < 0.05$). The means of serum FT_3 and TT_4 at presentation were correlated with the development of hypothyroidism after RAI therapy. Logistic regression analysis showed serum FT_3 concentration at presentation to be significant contributing factor to failure to respond to a single dose of RAI. Patients who had higher FT_3 concentrations at diagnosis were more likely to fail to respond to RAI therapy.

Conclusions: The results of the present study of a cohort of patients with hyperthyroidism demonstrate that a single fixed dose of 10 mCi of RAI is highly effective in curing GD as well as toxic nodular hyperthyroidism. Therefore, treatment potocols for these groups should be identical. The most important factors that determine efficacy of RAI treatment are serum FT_3 concentrations at diagnosis before the initiation of treatment and goiter size. Therefore, these factors should be taken into consideration when planning treatment. If such factors are present, the initial dose of RAI should be increased.

Key Words: Hyperthyroidism; radioiodine therapy; prognostic factors; clinical outcome.

Hyperthyroidism is a substantial health issue, affecting approx 3 in 1000 patients each year, leading to a population prevalence of up to 3% of thyroxicosis-related disease *(1,2)*. The majority of thyroxicosis is caused by Graves' disease (GD) or toxic nodular goiter (TNG); their relative proportions vary with demography and geography *(3)*. Patients with hyperthyroidism are treated by surgery, antithyroid drug (ATD) medication or radioactive iodine (RAI). Local traditions, severity of the disease, sex, and age are some of the factors that influence the type of treatment chosen. The mainstay of drug therapy is inhibition of thyroid hormone synthesis with thionamides. In TNG drug therapy is used prior to RAI or surgery, or as an alternative, as life-long therapy. In GD 1–2 yr of medication is the primary treatment is most centers, leading to euthyroidism in approx 50% after discontinuation of the drugs *(4)*. Subtotal or near total thyroidectomy, indicated when drug treatment or RAI seem undesirable, has few complications in experienced hands; nevertheless, vocal cord paralysis, hypoparathyroidism, bleeding, and infections occur *(5)*.

RAI therapy for hyperthyroidism was first introduced in the 1940s and is today the treatment of choice in many clinics *(6)*. The aim of treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patients either euthyroid or hypothyroid. Although it is highly effective, with a cure rate approaching 100% after one or more treatments *(7)*, it has proved impossible to titrate doses for individual patients accurately to guarantee an euthyroid state

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Table 1
Clinical and Laboratory Characteristics of Patients with Graves' Hyperthyroidism, TMNG, and Toxic Adenoma Treated by RAI

	GD (n = 13)	TMNG (n = 79)	Toxic adenoma (n = 23)	p
Females	11(84.6%)	60 (75.9%)	14 (60.9%)	0.2263*
Males	2 (15.4%)	19 (24.1%)	9 (39.1%)	
Mean age and range (yr)				
Females	50.64 ± 10.74 (32–70)	62.58 ± 7.63 (43–80)	61.64 ± 12.64 (38–78)	0.0001**
Males	49.50 ± 7.78 (44–55)	62.32 ± 10.44 (38–83)	61.56 ± 10.17 (40–71)	
Total	50.46 ± 10.1 (32–70)	62.55 ± 8.4 (38–83)	61.61 ± 11.5 (38–78)	
Goiter				
None	2 (15.4%)	0 (0%)	1 (4.3%)	0.004*
Small	1 (7.7%)	11 (13.9%)	3 (13%)	0.8800
Medium/large	10 (76.9%)	68 (86.1%)	19 (82.6%)	0.5555
At diagnosis				
FT_3 (pg/mL)	13.35 ± 6.20	6.70 ± 3.33	7.41 ± 3.41	0.001***
TT_3 (ng/mL)	9.87 ± 30.56	5.34 ± 2.19	6.37 ± 27.38	0.001
FT_4 (ng/dL)	3.02 ± 2.07	2.43 ± 1.16	3.41 ± 2.77	0.609
TT_4 (ng/mL)	44.46 ± 77.21	35.00 ± 70.03	20.88 ± 22.08	0.682
TSH (μU/mL)	0.003 ± 0.005	0.005 ± 0.009	0.007 ± 0.199	0.767

*Chi-square test.
**Variance analysis.
***Kruskal–Wallis variance analysis.
GD: Graves' disease; TMNG: Toxic multinodular goiter; FT_3: Free triiodothyronine; FT_4: Free thyroxine; TT_3: Total triiodothyronine; TT_4: Total thyroxine; TSH: Thyroid stimulating hormone.

