Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma

Maurice J. H. M. Pluijmen*, Carmen Eustatia-Rutten*, Bernard M. Goslings*, Marcel P. Stokkel†, Alberto M. Pereira Arias*, Michaela Diamant*, Johannes A. Romijn* and Jan W. A. Smit*
Departments of *Endocrinology and Metabolism and †Nuclear Medicine, Leiden University Medical Center, Leiden, the Netherlands

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Summary

OBJECTIVE Most patients with differentiated thyroid carcinoma (DTC) undergo total thyroidectomy followed by routine radioiodide thyroid remnant ablation. Most centres that routinely perform radioiodide ablation prescribe a low-iodide diet (LID) to increase the radioiodide accumulation in thyroid remnants. The efficacy of an LID on thyroid remnant ablation, however, has never been demonstrated convincingly.

DESIGN AND METHODS In a retrospective study, we studied two groups of DTC patients without distant metastases, who had received either a standard diet or an LID during ablation (LID group, n=59, and control group, n=61). Both groups were compared for radioiodide uptake in thyroid remnants during ablation and efficacy parameters of remnant ablation, 6 months after ablation. A subgroup without extrathyroidal tumour growth was analysed separately (stages T1–3, N0).

RESULTS In the total group, the LID during ablation decreased the 24-h urinary iodide excretion to 26.6 mm per mm compared with 158.8 mm per mm in controls whereas radioiodide uptake in thyroid remnants was increased by 65% (P<0.001). Six months after ablation, patients were investigated after thyroid hormone withdrawal. In the total group, no significant effects of the LID during ablation were observed on thyroglobulin (Tg) or the percentage of patients with persistent neck activity after 185 MBq \(^{131}\)I. However, in the LID group, 65% of patients without Tg antibodies had undergone successful ablation (defined by absent neck activity and Tg < 2 \(\mu\)g/l) compared with 48% in the control group (P<0.001). In the subgroup (T1–3, N0), 8% of the patients who had undergone the LID had Tg ≥ 2 \(\mu\)g/l vs. 32% in the control group (P=0.012), whereas successful ablation was achieved in 71% of patients without Tg antibodies in the LID vs. 45% in the control group (P<0.001).

CONCLUSION We conclude from this study that a low-iodide diet during thyroid remnant ablation improves the efficacy of this treatment.

Differentiated thyroid carcinoma (DTC) has a relatively favourable prognosis (Hundahl et al., 1998). However, subgroups of patients are at higher risk for recurrent disease or death (Gilliland et al., 1997; Schlumberger, 1998; Mazzaferri & Kloos, 2001). The initial therapy consists of near-total thyroidectomy. Although controversy exists about the routine application of postsurgical radioiodide ablation of thyroid remnants, many clinics follow this procedure. An argument in favour of thyroid ablation is the beneficial effect on recurrence and mortality in patients with higher tumour stages and those with evident residual tumour after initial surgery (Simpson et al., 1988; DeGroot et al., 1990; Samaan et al., 1992; Mazzaferri & Jhiang, 1994; Mazzaferri, 1997). In patients with small (<1–1.5 cm) intrathyroidal tumours, no clear effect of thyroid ablation on recurrence and mortality rates appears to be present (DeGroot et al., 1990; Hay et al., 1992; Mazzaferri, 1997). Another argument in favour of thyroid ablation is the possibility to include the results of post-ablative whole-body scintigraphy (WBS) in the post-surgical TNM staging procedure. In addition, during follow-up the specificity of detectable serum thyroglobulin (Tg) and positive WBS for persistent or recurrent tumour measurements is higher (Utiger, 1997; Schlumberger, 1998; Mazzaferri & Kloos, 2001).

