

THERAPEUTIC NUCLEAR MEDICINE

The Increasing Incidence of Hypothyroidism within  
One Year after Radiolodine Therapy  
for Toxic Diffuse Goiter

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*Patients treated with 10 mCi of I-131 for toxic diffuse goiter in the period January 1974–June 1976 were evaluated for development of hypothyroidism. Fifty percent were hypothyroid within 3 mo and 69% within 1 yr of treatment. Our data suggest that there is a higher incidence of hypothyroidism after standard doses of I-131 in the 1970s as contrasted with treatment groups in the 1950s and 1960s. The pathophysiology of this increased incidence is not known with certainty; however, infrequent use of thionamide medication, together with recent increases in dietary iodine, may render the gland more radiosensitive.*

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The occurrence of hypothyroidism after radioactive iodine therapy for toxic diffuse goiter (TDG) is a well-described entity (1–8). Evidence that its incidence might be increasing was apparent from two recent studies: a preliminary review of our own patients, and a report by workers from Australia (1,2). A detailed review of our total patient population has again demonstrated this apparent increase in occurrence of hypothyroidism after I-131.

METHODS

Records of patients treated for TDG with I-131 at our Medical Center from January 1974 to June 1976 were reviewed. The primary objective of this study was to determine the percentage of patients developing hypothyroidism within a year of therapy. The Medical Center is a 1,000-bed hospital that functions as a world-wide referral and training center for the U.S. Air Force.

The diagnosis of TDG was based on the following: a) elevated blood levels of  $T_3$ - $T_4$  by radioimmunoassay (RIA), b) elevated  $T_3$  resin uptake ( $T_3$ RU), c) elevated 24-hr I-131 uptake (in most cases), and d) a characteristic clinical appearance (Table 1). Excluded were all patients with a multinodular gland or with a single toxic nodule. With a few exceptions (patients with complicating medical problems) our policy has been the administration of 10 mCi I-131

to patients with TDG regardless of the size of the thyroid gland, results of thyroid-function tests, or 24-hr I-131 uptakes. This report deals with the 54 patients who were treated with an initial dose of 10 mCi of I-131 and were followed in our thyroid clinic during the above time period.

The patients' age range was 15–55 yr. There were 19 males and 35 females. Only two of the patients were black. Thirteen received thionamide preparations before receiving I-131.

The determination of hypothyroidism was based on symptoms plus the following: a) low serum  $T_4$  (RIA), b) low  $T_3$ RU, c) disappearance of goiter and, d) low free thyroxine index (FTI). (Free thyroxine index =  $T_4$ (RIA)  $\times$   $T_3$ RU divided by average normal  $T_3$ RU. Normal range 5–12  $\mu$ g %.) (1). The last was an absolute requirement for the diagnosis of hypothyroidism. Serum  $T_3$ (RIA) and serum thyrotropin (TSH by RIA) were also obtained. These two tests were not used in any decision to begin thyroid replacement therapy in otherwise hypothyroid patients, since these are occasionally misleading (9,10). Methods for measuring  $T_4$ (RIA),

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TABLE 1. THYROID-FUNCTION TESTS IN PATIENTS BEFORE THERAPY AND WHEN HYPOTHYROID WITHIN 1 YR AFTER RADIOIODINE TREATMENT FOR TOXIC DIFFUSE GOITER\*

Patient's status	T <sub>4</sub> (RIA) μg%	T <sub>3</sub> RU %	T <sub>4</sub> (RIA) ng%	TSH μU/ml	RAIU %
Hyperthyroid (N = 48)	22.1† (12-43)	41 (20-54)	640 (208-3765)	Not done	53 (16-83)
Hypothyroid (N = 33)	2.3‡ (0.5-5.7)	22 (15-28)	61 (0-129)	60 (2.8-330)	Not done
Normal values	5-12	25-35	80-220	<6	5-30

\* T<sub>4</sub>(RIA) = serum thyroxine by radioimmunoassay; T<sub>3</sub>RU = tri-iodothyronine resin uptake; T<sub>4</sub>(RIA) = serum tri-iodothyronine by radioimmunoassay; TSH = serum thyrotropin by radioimmunoassay, performed in only 22 hypothyroid patients (elevated in 21); RAIU = 24-hr radioactive iodine uptake.

