Low-Iodine Diet of 4 Days Is Sufficient Preparation for I-131 Therapy in Differentiated Thyroid Cancer Patients

Dekker, Bernadette L.; Links, Mirthe H.; Kobold, Anneke C. Muller; Swart-Busscher, Linda G.; Kars, Marleen; Bons, Judith A. P.; Brouwers, Adrienne H.; Links, Thera P.; Van der Horst-Schrivers, Anouk N. A.

Published in:
Journal of Clinical Endocrinology & Metabolism

DOI:
10.1210/clinem/dgab691

Publication date:
2022

The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 2, e604–e611
https://doi.org/10.1210/clinem/dgab691
Clinical Research Article

Clinical Research Article

Low-Iodine Diet of 4 Days Is Sufficient Preparation for ^{131}I Therapy in Differentiated Thyroid Cancer Patients

Bernadette L. Dekker,[1] Mirthe H. Links,[1] Anneke C. Muller Kobold,[2] Linda G. Swart-Busscher,[3] Marleen Kars,[4] Judith A.P. Bons,[5] Adrienne H. Brouwers,[6] Thera P. Links,[1] and Anouk N. A. van der Horst-Schrivers[1,4]

[1]University of Groningen, University Medical Center Groningen, Internal Medicine, Department of Endocrinology, 9700 RB Groningen, the Netherlands; [2]University of Groningen, University Medical Center Groningen, Department of Laboratory Medicine, 9700 RB Groningen, the Netherlands; [3]University of Groningen, University Medical Center Groningen, Department of Paramedical Sciences, 9700 RB Groningen, the Netherlands; [4]Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Center, 6202 AZ, Maastricht, the Netherlands; [5]Central Diagnostic Laboratory, Maastricht University Medical Center, 6202 AZ, Maastricht, the Netherlands; and [6]University of Groningen, University Medical Center Groningen, Department of Nuclear Medicine and Molecular Imaging, 9700 RB Groningen, the Netherlands

ORCiD numbers: 0000-0002-4785-9723 (B. L. Dekker); 0000-0003-3457-4179 (A. C. Muller Kobold); 0000-0003-2698-1516 (A. H. Brouwers); 0000-0001-5327-1718 (T. P. Links); 0000-0002-1181-5032 (A. N. A. van der Horst-Schrivers).

Abbreviations: ^{131}I, radioactive iodine; DTC, differentiated thyroid cancer; gCr, grams of creatinine; I/Cr, iodine to creatinine ratio; IQR, interquartile range; LID, low-iodine diet; MUMC+, Maastricht University Medical Center+; NIS, sodium-iodine symporter; rhTSH, recombinant human thyrotropin; THW, withdrawn from thyroid hormone; TSH, thyrotropin; UIE, urinary iodine excretion; UMCG, University Medical Center Groningen.

Received: 29 June 2021; Editorial Decision: 13 September 2021; First Published Online: 17 September 2021; Corrected and Typeset: 7 October 2021.

Abstract

Context: No consensus exists about the optimal duration of the low-iodine diet (LID) in the preparation of ^{131}I therapy in differentiated thyroid cancer (DTC) patients.

Objective: This work aimed to investigate if a LID of 4 days is enough to achieve adequate iodine depletion in preparation for ^{131}I therapy. In addition, the nutritional status of the LID was evaluated.

Methods: In this prospective study, 65 DTC patients treated at 2 university medical centers were included between 2018 and 2021. The patients collected 24-hour urine on days 4 and 7 of the LID and kept a food diary before and during the LID. The primary

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

outcome was the difference between the 24-hour urinary iodine excretion (UIE) on both days.

Results: The median 24-hour UIE on days 4 and 7 of the LID were not significantly different (36.1 mcg [interquartile range, 25.4-51.2 mcg] and 36.5 mcg [interquartile range, 23.9-47.7 mcg], respectively, $P = .43$). On day 4 of the LID, 72.1% of the DTC patients were adequately prepared (24-hour UIE < 50 mcg), and 82.0% of the DTC patients on day 7 ($P = .18$). Compared to the self-reported regular diet, DTC patients showed a significantly ($P < .01$) lower percentage of nutrient intake (calories, protein, calcium, iodine, and water) during the LID.

Conclusion: The 24-hour UIE on day 4 of the LID did not differ from day 7, and therefore shortening the LID from 7 to 4 days seems justified to prepare DTC patients for ^{131}I therapy in areas with sufficient iodine intake and may be beneficial to maintain a sufficient nutritional intake during DTC treatment.