(8). Despite more than half a century of experience, there is little agreement regarding the most appropriate dose regimen *(9,10)*. Regimens used have included low doses [80 megabequerels (MBq)] *(7,11)*, various fixed doses (185, 370, and 555 MBq) *(7,11,12)*, and doses calculated on the basis of thyroid size, the uptake of RAI, or the turnover of RAI *(12,13)*. Despite these potential benefits of calculated doses, several studies have failed to demonstrate improvements in cure rate over fixed doses *(12,14)*. Furthermore, there is little evidence that using a calculated dose has any advantage over a fixed-dose regimen, in terms of preventing hypothyroidism *(15)*, so many centers use a single fixed dose *(16)*. Opinions also vary about the need for longer doses of RAI in TNG, as compared with GD *(17)*. Patients with toxic nodular hyperthyroidism are perceived to be relatively radioresistant, compared with those with GD *(18)*, although evidence is conflicting. However, some studies suggest that persistent hyperthyroidism is more common in patients with GD *(17)*.

The influence of ATDs on outcome of RAI treatment has also received attention. Some studies have suggested relative radioresistance in those prescribed ATDs before or after RAI *(19)*, but others have shown no effect *(13)* or an effect confined to propylthiouracil *(20)*.

In the present study, we assessed the effectiveness of RAI treatment on hyperthyroidism and to evaluate prognostic factors affecting outcome.

Results

The demographic, clinical, and laboratory characteristics at presentation of the cohort are summarized in Table 1. Of the 115 patients, 13 (11.3%) were classified as having GD, 79 (68.7%) as cases of TMN hyperthyroidism, and 23 (20%) as cases of toxic adenoma. As expected, patients with GD presented with hyperthyroidism at an earlier age than those with TNG ($p < 0.0001$). In contrast, patients with GD had significantly more severe hyperthyroidism, as determined by serum free T_3 and TT_3, at diagnosis than those with TNG ($p < 0.001$).

Gender, FT_4, TT_4, and TSH were similar for patients GD and TNG. Goiter was nonpalpable in 15.4% of patients with GD, in 0% of patients with TMNG, and in 4.3% of patients with toxic adenoma. The difference was significant ($p < 0.001$).

Characteristics of males and females at presentation of hyperthyroidism were similar (Table 2). The prevalence of palpable goiter were similar in both gender.

Table 2
Serum Concentrations of FT_3 and FT_4 and Palpable Goiter at Diagnosis by Gender

	Females	Males	*p*
Mean FT_3 at diagnosis	7.30 ± 4.36	7.65 ± 2.94	0.702*
Mean FT_3 at diagnosis	2.55 ± 1.48	3.01 ± 2.57	0.232*
Palpable goiter	71 (83.5%)	28 (93%)	0.502**

*Student's *t* test.
**Chi-square test.

Table 3
Outcome of a Single Fixed-Dose of RAI for Patients with GD, TMNG, and Toxic Adenoma

	Euthyroid		Hypothroyid		Hypothyroid + euthyroid (cure)		Persistent hyperthyroid	
	n	%	*n*	%	*n*	%	*n*	%
GD (*n* = 13)	3	23	6	46.2	9	69.2	4	30.8
TMNG (*n* = 79)	50	63.3	7	8.9	57	72.2	22	27.8
Toxic adenoma (*n* = 23)	15	65.2	2	8.7	17	73.9	6	26.1
Total (*n* = 115)	68	59.1	15	13	83	72.1	32	27.8
p (chi-square test)	0.019		0.0008		0.956		0.9556	

GD, Graves' disease; TMNG, toxic multinodular goiter.

Table 3 shows results of RAI therapy. There was no significant difference in the cure rate betweeen GD and TNG, but Graves' patients had a significantly higher incidence of hypothyroidism ($p < 0.001$). In contrast, incidence of euthyroidism was significantly increased in TNG than those of the patients with GD ($p < 0.05$).

Table 4 reveals the releationships between clinical characteristics and outcome of RAI therapy in hyperthyroid patients. The incidences of hyperthyroidism, euthyroidism, cure rate, and persistent hyperthyroidism did not vary significantly between females and males. Age at onset of hyperthyroidism at diagnosis was not associated with outcome of RAI therapy. The incidence of hypothyroidism in patients who had nonpalpable goiter was higher than those in patients who had medium or large goiter ($p < 0.05$). The means of serum FT_3 and TT_4 at presentation were correlated with the development of hypothyroidism after RAI therapy. We did not find an association between the use of ATDs and outcome of RAI treatment.