† Mean value (range in parentheses).

‡ Free thyroxine index was low in every case (free thyroxine index = T<sub>4</sub>(RIA) × T<sub>3</sub>RU ÷ average normal T<sub>3</sub>RU).

T<sub>3</sub>(RIA), T<sub>3</sub>RU, and TSH have been described previously (11).

# RESULTS

Of the 54 patients who received 10 mCi of I-131 as initial treatment for TDG, data sufficient to determine the ultimate outcome of therapy were available in 48. Of these, 11 had been on a thionamide preparation before receiving I-131. The incidence of hypothyroidism occurring in this group of 48 within 3 mo of therapy was 50% (24/48). Within 12 mo of therapy 69% (33/48) had developed hypothyroidism. At the time hypothyroidism was diagnosed and treated, mean T<sub>4</sub>(RIA) was 2.3 μg% (normal 5-12%), with a range of 0.5-5.7 μg%; and mean T<sub>3</sub>RU was 22% (normal 25-35%), with a range of 15-28% (Table 1). Four patients had a low-normal T<sub>4</sub>(RIA) but a low T<sub>3</sub>RU; in these the diagnosis of hypothyroidism was based on a low FTI. All other hypothyroid patients had a low T<sub>4</sub>(RIA), as well as a low FTI. The mean serum T<sub>3</sub>(RIA) was 61 ng% (normal 80-220%) with a range of 0-129 ng%. Serum TSH values were available in 22 hypothyroid patients and were elevated in 21. One patient had a TSH value of 2.8 μU/ml

when hypothyroid 3 mo after therapy. The mean TSH was 60 μU/ml (normal <6 μU/ml).

Two thirds of our patients had definite symptoms of hypothyroidism at the time their thyroid tests were low. The remainder had only minimal symptoms. They were started on L-thyroxine therapy with the first symptoms of hypothyroidism if they had both definite shrinkage of the goiter and extremely low FTI.

Fifteen of the 48 patients did not become permanently hypothyroid during the first year after treatment, although four went through a stage of transient hypothyroidism (1). Of these fifteen, six were euthyroid at 12 mo after only one dose of 10 mCi I-131, whereas nine were retreated (Table 2). Examination of our patient data revealed that in those 11 patients who received thionamide preparations before I-131, the incidence of hypothyroidism (55%) was significantly lower than the incidence (73%) of 37 patients not pretreated with these medications (p < 0.01 by Chi square). Patients pretreated with thionamides were selected for such treatment not because of a particular clinical presentation, gland size, or the results of thyroid test, but merely according to the preference of the individual referring

TABLE 2. OUTCOME OF THERAPY OF PATIENTS TREATED WITH 10 mCi I-131 FOR TOXIC DIFFUSE GOITER

Number treated and followed	Hypothyroid within 3 mo of therapy	Cumulative number hypothyroid within 1 yr of therapy	Number of patients other than hypothyroid 1 yr after therapy	
48	24 (50%)	33 (69%)	15 (31%)	
			Euthyroid*	Persistent hyperthyroidism requiring retreatment*
			6 (12%)	9 (19%)

\* Two patients in each group had transient hypothyroidism.

physicians. Since these patients demonstrated persistent TDG after 6–12 mo of therapy, they were referred for radioiodine therapy. Thus, the use of thionamides appeared to be the important variable that determined the difference in response to I-131 between these two groups.

As mentioned initially, only 48 patients had sufficient data for full evaluation of results of I-131 therapy. Six other patients were lost to followup. A review of records of these six indicated that: a) they probably had moved (reassigned to another military installation), therefore lack of followup could not be attributed to euthyroidism and disinclination to return; b) they did not differ in terms of clinical presentation, size of thyroid, and thyroid-function tests from our group of 48. We therefore do not believe that exclusion of these six patients biases our results. Even if we considered all six to be euthyroid, the overall incidence of hypothyroidism would still be 61% at 1 yr.