Key Words: low-iodine diet, radioactive iodine therapy, urinary iodine excretion, iodine intake, nutrition diary, individual perceptions

In a substantial number of patients with differentiated thyroid cancer (DTC), radioactive iodine (^{131}I) therapy after a (near) total thyroidectomy is recommended, with the primary goal of destroying residual normal thyroid tissue and potentially cancerous tissue. Several (inter)national guidelines advise a low-iodine diet (LID), with the aim of less than 50 mcg iodine intake per day, to improve the outcome of ^{131}I therapy (1-4). A LID depletes the overall iodine body storage, and it is postulated that this leads to an increased expression of the sodium-iodine symporter (NIS), which results in an increased uptake of ^{131}I, thereby augmenting the effect of ^{131}I (5-7). In addition, stimulation of the thyrotropin (TSH) receptor plays an important role in upregulating NIS expression and, therefore, in the uptake of ^{131}I (8).

Consensus about the optimal duration of the LID in different guidelines is lacking. The American and British Thyroid Associations recommend a LID of approximately 1 to 2 weeks, the European Thyroid Association advises a LID of 3 weeks, and the European Association of Nuclear Medicine recommends an optional LID of 1 to 2 weeks (1-4).

At the beginning of this century, 2 studies recommended a LID of 2 weeks for optimal ^{131}I therapy preparation (9, 10). These studies were followed by more recent findings suggesting an adequate depletion can already be accomplished with a LID of 1 week (11-13). In these studies, several definitions of an adequate depletion differed significantly; 24-hour urinary iodine excretion (UIE) less than 66.2 mcg/g creatinine (gCr) or less than 50 mcg/L or less than 50 mcg/gCr or less than 100 mcg/gCr (9-13). One study with historical cohorts showed that adequate depletion using the strict reference standard of 24-hour UIE less than 50 mcg/24h had been achieved in some patients after only 4 days; however, this study included only a subgroup of patients who followed the LID (14).

Adherence to a LID can be stressful, distasteful, and overwhelming during a period of thyroid cancer treatment, even more so for patients suffering from complaints of hypothyroidism due to thyroid hormone withdrawal. In addition, minimizing iodine intake also complicates achieving a balanced diet, which is essential in any cancer recovery, and therefore, shortening the LID from 1 to 2 weeks to 4 days could be beneficial for DTC patients (15, 16).

For this reason, we prospectively investigated if a LID of 4 days is enough in areas with sufficient iodine intake to achieve adequate iodine depletion in preparation for ^{131}I therapy by comparing the 24-h UIE on day 4 of the LID to day 7 of the LID. Second, we aimed to assess the nutritional status of patients while on a LID and evaluated the individual perception of DTC patients regarding the LID.

Materials and Methods

Patients

In this prospective multicenter study, consecutive DTC patients (age ≥ 18 years) who were scheduled for ^{131}I therapy, between May 2018 and March 2021, at the University Medical Center Groningen (UMCG) or between May 2020 and March 2021 at the Maastricht University Medical Center+ (MUMC+), were asked to participate in this study. Exclusion criteria were the use of iodine-containing drugs (like amiodarone), a diagnostic scan with iodinated contrast within 3 months before the ^{131}I therapy, and the inability to understand the Dutch language.

Patients were treated according to the Dutch DTC guidelines; in general, a (near) total thyroidectomy

with or without additional lymph node dissection was performed (17). In preparation for the subsequent ^{131}I therapy, patients were withdrawn from thyroid hormone (THW, with the aim of a TSH level > 25 mU/L before ^{131}I therapy) or received recombinant human (rh)TSH on clinical indication with the continuation of thyroid hormone substitution, and had to follow a LID of 7 days, with an iodine intake of less than 50 mcg/24h. They received written instructions, a sample menu, a link to a website containing low-iodine recipes (www.jodiumarm.nl), and contact details of the dietician who could be contacted as needed.

Medical records were used to obtain medical history, diagnosis, and treatment details. DTC was defined as papillary and follicular thyroid carcinoma (including all subtypes). Tumors were staged and reclassified according to the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM. The TSH value was determined, during THW or rhTSH, one day before or the day of ^{131}I administration.

Study approval by the medical ethics committee of the UMCG (No. METc 2017/647) and MUMC+ (No. RvB/300674) was waived because this study is not clinical research with humans as intended in the Medical Research Involving Human Subjects Act (WMO). All participants gave written informed consent.