The efficacy of radioiodide therapy depends on the radiation dose delivered to the thyroid remnant or tumour (Maxon et al.,...
Arturipared with normal thyroid (Cavalieri, 1997; Maxon et al., 1997; Arturi et al., 1998; Lazar et al., 1999). Strategies to increase radioiodide uptake include the establishment of high TSH levels, either by thyroid hormone withdrawal or by therapy with recombinant human TSH (Ladenson et al., 1997; Haugen et al., 1999). Another method to enhance uptake is to deplete the plasma inorganic iodide pool before the administration of radioiodide. The theoretical rationale for this method is that low plasma iodide concentrations may increase the expression of the sodium iodide symporter (hNIS) (Stanbury et al., 1952; Barakat & Ingbar, 1965; Cavalieri, 1997; Uyttersprot et al., 1997; De la Vieja et al., 2000) and leads to a higher specific activity of radioiodide.

Iodide depletion can be achieved by limiting iodide intake through a low-iodide diet (LID). Many clinics now use an LID before thyroid ablation. Thus far, only a few studies have investigated the LID during thyroid ablation therapy (Barakat & Ingbar, 1965; Goslings & Hannon, 1973; Maxon et al., 1983a; Lakshman et al., 1988; Morris et al., 2001). In a study from our hospital in patients with metastasized follicular carcinoma, a 4-day LID decreased iodide excretion from 121·6 ± 36·9 µg/day to 30·0 ± 9·7 µg/day (Goslings & Hannon, 1973). An LID appears to increase radioiodide uptake by 17–123%, whereas an increase in the effective half-life of radioiodide was observed as well, both of which contributed to an increase in radiation dose of 51–146% (Goslings & Hannon, 1973; Goslings, 1975; Maxon et al., 1983a; Maruca et al., 1984).

However, these studies involved small patient groups and only changes in urinary iodide excretion, radioiodide uptake and calculated tumour radiation dose were investigated, rather than parameters of therapeutic efficacy. Only one recent study has reported the effect of a preablative LID on the efficacy of ablation in a large group of patients (Morris et al., 2001). In this study, no apparent benefit of LID vs. a normal diet was found. Limitations of that study, however, were the remarkably high urinary iodide excretions in the LID group and the significantly higher ablation activities administered to the control group. Furthermore, no data were given on preablative radioiodide uptake measurements or thyroid function parameters such as TSH and Tg levels.

In the present study, we investigated the influence of a stringent LID, as defined by a maximal iodide urinary excretion of 49-4 µg/day (Goslings, 1975), on the effectiveness of thyroid remnant ablation in a cohort of Dutch patients with DTC, as determined both by diagnostic radioiodide scintigraphy and by serum Tg levels during follow-up. The Netherlands is nowadays regarded as an iodide-replete area, meeting the internationally set standards for dietary iodide content (Brussaard et al., 1997b).

Patients and methods

Initial therapy and evaluation

The Leiden University Medical Center (LUMC) is a large referral centre for the treatment of DTC in the Netherlands. Therapy for DTC consists of near-total thyroidectomy, followed 4 weeks later by thyroid ablation therapy. Thyroid surgery for DTC in the Leiden area is performed according to guidelines formulated by the Regional Comprehensive Cancer Centre. Before thyroid ablation, 24 h after the administration of 37 MBq $^{131}$I, scintigraphy of the neck region is performed and the 24-h thyroid uptake of radioiodide is measured. Thyroid ablation is performed with an average activity of 2800 MBq. When the tumour has not been removed radically according to surgical reports or pathological examination and when metastases are present, 6000 MBq is administered. Before 1992, patients were not routinely prescribed an LID during ablation. From 1992 onwards, an LID as described in the following section was routinely incorporated in the thyroid ablation protocol. Six days after ablation, WBS is performed. After ablation, thyroxine replacement therapy is initiated, aiming at serum TSH levels < 0·1 mU/l.

Efficacy of ablation therapy is evaluated 6 months after ablative therapy. Levothyroxine substitution therapy is discontinued and replaced by liothyronine substitution for 2 weeks. Two weeks after discontinuation of liothyronine, 185 MBq $^{131}$I is administered and WBS is performed 3 days thereafter. At the time of thyroid ablation and during evaluation of ablation TSH, total T4, Tg and Tg antibodies (TgAb) are measured.