Durations of hypothyroidism (6.4 ± 5.8 mo) and euthyroidism (5.9 ± 5.6 mo) were similar in patients with GD and TNG. In a 57-yr-old female, hyperthyroidism relapsed at the 36th mo after RAI therapy. Goiter size at presentation was not associated with mean FT_4 at presentation and age at onset of hyperthyroidism.

Logistic regression analysis showed serum FT_3 concentration of presentation to be a significant contributing factor to failure to respond to a single dose of RAI (Table 5). Patients who had higher FT_3 concentrations at diagnosis were more likely to fail to respond to RAI therapy. Ten patients received RAI therapy twice and 1 patient received RAI therapy four times. Nineteen of 32 patients with persistent hyperthyroidism received antithyroid drug therapy (propylthiouracil or methimazole) to establish euthyroidism. Eight of patients with persistent hyperthyroidism have undergone to surgical therapy and five of them received second dose a RAI therapy. Also, no GD patients' eyes worsen after ^{131}I therapy.

Discussion

RAI treatment of hyperthyroidism is easy to perform, is of low cost, and has a low risk of adverse effects. Although the choise of treatment modality for hyperthyroidism still differs between centers and countries *(21–23)*, today RAI treatment is the preferred therapy of middle-aged and elderly

Table 4
The Relationship of Clinical Factors with Outcome of RAI Treatment

	Hypothyroidism		Euthyroidism		Total (Cure)		Persistent hyperthyroidism		*p*
	n	%	*n*	%	*n*	%	*n*	%	
Males	3	10	20	66.7	23	76.7	7	23.3	0.615*
Females	12	14.1	48	56.5	60	70.6	25	29.4	
Goiter									
None	2	66.7	1	33.3	3	100	0	0	
Small	1	7.7	8	61.5	9	69.2	4	30.8	0.009*
Medium/large	8	10	48	60	56	70	24	30	
p	0.009		0.643		0.07		0.26		
At diagnosis									
FT_3 (pg/dL)	7.31 ± 5.60		6.77 ± 3.07		7.50 ± 4.15		9.45 ± 5.16		0.045**
TT_3 (ng/mL)	3.85 ± 2.05		6.58 ± 29.16		6.94 ± 26.94		9.20 ± 26.11		0.035
FT_4 (ng/dL)	2.52 ± 1.96		2.55 ± 1.71		2.80 ± 2.16		3.10 ± 1.53		0.100
TT_4 (ng/mL)	50.18 ± 83.69		21.07 ± 28.77		33.64 ± 64.31		53.60 ± 98.23		0.132
TSH (μU/mL)	0.005 ± 0.007		0.006 ± 0.141		0.006 ± 0.101		0.003 ± 0.006		0.327
The use of ATDs									
Yes (*n* = 103)	14	13.6	61	59.2	75	72.8	28	27.2	0.828*
No (*n* = 12)	1	8.3	7	58.3	8	66.6	4	33.3	

*Chi-square test.
**Mann–Whitney U test.

Table 5
Factors Predictive of an Unsuccessful Response to One Dose RAI Using Logistic Regression Analysis

	OR	95% CI	*p*
Male sex	0.81	0.23–2.81	0.739
At presentation			
FT_4 (ng/dL)	1.05	0.76–1.46	0.753
FT_3 (pg/dL)	1.16	1.01–1.34	0.033
Medium/large goiter	1.70	0.34–8.44	0.518
Age (yr)	1.02	0.96–1.09	0.531

