AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Clinical
THYROIDOLOGY

VOLUME 24 • ISSUE 2 FEBRUARY 2012

Is There a Place for a Combined Treatment of Athyreotic Patients With Thyroxine and Triiodothyronine?

Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011;6:e22552. Epub August 1, 2011.

SUMMARY

Background

It is well established that in an area with a sufficient iodine supply, thyroidal secretion contributes approximately 10% to 20% to the daily T_3 production. In the presence of iodine deficiency, this percentage can drastically increase. Therefore, the peripheral tissues of a normal subject are not entirely dependent on T_3 generated by conversion from T_4. In T_4-substituted athyreotic subjects, the lack of thyroid-generated T_3 is compensated for by higher serum T_4 values. Conversion of T_4 to T_3 is a variable process, depending on metabolic parameters. An example is the strong reduction of conversion due to fasting. Since the publication of a controversial article in the New England Journal of Medicine (1), the question of whether some athyreotic subjects could benefit from a mixture of thyroxine and triiodothyronine has been extensively studied, ending with the general conclusion that there is no clinical advantage to adding triiodothyronine to thyroxine treatment (2). The authors of the present article performed a large retrospective study trying to develop arguments that thyroxine treatment alone is not always sufficient.

Methods and Results

In this retrospective study covering the years 2002 to 2007, serum thyroid hormone parameters were studied in athyreotic subjects with a serum TSH between 0.4 and 4 mU/L. One third of these patients had had previous ^{131}I treatment. Patients with thyroid antibodies were excluded. Women predominated (81%) and 69% of the subjects were less than 60 years of age. The control subjects consisted of 3875 euthyroid subjects, investigated in the clinic for a nonfunctioning nodule of less than 2 cm in diameter. For statistical analysis nonparametric tests were applied.

In the control group, there were some minor and expected differences in FT_4 and FT_3 values according to sex and age. Over the range of 0.4 to 4 mU/L for serum TSH, FT_3 values did not change when plotted against the log TSH values.

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In the athyreotic group, mean serum TSH levels were similar to those in the euthyroid control group (1.2 vs. 1.4 mU/L). As expected, serum FT_4 values were slightly higher and FT_3 values slightly lower. As a consequence, the median individual FT_3:FT_4 ratio was lower in thyroxine-treated patients (0.24 vs. 0.32, P<0.001). There was a minimal but significant decrease of FT_3 in elderly male subjects.

Despite normal serum TSH levels, 15% of the athyreotic subjects had FT_3 values below the normal range and 7% had FT_4 values above the normal range. The results of the linear regression analysis between serum TSH and FT_4 were significantly steeper in T_4-treated subjects; in other words, in case subjects, larger changes in serum thyroxine were needed to adjust serum TSH than in control subjects. Interestingly, within the group of thyroxine-substituted patients the FT_3:FT_4 ratio decreased with higher administered doses, possibly reflecting an inhibition of deiodinase type 2 activity by circulating T_4 values.

CONCLUSIONS

Despite perfect control of serum TSH in athyreotic subjects (mean TSH, 1.2 mU/L, vs. 1.4 mU/L in control subjects; range 0.4 to 4), 15% of these patients had decreased serum T_3 levels, possibly indicating some thyroid hormone deficiency. Athyreotic patients had a lower FT_3:FT_4 ratio than control subjects. This ratio tends to decrease with a higher therapeutic dose of thyroxine. In patients, serum T_3 levels correlated with serum T_4, while in control, subjects serum T_3 levels remained constant despite differences in serum T_4. In addition, the pituitary TSH response to thyroxine was significantly different between the two groups, indicating a less refined feedback mechanism in athyreotic patients.

ANALYSIS AND COMMENTARY

The authors confirm the fact that the thyroid parameters of thyroxine-treated patients do not fully match those of the control subjects. In fact, serum FT_4 levels had to be higher in the treated patients in order to achieve similar FT_3 levels. This is well known. There was, however, an additional difference between patients and control subjects: In patients, the serum FT_3 values increased in close correlation with increasing serum FT_4 values, while in control subjects, serum FT_3 values remained constant and, thus, did not correlate with the serum FT_4 values. This finding may reflect the advantage of normal thyroid function over substitution therapy. The authors postulate that a relatively large fraction of athyreotic, T_4-treated patients, deemed to have satisfactory substitution according to serum TSH levels, may in fact have partial T_3 deficiency. This is possible, albeit not proven, since blood levels are not a clear reflection of intracellular T_3 pools. The circulating T_3 represents only 20% of the total T_3 pool. Clinical signs of thyroid deficiency were absent. We know that thyroid hormone effects are robust. In general, serum TSH needs to be 10 mU/L or more before clinical symptoms appear (3). This may reflect difficulties in finding sensitive criteria for hypothyroidism. At the present state of the art of therapy, one is tempted to conclude that these findings are interesting but clinically irrelevant. One word of caution: During pregnancy it is recommended that an abnormally low FT_3 be avoided. A technical remark: It is likely that during the 7 years of observation, several patients had repeated determinations of thyroid parameters, but this was not reported.

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