EDITORIAL Levothyroxine therapy alone restores normal serum FT_3 levels after total thyroidectomy

A small but significant proportion of patients placed on levothyroxine (L-T_4) following thyroidectomy report not achieving their preoperative sense of well-being in spite of achievement of euthyroid reference range thyrotropin (TSH) values. While 80% of circulating serum triiodothyronine (T_3) is derived from the peripheral monodeiodination of L-T_4, thyroidectomy theoretically deprives the individual of the 20% contribution of direct T_3 secretion from the thyroid. That the nonspecific symptoms might be due to consequent relative T_3 insufficiency led to over a dozen studies in the past decade examining whether T_4/T_3 combination therapy would result in an improved sense of well-being and cognitive function as compared with therapy with L-T_4 alone. Essentially all studies but one (1) found no significant difference in outcomes irrespective of the form of thyroid hormone replacement (2).

One key consideration in assessing outcomes is whether comparable levels of serum T_3 are achieved with L-T_4 therapy alone versus T_4/T_3 combination therapy. When serum T_3 levels were compared in all of the studies published to date, the comparison was done in patients with hypothyroidism who were already taking L-T_4 who were either continued on L-T_4 therapy or switched to T_4/T_3 combination therapy. Although the observations were paired, with the patients serving as their own controls, the comparison was of T_3 levels while taking L-T_4 alone as compared with taking L-T_4/T_3. Thus, there were no data on true baseline or premorbid serum T_3 levels—that is, either prior to development of hypothyroidism or prior to thyroidectomy. The rather simple study by Jonklaas et al.(3) fairly definitively addresses the issue of whether we can achieve levels of serum T_3 with L-T_4 replacement alone that are just as "normal" as a given patient's preoperative serum T_3 levels. If the basis for reports of mood or motor dysfunction were due to T_3 insufficiency, patients achieving postoperative T_3 levels comparable to their baseline preoperative T_3 levels should feel no different once recovered from any perioperative symptoms unrelated to thyroid hormone replacement. In the study by Jonklaas et al., reference-range TSH levels were achieved in 94% of patients by the end of the study, although many patients had higher TSH levels shortly after surgery that required titration with an increased dosage of L-T_4.

Because T_4 is converted to T_3, it would follow that ultimately near-normal concentrations of serum T_3 could be restored by administering T_4 alone, providing enough L-T_4 is given. As had been seen in earlier published studies, attainment of T_3 levels in the normal range requires a dosage of L-T_4 that is associated with free thyroxine (FT_4) levels on replacement that are higher than preoperative basal FT_4 values. Nevertheless, the study provides proof of principle that sufficient levels of serum T_3, statistically no different from patients' preoperative basal T_3 levels, can be achieved during treatment with L-T_4 alone, and are associated as well with comparably normal TSH levels. Unfortunately, Jonklaas et al. did not assess patient satisfaction, mood, cognition, or responses to symptom questionnaires. It would have been of interest to determine whether restoration of serum T_3 levels to their original values was associated with a universal sense of well-being in all subjects or whether there was a subgroup who failed to achieve their baseline sense of well-being in spite of having comparable serum T_3 levels.

While there may be other, yet poorly understood, reasons why some patients continue to report reduced mood, memory, and psychomotor function while on replacement therapy with L-T_4 alone, this study confirms that such symptoms are not due to T_3 insufficiency, given an adequate L-T_4 dosage and normalization of TSH. In view of the controversy over what constitutes a "normal" TSH level (4) and because achievement of a TSH level within the population reference range may not be equivalent to achieving a patient's individual "normal" range (5), perhaps we should be titrating L-T_4 dosages to achieve both the latter "personal best" TSH level and the premorbid or presurgical T_3 levels when known. Is it possible that the fraction of patients who report symptoms are those whom we have failed to truly restore to euthyroidism? Indeed, several studies have shown that 15 to 27% of patients treated by endocrinologists are undertreated (6,7). Moreover, these figures are based on TSH values at an upper limit of the reference range of 4.5 to 5.3 mIU/L, and the percentages of undertreated patients would be considerably higher given an upper limit of normal for TSH of 3 to 3.5 mIU/L. Conceivably, the number of patients with these persistent symptoms would be much reduced if patients were treated with sufficient L-T_4 to bring TSH levels to the range of 1.0 to1.5 mIU/L.

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Citation

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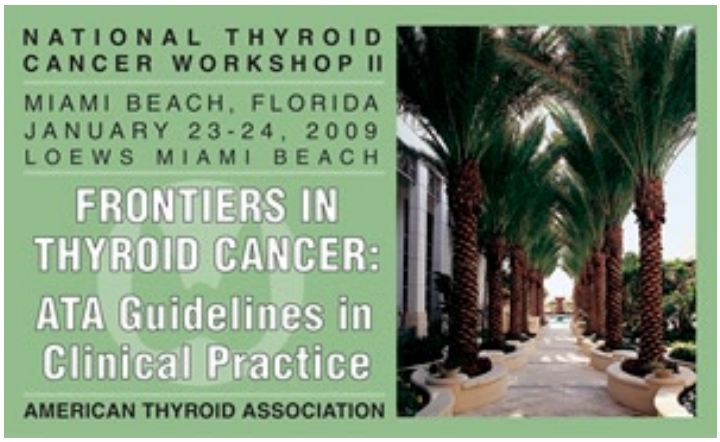

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