patients with hyperthyroidism. Furthermore, younger patients are now offered RAI earlier in the course of their disease *(5)*, because evidence suggests that onset of GD at a young age is associated with increased likehood of relapse after medical treatment *(24)*. Regimens used have included various fixed doses and doses calculated on the basis of the size of the thyroid gland by means of ultrasonography or isotope scans, these methods being superior to assessment of thyroid size by palpation *(25)*. Some formulas also incorporate measurements of isotope uptake or turnover. Most dosimetric methods incorporate thyroid size in their formulas, because this has been considered to be an important prognostic factor for success after RAI treatment. Despite this, the evidence from several studies is that not calculated doses of RAI do not have any benefit over fixed doses, in terms of improving cure rates *(14,26)* or in preventing the development of hypothyroidism *(13)*, so many clinicians prefer the use of a fixed-dose regimen *(9)*. The development of long-term hypothyroidism seems to be inevitable, irrespective of the amount of RAI administered, with an incidence of 2–3% per year after therapy *(7,23)*. Some clinicians now prefer to give a large ablative dose (15 mCi and upward), which results in early hypothyroidism, so that the need for long-term follow-up of thyroid function in euthyroid patients is obviated. It may be possible to improve cure rates using a single fixed-dose regimen without increasing the dose in all patients. This might be achieved by the identification of subjects with poor prognostic factors who are unlikely to respond to standard doses and by administering larger doses only to these individuals.

Allahabadia et al. reported that the incidence of hypothyroidism was 60.8% for patients treated with a first dose of 10 mCi, at 1 yr after RAI treatment *(27)*. In this study, Graves' patients had a significantly higher incidence of hypothyroidism (54.5%) than those of the patients with TNG (31.7%), but there was no significant difference in the cure rates, after one dose of RAI, between GD and TNG, such as in our study. In some studies, it was reported that incidence of hypothyroidism after RAI treatment for TNG was 14% *(28,29)*, as in our study.

Several factors have been considered to influence the outcome of RAI treatment. Many studies have demonstrated that patients with larger-volume thyroid glands *(11)* and severe hyperthyroidism *(17,30,31)* are more likely to fail to respond to a single dose of RAI. In addition to the amount of RAI administered, these two clinical factors are widely regarded as the most reliable predictors of response to treat-

ment. Patients with TNG have often been stated to be more resistant to RAI than those with GD and have consequently received larger doses *(18)*. Our present findings, however, have not shown an excess of persistant hyperthyroidism in patients with toxic nodular hyperthyroidism. This finding is consistent with study performed by Allahabadia et al. *(27)*. Although ATDs are known to confer a degree of radioresistance, results have been conflicting, with some *(19)*, but not all *(32)*, studies reporting a reduction in the response rates to RAI if patients have received pretreatment with ATDs. Furthermore, some studies have shown an effect only with propylthiouracil alone *(20)*. In our study, there was no relationship between the use of ATDs and outcome of RAI treatment.

It should be noted that serum TSH concentrations remained suppressed in a number of subjects assigned to the cured group. It is well recognized that TSH suppression can persist for several months, or even years, after successful treatment of hyperthyroidism with thionamide drugs or RAI *(33)*. Whether such patients should be considered euthyroid or considered for further antithyroid treatment is controversial and a subject for debate *(34)*. Our data from the present study demonstrated a significantly greater response to a single fixed dose of RAI of 10 mCi, with only approx 10% of patients who were given the former dose requiring treatment with a second dose to achieve cure of hyperthyroidism.

Despite previous reports of lower response rates in TNG *(18)*, we found almost similar cure rates in patients with GD and TNG. Patients with TNG were predictably less likely to develop hypothyroidism, presumably because uptake of RAI was restricted mainly to hyperfunctioning autonomous areas within the gland. Although RAI is clearly successful in curing hyperthyroidism in such patients, surgery should be discussed as a treatment option because of the small risk of malignancy within residual nonfunctioning thyroid nodules *(1)*.

Allahabadia et al. reported that male hyperthyroid patients has a significantly worse outcome after RAI treatment than females, and that this observation was even more marked in those with GD *(27)*. In the other study, gender has not been demonstrated to be a significant prognostic factor for response to RAI treatment of hyperthyroidism *(35)*. We did not find a relationship between gender and outcome and RAI treatment.

The results of the present study of a cohort of patients with hyperthyroidism demonstrate that a single fixed dose of 10 mCi of RAI is highly effective in curing GD as well as toxic nodular hyperthyroidism. In contrast to previous studies, we have not demonstrated any difference in response to treatment between these three categories of patients; and therefore, treatment potocols for these groups should be identical. The most important factors which determine efficacy of RAI treatment are serum FT3 concentrations at diagnosis before the initiation of treatment and goiter size. Therefore, these factors should be taken into consideration when planning treatment. If such factors are present, the initial dose of RAI should be increased. The most important outcome of RAI therapy is hypothyroidism. Hypothyroidism can be easily diagnosed because of regularly follow-ups and TSH measurements and it can be controlled easily with L-thyroxine replacement treatment.