#### DISCUSSION

Reports from the 1950s and 1960s on the incidence of hypothyroidism after therapeutic I-131 used the criteria of symptoms and decreased protein-bound iodine or serum thyroxine to establish the diagnosis. Since then the diagnosis of hypothyroidism following I-131 has become less clear cut. Some more recent reports state that low serum thyroxine and protein-bound iodine values may be seen in clinically euthyroid patients (whose metabolism is maintained by a normal to elevated  $T_3$ (RIA) in the presence of elevated TSH (12,13). Even though they lack symptoms, some such patients may not be truly "euthyroid," since they fail to respond normally to exogenous TSH (14). Review of Sterling's data on these "euthyroid" patients reveals that none had a  $T_3$ (RIA) less than 143 ng% or TSH greater than 30  $\mu$ U/ml (12). In contrast, none of our patients had a  $T_3$ (RIA) greater than 129 ng% (mean 61 ng%), and our mean TSH was 60  $\mu$ U/ml. Thus our patients were hypothyroid by even the most stringent criteria.

Although one third of our patients were not clinically hypothyroid, we feel the diagnosis is well established because of the extremely low thyroid function studies and the disappearance of the goiter, usually to the point of a nonpalpable thyroid (1). Patients were seen every 4 to 6 wk and thyroid hormone replacement was instituted at the first suggestive symptoms when the tests were unequivocally abnormal and the goiter was disappearing. Although we did not stimulate treated patients with TSH or attempt to withdraw replacement therapy at a later date, we believe they were permanently hypothyroid.

Furthermore, we identified four patients with transient hypothyroidism and excluded them from the permanent hypothyroid group (1). This is the expected proportion of patients whose hypothyroidism would be transient based on previous larger studies (14). The fact that they remain euthyroid, with normal thyroid-function studies, on standard replacement doses of L-thyroxine (.15–.2 mg/day) further indicates that all tissue capable of autonomous production had been destroyed.

At first impression, our high incidence of hypothyroidism might be viewed as secondary to the use of a relatively large dose of I-131. Therefore, for purposes of comparison, we reviewed previous reports in which patients with Graves' disease (i.e., TDG) were given doses of I-131 similar to ours (1–8) (Table 3). Nofal et al. obtained followup studies on a large group of patients treated with I-131 between 1948 and 1963 (3). Fifty percent received a total dose of I-131 of 10–20 mCi, and 24% received 10 mCi or less. The cumulative incidence of hypothyroidism at 5 or more years was 54%. In a prospective study performed between 1962 and 1964, Skillman found a roughly 50% incidence of hypothyroidism at 2½ yr in patients given either 9 or 12 mCi I-131 (4). The incidence of hypothyroidism at 2½–5 in these two series was lower than that of the present report at 1 yr. Reports that specifically mention results at 1 yr indicate an even more impressive difference from this study. A large study using an average dose of 8.9 mCi during the 13 yr before 1969 found an incidence of hypothyroidism of 31% at 1 yr and 44% at 5 yr (5). Several reports from the past 5 yr cite incidences of hypothyroidism similar to those just mentioned, but the doses of I-131 were more variable (6–8).

In contrast to these results, we found an incidence

**TABLE 3. INCIDENCE OF HYPOTHYROIDISM IN SEVERAL SERIES OF I-131-TREATED PATIENTS**

Source of data	Date of report	Dosage* (mCi)	Incidence of hypothyroidism (%)
Nofal (3)†	1966	10–20	54 (5)‡
Skillman (4)	1969	9 or 12	50 (2½)
Burke (5)	1969	8.9	31 (1)
Cevallos (6)	1974	7.4	40 (1)
Safa (7)	1975	12.7	32 (¼)
Douglas (8)	1973	8.8	38 (1)
Wise (2)	1975	10–12	92 (½)
Present Series	1977	10	69 (1)

\* Values represent mean doses or dosage ranges with which most patients were treated.

† Reference numbers are in parentheses.