Urinary Iodine Measurements

Patients collected 24-hour urine on day 4 and day 7 of the LID, volume was determined, and a urine sample was stored at –20 °C until processing. All samples were analyzed at the UMCG, and for determination of the urinary iodine, creatinine, and sodium, a sample of the 24-hour urine collection was used.

Urinary iodine was measured using an inductively coupled plasma mass spectrometer (ICP-MS, Thermo Scientific iCap-TQ). The total interassay and intra-assay coefficient of variation values were 2.1% to 2.9% at 40.0 mcg/L and 2.2% to 3.5% at 225 mcg/L. The limit of quantification was 10 mcg/L (coefficient of variation of 8.9%).

Urinary creatinine was analyzed using the enzymatic creatinine assay on the Roche cobas c system (Roche) based on the conversion of creatinine with creatininase, creatinase, and sarcosine oxidase to glycine, formaldehyde, and hydrogen peroxide.

Urinary sodium was analyzed by an ion-selective electrode on the Roche cobas c analyzer.

Serum TSH was measured using an electrochemiluminescent immunometric assay (Cobas 8000 instrument, Roche Diagnostics).

The UIE was expressed as 24-hour UIE (mcg/24h) and as the iodine to creatinine ratio (I/Cr, mcg/gCr) based on the 24-hour urine collection.

Our primary outcome was the difference between the 24-hour UIE on day 4 and day 7 of the LID. An incomplete 24-hour urine collection (< 600 mL) was excluded from the 24-hour UIE analysis. To ensure we could use the iodine to creatinine ratio, we correlated 24-hour UIE (gold standard) with I/Cr. Several definitions were used to define an adequate LID preparation to compare the success rates between both days: 24-hour UIE less than 50 mcg/24h (strict reference standard), I/Cr less than 50 mcg/gCr; and I/Cr less than 100 mcg/gCr (9, 10, 13, 14).

Nutritional Evaluation

To evaluate the nutritional status, patients noted their food and dietary supplement intake 3 days before and 4 days during the LID in a food diary (Supplementary Table S1) (18). The food intake before the LID provided information about the everyday choices (regular diet) of the patients. The dietary intake was evaluated by a dietician (L.S.B.) using the guidelines of the Health Council of the Netherlands; the intake of several macronutrients and micronutrients (calories, protein, calcium, sodium, iodine, and water) was expressed as the percentage of the dietary reference intake (19). In the week before the LID, sufficient iodine intake was defined as more than 150 mcg/24h (20). In the Netherlands, on a population basis, the daily intake of iodine is optimal (21, 22). The self-reported salt intake was based on the total amount of salt intake during the day, including salt-containing products; patients were informed to use noniodinated salt during the LID.

In addition, to evaluate the individual perception toward the LID, patients were asked to answer 11 questions after following the LID of seven days (Supplementary Table S2) (18).

Statistical Analysis

The primary end point was the difference between the 24-hour UIE on days 4 and 7 of the LID. We hypothesized a significantly lower 24-hour UIE on day 7 of the LID (SD = 0.25). The sample size required to provide more than 80% power with a one-sided α level of .05 was calculated to be 65 patients. Data were expressed as mean with ± SD or median with interquartile range (IQR). For paired data, we used the Wilcoxon signed rank test and the McNemar test. For unpaired data, the Pearson chi-square test and Fisher exact test were used. In addition, the Spearman correlation was used to

correlate the 24-hour UIE and I/Cr. We calculated the median of the individual percentage differences of the 24-hour UIE between days 4 and 7 of the LID. To calculate this individual percentage difference, the following formula was used: ((24h UIE day 4 – 24h UIE day 7)/(24h UIE day 4)) × 100. *P* values less than .05 were considered significant. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp) was used for statistical analysis of the data.

Results

Patient Characteristics

A total of 124 DTC patients were eligible for inclusion. Two were excluded from participation because they could not understand the Dutch language, and 57 patients did not want to participate. All 59 excluded patients followed a LID in preparation for their ^{131}I therapy.

Sixty-five patients with a mean age of 54 years (SD ± 14.8) were included. Forty-one patients (63.0%) were female, and 40 patients (61.5%) were diagnosed with papillary thyroid carcinoma. Three patients (4.6%) received rhTSH before ^{131}I therapy, and 62 patients (95.4%) were prepared with THW. TSH levels were more than 25.0 mU/L before or the day of receiving ^{131}I therapy in all patients. For clinical and treatment characteristics, see Table 1.

