Radioiodine-Induced Hypothyroidism in Graves' Disease: Factors Associated with the Increasing Incidence

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A retrospective analysis was done of the records of 454 patients who received their first I-131 treatment for Graves' disease during six periods covering 1951 to 1978. In the earliest group, 3% of patients were hypothyroid 3 mo after I-131 use, and 40% were hypothyroid at 1 yr. In the most recent group, 36% of patients were hypothyroid at 3 mo and 91% were myxedematous at 1 yr. Although no obvious trends were noted, whether in the number of patients pretreated with thionamide drugs, in the mean 24-hr I-131 uptake, or in the calculated dose of I-131 (μCi/estimated gram of thyroid tissue) during the years of the study, the initial mean dose of I-131 administered increased from 8.1 mCi in the earliest group to 13.8 mCi in the latest group. Concurrently, estimates of gland size increased from a mean of 26 g in the first group to 43 g in the last. If, in patients with Graves' disease, the thyroid gland size did not truly increase during the years of the study, the increasing occurrence of early hypothyroidism seen after I-131 use may reflect the conscious or unconscious decision to use larger doses of I-131 calculated on the basis of inflated estimates of thyroid gland weight.

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Von Hofe et al. (*1*) reported that, within 12 mo of treatment with 10 mCi of radioactive iodine, 69% of their 48 patients with diffuse toxic goiter treated during 1974 to 1976 developed hypothyroidism. Wise et al. (*2*) found that 92% of 50 patients were hypothyroid within 6 mo after I-131 therapy. These two reports demonstrated a percentage of postradioiodine myxedema considerably higher than was found in earlier studies (*3–12*). In addition to the suggestion by Von Hofe and colleagues (*1*) that the absolute percentage of hypothyroidism after I-131 administration has increased in recent years, previous authors have described a progressive increase—independent of dose and year of treatment—in the proportion of late myxedema after I-131 use (*3–9*).

The largest study of outcome to date is that of Becker et al. (*3*), who reported on the results of the Cooperative Thyrotoxicosis Therapy Follow-Up Study. They noted approximately 40% hypothyroidism at 10 yr after treatment with 100 to 125 μCi of radioiodine per estimated gram of thyroid tissue and concluded that doses above this range did not significantly increase the probability of myxedema or reduce the need for retreatment with I-131.

At our institution, the use of I-131 in Graves' disease began in 1946. This experience, covering three decades, was evaluated to examine the results of I-131 therapy in Graves' disease from a single institution, to define trends in treatment policy and outcome, and to compare our experience with that of other large series, particularly that of Holm et al. (*13,14*), who have described a very similar study in a Scandinavian population.

PATIENTS AND METHODS

We reviewed the records of all patients with Graves' disease who received their first treatment with I-131 in

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TABLE 1. DIAGNOSTIC CONFIRMATION OF HYPERTHYROIDISM

Confirmation means	Percentage of patients					
	1952	1957	1962	1967	1972	1977
Basal metabolic rate (BMR)	41	48	26	2	1	0
Protein-bound iodine or butanol-extractable iodine (BEI)	3	2	6	4	0	0
Both BMR & BEI	54	41	68	91	1	0
Total T_4 or free T_4	0	0	0	0	83	98
BMR + T_4	0	0	0	0	7	0
T_3	0	0	0	0	4	1
Clinical diagnosis	2	9	0	3	4	1
Total	100	100	100	100	100	100

the periods centered in 1952, 1957, 1962, 1967, 1972, and 1977. Each study "year" included a 2-yr period; for example, 1952 included findings from July 1, 1951, through June 30, 1953. Four hundred fifty-four patients were included. Exclusion was based on previous I-131 therapy, prior subtotal thyroidectomy, the presence of a nodular goiter, a history of x-ray irradiation to the thyroid region, or inadequate follow-up. Fourteen percent of patients were excluded because of inadequate follow-up. This percentage varied from 7% in 1952 to 20% in 1972 to 8% in 1977.

The diagnosis of hyperthyroidism secondary to Graves' disease was based on clinical judgment supported by laboratory data. Some tests used to confirm the diagnosis (for example, protein-bound iodine and basal metabolic rate) were supplanted by more modern methods in later years (Table 1), but each patient had a measurement of diagnostic 24-hr radioiodine uptake. Few of our patients had thyroid scans. Palpation alone was used to determine whether the patient had diffuse thyroid enlargement.