Materials and Methods

Our cohort comprised 115 consecutive patients with hyperthyroidism treated with RAI at the Endocrinology Clinic at the Farabi Hospital, Trabzon, between 1994 and 2002. Data were retrieved from endocrinology clinic database. Patients were categorized, by simple clinical and immunological criteria, into three diagnostic groups: GD, toxic multinodular (TMN) hyperthyroidism, and toxic adenoma. GD was defined as the presence of biochemical hyperthyroidism (raised serum total T_4, total T_3, free T_4 and free T_3 concentrations, and suppressed TSH) together with the presence of two of the following: a palpable diffuse goiter, a significant titer of thyroid peroxidase, Tg autoantibodies and/or TSH receptor antibodies, and/or the presence of ophthalmopathy. All 13 patients with GD were relapsed GD and they used to take antithyroid drug therapy (propylthiouracil or methimazole). The diagnosis of TMN goiter was based on the presence of thyroid nodules at palpation and an irregular distribution and/or multiple hyperactive nodules of technetium-99m pertechnetate on a thyroid scan. Toxic adenoma was defined as hyperthyroidism in the presence of solitary nodule at palpation and a solitary hyperactive nodule and completely suppression in the rest of the thyroid on a thyroid scan. Thyroid RAI uptakes of all patients prior to therapy were increased.

The size and type of goiter at diagnosis was categorized on the basis of physical examination: none (gland impalpable or normal size), small (thyroid palpably enlarged but not visible), and medium or large (palpable and visible goiter). The following factors were defined at diagnosis (before initiation of treatment) and recorded in the database: gender, age, serum total and free thyroid hormones (TT_3, TT_4, FT_3, and FT_4) at diagnosis; the presence of the eye disease; presence, size, and type of goiter; autoantibody status and titer; and serum concentrations of free T_4. Information regarding duration of ATDs; dose and timing of RAI and outcome after RAI was also recorded.

Over the period of the study our policy was to offer a single fixed first dose (10 mCi) ^{131}I to all patients with TNG for the first time and to all patients with relapsed GD. ATDs, if given, were withdrawn a week before RAI therapy and not recommended for a minumum of 5 d after therapy. Thyroid status was assessed at monthly intervals after RAI administration. Patients were judged to be euthyroid if serum free T_4 concentrations off ATD therapy were within the normal range; patients classified as persistently hyperthyroid if free T_4 remained elevated; and hypothyroid if serum free T_4 was below the normal range and serum TSH was elevated.

In those with normal serum free T_4 and elevated serum TSH (subclinical hypothyroidism) and in those with only modest reduction in free T_4 and elevation of serum TSH, T_4 replacement therapy (if commenced) was later withdrawn and thyroid status reassessed to exclude cases and transient hypothyroidism. Patients who remained hyperthyroid at 6 mo were retreated with a second dose of RAI. Cure was defined as hypothyroidism and/or euthyroidism.

Statistical Analysis

Statistical analyses were carried out by variance analysis (Kruskal–Wallis–variance analysis followed by Mann–Whitney U test). In addition, chi-square test was applied for data obtained by count. Logistic regression analysis was used to established the factors affecting RAI therapy.