Urinary Iodine Excretion During the Low-Iodine Diet

Eight out of 130 24-hour urine collections were incomplete. Sixty-one 24-hour urine collections on day 4 and 61 24-hour urine collections on day 7 were available for data analysis on 24-hour UIE. All 130 24-hour urine collections (65 paired) were used for data analysis on I/Cr.

The median 24-hour UIE on days 4 and 7 of the LID were 36.1 mcg (IQR, 25.4-51.2 mcg) and 36.5 mcg (IQR, 23.9-47.7 mcg), respectively (*P* = .43, Fig. 1). The median of the individual percentage differences of the 24-hour UIE between days 4 and 7 of the LID was 4.7% (decrease). The correlations between the 24-hour UIE and I/Cr were good on days 4 and 7 of the LID (ρ = 0.718, *P* < .01, and ρ = 0.727, *P* < .01, respectively).

Using the definition of 24-hour UIE less than 50 mcg/24h as an adequate LID preparation, 44 of the 61 patients (72.1%) were already adequately prepared on day 4, and 50 of the 61 patients (82.0%) on day 7 (*P* = .18, Fig. 2 and Table 2). The percentages of DTC patients fulfilling the criteria of an adequate LID by other definitions are illustrated in Table 2.

Table 1. Characteristics of the study population

	Total study population
No.	65
Sex, No.	
Male/female	24/41
Age during LID, y	53.7 ± 14.8
Histology, No.	
Papillary/follicular	40/25
TNM, %	
T1-T2	38 (58.5)
T3-T4	27 (41.5)
N0	43 (66.2)
N1a-N1b	22 (33.8)
M0	62 (95.4)
M1	3 (4.6)
AJCC stage, %	
1	42 (64.6)
2	19 (29.2)
3	2 (3.1)
4A	–
4B	2 (3.1)
ATA risk stratification, %	
Low	14 (21.5)
Intermediate	42 (64.6)
High	9 (13.8)
^{131}I therapy[a], %	
First	48 (73.8)
Second	17 (26.2)
TSH[b], mU/L	82.0 (66.5-106.0)

Data are expressed as mean (± SD), median (interquartile range) or number (%).

Abbreviations: ^{131}I, radioactive iodine; AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; LID, low-iodine diet; TSH, thyrotropin.

[a]Number of ^{131}I therapies at the moment of study participation; first ^{131}I therapy indicates ablation therapy, and second ^{131}I therapy indicates additional treatment when indicated.

[b]Before ^{131}I therapy during thyroid hormone withdrawal (n = 62) or recombinant human TSH (n = 3).

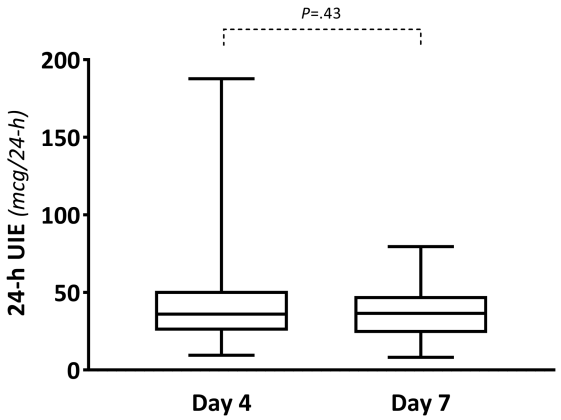

Figure 1. Twenty-four–hour urinary iodine excretion (mcg/24-h) on days 4 and 7 of the low-iodine diet in preparation of ^{131}I therapy. Data expressed as median (interquartile range) and minimum and maximum values.

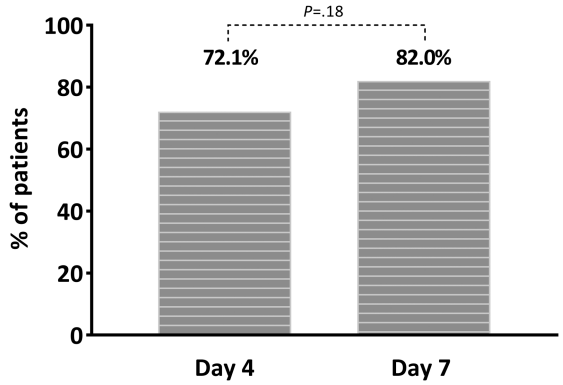

Figure 2. Percentage of differentiated thyroid cancer patients with a 24-hour urinary iodine excretion less than 50 mcg on days 4 and 7 of the low-iodine diet in preparation of ^{131}I therapy. Data expressed as percentage (%).