Data included age, sex, presence of any prior medical treatment, date of I-131 treatment, thyroid weight estimated by palpation, diagnostic 24-hr I-131 uptake, and the I-131 administered, expressed both in mCi and in μCi per estimated gram of thyroid tissue. After treatment, the adjunctive use of potassium iodide commencing within 1 wk of I-131 therapy, or the use of additional I-131, was noted, and the thyroid status at 3, 6, 12, and 24 mo, as well as at last contact, was recorded. The cumulative dose in mCi for each patient was calculated.

The mode of diagnosis of hypothyroidism was noted, and the date of that diagnosis was taken as the date on which permanent replacement therapy was prescribed.

At 1 yr after treatment, 86% of the 454 patients were available for study. That percentage decreased to 70% at 2 yr and to 32% at 10 yr.

Standard life-table techniques were used to estimate the probability of hypothyroidism at intervals after treatment.

RESULTS

From 1952 to 1977, mean patient age decreased from 56 to 44 yr (Table 2). Sex ratios varied inconsistently throughout the years; for example, 63% of patients in 1952 were females compared with 56% in 1957, 68% in 1967, and 79% in 1977. The percentage of patients pretreated with thionamide drugs also failed to follow any definite pattern.

The mean diagnostic uptake of I-131 did not change significantly during the study years; it was 62% in 1952 and 1957, 50% in 1967, and 60% in 1977. Estimated thyroid size increased 65%, from 26 g in 1952 to 43 g in 1977. The amount of I-131 administered, expressed as μCi per estimated gram of thyroid tissue, was highest in 1952 at 197 μCi/g and lowest in 1957 at 152 μCi/g, then increased progressively to 178 μCi/g in 1977. The administered I-131 activity, expressed as mCi per patient, increased from 8.1 mCi in 1952 to 13.8 mCi in 1977 (Table 2).

The number of patients receiving adjunctive potassium iodide within 1 wk after I-131 use decreased from 82% in 1952 to 52% in 1977. Nineteen percent of patients required retreatment with I-131 in 1952; the percentage decreased to 8% in 1967 and to 3% in 1977. None of the 454 patients required thyroidectomy for refractory hyperthyroidism.

The actuarial estimate of the proportion of hypothyroidism was computed for each study period at time intervals after treatment (Fig. 1). Except for a transient reversal of the trend at 10 yr in the 1962 group, the proportion with post-therapeutic myxedema increased steadily from one period to the next for the entire period of follow-up. For example, 3 mo after treatment in 1952, 6% of patients were receiving permanent replacement therapy. The percentage increased to 18% at 3 mo in 1967 and to 36% at 3 mo in 1977. At 1 yr after treatment, 40% of the 1952 group and 68% of the 1967 group were hypothyroid, and in 1977, 91% of patients were permanently myxedematous at 1 yr. Similar trends were seen during a 10-yr span (Fig. 2); namely, a progressive increase in hypothyroidism was noted at given intervals after treatment, with earlier groups (even at 10 yr) not

TABLE 2. DEMOGRAPHIC AND TREATMENT VARIABLES FOR PERIODS OF STUDY

Variable	1952	1957	1962	1967	1972	1977
No. of patients	68	59	62	95	81	89
Mean age (yr)	56	56	52	44	48	44
Females (% of pts)	63	56	76	68	74	79
Previous thionamide therapy (% of pts)	16	26	21	26	23	17
Mean I-131 uptake (%)*	62	62	57	50	58	60
Est. thyroid wt (g)†	26	28	32	34	36	43
Adjunctive KI (% of pts)‡	82	93	90	66	57	52
Mean I-131 dose						
Calculated (μCi/g)	197	152	154	159	163	178
Initial (mCi)¶	8.1	7.3	9.0	11.8	10.8	13.8
Cumulative (mCi)	11.2	9.5	9.7	13.3	11.6	14.7
Retreatment with I-131 (% of pts)	19	19	6	8	6	3
Follow-up at 1 yr (% of pts)	84	86	89	77	87	86

* 24-hr diagnostic I-131 uptake.

† By palpation.

‡ Percentage of treatment group receiving KI within 1 wk after therapeutic I-131.

¶ Delivered according to formula:

$$\text{Activity (mCi)} = \frac{\text{est. gland wt (g)} \cdot \text{therapeutic } \mu\text{Ci per est. g}}{\%\ \text{I-131} \cdot 10}.$$

achieving a percentage hypothyroid as great as that seen in the 1972 and 1977 groups at 1 or 2 yr. We note that only 32% of the patients were available for follow-up at 10 yr.