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References

1 Turnbridge, W. M. G., Evered, D. E., Hall, R. E., et al. (1977). *Clin. Endocrinol.* **7,** 481–493.
2. Davies, T. F. (2000). In: *The thyroid.* Braverman, L. E. and Utiger, R. D. (eds.). 8th ed. Lippincott, Philadelphia, pp. 518–531.
3 Kok, S. W., Smit, J. W., De Craen, A. J. M., Goslings, B. M., van Eck-Smith, B. L. F., and Romijn, J. A. (2000). *Nucl. Med. Commun.* **21,** 1071–1078.
4 Feld-Rasmussen, U., Schleusener, H., and Carayon, P. (1994). *J. Clin. Endocrinol. Metab.* **78,** 98–102.
5 Hennemann, G., Krenning, E. P., and Sankaranarayanan, K. (1986). *Lancet* **1,** 1369–1372.
6 Hall, P., Lundell, G., and Holm, L.-E. (1993). *Acta Endocrinol.* **128,** 230–234.
7 Franklyn, J. A., Daykin, J., Drolc, Z., Farmer, M., and Sheppard, M. C. (1991). *Clin. Endocrinol.* **34,** 71–76.
8 Allahabadia, A., Daykin, J., Holder, R. L., Sheppard, M. C., Gough, S. C., and Franklyn, J. A. (2000). *J. Clin. Endocrinol. Metab.* **85,** 1038–1042.
9 Franklyn, J. A. (1994). *N. Engl. J. Med.* **330,** 1731–1738.
10 Shapiro, B. (1993). *J. Nucl. Med.* **34,** 1638–1641.
11 Nordyke, R. A. and Gilbert, F. I. Jr. (1991). *J. Nucl. Med.* **32,** 411–416.
12 Jarlov, A. E., Hegedus, L., Kristensen, L. O., Nygaard, B., and Hansen, B. M. (1995). *Clin. Endocrinol.* **43,** 325–329.
13 Sridama, V., McCormick, M., Kaplan, E. L., Fauchet, R., and DeGroot, L. J. (1984). *N. Engl. J. Med.* **311,** 426–432.
14 Catargi, B., Leprat, F., Guyot, M., Valli, N., Ducassou, D., and Tabarin, A. (1999). *Eur. J. Endocrinol.* **141,** 117–121.
15 Turner, J., Sadler, W., Brownlie, B., and Rogers, T. (1985). *Eur. J. Nucl. Med.* **11,** 191–193.
16 Hedley, A. J., Lazarus, J. H., McGhee, S. M., et al. (1992). *J. Roy Coll. Physic. Lond.* **26,** 348–351.
17. Franklyn, J. A., Daykin, J., Holder, R., and Sheppard, M. C. (1995). *Q. J. Med.* **88,** 175–180.
18 Farrar, J. J. and Toft, A. D. (1991). *Clin. Endocrinol.* **35,** 207–212.
19 Sabri, O., Zimny, M., Schultz, G., et al. (1999). *J. Clin. Endocrinol. Metab.* **84,** 1229–1233.
20 Imseis, R. E., Van Middlesworth, L., Massie, J. D., Bush, A. J., and Vanmiddlesworth, N. R. (1998). *J. Clin. Endocrinol. Metab.* **83,** 685–687.
21 Berg, G., Michanek, A., Holmberg, E., and Nyström, E. (1996). *J. Intern. Med.* **239,** 165–171.
22 Wartofsky, L., Glinoer, D., Solomon, B., et al. (1991). *Thyroid* **1,** 129–135.
23 Huysmans, D. A. K. C., Hermus, A. R. M. M., Corstens, F. H. M., and Kloppenborg, P. W. C. (1993). *Eur. J. Nucl. Med.* **20,** 1056–1062.
24 Vitti, P., Rago, T., Chiovato, L., et al. (1997). *Thyroid* **7,** 369–375.
25 Jarlov, A. E., Nygaard, B., Hegedus, L., Hartling, S. G., and Hansen, J. M. (1998). *Thyroid* **8,** 393–398.
26. Peters, H., Fischer, C., Bogner, U., Reiners, C., and Schleusener, H. (1995). *Eur. J. Clin. Invest.* **25,** 186–193.
27 Allahabadia, A., Daykin, J., Sheppard, M. C., Gough, L., and Franklyn, J. A. (2001). *J. Clin. Endocrinol. Metab.* **86,** 3611–3617.
28 Clerc, J., Dagousset, F., Izemart, M., et al. (1995). *J. Nucl. Med.* **36,** 217–223.
29 Nygaard, B., Hegedus, B., Ulriksen, P., Nielsen, K. G., and Hansen, J. M. (1999). *Arch. Intern. Med.* **159,** 1364–1368.
30 Watson, A. B., Brownlie, B. E., Frampton, C. M., Turner, J. G., and Rogers, T. G. (1988). *Clin. Endocrinol.* **28,** 487–496.
31 Roudebush, C. P., Hoye, K. E., and DeGroot, L. J. (1977). *Ann. Intern. Med.* **87,** 441–443.
32 Marcocci, C., Gianchecchi, D., Masini, I., et al. (1990). *J. Endocrinol. Invest.* **13,** 513–520.
33 Davies, P. H., Franklyn, J. A., Daykin, J., and Sheppard, M. C. (1992). *J. Clin. Endocrinol. Metab.* **74,** 1189–1194.
34 Utiger, R. D. (1994). *N. Engl. J. Med.* **331,** 1302–1303.
35. Kahraman, H. (1990). Uzmanlik tezi, Istanbul University, Faculty of Medicine, Istanbul, pp. 98–101.