

Two-Week Low Iodine Diet Is Necessary for Adequate Outpatient Preparation for Radioiodine rhTSH Scanning in Patients Taking Levothyroxine

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We evaluated a self-managed, outpatient, low iodine diet (LID) ($<50 \mu\text{g}/\text{day}$) designed to decrease total body iodine (TBI) in preparation for radioiodine (^{131}I) scans. However, levothyroxine (LT_4) ingestion is a significant source of dietary iodine in recombinant human TSH (rhTSH)-stimulated studies. Measuring urine iodine to creatinine ratios (I/Cr), a reflection of TBI, we evaluated the LID for 7-day and 14-day periods to determine the efficacy of our LID to deplete TBI, with and without LT_4 . Patients following the LID for 14 days ($n = 28$) without LT_4 attained the goal of an iodine deficient state (I/Cr $<50 \mu\text{g}/\text{g}$) in 78% of cases, establishing the diet's efficacy in significantly reducing TBI. In patients taking LT_4 , 7 days of the LID was insufficient to attain this goal of true iodine deficiency. However, a 14 day LID while taking LT_4 resulted in 21% of patients being iodine deficient. For diagnostic purposes, a 7 day LID period ($n = 21$) suboptimally but adequately (I/Cr $<100 \mu\text{g}/\text{g}$) prepared 41% of the patients, whereas 14 days on the diet ($n = 24$) adequately prepared 71% of the patients taking LT_4 . Our simple, self-managed, outpatient, LID effectively makes patients iodine deficient. Though less efficacious when taking LT_4 , this LID adequately reduces TBI for rhTSH-stimulated ^{131}I uptake scans when followed for 14 days.

Introduction

MONITORING FOR RECURRENT THYROID CARCINOMA is a lifelong process. The most sensitive method for identifying recurrent thyroid carcinoma has been radioiodine (^{131}I) whole body scanning to localize tumor sites in combination with serum thyroglobulin (Tg) levels (1,2). To enhance ^{131}I uptake in whole body scans, thyrotropin (TSH) levels need to be markedly elevated (3). Typically, this has been done by withdrawal of thyroid hormone therapy prior to the administration of the ^{131}I tracers. This approach causes symptomatic hypothyroidism prior to and during the testing period (4). Administration of recombinant human TSH (rhTSH) (Thyrogen[®]) in euthyroid patients increases serum TSH prior to ^{131}I whole body scans, and has been demonstrated to be a safe and equally efficacious alternative to thyroid hormone withdrawal without hypothyroid sequelae (5).

As a result of iodine fortification of foods in the American diet, radioactive iodine uptake by the thyroid gland in standard scans has been reported to be reduced (6,7). This decline in medical iodine uptake supports the necessity of routinely preparing thyroid cancer patients prior to ^{131}I scans with LID, though the effect of LID on diagnostic efficacy has never been demonstrated. In order to increase uptake in di-

agnostic studies, and potentially enhance the effectiveness of ^{131}I therapy, various LIDs have been developed to decrease total body iodine prior to radioiodine administration (8–12). Many of the previously published diets varied in duration prior to treatment and usually involved oversight by or consultation with trained dietitians (9,10). Dietary iodine restriction has been clearly shown to be equally efficacious in lowering urinary iodine levels in both the euthyroid and hypothyroid state (10). While this approach has been successful in reducing total body iodine content as determined by a decrease in urinary iodine excretion (1,2), the expense and availability of trained dietitians does not always make this feasible. In this study we assessed the utility and effectiveness of a self-managed, outpatient, LID with respect to the length of the diet period and efficacy while taking LT_4 .

Materials and Methods

Patients

For over 15 years, a simple LID has been supplied to thyroid cancer patients in the Division of Endocrinology at Rhode Island Hospital in preparation for ^{131}I uptake scans to monitor for residual and recurrent thyroid carcinoma. Traditionally the standard of care at this institution had been a

two-week LID period prior to thyroprivic studies. However, with the development of rhTSH and its use in diagnostic thyroid scanning, a shorter LID period was presented as a component of the standardized protocols. This shorter, one-week diet period was adopted at this institution as the standard in rhTSH studies only. We questioned the efficacy of this change in our population with our simple LID. As a result of our initial findings, the diet protocol in the rhTSH studies was changed to our original diet protocol in use for the past two decades. As part of our standard protocol, spot urinary iodine and creatinine levels have been collected prior to ^{131}I administration to assure adequate diet preparation has been achieved when interpreting scan results. Since the urinary iodine results are not routinely available prior to scanning, the urinary iodine content does not influence clinical decision-making, just interpretation of results.