Table 2. Percentages of differentiated thyroid cancer patients fulfilling the criteria of adequate low-iodine diet

Definition of adequate LID	D 4, %	D 7, %	*P*
< 50 mcg/24 h	72.1	82.0	.18
< 50 mcg/gCr	79.7	73.4	.42
< 100 mcg/gCr	98.4	100	≥ .999

Data expressed as percentages (%).
Abbreviations: gCr, grams of creatinine; LID, low-iodine diet.

Nutritional Evaluation and Individual Perceptions Regarding the Low-Iodine Diet

Compared to the regular diet, during the LID, DTC patients showed a significantly ($P < .01$) lower percentage of the dietary reference intake with regard to calories, protein, calcium, iodine, and water (Table 3). No difference was found between the first 3 days of the LID and day 6 concerning the daily self-reported iodine intake (55.0 mcg [IQR, 37.5-67.0 mcg] and 54.0 mcg [IQR, 35.5-71.0 mcg], respectively, $P = .83$). The daily self-reported iodine intake before the LID was significantly higher (145 mcg [IQR 120.5-181.0 mcg]) compared to the intake during the LID (55.0 mcg [IQR, 37.3-71.5 mcg]; $P < .01$).

The median self-reported salt intake during the regular diet was 4.8 g/day (IQR, 3.9-5.8 g/day], which was significantly ($P < .01$) higher than the self-reported salt intake during the diet week (2.2 g/day [IQR, 1.7-3.1 g/day]). Based on the urinary sodium excretion on days 4 and 7 of the LID, the median salt intake was 3.6 g/day (IQR, 2.1-4.6 g/day) and 3.0 g/day (IQR, 1.9-4.3 g/day) on days 4 and 7 of the LID, respectively.

Fifty-nine of the 65 DTC patients (90.8%) reported compliance with the diet for the recommended 7 days. Patients who were not adequately prepared (24h UIE ≥ 50 mcg/24h) did not report significant differences compared to adequately prepared DTC patients, concerning difficulties in maintaining the LID, composing a daily menu, and the individual perception toward the LID in terms of taste and nutritiousness (Table 4).

Table 3. Comparison of nutritional status of self-reported regular diet and low-iodine diet in differentiated thyroid cancer patients

	Before LID	LID	*P*
No.	57[a]	64[b]	
Calories, % of DRI	83.0 (66.5-95.5)	64.0 (52.3-79.5)	< .01
Protein, % of DRI	133.0 (112.0-154.5)	100.0 (82.3-117.0)	< .01
Calcium, % of DRI	73.0 (46.0-101.5)	41.0 (33.0-54.0)	< .01
Iodine, % of DRI	97.0 (80.0-120.5)	36.5 (24.5-47.8)	< .01
Water, % of DRI	75.0 (56.0-133.5)	60.0 (43.3-109.0)	< .01

Data are expressed as median (interquartile range).
Abbreviations: DRI, dietary reference intake; LID, low-iodine diet.
[a]Eight DTC patients did not report their food intake before LID, hence n = 57.
[b]One DTC patient did not report his food intake before LID, hence n = 64.

Discussion

In this prospective multicenter study, we demonstrate that the 24-hour UIE on day 4 of the LID did not differ from the 24-hour UIE on day 7 of the LID, supporting that a LID of 4 days is equivalent to a LID of 7 days in the preparation of DTC patients for ^{131}I therapy. Depending on the definition used for adequate LID preparation, most of the included DTC patients (72.1%-98.4%) achieved an adequate preparation for ^{131}I therapy with a LID of 4 days. In addition, the self-reported intake of macronutrients and micronutrients of the DTC patients during the diet decreased substantially compared to their regular intake.

