Clinical THYROIDOLOGY
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# Should We Treat Patients with Hypothyroidism with $T_4$ and $T_3$ Instead of $T_4$ Alone?

Ito M, Miyauchi A, Morita S, Kudo T, Nishihara E, Kihara M, Takamura Y, Ito Y, Kobayashi K, Miya A, Kubota S, Amino N. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. Eur J Endocrinol, June 18, 2012 [Epub ahead of print].

## SUMMARY

### Background

The mean serum TSH of a normal population is 1.4 to 1.6 mU/L, with the range varying from 0.4 to 3 or 4. It is generally accepted that serum TSH levels within these reference values indicate an adequate substitution with thyroxine in patients with hypothyroidism. With thyroxine treatment, all available $T_3$ has to be generated by conversion from $T_4$, while in normal subjects approximately 10 to 20% of $T_3$ is provided by thyroidal secretion. It is well established that the control of serum TSH is a very complex mechanism. In the pituitary there is an active local conversion of $T_4$ to $T_3$ and circulating $T_3$ probably plays a minor role in governing TSH secretion. Therefore, a slight decrease of serum $T_3$ levels may be of little importance for adequate pituitary function, the local $T_4$ concentration being the decisive factor. This raises the question of whether using serum TSH as the only monitor of adequate thyroid substitution is a fully adequate procedure. Comparing serum $FT_4$ and $FT_3$ concentrations in subjects who undergo thyroidectomy offers an excellent opportunity to test circulating thyroid hormone levels versus TSH secreted by the pituitary. The many patients with thyroid cancer who are treated with different doses of thyroxine with the aim of achieving serum TSH levels appropriate to control the disease are an ideal population in which to address this problem. This is particularly true if preoperative thyroid hormone levels are available, as they were in Ito et al.'s study.

### Methods and Results

This was a retrospective study of 135 patients with thyroid cancer. Blood samples were obtained on two occasions before operation. The sample was deep-frozen. Patients with any possible interfering factor (thyroid disease other than a nodule, thyroid antibodies, any nonthyroid disease and or interfering drug treatment) were excluded. The mean dosage of thyroxine was approximately 2 μg per kilogram of body weight, adjusted according to the presumed prognosis of the thyroid cancer. Postoperative samples were obtained after at least 3 to 6 months of stable treatment and approximately 2 to 4 hours after the ingestion of thyroxine. At the end of the study, all serum $FT_3$ levels were remeasured from the deep-frozen samples in one single assay.

The serum TSH levels were stratified as follows: group 1: <0.03 mU/L; group 2: 0.03 to 0.3 mU/L; and group 3: 0.3 to 3 mU/L; each group corresponded to the specific risk group of thyroid cancers.

As expected, after operation serum $FT_4$ levels were higher than before operation. The patients with serum TSH levels of <0.03 mU/L had clearly increased serum $FT_3$ levels. Yet, in the group with moderately decreased serum TSH levels (0.03 to 0.3 mU/L), serum $T_3$ levels were identical to those before treatment (before, 3.01 ng/L; after, 2.98; for $FT_4$, 10.1 vs. 13.9 ng/L) and with serum TSH levels in the normal range (0.3 to 3 mU/L), serum $FT_3$ levels were significantly lower than before operation.

### Conclusions

In this well-conducted study the authors compared serum $FT_3$ levels before and after total thyroidectomy followed by thyroxine treatment. Their findings indicate that $FT_3$ levels are equal those before operation only if serum TSH is in the slightly decreased range, between 0.03 and 0.3 mU/L. Serum TSH levels from 0.3 to 3 mU/L went along with a mean $FT_3$ of 2.62 ng/L, a small but significant dif-

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ference from 3.08 ng/L. The clinical significance of this difference is difficult to appreciate since the informative value of clinical testing of well-being is limited. The article, however, stresses the point that the definition of adequacy of thyroxine treatment is different if it is based on serum TSH or on peripheral thyroid hormones.

## ANALYSIS AND COMMENTARY

The study has great merit insofar as serum $FT_3$ levels were measured altogether in one single essay. The interassay variability is therefore excluded. The absolute values may vary from one laboratory to another but for this particular study, this is irrelevant. The study was done in patients with thyroid cancer who were scheduled for surgery. Thus, preoperative values were readily available. The therapeutic goal in these patients is not a perfect euthyroid state but a suppressed serum TSH that can be obtained only with a supraphysiological thyroxine dosage. The data show that there is a small but significant imbalance between the circulating hormones and TSH levels. Indeed, within the normal range of serum TSH, defined here as values from 0.3 to 3 mU/L, serum $T_3$ levels were slightly decreased while serum $T_4$ levels were higher than in a normal population. This is most likely the consequence of the all-important mechanism of local $T_4$ conversion in the pituitary as opposed to the periphery. In normal persons the $T_3$ secreted by the thyroid is compensating for the difference. In patients with low-risk cancers and in primary hypothyroidism it is usual to adjust thyroxine therapy according to serum TSH levels, which need to be within the normal range. This is justified by the possible side effects of long-term subclinical hyperthyroidism, such as atrial fibrillation and osteopenia. On the other hand, a slightly decreased serum $T_3$ level has no measurable clinical manifestations. Some patients may report the inadequateness of thyroid hormone treatment despite normal serum TSH, yet our means to document such reports by clinical tests of thyroid hormone action are for the moment nonexistent. Nevertheless, it is interesting that the European Thyroid Association has addressed this question on their website.

The authors do not discuss the possible role of the frankly increased $FT_4$ levels. $T_4$ is considered a prohormone, yet it has some direct effects, such as the inactivation of deiodinase type II. Therefore, if biochemically the aim is to achieve a perfect substitution, then a combination treatment of thyroxine and triiodothyronine may be necessary.

As for the science, as a clinician I am inclined to consider this small difference in serum $T_3$ levels as clinically insignificant and therefore to routinely use levothyroxine as the sole treatment for hypothyroidism. Some patients are not satisfied with the treatment; rarely, I may add 12.5 μg of triiodothyronine.

**— Albert G. Burger, MD**