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Is Serum TSH Not the Gold Standard for Thyroxine Treatment?

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Hoermann R, Midgley JE, Larisch R, Dietrich JW. Is pituitary thyrotropin an adequate measure of thyroid hormone-controlled homeostasis during thyroxine treatment? Eur J Endocrinol. November 26, 2012 [Epub ahead of print].

SUMMARY

Background

This article is complementary to several recent articles, one from the authors of the current article and one recently reviewed by me in Clinical Thyroidology (1-3). The authors raise the question of whether the current approach, monitoring thyroxine treatment with the serum TSH alone, is adequate. To answer this question, they studied serum FT_4 and FT_3 levels in thyroxine-treated patients and compared them with those of untreated subjects.

Methods

The study was done between October 2006 and January 2007. The first blood samples of 1994 patients seen in a thyroid clinic were studied. The median age of the patients (predominantly women) was 61 years. Thyroid antibodies were not measured routinely. A total of 1059 patients were untreated—they did not receive any thyroid hormone or other drug treatment; 50 patients were given iodine supplementation alone (100 to 200 µg per day). Of the 190 patients with hypothyroidism, only 53 (28%) had autoimmune disease; in the rest of the group, hypothyroidism was due to surgery and radioactive iodine treatment.

The patients were treated with 50 to 200 µg of levothyroxine daily. Subclinical hyperthyroidism was defined by a serum TSH below the reference range (<0.2 mU/L) and FT_4 and FT_3 in the reference range. A complex mathematical model postulated interference of various factors, among which the deiodinases were prominent.

Results

The authors confirmed their earlier work and the remarkable work of Ito et al. (1). In T_4-substituted subjects, serum FT_3 levels are low as compared with those of untreated patients with an equal serum TSH value. They used complex mathematical correlations that showed that for a given serum TSH, FT_3 values were clearly lower than those in control subjects. Obviously, serum FT_4 levels were higher in control subjects than in levothyroxine-treated subjects for a similar TSH. Based on their mathematical program, these authors postulated that the deiodinases (types 1 and 2) in the pituitary are still functioning, with high T_4 levels resulting in an inhibited serum TSH. According to the authors, under thyroxine treatment the peripheral deiodinases are less active, resulting in lower FT_3 levels as compared with the serum TSH in normal subjects.

Conclusions

In a group of levothyroxine-treated patients with serum TSH from 0.2 to 4 mU/L, the levels of serum FT_3 are below the normal reference range of healthy subjects. The authors conclude that in patients undergoing thyroxine substitution, TSH cannot be considered to be the gold standard of adequate substitution. Based on the mathematical program, they postulate that deiodinases type 1 and 2 are more effective in the pituitary than in the periphery.

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ANALYSIS AND COMMENTARY

This article is highly based on mathematical considerations. Most clinicians, including myself, are not capable of understanding the mathematical part of the article. Nevertheless, the present work is confirmatory of many earlier reports, some dating back 15 years.

It is well established that in normal subjects, 15% to 20% of the circulating T_3 is directly secreted from the thyroid. In hyperthyroidism, this percentage is even higher. Thyroxine treatment lacks this contribution to the circulating T_3. This is so well recognized that approximately 20 years ago a patent was granted for a slow release T_3 that would have overcome the problem of the relatively short half-life of triiodothyronine (Cytomel). Yet the compound was never developed. One could argue that with a combined thyroxine and slow-release T_3 treatment, patients with hypothyroidism could be monitored not only according to their serum TSH but also according to their FT_3 and FT_4 values. This would be particularly adequate in patients who were euthyroid before thyroidectomy, whose own serum values could be used as an individual reference range. However, this argument falls short by not taking into consideration the normal fluctuations of serum T_3 values due to many nonthyroidal factors, such as fasting, disease, iodine supply, and depression. At present, there are no objective criteria comparing the true value of the two treatments, since we have no objective tests measuring clinically subtle but potentially relevant differences.

From their mathematical program, the authors infer differences between peripheral and pituitary deiodinases. This is not well documented. It is much more likely that the lack of thyroidal secretion of T_3 explains the difference. Also, all mathematical programs can produce results only from the data that were put into them. TSH control cannot be explained by deiodinases. Leptin, transporters of T_4 and T_3, and such are only some examples of other possible factors affecting the regulation of serum TSH.

As stated in my recent review (3), I believe that for practical reasons thyroxine treatment alone of patients in need of thyroid hormone replacement is adequate. I do not exclude the occasional use of a combination of thyroxine and triiodothyronine in an exceptional patient.

References

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3. Burger AG. Should we treat patients with hypothyroidism with T_4 and T_3 instead of T_4 alone? Clin Thyroidol 2012:24:8-9.