Hypothyroid scans

Retrospectively, 15 of the patients undergoing rhTSH scans underwent one or more previous thyroprivic scans prepared with the same diet over a two week period. Each diet period and scan event was considered individually. These patients were not taking their thyroid replacement medications, so dietary iodine was from food alone, while following the prescribed diet.

Recombinant human thyrotropin scans

Prospectively, 21 consecutive patients followed by 24 consecutive patients undergoing rhTSH scans to monitor for re-

current thyroid carcinoma were prepared with a one-week and a two-week self-administered LID, respectively. After receiving an outline of diet recommendations (Table 1), the diet was started one or two weeks prior to the first of two rhTSH injections followed by ^{131}I administration. No patients had received iodinated contrast materials in the six months prior to any of the diagnostic scans done in these studies.

Low iodine diet

During a regular office visit, the LID was explained to the patients. The patients were then sent home with a simple, one-page list of dietary recommendations (Table 1) to limit iodine intake for the period prior to ^{131}I administration and diagnostic scan. This diet is similar to previously published diets limiting daily iodine intake to 50 μg daily (9,10). We did not objectively monitor dietary compliance, as the urinary iodine levels were anticipated to document compliance. Patients were asked to follow the diet and most reported compliance, but detailed data on the patients' assessment of compliance was not routinely recorded.

Serum and urine measurements

Prior to ^{131}I administration, urine iodine and creatinine levels were collected from all subjects along with serum TSH determinations in those undergoing thyroprivic scans. Studies in the thyroprivic subjects were included only if the serum TSH was greater than 25 $\mu\text{U}/\text{L}$ prior to ^{131}I administration. The specific TSH results are not reported.

Urine iodine was measured by mass spectrometry with a

TABLE 1. DIETARY RECOMMENDATION SHEET

Low iodine diet

Avoid the following foods prior to your radioactive iodine test and until your scan and treatment, if needed, are complete:

1. Iodized salt, sea salt
2. Milk or other dairy products, including ice cream, cheese, yogurt, etc.
3. Eggs
4. Seafood, including fish, shellfish, kelp, or seaweed
5. Foods that contain the additives carragen, agar-agar, algin alginates
6. Cured and corned foods (ham, lox, corned beef, sauerkraut)
7. Breads made with iodinated dough conditioners
8. Foods and medications containing red food dyes
9. Chocolate
10. Molasses
11. Soy products (soy sauce, soy milk)

Additional Guidelines:

1. Avoid restaurant foods since there is no reasonable way to determine which restaurants use iodized salt
2. Foods that contain small amounts of milk or eggs may be used
3. Non-iodized salt may be used as desired
4. Consult your doctor before discontinuing any red-colored medication

Sample Meal Patterns:

Breakfast	Lunch	Dinner
Orange juice	Turkey sandwich	London broil
Cream of wheat	Lettuce & tomato	Mushroom sauce w/margarine
Whole wheat toast	Italian dressing	Green beans
Margarine	Fresh apple	Cucumber vinaigrette
	Graham crackers	Small roll
Coffee	Iced tea	Iced tea

Perkin-Elmer Elan 6000 at the Mayo Clinic. Urine samples are diluted 1:50 in 1% tetramethyl ammonium hydroxide containing 50 μg tellurium/L, and assessed for iodine content by mass spectrometry. Samples are compared to known values of iodine simultaneously analyzed with each batch. In addition, the urine sample is compared to itself before and after being spiked with 1000 $\mu\text{g}/\text{L}$ of iodine. The resulting concentration calculated from the spiked samples must be within 15% of the expected concentration.