The probability of hypothyroidism 1 yr after therapy was plotted for each of the years studied and for the entire group, as a function of sex, prior thionamide treatment, age, and adjunctive potassium iodide use (Table 3). The overall percentage of hypothyroidism after I-131 use was 68% for males compared with 72% for females, and both groups showed progressive increase in hypothyroidism from 1952 to 1977 (for example, 36% for males in 1952 and 84% for males in 1977). Similar trends were seen for patients who received previous thionamide treatment compared with those who did not—73% and 66%, respectively, over all years. Within each group, the occurrence of hypothyroidism increased dramatically from 1952 to 1977. Overall, 86% of the patients 40 years old or younger had myxedema, against only 65% of those more than 40 years old. Those receiving potassium iodide within 1 wk after I-131 therapy had an overall probability of hypothyroidism of 65% at 1 yr against 86% for those without potassium iodide. Thus, although age or potassium iodide use was associated with larger overall differences in outcome than was sex or previous thionamide use, progressive increases in hypothyroidism after I-131 use were noted within each category from 1952 to 1977.

The increasing incidence of hypothyroidism was not attributable to the introduction of more refined diagnostic tests. Throughout the study period, the basal metabolic rate and a measurement of thyroid hormone in blood were used to confirm the diagnosis of hypothyroidism. Even when immunoassay of thyroid-stimulating hormone became available, it was used to support the diagnosis of hypothyroidism in only 13% of patients in

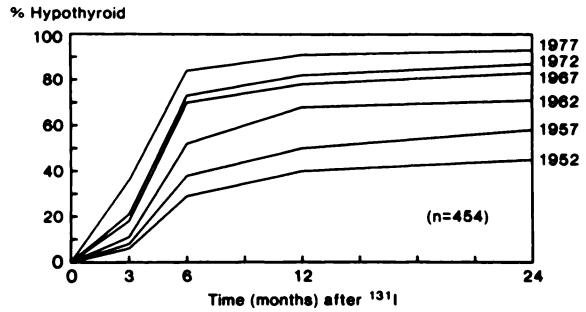

FIG. 1. Actuarial estimate of percentage of patients becoming hypothyroid during first 2 yr after initial treatment with I-131.

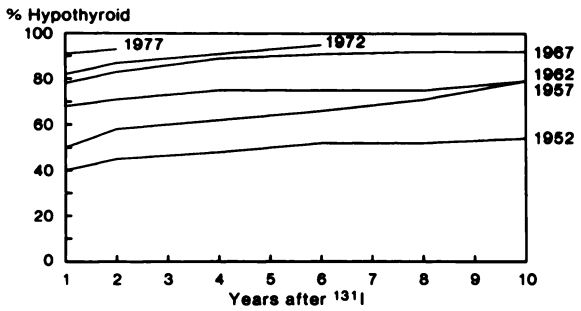

FIG. 2. Actuarial estimate of percentage of patients becoming hypothyroid during 1 to 10 yr after initial treatment with I-131.

TABLE 3. PROBABILITY OF HYPOTHYROIDISM DEVELOPING WITHIN 1 YEAR AFTER I-131 USE

	Percentage						
	1952	1957	1962	1967	1972	1977	1952–77
Sex							
Males (n = 136)	36	54	73	87	78	84	68
Females (n = 318)	42	47	66	74	84	93	72
Previous therapy							
Thionamide before I-131 (n = 123)	36	40	75	87	73	86	73
No thionamide (n = 323)	42	58	65	75	87	92	66
Age							
≤40 yr (n = 118)	...	...	80	80	84	97	86
>40 yr (n = 336)	40	49	65	77	81	86	65
Potassium iodide							
Within 1 wk after I-131 (n = 332)	36	50	64	72	78	95	65
None (n = 128)	64	...	...	93	88	86	86

1972 and 22% of patients in 1977.

As mentioned above, Becker et al. (*3*) reported the probability of hypothyroidism at 10 yr and the need for additional I-131 treatment, both as functions of radioiodine dose. Our patients had a higher probability of hypothyroidism at all doses used, as well as a correspondingly lesser need for additional I-131 treatment (Fig. 3).

