

Changing Annual Incidence of Hypothyroidism After Iodine-131 Therapy for Hyperthyroidism, 1951–1975

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The incidence of hypothyroidism was analyzed in 4,553 hyperthyroid patients treated with I-131 between 1951 and 1975. The average annual rate of hypothyroidism during the first 7 yr after therapy increased continuously for each 5-yr period of treatment, from 3.6% for patients treated between 1951 and 1955 to 7.7% for patients treated during the period from 1971 through 1975 ($p < 0.001$). The increase in the incidence of hypothyroidism was seen before the introduction of TSH assays and when allowance was made for thyroid gland size, the age of the patient, and the experience of the radiotherapist. The use of TSH assays has probably resulted in an earlier recognition of hypothyroidism, which may explain why the most marked rise in the incidence of hypothyroidism was observed after the introduction of TSH assays.

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In a recent study in this *Journal*, it was suggested that standard doses of I-131 would cause a higher proportion of hypothyroidism in patients treated for hyperthyroidism in the 1970s than in patients treated in the 1950s and 1960s (1). A less frequent use of thionamide medication in the 1970s, together with an increase in dietary iodine intake, were suggested as possible explanations for this rise in the incidence of hypothyroidism (1).

The purpose of the present study was to analyze a large series of hyperthyroid patients uniformly treated with I-131 at one hospital in order to determine whether there has been any change in the incidence of hypothyroidism during the period 1951–1975.

MATERIALS AND METHODS

The study comprised 4553 hyperthyroid patients (3827 women and 726 men) given I-131 therapy at

Radiumhemmet between 1951 and 1975. The patients were divided into five groups according to the year of I-131 therapy: 1951–1955 ($n = 713$), 1956–1960 ($n = 929$), 1961–1965 ($n = 998$), 1966–1970 ($n = 972$), and 1971–1975 ($n = 941$). The mean age was 56 yr for the whole series (range 14–91 yr), and rose gradually from 52 yr in the 1951–1955 period to 58 yr in 1971–1975.

Fifty-one percent of the patients had clinically diffuse thyroid glands and 49% had one or more palpable nodules. The proportion of nodular thyroids increased from 32% in the period 1951–1955 to 64% 1971–1975. Five percent of the thyroids were judged normal in weight (≤ 30 g), 86% were between 31 and 60 g, and 9% were larger. The distribution of gland weights remained unchanged over the five treatment periods.

The principles of I-131 therapy for hyperthyroidism at our clinic (2–4) have remained unchanged during the period of study. The radiation dose delivered to the thyroid glands aimed at 6,000–10,000 rad per treatment, with the upper dose range for nodular glands. Eighty patients with a hyperfunctioning nodule, however, were usually given 20,000–30,000 rad per treatment.

The follow-up period was reckoned from the time of

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the first I-131 treatment until December 1978, or until the time when hypothyroidism occurred, or until death. The follow-up procedure and the criteria for diagnosis of hypothyroidism have been described (3). In the comparisons between the five treatment periods, the average annual rate of hypothyroidism for the first 7 yr after I-131 therapy was calculated. The expected rate of hypothyroidism was calculated using the standard life-table technique. The statistical method used was the logrank test (5).

RESULTS

The rate of developing hypothyroidism after I-131 therapy rose for each treatment period (Fig. 1). The numbers of patients successfully followed for 7 yr in each treatment group were, respectively, 521, 686, 823, 801, and 421. The annual rise in the incidence of hypothy-

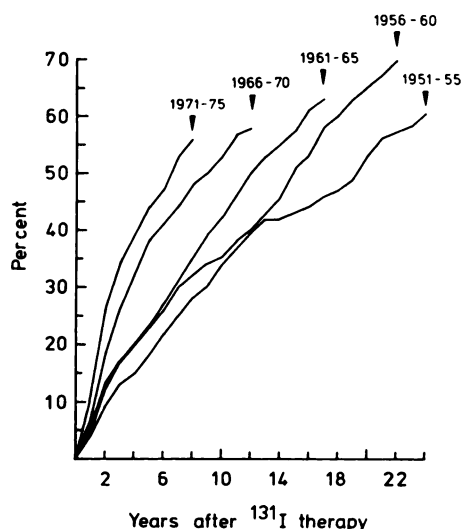


FIG. 1. Average annual incidence rate for hypothyroidism after I-131 therapy for hyperthyroidism in relation to treatment period.