Urine creatinine was measured using the Kodak Ektachem¹ system (Rochester, NY.) A creatinine-containing urine sample diluted 1:19 was placed on a slide with two gel layers incubated at 37°C. The two layers contain creatinine hydrolase and creatine hydrolase to ultimately convert creatinine into sarcosine. The creatinine, creatine, and sarcosine diffuse into the lower gel layer where sarcosine oxidase produces peroxide. In this gel layer the peroxide reacts with Leuco dye in the presence of a peroxidase to elicit a color change proportional to creatinine concentration. The optical density of the reaction is measured at 3.85 and 5 minutes at 670 nm. The rate of change between the two readings is proportional to the creatinine concentration. The system is calibrated with standardized Ektachem Verifiers[®].

Statistical analysis

Clinical categories for urinary iodine content are defined as excellent, adequate, inadequate, and poor for iodine/creatinine ratios of <50 $\mu\text{g}/\text{g}$, 51–100 $\mu\text{g}/\text{g}$, 101–250 $\mu\text{g}/\text{g}$, and >250 $\mu\text{g}/\text{g}$, respectively. These clinical categories were arbitrarily defined based on the clinical definition of iodine deficiency and previously defined regional normal urinary iodine levels. Values <50 $\mu\text{g}/\text{g}$ reflect an iodine deficient state (13), whereas values >100 $\mu\text{g}/\text{g}$ are consistent with a normal iodine diet (12). The designations of inadequate and poor reflect a failure to attain the dietary iodine goals of reduced urinary iodine. The “poor” designation reflects a urinary I/Cr two-fold greater than the normal median I/Cr for the northeastern United States (Table 2). Results are presented as mean \pm standard deviation, median, or as a percent of the total patient population in the study. Non-parametric Mann-Whitney rank tests were employed for sta-

tistical analysis. All results were attained as part of the standardized and usual care of thyroid carcinoma patients in the Division of Endocrinology at Rhode Island Hospital.

Results

Diet efficacy

Examining casual urinary samples prior to ¹³¹I administration in thyroprivic studies provides a patient population with no significant dietary iodine, if they conform to the LID. Though the male population in these studies was substantially smaller than the female population, no significant differences were identified between genders due to the wide variability in the results between patients. After two weeks on this outpatient LID, 78% of the thyroprivic patients were iodine deficient (<50 $\mu\text{g}/\text{g}$) (Fig. 1). The remaining 22% of patients had values representing total body iodine consistent with normal dietary iodine intake.

Levothyroxine as an iodine source

As in the thyroprivic studies, patients undergoing the studies with rhTSH followed the LID for a two-week period prior to ¹³¹I administration. However, due to the nature of the rhTSH methods, patients continue to take their LT₄ throughout the study preparation and scan. The presence of daily LT₄ provides a significant source of daily iodine intake for which the LID does not account. Twenty-four consecutive patients were prepared with the LID for a two week period while continuing their regular suppressive doses of LT₄ prior to a rhTSH-stimulated radioiodine study. Though only 15–25% of the patients were male, no significant gender specific differences were identified (Table 2). LT₄ significantly reduces the efficacy of the LID in lowering the urinary iodine to creatinine ratio to iodine deficient levels compared to patients not taking LT₄ (median iodine to creatinine ratio, $p < 0.001$). In the patients taking LT₄, 21% attained an iodine deficient state (Fig. 2B). In contrast, in the patient population not taking thyroid hormone while on the same diet, 78% attained an iodine deficient state (Fig. 1). However, despite continued LT₄ therapy, an additional 50% of the patients attained iodine to creatinine ratios which we categorized as

TABLE 2. URINARY IODINE/CREATININE ($\mu\text{g}/\text{g}$) AFTER LOW IODINE DIET PREPARATION: TWO-WEEK PERIOD WITH AND WITHOUT LEVOTHYROXINE (LT₄)

		All	Male	Female
Without LT ₄	Mean \pm SD	59.59 \pm 75.95	84.45 \pm 72.83	52.82 \pm 77.00
	Median	26.17 ^a	45.02	22.02
	n	28	6	22
	Urine [I-] ($\mu\text{g}/\text{L}$)	110.71 \pm 136.19	186.00 \pm 174.67	92.64 \pm 122.76
	n	31	6	25
With LT ₄	Mean \pm SD	84.69 \pm 44.03	66.27 \pm 28.38	88.37 \pm 46.38
	Median	76.91 ^a	56.52	82.5
	n	24	4	20
	Urine [I-] ($\mu\text{g}/\text{L}$)	123.88 \pm 82.89	130.25 \pm 115.99	122.73 \pm 79.05
	n	26	4	22
No diet	Mean \pm SD	118.5 \pm 5.5 ^b		

^aDenotes significance ($p < 0.001$) as determined by nonparametrical analysis with the Mann-Whitney rank test.