Several studies showed that a LID of 7 days is sufficient to achieve target UIE values for the preparation of ^{131}I therapy (11-13). Only the retrospective study by Pluijmen et al (14) showed that the strict reference UIE target of less than 50 mcg/24h can be achieved in 4 days; however, an unknown number of patients with a 24-hour UIE greater than 49.4 mcg/24h was excluded. Our prospective study shows that 72.1% of DTC patients can achieve this strict reference target within 4 days, and that after 4 days, the additional decrease is negligable (4.7%). Our results are also supported by 2 Korean studies that nicely illustrated the pattern of UIE during a LID of 14 days (11, 13). They

Table 4. Individual perceptions of differentiated thyroid cancer patients regarding low-iodine diet

	24-h UIE < 50[b]	24-h UIE ≥ 50	*P*
No.[a]	44	17	
It was *hard* to maintain the LID	3.0 (2.0-3.0)	3.0 (2.0-3.0)	.38
It was *hard* to compose a daily menu during the LID	3.0 (2.0-3.0)	3.0 (2.0-3.0)	.85
The LID was *not* nutritious	3.0 (2.0-3.0)	2.0 (2.0-3.0)	.18
The LID was *not* tasty	3.0 (2.3-3.0)	2.0 (2.0-3.0)	.12
How many days did you maintain the LID, %			.61
5	1 (2.3)	1 (5.9)	
6	3 (6.8)	1 (5.9)	
7	40 (90.9)	15 (88.2)	
Fish consumption per wk in regular diet, %			.25
Never	16 (36.4)	3 (17.6)	
1	27 (61.4)	14 (82.4)	
> 1	1 (2.3)	–	
Bread consumption per wk in regular diet, %			.89
Never	–	–	
1-2	4 (9.1)	1 (5.9)	
3-5	6 (13.6)	3 (17.6)	
6-7	34 (77.3)	13 (76.5)	

A 4-point scale was used from 1 (strongly agree) to 4 (strongly disagree). Values are expressed as median (interquartile range) or number (%).
Abbreviations: LID, low-iodine diet; UIE, urinary iodine excretion.
[a]Data missing for 4 differentiated thyroid cancer patients.
[b]Day 4 of the LID.

showed a significant drop of the UIE, measured as urine I/Cr ratio, within the first 3 days, followed by a flattened line during the rest of the diet.

Guidelines advise a LID to deplete the overall iodine body store. However, until now, randomized prospective trials that show that a LID improves ablation success have been lacking. Theoretically, a depleted iodine plasma concentration increases the NIS expression, and, therefore, optimizes ^{131}I uptake. An animal study with pregnant rats showed that iodine deficiency induces NIS messenger RNA expression in the thyroid gland of the fetus and the fetal side of the placenta (23).

In clinical practice, the advice on how long and strict the LID should be differs between countries and even between hospitals of one country (24), which can be very confusing for patients.

The intake of the self-reported different nutrients decreased significantly during the LID compared to the regular dietary intake of the DTC patients. Similar findings were reported by a Korean study and represent the difficulties for DTC patients to maintain a balanced diet with iodine intake restriction (25). We did not measure the patients' weight in this study, but a hypothyroid state nullifies a possible weight loss. In a previous study, we found an increase in body weight after the LID compared to the weight a couple of weeks before the LID (26). In addition, we also found low salt intake during the LID, which illustrates that patients confuse the LID with a low-salt diet (14). In the literature, the development of hyponatremia by following a LID, especially in vulnerable patients, has been described several times (27-29).

In general, the participants in our study did not have a strong opinion about perceived barriers regarding the LID. Some individuals reported difficulties composing a daily menu and experienced stress about contributing to treatment failure when not following the diet correctly, experiences also described in other countries (30, 31).

The strengths of this study are the prospective design, the collection of 24-hour urine to evaluate the body iodine pool, and the extrapolation to daily care practice in countries with sufficient iodine intake. This study also has some limitations. First, a LID of 4 days might not be suitable for iodine-rich areas. Second, the self-reported nutrition diaries could be vulnerable to underestimation of the dietary intake. Finally, there was no documentation of the baseline 24-hour UIE before the LID to confirm that the 24-hour UIE decreased during the LID. However, there was a substantial decrease in the iodine intake during the LID compared to the regular diet, and previous data from the Dutch population show that the Netherlands is a country with optimal iodine nutrition status with a substantially higher 24-hour UIE than the reported 24-hour UIE during the LID (22, 32).

Continued levothyroxine in patients prepared for ^{131}I therapy with rhTSH may lead to an increased iodine body pool. Until now, studies have not suggested that these patients have to follow a LID of a longer duration (13, 33). However, we cannot be sure whether 4 days is enough for these patients since we included only 3 patients prepared with rhTSH. It is also not possible to draw separate conclusion for low- or high-risk-patients. In general, there is a tendency toward less-aggressive management for low-risk DTC patients; an optimal or strict LID might be less important in patients with an excellent prognosis.

