Levothyroxine therapy alone restores normal serum FT_3 levels after total thyroidectomy

Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA 2008;299:769-77.

SUMMARY

BACKGROUND Clinical trials have demonstrated that adding liothyronine (T_3) to levothyroxine (L-T_4) confers no consistent benefit to patients being treated for hypothyroidism. However, there is no direct evidence that subtle T_3 deficiency is avoided by using L-T_4 alone. This study is designed to compare preoperative serum T_3 levels in patients with normally functioning thyroid glands with the T_3 levels in the same patients after they became surgically athyreotic and were being treated with L-T_4 alone.

METHODS The study subjects were 50 euthyroid patients aged 18 to 65 years who were scheduled for total thyroidectomy for suspected or known thyroid cancer, goiter, or benign nodular thyroid disease. Thyroid hormone levels were measured before thyroidectomy in individuals not receiving thyroid hormone therapy, and again after surgery when they were being treated with L-T_4 alone. Postoperatively, patients with benign thyroid disease were given L-T_4 (1.7 µg/kg daily) replacement therapy aimed at keeping the serum TSH levels in the normal range, and others were given L-T_4 (2.2 µg/kg daily) to maintain the serum TSH level below normal for the treatment of thyroid cancer. The L-T_4 doses were adjusted during the two postoperative (third and fourth) thyroid profiles to achieve the treatment goals. Patients underwent a complete history and physical examination and had two separate thyroid profiles before and two after thyroidectomy when they were taking L-T_4 and had achieved stable serum thyrotropin (TSH) levels. At the end of the study, the medication history and physical examination were repeated.

RESULTS Of the 50 subjects who completed the study, 37 (74%) were female, 19 (51%) of whom were premenopausal and 18 (49%) menopausal. The mean age of the subjects was 49 years. Thyroidectomy was performed for benign disease in 33 patients (66%) and for thyroid cancer in 17 others (34%). In all, 34 (68%) required an alteration of their L-T_4 dose in the third time point to maintain the target TSH level, which was achieved by the fourth time point. The serum TSH levels were significantly higher than the prethyroidectomy values at time point 3 but not at time point 4 (Figure 1). The serum free T_4 (FT_4) levels increased significantly at postthyroidectomy time points 3 and 4 as compared with prethyroidectomy FT_4 levels at the first and second time points; however, the serum FT_4 levels did not differ between time points 3 and 4 (Figure 2). As would be expected the serum TSH levels were significantly lower and the serum FT_4 levels were significantly higher in patients with thyroid cancer as compared with preoperative values (Figures 1 and 2). By the end of the study, there were no significant decreases in serum T_3 levels in patients receiving L-T_4 therapy as compared with their prethyroidectomy

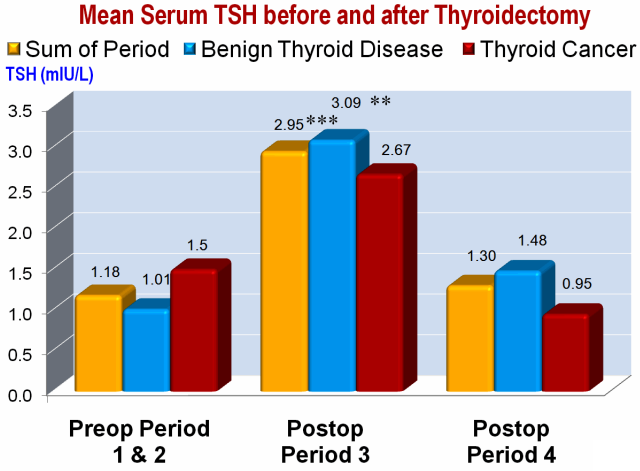

Figure 1. Mean serum TSH concentrations during preoperative periods 1 and 2 combined and postoperative periods 3 and 4. Figures are drawn from data in Table 2 of Jonklaas et al. To convert FT_4 to pmol/L, multiply by 12.871; and T_3 to nmol/L, multiply by 0.0154. Time points 3 and 4 were each compared with the mean of the time points 1 and 2. Significance was tested by Wilcoxon signed rank test. **P = 0.02, ***P = 0.03, ****P = 0.04 †P = 0.01, §P = 0.46 comparing time points.

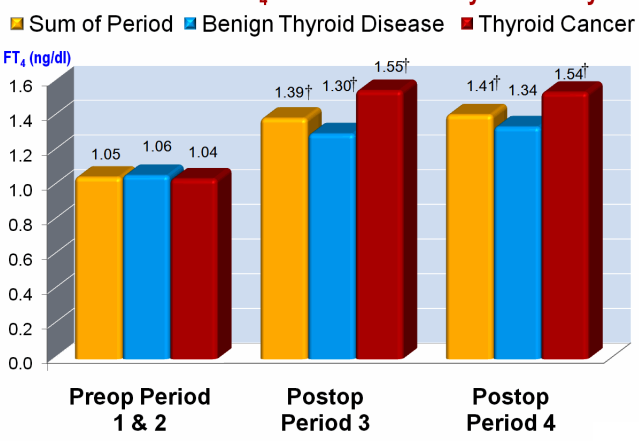

Figure 2. Mean serum FT_4 levels before and after thyroidectomy. See Figure 1 legend for explanation of symbols.

T_3 levels (mean, 127.2 vs. 129.3 ng/dl) as measured by T_3 immunometric assay or by liquid chromatography tandem mass spectrometry (Figures 3 and 4).