^bNHANES III Data for Northeastern United States (12).

[I-] presented as mean \pm SD.

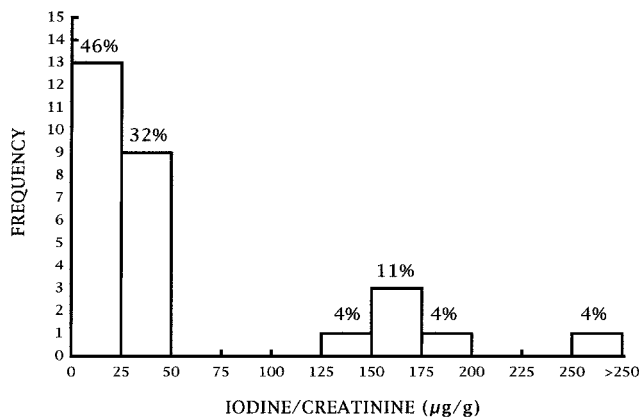


FIG. 1. Urinary iodine to creatinine ratio (I/Cr) following a two week low iodine diet (LID) in preparation for thyroprivic scans. Frequency of patients with urinary iodine/creatinine ratios within 25 µg/g intervals following a LID for two weeks in preparation for a thyroid hormone withdrawal radioiodine (¹³¹I) uptake scan. The desired goal was a urinary I/Cr <50 µg/g consistent with an iodine deficient state. A ratio of <100 µg/g was categorized adequate for radioiodine uptake and scanning. Ratios >100 µg/g were considered inadequate and consistent with a normal iodine diet. All patients studied had serum TSH levels >25 µU/L just prior to ¹³¹I administration.

adequate. Thus, 71% of the patients on LT₄ adequately reduced their total body iodine content while following this diet for two weeks. Notably, urine iodine concentrations (Table 2) after two weeks of LID with and without LT₄ were not significantly different ($p = 0.15$). This finding supports the necessity of normalizing the urine iodine concentration to a simultaneous urine creatinine concentration to adjust for the patient's hydration status and provide a more accurate representation of total body iodine.

Effect of diet period on efficacy

A two-week diet period significantly reduces total body iodine whether taking LT₄ or not. To understand the nature of the diet's efficacy, a one-week diet period was examined in 21 consecutive patients preparing to undergo an rhTSH ¹³¹I uptake study. Though one-fourth of the patients were male, no gender-specific differences were identified. The one week diet period was clearly less efficacious (median, $p < 0.003$) (Table 3). Although 41% of patients attained adequate low iodine status, 59% did not (Fig. 2A). Of those attaining adequate reduction in their total body iodine, none attained an iodine deficient state (<50 µg I/g Cr). Furthermore, a significant number of patients (27%) had iodine to creatinine ratios >250 µg/g, suggesting significant dietary iodine intake.

Since LT₄ was the only unaccounted-for source of dietary iodine in these patients, we correlated urinary iodine to creatinine content to LT₄ dose per kg body weight. Using least squares linear regression analysis, total body iodine correlated poorly to LT₄ dose in patients on the LID for one week. However, increasing the length of the diet period increased the correlation with LT₄ dose (Fig. 3). Extrapolating the expected mean urinary I/Cr when the LT₄ dose is zero gives a calculated I/Cr of 51 µg/g after two weeks on the diet. This calculated value closely approximates our measured mean urinary I/Cr when patients were on the diet without LT₄ for two weeks (Table 2). Age was also considered, but age correlated poorly with iodine to creatinine ratios in all groups (data not shown).