To conclude, the 24-hour UIE on day 4 of the LID did not differ from day 7. Therefore, shortening the LID from 7 to 4 days seems justified to prepare DTC patients for ^{131}I therapy in areas with sufficient iodine intake. Shortening the LID may benefit DTC patients to maintain a sufficient nutritional intake during their treatment.

Acknowledgments

We would like to thank J. IJmker of the Department of Clinical Pharmacy and Pharmacology of the University Medical Center

Groningen, H. Breukelman of the Central Freezer Facility of the University Medical Center Groningen, M. Goessens of the Central Diagnostic Laboratory of the Maastricht University Medical Center, and H. Tjon-A-Fat of the Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Center, for their help.

Financial Support: This work was supported by Junior Scientific Masterclass Groningen (to B.L.D.).

Author Contributions: Study concept and design: Dekker, Muller Kobold, Links (T.P.), van der Horst-Schrivers. Acquisition, analysis, or interpretation of data: Dekker, Links (M.H.), Muller Kobold, Swart-Busscher, Kars, Links (T.P.), van der Horst-Schrivers. Drafting of the manuscript: Dekker, van der Horst-Schrivers. Critical revision of the manuscript for important intellectual content: Links (M.H.), Muller Kobold, Swart-Busscher, Kars, Bons, Brouwers, Links (T.P.). Obtained funding: Dekker, Muller Kobold, Links (T.P.), van der Horst-Schrivers. Administrative, technical, or material support: Muller Kobold, Swart-Busscher, Bons. Final approval of the version to be published: all authors.

Additional Information

Correspondence: Anouk N. A. van der Horst-Schrivers, MD, PhD, Maastricht University Medical Center, Division of Endocrinology, Postbus 5800, 6202 AZ, Maastricht, the Netherlands. Email: anouk.schrivers@mumc.nl.

Disclosures: The authors have nothing to disclose.

Data Availability: Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;**26**(1):1-133.
2. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol*. 2006;**154**(6):787-803.
3. Perros P, Boelaert K, Colley S, et al; British Thyroid Association. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014;**81**(Suppl 1):1-122.
4. Luster M, Clarke SE, Dietlein M, et al; European Association of Nuclear Medicine (EANM). Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging*. 2008;**35**(10):1941-1959.
5. Goslings BM. Proceedings: effect of a low iodine diet on 131-I therapy in follicular thyroid carcinomata. *J Endocrinol*. 1975;**64**(3):30P.
6. Sawka AM, Ibrahim-Zada I, Galacgac P, et al. Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. *Thyroid*. 2010;**20**(10):1129-1138.
7. Li JH, He ZH, Bansal V, Hennessey JV. Low iodine diet in differentiated thyroid cancer: a review. *Clin Endocrinol (Oxf)*. 2016;**84**(1):3-12.
8. Spitzweg C, Morris JC. The sodium iodide symporter: its pathophysiological and therapeutic implications. *Clin Endocrinol (Oxf)*. 2002;**57**(5):559-574.
9. Park JT II, Hennessey JV. Two-week low iodine diet is necessary for adequate outpatient preparation for radioiodine rhTSH scanning in patients taking levothyroxine. *Thyroid*. 2004;**14**(1):57-63.
10. Tomoda C, Uruno T, Takamura Y, et al. Reevaluation of stringent low iodine diet in outpatient preparation for radioiodine examination and therapy. *Endocr J*. 2005;**52**(2):237-240.
11. Kim HK, Lee SY, Lee JI, et al. Daily urine iodine excretion while consuming a low-iodine diet in preparation for radioactive iodine therapy in a high iodine intake area. *Clin Endocrinol (Oxf)*. 2011;**75**(6):851-856.
12. Lee M, Lee YK, Jeon TJ, et al. Low iodine diet for one week is sufficient for adequate preparation of high dose radioactive iodine ablation therapy of differentiated thyroid cancer patients in iodine-rich areas. *Thyroid*. 2014;**24**(8):1289-1296.
13. Kang SW, Yap ZZ, Lee CR, et al. Pattern of urine iodine excretion with low iodine diet during preparation for radioactive iodine ablation in patients with thyroid cancer. *Head Neck*. 2019;**41**(2):381-387.
14. Pluijmen MJ, Eustatia-Rutten C, Goslings BM, et al. Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)*. 2003;**58**(4):428-435.
15. Moon JA, Yoo CH, Kim MH, et al. Knowledge, self-efficacy, and perceived barriers on the low-iodine diet among thyroid cancer patients preparing for radioactive iodine therapy. *Clin Nutr Res*. 2012;**1**(1):13-22.
16. Morris LF, Wilder MS, Waxman AD, Braunstein GD. Reevaluation of the impact of a stringent low-iodine diet on ablation rates in radioiodine treatment of thyroid carcinoma. *Thyroid*. 2001;**11**(8):749-755.
17. Guideline database. Federation Medical Specialists. Richtlijn voor de diagnostiek, behandeling en follow-up van patiënten met gedifferentieerd (niet-medullair) schildkliercarcinoom. 2014. Accessed August 30, 2021. https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html
18. Dekker BL, Links MH, Muller Kobold AC, et al. LID of four days in DTC patients–Supplemental data. 2021. https://doi.org/10.6084/m9.figshare.14852085.v1
19. Dutch Health Council (Gezondheidsraad) (2015) Dutch dietary guidelines 2015 (Richtlijnen goede voeding 2015). Publication No. 2015/24. ISBN 978-94-6281-089-1. The Hague.
20. WHO, UN Children's Fund, International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. A Guide for Programme Managers*. 3rd ed. World Health Organization; 2007.
21. Geurts M, Verkaik-Kloosterman J. De jodiuminname van de Nederlandse bevolking na verdere zoutverlaging in brood. *RIVM Briefrapport*. 2014:1-37.
22. Wilson-van den Hooven C, Fransen H, Ris-Stalpers C, Ock M. 24-uurs urine-excretie van jodium; Voedingsstatusonderzoek bij volwassen Nederlanders. *RIVM Briefrapport*. 2007:1-20.

