Results

The authors confirmed their earlier work and the remarkable work of Ito et al. (1). In T₄-substituted subjects, serum FT₃ 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, FT₃ values were clearly lower than those in control subjects. Obviously, serum FT₄ 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 T₄ levels resulting in an inhibited serum TSH. According to the authors, under thyroxine treatment the peripheral deiodinases are less active, resulting in lower FT₃ 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 FT₃ 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.

continued on next page
Is Serum TSH Not the Gold Standard for Thyroxine Treatment?

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