Low-iodide diet

The LID in our hospital involves 4 days of iodide restriction aiming at a maximum excretion of 49-4 µg/day (Goslings & Hannon, 1973; Goslings, 1975). Patients receive written instructions and are assisted by a dietician (Table 1). To assess the efficacy of the LID, 24-h urine samples are collected on the fourth day of the diet for determination of urinary iodide and creatinine excretion.

Study design

The aims of the present study were to assess the effects of a preablative LID on the uptake of radioiodide at ablation and to assess the influence of a preablative LID on the efficacy of ablation, as assessed 6 months later. The study could be carried out because the LID was given during the evaluation of ablation from 1980 onwards, whereas it was introduced for thyroid ablation in 1992. This enabled us to compare two groups: one group (1986–91) had not received the LID during thyroid ablation, whereas the second group (1992–98) received the LID during ablation. Both groups received the LID during evaluation of thyroid ablation. Patients were selected from 416 patients who were treated for...
DTC in the LUMC between 1986 and 1998. All patients had undergone near-total thyroidectomy. When operated on in another hospital, surgery reports were examined and pathological material was reviewed. The following categories of patients were excluded: patients receiving high-activity $^{131}$I because of non-radical surgery and/or the presence of distant metastases, patients who had received additional external radiotherapy, patients with insufficient TSH levels (< 25 mU/l) during ablation or evaluation of ablation, patients with a > 1-year interval between surgery and ablation, and patients who had followed an LID, but whose 24-h urine iodide excretion was > 49.4 mg/day. Lymph node resection was optional and was registered as ‘modified radical neck dissection (MRND)’, ‘picking out procedure’ and ‘no lymph node resection’. The 120 remaining patients were divided into two groups, according to the prescription of an LID during ablation from 1992 onwards (LID group) and the patients who did not follow an LID during thyroid ablation (control group, 1986–91). To assess the influence of extrathyroidal tumour growth, separate analyses were carried out for all patients and for the subgroup of patients with stage pT1–3, N0.

Study parameters

The ability of an LID to create a state of iodide depletion was examined by measuring 24-h urinary iodide excretion. To determine the influence of an LID on radioiodide uptake in the thyroid region, preablative radioiodide uptake in the neck was measured after the administration of 37 MBq $^{131}$I. To evaluate the effectiveness of ablation therapy, patients were analysed during evaluation of thyroid ablation by the measurement of serum Tg levels and by 185-MBq $^{131}$I WBS.

Serum Tg levels were expressed as absolute concentrations and as ‘elevated’ or ‘not elevated’, based on a threshold of 2 μg/l. When TgAbs were detectable, Tg was considered as ‘not interpretable’, and not included in analyses. Serum T4 levels were registered as absolute levels and as ‘detectable’ or ‘undetectable’, based on the detection limit of 13.5 nmol/l. WBS scans were evaluated by two nuclear medicine physicians, who were unaware of LID adherence, for the presence of uptake in the neck by consensus reading. They were classified as ‘positive’ or ‘negative’ for $^{131}$I accumulating lesions.

Laboratory methods

Serum total T4 levels are measured by fluorescence polarization immunoassay (Axsym, Abbott, Chicago, IL, USA). Detection limit is 13.5 nmol/l, interassay variability 3.1–8.5%. TSH levels were measured by means of an immunofluorometric assay (IFMA) with the Delfia® (Wallac, Turku, Finland) until 1997. Thereafter, an immunoluminometric assay (ILMA) was used with the Elecsys® (Boehringer Mannheim, Germany). Correlation between both methods is 0.95 ± 0.06 (own data). Serum Tg was measured by using an immunoradiometric assay (IRMA), the Dynostest TG® (Brahms Diagnostica GmbH, Germany), sensitivity 1 μg/l. As of January 1997 the Dynostest TG-s (Brahms Diagnostica GmbH) was used, with a sensitivity of 0.05 μg/l and an

Table 1 Summary of the 4-day low-iodide diet as used in the Leiden University Medical Center