‡ Numbers in parentheses represent years of followup.

of 69% at 1 yr after only 10 mCi of I-131. This is the highest incidence of hypothyroidism at 1 yr of which we are aware, with the exception of a recent report from Australia by Wise (2). Using doses similar to ours in 80% of his patients, Wise found 92% hypothyroid after 6 mo followup. Exactly what the incidence of hypothyroidism was in those receiving only 10 mCi is not clear from the data presented. It is apparent from these studies that the current incidence of hypothyroidism has increased over that of the 1950s and 1960s, and perhaps that of the 1970s. The reason for this apparent increase is not clear.

Several factors have been reported to correlate with the development of hypothyroidism after I-131: (a) the presence of antibodies to thyroid cytoplasmic antigen; (b) the age of the patient at the time of treatment (those over 55 have a higher incidence); (c) the race of the patient (nonblacks appear to have a higher incidence than blacks); and (d) pretreatment with thionamide drugs (such treatment is associated with a lower incidence of hypothyroidism) (15-19).

We do not have antibody studies in our patients, but in order to implicate this as a factor one would have to assume an increase in autoimmune mechanisms in these patients. Age would not appear to be a factor, since our oldest patient was 55. The fact that 46 of our 48 patients were nonblack might be of some significance in our high incidence of hypothyroidism. The influence of race on response to I-131 certainly needs more investigation. Eleven of our 48 patients (23%) had been treated with thionamide preparations before receiving I-131. Five of these 11 (46%) required retreatment, whereas only four of the 37 (11%) not on thionamide before I-131 required retreatment. Viewed differently, six of 11 (55%) on thionamides became hypothyroid after one dose of I-131, as contrasted with 27 of 37 (73%) not on these medications. This apparent radioprotective effect of thionamides agrees with the findings of others (18-19). It is possible that our high incidence of hypothyroidism results mainly because only 23% of our patients received these preparations before I-131. In general the older literature with which we are comparing results does not state the number of patients who received prior treatment with thionamides. Although their study group included some patients with nodular glands, Nofal et al. reported that at least 51% of the patients treated between 1948 and 1963 received either propylthiouracil or iodine plus propylthiouracil before I-131 therapy (3). The overall incidence of hypothyroidism was 45% at 1 yr, but the relative incidence in those not pretreated with thionamides was not stated.

More recent data from Wise, indicating a 92% incidence of hypothyroidism at 6 mo, could be explained by the fact that only two of 50 patients had been pretreated with thionamide compounds (2). It is possible, therefore, that the lower incidence of hypothyroidism in earlier studies was because a larger percentage of patients were "protected" with these medications.

Several lines of evidence indicate that intrathyroidal iodine content is one factor that determines, in part, the response to both antithyroid drugs and radioiodine. Thionamide therapy leads to intrathyroidal iodine depletion (20). Patients given physiologic doses of iodine after discontinuing thionamides have a higher recurrence rate of thyrotoxicosis than similar patients not given iodine. In contrast, administration of pharmacologic amounts of iodine after I-131 treatment predisposes to hypofunction of the gland (21).

A recent increase in the iodine content of the diet in the U.S.A. has been described (22-24). Increased dietary iodine could therefore be a factor in both the increased recurrence rate after thionamide therapy and our increased incidence of hypothyroidism after I-131. One could then postulate that the radioresistance of patients given thionamides is due to intrathyroidal iodine depletion caused by these drugs.

We have addressed specifically the increased incidence of hypothyroidism after an average of 10 mCi of I-131 therapy. Given the above mechanisms to explain this increase, it is reasonable to assume that one would also see a higher incidence of hypothyroidism after smaller doses of I-131 than has been reported in the past.

A 2% per year incidence of hypothyroidism after the first year of followup in patients previously given radioiodine has been described (25). Whether in our population we will continue to see such an incidence is not known. Conceivably we have "selected out" those patients who are likely to become hypothyroid and merely brought this to bear within 1 yr of therapy.

In summary, we have presented data indicating a higher incidence of hypothyroidism within 1 yr after I-131 treatment for toxic diffuse goiter than would be expected from older series. This high incidence may be explained largely by a combination of increased dietary iodine and decreased use of thionamide preparations in recent years.

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