23. Schröder-van der Elst JP, van der Heide D, Kastelijn J, Rousset B, Obregón MJ. The expression of the sodium/iodide symporter is up-regulated in the thyroid of fetuses of iodine-deficient rats. *Endocrinology*. 2001;**142**(9):3736-3741.
24. England CY, Moss L, Beasley M, Haupt-Schott I, Herbert G, Atkinson C. A survey of UK centres on low iodine diet recommendations prior to radioiodine ablation therapy for differentiated thyroid cancer. *Eur Thyroid J*. 2020;**9**(3):132-138.
25. Ju DL, Park YJ, Paik HY, et al. Dietary evaluation of a low-iodine diet in Korean thyroid cancer patients preparing for radioactive iodine therapy in an iodine-rich region. *Nutr Res Pract*. 2016;**10**(2):167-174.
26. Jagersma RJ, Muller Kobold AC, Swart LG, Dekker BL, Links TP, van der Horst-Schrivers ANA. The low iodine diet: time for improvement. Paper presented at: Program of the 39th Annual Meeting of the European Thyroid Journal; 2016, Copenhagen, Denmark; 164 (Abstract P3-06-10).
27. Kim SK, Yun GY, Kim KH, et al. Severe hyponatremia following radioactive iodine therapy in patients with differentiated thyroid cancer. *Thyroid*. 2014;**24**(4):773-777.
28. Krishnamurthy VR, McDougall IR. Severe hyponatremia: a danger of low-iodine diet. *Thyroid*. 2007;**17**(9):889-892.
29. Nozu T, Yoshida Y, Ohira M, Okumura T. Severe hyponatremia in association with I(131) therapy in a patient with metastatic thyroid cancer. *Intern Med*. 2011;**50**(19):2169-2174.
30. Herbert G, Searle A, England CY, et al. Experiences of low iodine diets in the treatment of differentiated thyroid cancer with radioactive iodine ablation therapy. *Clin Nutr ESPEN*. 2020;**39**:190-197.
31. Lee KJ, Chang SO, Jung KY. Experiences with a low-iodine diet: a qualitative study of patients with thyroid cancer receiving radioactive iodine therapy. *Eur J Oncol Nurs*. 2016;**23**:43-50.
32. Dekker BL, Touw DJ, van der Horst-Schrivers ANA, et al. Use of salivary iodine concentrations to estimate the iodine status of adults in clinical practice. *J Nutr*. 2021. doi: 10.1093/jn/nxab303
33. Fujimoto K, Hataya Y, Okubo M, Matsuoka N. Influence of levothyroxine with recombinant human TSH on urine iodine excretion before radioactive iodine administration. *Endocr Pract*. Published online April 6, 2021. doi:10.1016/j.eprac.2021.03.012