TABLE 1. AVERAGE ANNUAL INCIDENCE RATE FOR HYPOTHYROIDISM DURING THE FIRST 7 YR AFTER I-131 THERAPY FOR HYPERTHYROIDISM, IN RELATION TO TREATMENT PERIOD AND TO TYPE OF THYROID DISEASE

Treatment period	Diffuse %	Nodular %	All patients %
1951-1955	4.0	2.7	3.6
	(p<0.05)	(n.s.)	(n.s.)
1956-1960	5.1	2.9	4.2
	(n.s.)	(n.s.)	(n.s.)
1961-1965	5.3	3.3	4.4
	(p<0.001)	(p<0.001)	(p<0.001)
1966-1970	8.4	4.7	5.9
	(p<0.01)	(n.s.)	(p<0.01)
1970-1975	10.4	5.9	7.3

TABLE 2. AVERAGE ANNUAL INCIDENCE RATE FOR HYPOTHYROIDISM DURING THE FIRST 7 YR AFTER I-131 THERAPY FOR HYPERTHYROIDISM, IN RELATION TO ANTITHYROID PREMEDICATION AND TO AGE

Treatment period	Patients with antithyroid premedication, %	All patients, %	
		<50 yr old	≥50 yr old
1951-1955	2.4	4.3	3.0
	(n.s.)	(n.s.)	(p<0.05)
1956-1960	3.1	4.7	3.9
	(p<0.05)	(n.s.)	(n.s.)
1961-1965	4.7	5.3	4.0
	(n.s.)	(p<0.001)	(p<0.001)
1966-1970	5.9	7.3	5.9
	(p<0.01)	(p<0.001)	(n.s.)
1971-1975	8.0	10.0	6.6

TABLE 3. AVERAGE ANNUAL INCIDENCE RATE FOR HYPOTHYROIDISM DURING THE FIRST 7 YR AFTER I-131 THERAPY, IN RELATION TO EXPERIENCE OF FIVE RADIOTHERAPISTS AND TO TREATMENT PERIOD

Treatment period	Radiotherapist				
	A	B	C	D	E
1951-1955	3.7 (n.s.)	3.3 (n.s.)	—	—	—
1956-1960	4.7	4.0 (n.s.)	4.4 (n.s.)	—	—
1961-1965	—	4.0 (p<0.001)	5.0 (n.s.)	—	—
1966-1970	—	6.7 (n.s.)	6.1	6.3 (p<0.05)	—
1971-1975	—	7.4	—	8.0	7.4
No. of patients treated	788	1,473	580	809	278

roidism was higher for patients with diffuse goiter than for those with nodular thyroids (Table 1), and increased by a factor of 2.6 for patients with diffuse and of 2.2 for those with nodular thyroids from 1951-1955 to 1971-1975.

In patients treated with only one dose of I-131, the average annual incidence rate of hypothyroidism was 4.2% during the 1950s, compared with 5.0% during the 1960s ($p<0.025$) and 6.9% for patients treated during the 1970s ($p<0.001$). The annual incidence of hypothyroidism also increased with time in patients who had received antithyroid premedication (Table 2), as well as in patients less than 50 yr of age and in those aged 50 yr or more (Table 2).

The treatment period itself appeared to be of greater importance in affecting the incidence of hypothyroidism than the experience of the treating radiotherapists, measured as the number of patients treated (Table 3). There was no difference in the incidence of hypothyroi-

dism within each treatment period between patients treated by the physicians evaluated.