Discussion

Studies demonstrating the efficacy of administering rhTSH prior to ¹³¹I diagnostic scans have had mixed results when compared to scans performed after thyroid hormone withdrawal (14). The initial rhTSH studies did not report the routine use of LID prior to ¹³¹I administration (3,14). Later studies assessed urinary iodine output in trial patients, but did not report those results (3). The most recently reported

TABLE 3. URINARY IODINE/CREATININE (µg/g) AFTER LOW IODINE DIET PREPARATION: ONE- VS. TWO-WEEK PERIOD WHILE ON LEVOTHYROXINE (LT₄)

		All	Male	Female
One week	Mean ± SD	199.87 ± 169.53	158.99 ± 87.96	212.64 ± 188.49
	Median	109.78 ^a	145.16	107.07
	n	21	5	16
	LT ₄ dose (mg)	0.148 ± 0.047 ^b		
	Urine [I-] (ug/L)	258.78 ± 215.93	231.40 ± 102.18	273.82 ± 245.25
	n	23	5	17
Two weeks	Mean ± SD	84.69 ± 44.03	66.27 ± 28.38	88.37 ± 46.38
	Median	76.91 ^a	56.52	82.5
	n	24	4	20
	LT ₄ dose (mg)	0.139 ± 0.033 ^b		
	Urine [I-] (ug/L)	123.88 ± 82.89	130.25 ± 115.99	122.73 ± 79.05
	n	26	4	22

^aDenotes significance ($p < 0.003$).

^bDenotes no significance ($p > 0.47$).

Significance determined by nonparametrical analysis with the Mann-Whitney rank test. [I-] and LT₄ dose presented as mean ± SD.

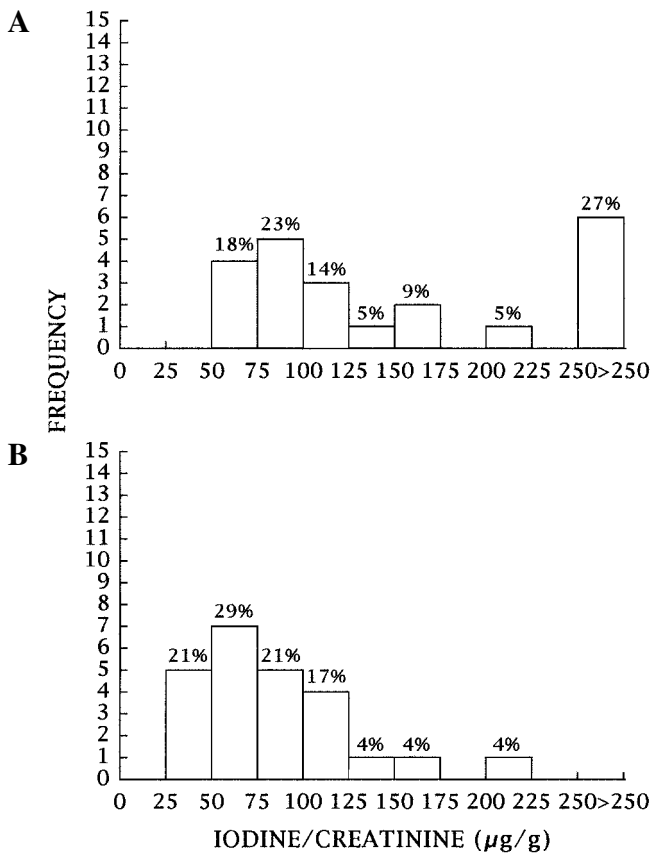


FIG. 2. Urinary iodine to creatinine ratios (I/Cr) following a one-week versus two-week LID period in patients taking levothyroxine (LT₄) in preparation for rhTSH-treated ¹³¹I uptake and scan. **A:** Frequency of patients with urinary I/Cr by 25 µg/g intervals following a LID for one week. **B:** Frequency of patients with urinary I/Cr by 25 µg/g intervals following a LID for two weeks. The desired goal urinary I/Cr was <50 µg/g, consistent with an iodine deficient state. A ratio of <100 µg/g was categorized adequate for radioiodine uptake and scanning. Ratios >100 µg/g were considered inadequate and consistent with a normal iodine diet.

trials comparing the efficacy of rhTSH with the thyroprivic scan protocols demonstrated an improved diagnostic efficacy compared to the previous studies, attributing the improvements to the standardization of their scanning techniques (5). However, this most recent study also recommended the use of LID prior to the diagnostic scans. Though this recommendation was apparently followed by a "majority of the investigators," the outcome of the LID suggested to participants prior to the administration of ¹³¹I was not reported nor considered in the determination of the relative efficacy between the two protocols (3).

