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Low-Iodine Diet in the Treatment of Differentiated Thyroid Cancer with Radioactive Iodine

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Introduction

In concert with the introduction of radioactive iodine as a treatment for thyroid cancer, attempts at improving uptake and retention of therapy doses of ^{131}I were made by limiting the amount of nonradioactive iodine in the diet, the so-called low-iodine diet (LID). It was postulated that the increased uptake of radioiodine facilitated by an LID would result in increased remissions of metastatic thyroid cancer. It is appropriate to evaluate the data for this postulate, particularly regarding inorganic iodine metabolism and the recent therapy with recombinant DNA–generated human thyrotropin (rhTSH).

Low-Iodine Diet

It was noted early *(1)* that in seven patients with metastatic follicular thyroid cancer, an LID for 4 d decreased iodine excretion from 121 ± 36.9 (SD) to 30.0 ± 9.7 (SD) μg/d on d 4. The tumor uptake before the LID was 0.6–8.3% of the dose at 24 h and increased modestly after 4 d of diet to 1.5–15.7 at 24 h. The effective half-life ($t_{1/2}$) before the LID had a range of 24–114 h (biologic $t_{1/2}$ of 1–11 d). After dietary treatment (30 μg of iodine/d), the effective $t_{1/2}$ was 30–125 h, an increase by a factor of 1.19 ± 0.15, of questionable significance. There was a suggested doubling (2.13 ± 0.79) of the tumor dose. Earlier studies *(2)* had indicated that in subjects with no thyroid disease, nontoxic goiter, and Graves disease in remission, acute depletion of extracellular iodide with an LID followed 24 h later by infusion of mannitol *(2,3)* led to changes in iodine metabolism. Iodide depletion resulted in decreased serum iodide (–0.24 ng/100 mL; $p < 0.01$), increased 24-h uptake of radioiodine by the thyroid (+11%; $p < 0.01$), and nonsignificant change in ^{127}I/24 h accumulation in the thyroid *(2)*. It was concluded *(2)* that the mechanism for the abrupt increase in thyroid uptake was not mediated by the pituitary, but rather by the thyroid. Although an LID led to a significant decrease in iodine excretion, there was only a modest or questionable effect on iodine kinetics or tumor dose.

The combined use of an LID and iv mannitol in seven thyroidectomized patients with residual thyroid cancer *(3)* was used to increase radioiodine uptake two- to threefold in normal and/or thyroid cancer without stimulation of radioiodine release produced by TSH. Subsequently, an LID, without osmotic diuresis, was instituted for 1 wk in 40 hypothyroid patients with well-differentiated thyroid cancer prior to radioiodine ablative therapy *(4)*. Twenty-one patients were on a regular diet and 19 patients received the LID *(4)*. The mean excretion (μg of iodine/g of creatinine) was significantly lower in patients on an LID compared to the regular diet (43 vs 347 μg/24 h; $p < 0.001$). Although an LID was useful in increasing the radiation dose per microcuries of ^{131}I administered in ablating residual thyroid tissue *(3)*, there was no impact on metastatic thyroid cancer lesions *(4)*.

While the patients were on triiodothyronine therapy,the last 4 wk included an LID *(4–6)*. In five patients *(6)*, the range of urinary iodine on the usual diet was 72–400 μg of iodine/g of creatinine (SEM: 209 ± 31). Prior to an LID, the urinary iodide was 16–370, and after an LID, the urinary iodide was 49 ± 4 μg/g of creatinine ($p < 0.01$). There was no change in iodine intake while the patients took triiodothyronine. Although an LID did indeed reduce urinary iodide *(4–6)* significantly, it was not readily apparent that the increased uptake *(5)* and retention by tumor tissue was sufficiently increased to increase the irradiation of well-differentiated thyroid cancer. This may have been related to the decreased renal clearance of radioiodine (40–71%) in three patients *(5)*. Although the lesion uptake increased 146%, this represented only a 46% gain relative to the total body dose *(5)*.

It has been recommended *(7)* that radioiodine uptake, scanning, and therapy should be performed 2 wk after triiodothyronine withdrawal when patients are minimally hypothyroid *(7)*. In 23 of 29 studies, individual uptakes and whole-body retentions were similar after 2 and 4 wk *(7)*. It has been reported *(8)* that in patients with differentiated thyroid cancer, 50 on a regular diet and 44 on a verbally instructed LID, for 10–14 d and then treated with 100–200 mCi of radioactive iodine (^{131}I), there was an insignificant difference in thyroid ablation rates (62 vs 68%; p 0.53). The urinary iodide levels were significantly decreased with an LID *(1,4,6,8)*.