DISCUSSION

Atkins (*15*) noted a number of factors known to influence the development of hypothyroidism after I-131 therapy. He included variables such as nodular goiter and previous thyroidectomy, which our study eliminated; other variables such as race and immune status were not analyzed in our study. Most of our patients were white. In comparison with the Cooperative Thyrotoxicosis Therapy Follow-Up Study, our investigation revealed that, in every study period a higher percentage of our patients became hypothyroid, and in each decade there was an increase in the percentage of our patients who became hypothyroid within a year of therapy. In an effort to explain these trends, we examined various factors known to influence the outcome of I-131 therapy.

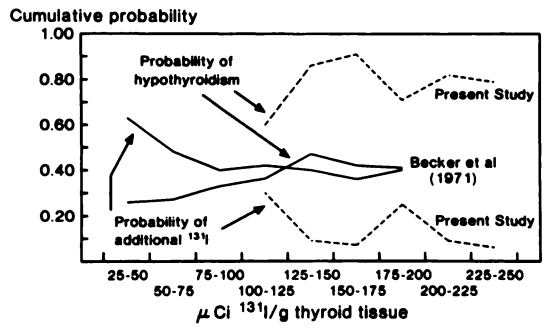

FIG. 3. Probability of hypothyroidism and need for additional I-131 treatment at 10 yr after initial dose of I-131.

Younger patients appear to have glands that are more radiosensitive and, therefore, more susceptible to the ablative effects of I-131 (*9,10*). We note that 7% of our patients in 1957 were 40 yr of age or younger. That percentage increased to 39% in 1967 and to 45% in 1977. Although age of 40 yr or younger was correlated with a higher percentage of hypothyroidism in our study (Table 3), the trend toward increasing hypothyroidism from 1952 to 1977 was demonstrated in those above age 40 as well as in those below. Holm (*14*) observed a similar trend.

Antithyroid drugs and potassium iodide have a protective effect on thyroid tissue if administered shortly before I-131 use (*3,10,16,17*). Insignificant changes in the percentage of our patients pretreated with thionamide drugs (Table 2) do not explain the increasing trend toward hypothyroidism seen during the study years. In contrast to our expectations, patients pretreated with thionamides had a slightly higher probability of developing hypothyroidism at 1 yr than did those not pretreated (Table 3). Holm et al. (*13*) observed no such trend, and our results varied in different decades. Pretreatment with thionamides probably does not significantly affect the incidence of postradioiodine hypothyroidism.

Higher uptake of I-131 theoretically produces a higher percentage of thyroidal ablation if the I-131 administered and other dose-modifying factors remain fixed. As noted in Table 2, the mean diagnostic 24-hr I-131 uptake by patients in our series remained relatively unchanged during the six time periods studied. This is interesting in view of the well-documented decrease in normal values of I-131 thyroid uptake observed during the past three decades (*18–21*). This decrease in normal uptake has been attributed to increased dietary iodine ingestion (*18,20*). Presumably the increase in thyroid hormone

production in patients with Graves' disease compensates for the larger amount of available iodine.

It has been suggested that use of potassium iodide shortly after I-131 administration increases the effective radiation delivered to the gland by inhibiting the release of radiolabeled thyroid hormone (*16*). In contrast, we found (Table 3) that patients receiving adjunctive potassium iodide had a lower probability of developing hypothyroidism at 1 yr (65%) than did those receiving no such treatment (86%). Since a larger percentage of patients in the later study years were not treated with potassium iodide, other factors operating during those years must have been responsible for the observed progressive increases in hypothyroidism after I-131 use.

There is a positive relationship between the amount of I-131 administered (whether as total mCi or as μCi/g) and the occurrence of early hypothyroidism; this was demonstrated by Goolden and Fraser (*5*), by Cevallos et al. (*6*), and by Smith and Wilson (*11*) in the treatment of patients receiving high- and low-dose regimens of I-131. The mean number of μCi/g delivered to our patients (Table 2) was highest in 1952, yet was associated with the lowest percentage of hypothyroidism in any of the six treatment periods. The increasing frequency of hypothyroidism, however, was associated with an increase in the mean dose of mCi administered—from 8.1 in 1952 to 13.8 in 1977.

Iodine-131 was administered according to the following formula:

$$\text{Activity (mCi)} = \frac{\text{est. gland wt (g)} \cdot \mu\text{Ci per est. g}}{\text{\% I-131 uptake} \cdot 10},$$

with individual variations in the μCi/g being determined by clinical judgment. We noted a relatively unchanging value in diagnostic I-131 uptake as well as in mean therapeutic μCi/g, which was highest in 1952; neither of these factors can completely account for the increasing mean dose of mCi of I-131 from 1952 to 1977.