CONCLUSION Levothyroxine therapy alone restores normal serum FT_3 levels after total thyroidectomy.

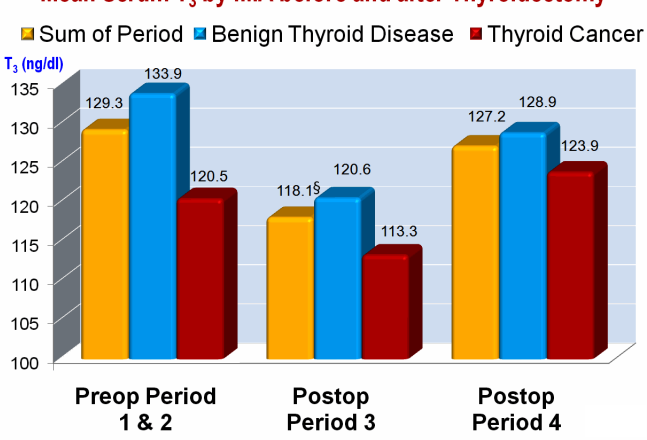

Figure 3. Mean serum free T_3 levels are measured by immunometric assay (IMA). See Figure 1 legend for explanation of symbols.

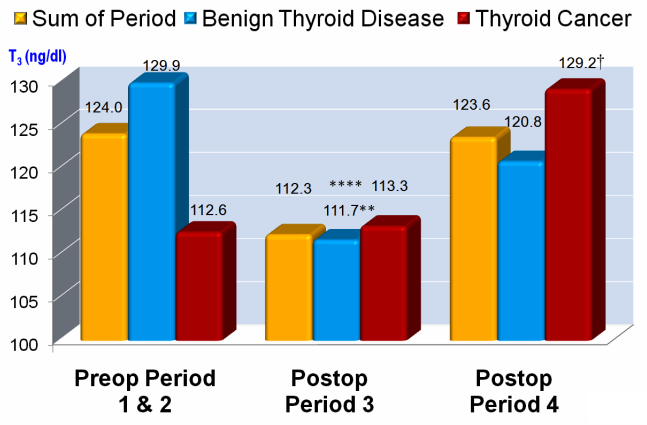

Figure 4. Mean serum free T_3 are measured by liquid chromatography–tandem mass spectrometry (LC-MS-MS). Time points 3 and 4 each were compared with the mean time points 1 and 2. Significance was tested by Wilcoxon signed rank test. **P = 0.02, ***P = 0.03, ****P = 0.04 †P = 0.01, §P = 0.46 comparing time points.

Reference

1. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ, Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999;340:424-9.

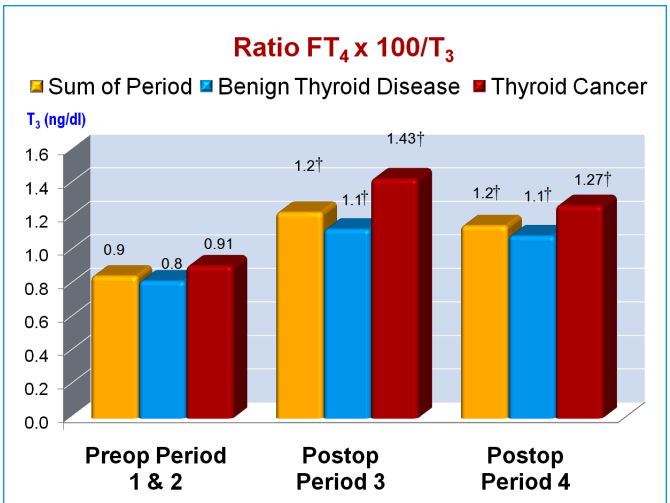

Figure 5. Mean Ratio FT_4 x 100/T_3 during preoperative periods 1 and 2 combined and postoperative periods 3 and 4. Figures are drawn from data in Table 2 of Jonklaas et al. To convert FT_4 to pmol/L, multiply by 12.871; and T_3 to nmol/L, multiply by 0.0154. Time points 3 and 4 were each compared with the mean of the time points 1 and 2. Significance was tested by Wilcoxon signed rank test. †P = 0.01 comparing time periods.

COMMENTARY

The treatment of hypothyroidism has been the subject of controversy for some time, mainly because a small group of patients with hypothyroidism do not feel entirely well with levothyroxine replacement therapy. As a consequence, some have suggested that thyroid hormone replacement with T_4 therapy alone may not precisely duplicate the normal thyroid hormone environment comprising both thyroxine (T_4)and triiodothyronine (T_3), causing the symptoms that some patients experience. Still, T_3 is normally converted from T_4 and nearly every published study has failed to find that the addition of T_3 to T_4 is beneficial, save for the study by Bunevicius et al.(1), which found that among patients with hypothyroidism, partial substitution of T_3 for T_4 may improve mood and neuropsychological function, suggesting a specific effect of the T_3 normally secreted by the thyroid gland. Despite the many studies exploring this question, none have measured serum T_3 levels before and after therapy in the same patients taking levothyroxine for various forms of hypothyroidism. This relatively simple approach, which was taken by Jonklaas et al., leaves little doubt that T_3 deprivation does not explain why some patients do not feel well when treated with levothyroxine.

Dr. Wartofsky explores this problem in the current issue of *Clinical Thyroidology*.

Ernest L. Mazzaferri, MD, MACP