<table>
<thead>
<tr>
<th>Not allowed</th>
<th>Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish and sea products</td>
<td>All fish and sea products*</td>
</tr>
<tr>
<td>Bread</td>
<td>Commercial bread</td>
</tr>
<tr>
<td>Salt</td>
<td>Iodide-enriched salt, seaweed</td>
</tr>
<tr>
<td>Water</td>
<td>Tapwater</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>All alcoholic beverages</td>
</tr>
<tr>
<td>Coffee, tea</td>
<td>Foreign cheese</td>
</tr>
<tr>
<td>Eggs</td>
<td>All eggs and products containing eggs</td>
</tr>
<tr>
<td>Dairy products</td>
<td>Salted butters and margarines</td>
</tr>
<tr>
<td>Meat</td>
<td>Game and poultry</td>
</tr>
<tr>
<td>Fruits</td>
<td>Specified fruits and fruit-juices</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Specified fresh vegetables</td>
</tr>
<tr>
<td>Soups and sauces</td>
<td>Commercial soups and sauces</td>
</tr>
<tr>
<td>Colourings/dyes</td>
<td>E-127 (erythrosine)</td>
</tr>
<tr>
<td>Medication, soap, shampoo</td>
<td>Specified iodide-containing products</td>
</tr>
</tbody>
</table>

*Not allowed from 1 week before radioiodide administration.
interassay variability of 0.3 μg/l. Serum TgAbs were measured by the Ab-HTGK-3 IRMA (DiaSorin Biomedics, Italy). Urinary iodide excretion was determined by addition of chloric acid to the urine sample, and subsequent reduction of the iodide formed with ceric ammonium sulphate (Garry et al., 1973).

**Statistical methods**

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean ± SD and compared between groups by an unpaired Student's t-test. Non-normally distributed continuous variables were expressed as median with range and compared between groups with the Mann-Whitney test. Categorical variables were presented as proportions and analysed between groups with the χ²-test. A P-value of < 0.05 was considered significant. Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Corporation, Chicago, IL, USA).

**Results**

**Patient characteristics**

One hundred and twenty patients (26 males, 94 females, age at diagnosis 43 ± 15 years) were analysed in this study. They were divided into an LID group (n = 59) and a control group (n = 61). Eighty-four per cent of patients had papillary carcinoma, 16% follicular carcinoma. At initial presentation 24% of the patients had lymph node metastases. According to the American Joint Committee on Cancer (AJCC) classification, 59% of patients had grade I, 29% grade II and 12% grade III (all patients with distant metastases were excluded). Patient characteristics did not differ significantly between the LID and control groups as illustrated in Table 2.

**Thyroid ablation**

Data for thyroid ablation are presented in Table 3 and Fig. 1. In the total group and in the subgroup (pT1–3, N0), the 4-day LID reduced the 24-h urinary iodide excretion to an average of 27 μg/day (Table 3). The 24-h urinary iodide excretion was only measured in nine patients who were not prescribed an LID and was 159 μg/day, which is comparable with the mean 24-h urinary iodide excretion in a healthy Dutch population (Brussaard et al., 1997a). The 24-h ¹³¹I uptake in the thyroid region was significantly higher after LID than in the controls in all patients (5.1 ± 3.8 vs. 3.1 ± 2.5%, P < 0.001) as well as in the subgroup (5.8 ± 4.0 vs. 3.3 ± 2.9%, P < 0.001, Table 3, Fig. 1a). Mean T4 was significantly lower in LID than in controls in the total group but the difference was not significant in pT1–3, N0 patients.