If an LID were to be included in the preparation for radioiodine therapy of thyroid cancer, it would be difficult to

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establish precisely the appropriate iodine intake. In euthyroid individuals, the euthryoidism has been assumed when TSH and thyroglobulin are at the lower end of the normal range, when urinary iodine is between 200 and 300 µg of iodine/g of creatinine *(9)*. To restrict the diet to be reliably "low iodine" might reduce patient acceptability and compliance.

LID and rhTSH Therapy

As discussed previously, prior to the introduction of rhTSH, attempts were made to increase the uptake of radioiodine in metastatic thyroid cancer by using an LID for periods of 3 d to 3 wk. This approach was employed in association with withdrawal of levothyroxine therapy for 4–6 wk, the last 2 wk or less with triiodothyronine replacing levothyroxine therapy. The LID and thyroid hormone withdrawal not only reduced stores of stable iodine but increased TSH production. Although radioiodine uptake by metastatic thyroid cancer was increased to some extent, it was not clear whether there was a proportionate increase in radiation dose owing to changes in the kinetics of the iodine pool and a decrease in iodine stores.

It has long been known that complete or partial thyroid hormone withdrawal may result in TSH elevation in as many as 90% of patients *(10,11)*. With the successful cloning of rhTSH and demonstration *(12)* of its diagnostic use in thyroid cancer patients, it was reasonable to compare its efficacy with thyroid hormone withdrawal in promoting elevated TSH levels in patients with metastatic thyroid cancer *(13–15)*. Although administered TSH stimulated radioiodine uptake in patients with thyroid cancer, the sensitivity of scanning after the administration of TSH was initially reported *(13)* to be less than after the withdrawal of thyroid hormone. This difference was not found to be statistically significant in subsequent studies (15). It is not clear whether the difference in these studies *(11–15)* may have been influenced by the LID recommended in the latter *(14,15)* patients as opposed to the earlier study *(14)*. Note that urinary excretion of iodide was not reported in any studies with rhTSH *(11–15)*. It is difficult to resolve the role of an LID of varying degrees in these studies without the accompanying dietary and urinary iodide determinations.

It is likely that decreased radioiodine clearance *(5,16)* owing to hypothyroidism with subsequent higher bioavailability for imaging after thyroid hormone withdrawal likely occurred in previous studies *(14,15)*. The rationale and efficacy of an LID to augment radioiodine uptake by metastatic thyroid cancer is questionable in the setting of the use of rhTSH rather than thyroid hormone withdrawal. Some patients continue with thyroxine replacement, a source of iodine, although patients are frequently changed to triiodothyronine, containing less iodine. A representative dose of levothyroxine (mol wt = 776.87) is about 200 µg/d and contains 126 µg of iodine. Triiodothyronine (mol wt = 650.97) at a daily dose of 50 µg would contain about 35 µg of iodine/d. This would be consistent with an LID of dietary origins. As already noted, LIDs have been formulated *(4,6)* that successfully induce iodine deficiency, as indicated by a decrease in urinary iodide, but do not significantly increase the radiation dose delivered to metastatic thyroid cancer *(11–15)*. Since most patients who are placed on an LID have not been studied under conditions of standard thyroid hormone withdrawal, the efficacy of an LID has not been validated in the setting of rhTSH treatment with thyroid hormone replacement *(11)*. In preparation for radioiodine therapy of thyroid cancer, there was no difference in diagnostic accuracy in residual differentiated thyroid cancer in patients with or without thyroid hormone replacement *(11–15)*.

Conclusion

It is eminently reasonable to exploit the properties of radioactive iodine for the treatment of thyroid cancer, which has a unique avidity for iodine. An LID that restricts nonradioactive iodine, ^{127}I, is rational if it allows greater radioactive iodine localization and delivery of tumoricidal doses of radiation. As discussed, the increased turnover of iodine on an LID and decreased pool size in thyroid cancer may compromise this goal.

An LID is variably palatable, and there are reservations about how many patients can rigorously adhere to such a diet for lengthy intervals. An LID can be formulated, recommended to patients, and validated by dietary urinary iodide analyses. It is noteworthy that in none of the studies of radioactive iodine treatment of thyroid cancer with rhTSH, in which an LID has been recommended and levothyroxine or triiodothyronine continued, has the ^{127}iodine availability been validated by dietary and urinary iodine analysis.

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