Low iodine diets prior to ¹³¹I uptake scans have become prudent in the United States and other countries where basic staples have been supplemented with iodine (11). Average daily levels of dietary iodine have been demonstrated to limit the efficacy of ¹³¹I uptake scans, which can be remedied by a period of low dietary iodine intake preceding the scans (8,15). The utility of simplifying such diets has already been recognized. Several simplified LID studies have been clearly shown to be as effective as earlier well-defined, rig-

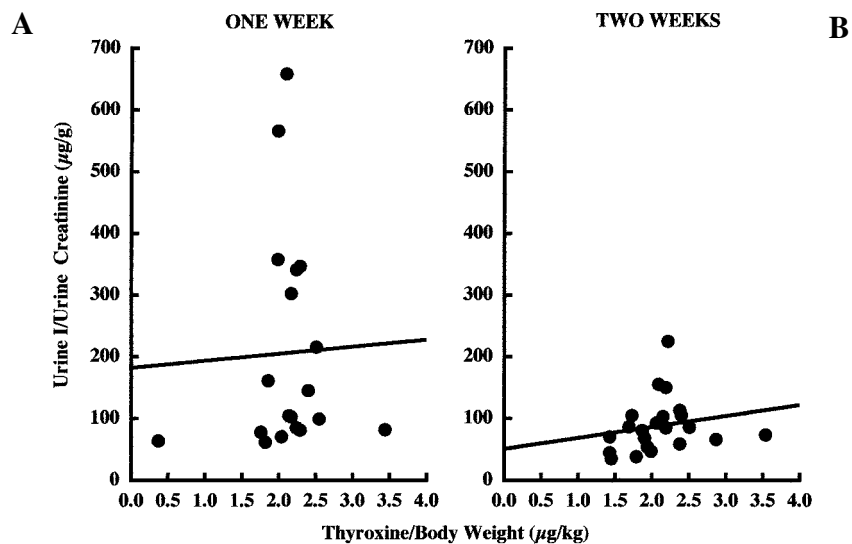


FIG. 3. Urinary iodine to creatinine ratios (I/Cr) correlate with LT₄ dose. Urinary I/Cr in patients preparing to undergo rhTSH ¹³¹I uptake scans while continuing to take LT₄ poorly correlates with the patient's LT₄ dose per kg body weight after one week on the LID. Extending the diet period increases the correlation between I/Cr and LT₄ /kg body weight. **A.** One-week diet preparation (m = 11.38, b = 182.16, R = 0.036). **B.** Two-week diet preparation (m = 17.66, b = 51.10, R = 0.195).

orous low iodine menus (9,10). These same LID studies also suggest that a one-week or shorter period is sufficient to lower urinary I/Cr to adequate levels for ^{131}I uptake and scans under study conditions. However, these previous studies rely significantly on dieticians or specific packaged meal plans (9,10,16,17).

A more recent study by Morris and colleagues also examined some outpatient LIDs in ^{131}I ablation patients and cited significant reductions in urinary iodine concentrations in this population (18). However, their reduction in urine iodine concentration was not associated with significantly increased ^{131}I ablation rates. Their urinary iodine results do not reflect total body iodine content. Without normalizing their urine iodine concentration to a simultaneous urine creatinine concentration, they do not account for each individual's hydration status. As such, for a given urine iodine content, a concentrated urine would yield a high urine iodine concentration, while a well hydrated individual with a dilute urine would have a low urine iodine concentration. Thus, urine iodine concentrations will vary independently from urinary iodine content and may not be representative of total body iodine. In our group, studies with our LID used in ^{131}I ablation preparations have yielded I/Cr results similar to values presented in this study. Unlike the results presented by Morris et al., preliminary observations in our ablation patients with our two-week diet period appear to have lower iodine levels and a higher percentage of successful ablations (19).