### Table 2  Baseline data of patients with differentiated thyroid carcinoma who were or were not prescribed a low-iodide diet (LID) during thyroid remnant ablation

<table>
<thead>
<tr>
<th></th>
<th>Total group</th>
<th>Control</th>
<th>P</th>
<th>pT1–3 N0</th>
<th>LID</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td></td>
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<tr>
<td>LID</td>
<td>59</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Males/Females (no. of patients)</td>
<td>11/48</td>
<td>15/46</td>
<td>0.429</td>
<td>0.429</td>
<td>6/39</td>
<td>7/29</td>
<td>0.457</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>43 ± 16</td>
<td>44 ± 14</td>
<td>0.597</td>
<td>0.597</td>
<td>43 ± 17</td>
<td>44 ± 14</td>
<td>0.597</td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
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<tr>
<td>Papillary/Follicular (no. of patients)</td>
<td>51/8</td>
<td>50/11</td>
<td>0.502</td>
<td>0.502</td>
<td>37/8</td>
<td>25/11</td>
<td>0.177</td>
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<td><strong>Stage (TNM)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>T1–3/T4</td>
<td>55/4</td>
<td>52/9</td>
<td>0.160</td>
<td>0.160</td>
<td>45/0</td>
<td>36/0</td>
<td>0.160</td>
</tr>
<tr>
<td>N0/N1</td>
<td>47/12</td>
<td>41/20</td>
<td>0.123</td>
<td>0.123</td>
<td>45/0</td>
<td>36/0</td>
<td>0.123</td>
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<tr>
<td><em><em>Stage (AJCC</em>)</em>*</td>
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<tr>
<td>I (no. of patients)</td>
<td>35</td>
<td>36</td>
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<tr>
<td>II</td>
<td>17</td>
<td>18</td>
<td>0.999</td>
<td>0.999</td>
<td>17</td>
<td>17</td>
<td>0.082</td>
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<tr>
<td>III</td>
<td>7</td>
<td>7</td>
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<tr>
<td><strong>Lymph node surgery</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>None (no. of patients)</td>
<td>44</td>
<td>39</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Picking out</td>
<td>11</td>
<td>15</td>
<td>0.450</td>
<td>0.450</td>
<td>2</td>
<td>5</td>
<td>0.203</td>
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<tr>
<td>MRND</td>
<td>4</td>
<td>7</td>
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</table>

*American Joint Committee on Cancer.

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Thyroid ablation evaluation

Data for thyroid ablation evaluation are presented in Table 3 and Fig. 1. Patients in LID and control groups all followed an LID during evaluation, resulting in similar urinary iodide excretion levels averaging between 24·5 and 28·5 mg/day. The proportion of patients with measurable T4 levels was significantly lower and mean TSH levels were significantly higher in the LID patients compared with controls both in the total group and in the subgroup. The mean Tg level and the proportion of patients with a Tg > 2 mg/l (8% vs. 32%) were significantly lower in LID patients than in controls in the patients without extrathyroidal tumour at diagnosis (pT1–3, N0) only.

The percentage of patients with persistent activity in the neck region at WBS after 185 MBq radioiodide did not differ between LID and controls in the total group and in the T1–3, N0 subgroup. However, in the patients without Tg antibodies, the percentage of patients with successful ablation, defined as both Tg < 2 μg/l and negative scintigraphy, was significantly higher in LID patients compared with controls in the pT1–3, N0 subgroup (71 vs. 45%) as well as in the total group (65 vs. 48%).

Discussion

The present study was performed to investigate the influence of an LID on the efficacy of thyroid remnant ablation in patients with DTC. Although the enhancement of radioiodide uptake by LID has been confirmed in small studies, as mentioned in the introduction, the question of whether the LID improves thyroid remnant ablation has not been answered convincingly. The theoretical rationale for the LID is to enhance the radioiodide dose through increased uptake by depletion of the plasma inorganic iodide concentration. The enhanced uptake of radioiodide may be the result of both increased hNIS gene expression (Stanbury et al., 1952; Barakat & Ingbar, 1965; Cavalieri, 1997; Uyttersprot et al., 1997; De la Vieja et al., 2000) and a lower specific activity of radioiodide because of a lower inorganic plasma iodide concentration. An alternative explanation may be that an LID indirectly stimulates radioiodide uptake by increasing the sensitivity of thyroid remnant to TSH, through receptor or postreceptor mechanisms.