As noted from Table 2, estimated thyroid gland size increased dramatically from 1952 to 1977 and, through its reflection in higher doses demanded by the above formula, may account for our observed increases in post-therapeutic myxedema during the years. Since the TSH assay was noted to diagnose hypothyroidism in only 13% of our patients in 1972 and 23% of patients in 1977, it cannot explain the trends already well established between 1952 and 1972, when the methods of diagnosis were fairly constant.

Smaller thyroid glands are more sensitive to the ablative effects of I-131 (*4,9,10*). The concurrence of larger estimates of gland size and a higher incidence of hypothyroidism is at variance with those observations. Experience has shown that, in the early years after the introduction of I-131, most patients with large glands were treated surgically. As confidence in the efficacy of I-131 increased, more patients were treated with this modality. At our institution, surgery is now rarely performed in adult nonpregnant patients with Graves' disease.

The estimates by clinicians of gland size in patients with Graves' disease increased approximately 65% from 1952 to 1977. During the years, these estimates were collected from more than 20 clinicians. A gradual consensus has developed among endocrinologists at our institution that early postradioiodine hypothyroidism is a desirable consequence of therapy. One may speculate that in the hope of ensuring the desired outcome, clinicians inflated their estimates of gland size when referring patients for I-131 treatment. This speculation was evaluated by circulating a questionnaire to the endocrinologists who estimate thyroid size before patient referral to a radiotherapist for I-131 treatment. Of 26 current staff members, 24 responded. Nine admitted that they consciously overestimated gland weight by amounts up to 30%. Among these nine were the five clinicians with the highest proportion of thyroid disease in their practice. If the average size of the glands in Graves' disease has truly increased during the last three decades, it has not been documented in the literature. The studies of Holm (*14*) and Holm et al. (*13*) deserve special comment. Their study population differed from ours in that 13% of their patients had previous thyroid surgery, and the number of patients in their series with nodular thyroids increased from 32% in 1951–1955 to 64% in 1971–1975. Patients who had previous surgery and patients with nodular thyroids were excluded from our study. Nevertheless, our results are strikingly similar in that both in Stockholm and Rochester the incidence of hypothyroidism increased steadily throughout the decades. Presumably because we used higher doses of I-131, the early frequency of hypothyroidism was much greater in our series (91% contrasted to approximately 10% in the Scandinavian series). It is of special interest that in the series described by Holm there was no increase over the decades in estimates of thyroid gland weight.

While our results support in general the conclusions drawn from the National Thyrotoxicosis Therapy Cooperative Study, we differ in several important regards. The Cooperative Study indicated that I-131 doses higher than 125 μCi/g did not add to the 40% probability of hypothyroidism at 10 yr, and did not diminish the need for retreatment with I-131, which was required in about 42% of their patients. With the higher administered activity that we used, only 3% of our patients required retreatment with I-131 in 1977, and the probability of hypothyroidism in that group at 1 year after therapy was already 91%. The threshold above which no additional thyroid ablative effect is to be anticipated is at a dose apparently higher than 125 μCi/g of estimated thyroid tissue.

Experience of more than 25 yr at our institution has indicated an increasing probability of hypothyroidism

developing after radioiodine therapy for Graves' disease and a concomitant decrease in the need for retreatment with radioiodine. The trend of increasing hypothyroidism was associated with lower ages of patients treated, with more radioiodine in the initial dose, with increasing estimates of gland size, and with less adjunctive use of potassium iodide. Whereas normal values for I-131 uptake at our institution have declined during the last 20 yr, the values for diagnostic I-131 uptake in patients with Graves' disease have remained unaltered.

Sex, prior thionamide therapy, age, or introduction of diagnostic use of the TSH radioimmunoassay did not account for the observed trends of increased postradioiodine hypothyroidism through the years covered by the study. However, in any given year, younger patients, and those who did not receive supplemental potassium iodide, had a higher probability of developing hypothyroidism.

In assessing reports of changes in outcome of radioiodine therapy over time, the possibility should be considered that estimates of thyroid gland size may have been inflated to influence the size of the administered dose. However, since similar trends toward increasing incidence of hypothyroidism have been observed in Scandinavia without a change in estimate of thyroid size among those patients, other factors, as yet unexplained, may contribute to the increasing incidence of thyroid underactivity after radioiodine therapy.

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