In our two studies we assessed our self-managed, outpatient LID. After preparation with one or two weeks of the LID, we measured spot urinary iodine levels prior to ^{131}I administration, since casual urine sampling for urine iodine and creatinine has been demonstrated to be a reliable representation of total body iodine (1,2). We identified categories of iodine depletion based upon the definition of iodine deficiency, urinary I/Cr $<50 \mu\text{g/g}$ (13), and established regional normal total body iodine content empirically determined for the northeastern United States (median urinary I/Cr, $118.5 \mu\text{g/g}$) (12). The goal urine iodine to creatinine ratio in these studies was true iodine deficiency, $<50 \mu\text{g}$ iodine/g creatinine. However, an iodine to creatinine ratio of $>50 \mu\text{g/g}$ but $<100 \mu\text{g}$ iodine/g creatinine, though suboptimal, was considered still adequate preparation for scanning. Based upon the reported value for the northeastern United States, urinary iodine to creatinine ratios greater than $100 \mu\text{g/g}$ were categorized as inadequate or poor preparation because they were consistent with a normal or elevated iodine diet.

LT_4 provides a significant source of daily iodine ingestion. Iodine makes up approximately 63.5% of the molecular weight of LT_4 . Every $100 \mu\text{g}$ of LT_4 contains $63.5 \mu\text{g}$ of iodine. The documented absorption of LT_4 ranges between 40% and 80% (20), with reported bioavailabilities of Synthroid® as high as 93% (20). Based on these reported bioavailabilities, $100 \mu\text{g}$ of LT_4 may provide anywhere from $25.4 \mu\text{g}$ to $59.1 \mu\text{g}$ of iodine daily. Because of this wide variability in bioavailability of iodine from LT_4 , we presented results as a function of total LT_4 per km body weight. Extrapolation of the LT_4 dose supports the idea that the LT_4 is the major source of iodine in the patients following the outpatient LID.

Adjusting the LT_4 dose prior to rhTSH administration theoretically may improve reduction in total body iodine by reducing dietary iodine intake. However, our results show the

importance of a two-week diet period. Though we do not have direct evidence for total body iodine reduction after one week on the diet without LT_4 , we can extrapolate the result from patients taking LT_4 . From these results, a mean urinary I/Cr after one week on the diet would be 182 g/g . In contrast, two weeks on the diet yields an extrapolated mean urine I/Cr of $51 \mu\text{g/g}$, which correlates with the measured mean urinary I/Cr in patients not taking LT_4 . This data suggests that a two-week LID is necessary to adequately reduce total body iodine prior to ^{131}I diagnostic studies.

The present study is one of the first to assess the viability and effectiveness of a self-motivated outpatient LID. Patients were merely given simple instructions and a general list of food types to avoid, and 78% of patients were able to reduce their total body iodine to an iodine deficient state as reflected in casual urinary iodine sampling, suggesting a diagnostic advantage in ^{131}I scans for residual thyroid carcinoma. These studies also demonstrate a reduction in diet efficacy due to continued daily LT_4 doses. However, the results with LT_4 in the diet support that a two-week course of the LID is more efficacious. Two weeks of preparation resulted in 71% of patients having a urinary iodine-creatinine ratio in the adequate range ($<100 \mu\text{g I/g Cr}$) versus 41% after one week. Though the diet was tested under differing conditions of thyroid status, previous studies have demonstrated that LIDs are equally effective in lowering urinary iodine output in both the euthyroid and hypothyroid states (10).

In conclusion, we suggest that rhTSH protocols for monitoring residual thyroid tissue or recurrent thyroid carcinoma may have an improved efficacy if patients are prepared with and monitored for compliance with an LID. Furthermore, we suggest an iodine deficient state prior to *any* radioiodine study or therapy may improve efficacy. These studies demonstrate the utility of simple, self-managed, outpatient LID guidelines to effectively reduce total body iodine content. These studies also support the necessity of a two-week diet preparation for adequate reduction in total body iodine.

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