We found a reduction in urinary iodide excretion by LID during ablation to an average of 27 μg/day, which is comparable...
with earlier studies (Goslings, 1975; Maxon et al., 1983a; Lakshmanan et al., 1988). Our results prove that an LID with a duration of 4 days is sufficient to achieve adequate iodide depletion. As the LID is cumbersome for most patients, we suggest that a 4-day LID instead of a longer period has considerable advantages.

In our study, the LID increased the 24-h $^{131}$I uptake without background correction by 65% in the total group and 75% in the subgroup compared with controls, which is compatible with a net twofold increase. These results are in agreement with our earlier studies (Goslings & Hannon, 1973; Goslings, 1975). Maxon et al. (1983a) reported a nonsignificant 51% augmentation of calculated radiation dose after an LID. At thyroid ablation, we found significantly lower T4 levels for the LID patients compared to controls. The lower T4 levels can be explained by a shift of T4 to T3 synthesis as a result of iodide deficiency. At ablation, the LID did not influence TSH levels. Therefore, the enhanced 24-h radioiodide uptake as observed in the LID group may be attributed to a direct effect of a reduced plasma iodide concentration on hNIS gene expression or by a higher specific activity of the radioiodide.

This study is one of the first to evaluate the influence of an LID on the efficacy of thyroid remnant ablation. We observed a significant reduction in the percentage of patients with elevated Tg (8% vs. 32%) in the subgroup of patients with stage pT1–3, N0. In addition, the percentage of patients with successful ablation, as measured by the absence of radioiodide uptake in combination with nonelevated Tg, was significantly higher after...
LID. These results cannot be attributed to differences in TSH levels, as patients in the LID group had lower T4 levels and higher TSH levels during evaluation, which would have influenced the results in the opposite direction. The disappointingly low ablation efficacy of 2800 MBq $^{131}$I without LID (48% for the total group and 45% for the subgroup) is in concurrence with the 43% found in a former study from our hospital (Goslings & Hannon, 1973; Sorge-van Boxtel et al., 1993). In a recent study by Morris et al. (2001) no difference in WBS was found between the LID group and the control group. However, as pointed out before, urinary iodide excretion after LID was higher than in our study and the ablation dose of $^{131}$I was significantly lower in the LID group than in their controls. Tg levels were not evaluated in that study.

We conclude that the higher percentage of patients with absence of neck activity in combination with nonelevated Tg and the lower percentage of patients with measurable Tg levels in the pT1–3, N0 subgroup after ablation represent a beneficial effect of LID.

A limitation of our study is the retrospective design. From a theoretical point of view, it could be assumed that the lower uptake of radiiodine as observed prior to ablation in the control group could be attributed to more extensive thyroid surgery. However, in the study period, thyroid surgery for DTC in the Leiden area has been performed according to guidelines as formulated and evaluated by the Regional Comprehensive Cancer Centre. In addition, thyroid surgery in the study period has largely been performed by the same surgeons. Furthermore, a detailed review of all pathological and surgery reports has been performed that did not reveal any difference in the surgical approach. We therefore consider that the differences observed between the LID and control groups are attributable to the LID.

Although we found a beneficial effect of the LID on thyroid ablation efficacy, it remains to be investigated whether this will lead to a better clinical outcome in the long term. A disadvantageous effect of the LID is the increase in plasma half-life of $^{131}$I, which is thought to be due to decreased renal iodide clearance (Maruca et al., 1984), and may lead to a higher total body dose. However, in our opinion, this disadvantage is outweighed by the fact that the absence of measurable Tg levels or activity at WBS after thyroid ablation will save the patient from subsequent high-activity radiiodine therapy and thus exposure to much higher doses.

In conclusion, in this study we demonstrate the efficacy of a 4-day low-iodide diet in increasing thyroid remnant radiiodine uptake, whereas the lower proportion of patients with measurable thyroglobulin levels and/or positive whole-body scintigraphy represents a beneficial effect on ablation efficacy.

References