The mean initial dose of I-131 and the mean dose administered per treatment were unchanged during the period of study for patients with diffuse glands, but decreased for patients with nodular glands (Table 4). The mean total dose of I-131 administered decreased for all patients, and particularly for those with nodular glands. The more frequent use of radiotherapy in the treatment of very large toxic nodular goiters during the earlier treatment periods has influenced this decrease. The mean 24-hr thyroid uptake of diagnostic amounts of I-131, and the mean effective half-time of the nuclide in the gland, did not differ much between the five treatment periods: 60-62% and 5.3-5.8 days, respectively.

The patients treated during 1951-1955 were cured after an average of 2.0 treatments. The corresponding figures for the subsequent periods were 1.9, 1.7, 1.6, and 1.4, respectively.

TABLE 4. AMOUNTS OF I-131 ADMINISTERED AND TAKEN UP BY THE THYROID GLAND, IN RELATION TO TREATMENT PERIOD

	Treatment period				
	1951-1955	1956-1960	1961-1965	1966-1970	1971-1975
Mean initial dose of I-131 administered (mCi)					
Diffuse glands	5.0	5.2	4.9	5.4	5.1
Nodular glands	12.7	11.8	10.4	10.2	8.5
Mean total dose of I-131 administered (mCi)					
Diffuse glands	9.3	9.6	8.6	8.3	7.2
Nodular glands	28.4	21.3	18.6	17.6	12.4
Mean dose of I-131 per treatment (mCi)					
Diffuse glands	5.0	5.2	4.9	5.2	4.9
Nodular glands	12.3	12.0	10.7	10.1	8.4

DISCUSSION

Von Hofe et al. (1) recently focused attention on a possible increase in the incidence of hypothyroidism in patients with toxic diffuse goiter treated with standard doses of I-131 in the 1970s, as compared with those treated earlier. Such an increase was observed in the present series of hyperthyroid patients. A suggested explanation for the lower incidence of hypothyroidism in earlier studies was the more frequent use of thionamide compounds at that time, a factor that could have operated against hypothyroidism to some extent (1). The rising incidence of hypothyroidism in the present study was also observed within the group of patients given antithyroid premedication. However, the duration of pretreatment (beyond 3 wk) is not known, so the data are incomplete on this point.

Stable iodine given in pharmacologic doses after I-131 therapy increases the proportion of hypothyroid patients (6). The dietary content of iodine has increased in the United States (7-9) as well as in Sweden (10,11). It is possible that such an increase may have contributed to the rise in the incidence of hypothyroidism after I-131 therapy, although a rise was noted in the present study even before 1966, when dietary iodine in Sweden was increased.

All patients were given I-131 therapy based on the same principles (2-4) throughout the entire period of study. The data in Table 4 make it hardly likely that the rising incidence of hypothyroidism can be attributed to a continuing increase in the radiation dose delivered to the thyroid glands.

It is not known whether there has been a rise in the antibody titers to thyroid antigens over the past decade, and particularly to those against cytoplasmic thyroid antigen. If such is the case, it would be one important explanation for the increasing incidence of hypothyroidism (12).

TSH assays were introduced in Sweden during the period 1968-1970, and have undoubtedly facilitated the diagnosis of hypothyroidism. The use of TSH is probably one of the most important explanations for an earlier recognition of hypothyroidism in the later treatment periods. An increase in the incidence of hypothyroidism was observed, however, even before the introduction of TSH assays, although to a lesser extent.

The early incidence of hypothyroidism can be reduced by lowering the radiation doses of I-131 (13-16). However, the rate with which the patients develop hypothyroidism several years after the I-131 therapy may be the same regardless of whether conventional I-131 radiation doses were administered or smaller doses (17,18).

It seems that the great majority of patients currently treated with I-131 will become hypothyroid if observed long enough. Higher doses of I-131 will cure hyperthy-

roidism more rapidly and hypothyroidism will occur earlier (19-21). A more aggressive I-131 therapy for hyperthyroidism, at least for patients above the age of 40 therefore seems warranted. Some of the problems associated with follow-up could then be diminished as well as the risk of insidious hypothyroidism in patients lost to follow-up.

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