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Thyroxine Plus Low-Dose, Slow-Release Triiodothyronine Replacement in Hypothyroidism: Proof of Principle

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Studies in hypothyroid rats show that, when infused with a combination of thyroxine (T4) plus triiodothyronine (T3) to normalize thyrotropin (TSH), euthyroidism in all organs is only ensured when T_4 and T_3 are administered in a ratio as normally secreted by the rat thyroid. As substitution with T_4-only results in an abnormal serum T_4/T_3 ratio, it is also possible that in humans, euthyroidism does not exist at the tissue level in many organs, considering that iodothyronine metabolism in the human and the rat share many similar mechanisms. Recent reports in which cognitive function and well-being are compared in patients with primary hypothyroidism substituted with T_4-only versus substitution with T_4 plus T_3 result in controversial findings in that either positive or no effects were found. In all these studies T_3 was used in the plain form that results in nonphysiologic serum T_3 peaks. In these studies it is suggested that substitution with T_3 should preferably be performed with a preparation that slowly releases T_3 to avoid these peaks. In the study reported here we show that treatment of hypothyroid subjects with a combination of T_4 plus slow-release T_3 leads to a considerable improvement of serum T_4 and T_3 values, the T_4/T_3 ratio and serum TSH as compared to treatment with T_4-only. Serum T_3 administration with slow-release T_3 did not show serum peaks, in contrast to plain T_3.

Introduction

The introduction of synthetic levothyroxine for thyroid hormone replacement therapy several decades ago signified an important improvement over the use of desiccated thyroid powder that contained thyroxine (T_4) plus triiodothyronine (T_3) in a varying ratio because it was only standardized in its iodine content. Recent interest to return to a now stable T_4/T_3 combination that mimics normal serum thyroid function parameters as closely as possible, stimulated studies comparing the effects of substitution with T_4 alone versus a fixed T_4/T_3 combination. These studies showed different results. Thus positive effects on health and well-being (1–3) as well as ineffectiveness (4–6) or even negative effects in some parameters (4) were noted. In two editorials (7,8) the pro and cons of these studies are discussed and suggestions were made for future studies to solve the discrepant findings. One of these recommendations is the use of T_3 in sustained release manner. "Plain" T_3 is rapidly absorbed into the bloodstream and also because of its short half-life of approximately 1 day, results in unwanted nonphysiologic serum peaks (9). Already in 1993 in a review on the use and misuse of thyroid hormone it was stated: "Perhaps the truly ideal substitution therapy for hypothyroidism might be a combination of LT_4, and LT_3 in a carefully determined ratio and in a form in which the LT_3 is slowly absorbed in a time-released form" (10).

In the present study we therefore addressed the following questions: (1) does a once-daily treatment with T_4 and slow-release (SR) T_3 lead to a constant serum T_3 level without peaks and (2) does the use of a combination treatment of T_4 plus SR-T_3 in a specific ratio results in normalization of serum thyrotropin (TSH) T_4, and T_3 concentrations? To these ends, patients treated with levothyroxine (LT_4) only for primary hypothyroidism were switched in an open, random, crossover manner to two regimens of substitution with a combination preparation of T_4 + plain (PL) T_3 and T_4 + SR-T_3.

Materials and Methods

Patients

Inclusion criteria were: patients of either gender with primary hypothyroidism, using between 100 and 175 μg LT4 (Thyrax®, Organon BV, The Netherlands), preferably 150 μg, for at least 3 months. They should otherwise be healthy. Each patient gave written informed consent. Exclusion criteria were: the use of any other medication and age of 80 years and above.

Eighteen patients were selected, fulfilling the inclusion criteria. One patient was excluded because of vaso-vagal col-

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lapse after (the first) vena-puncture, 1 patient because of a car accident and subsequently hospitalization during the study, and 1 patient because of improper use of study medication. The 15 included patients consisted of 12 females and 3 males, with a mean age of 50 years (range 26–79 years). Fourteen patients were using 150 μg LT_4 daily and 1 patient used 125 μg LT_4 daily. The causes of primary hypothyroidism were: ^{131}I treatment for Graves' disease, Hashimoto's thyroiditis, congenital hypothyroidism, neck irradiation for Hodgkin's disease and subtotal thyroidectomy for nodular goiter.

Study design

Three 6-week periods were discerned. In the first 6 weeks the patients were kept on their LT_4 dose that they were using before. Then patients were switched either to a combination therapy containing 125 μg T_4 (Thyrax®, Organon BV) and 6 μg PL-T_3 (inhouse normal release preparation using Cytomel® as T_3 compound) daily, or to a combination therapy containing 125 μg T_4 and 6 μg SR-T_3 (in-house slow-release preparation and using Cytomel® as T_3 compound) The combination treatments were performed in a randomized crossover design. During the sixth week of each study period, one blood sample was taken on day 3, and 5 serial blood samples were taken on day 5 at 8:00 AM (i.e., 15 minutes before ingestion of the medication), and at 09:45, 11:15, 2:15, and 5:15. Mean serum T_4 and T_3 and median serum TSH concentrations were calculated from the fifth day samples. It appeared that the T_4, T_3, and TSH values on the third day did not differ significantly from those on the fifth day at time point −15 minutes, indicating that equilibrium was reached. Patients were at rest at least half an hour before each blood sample was taken.

Laboratory methods

Serum T_4 and T_3 were measured by in-house radioimmunoassay (RIA); TSH by Amerlite 30 Amersham, United Kingdom. Within-assay coefficients of variation were 2%–8% for T_4, 2%–6% for T_3, and 2–5% for TSH.

Calculations

Statistical analysis was either done with the paired two tailed test for T_4, T_3, T_4/T_3 ratios, the maximal concentration of T_3 (C_{max}), the time of the maximal concentration (t_{max}), and the area under the T_3 curve from 0 to 24 hours (AUC_{0-24}) or with the Mann-Whitney two-tailed test for TSH. The AUC_{0-24}, was calculated by means of the linear trapezoidal rule, taking the predose value as the 24-hour point.

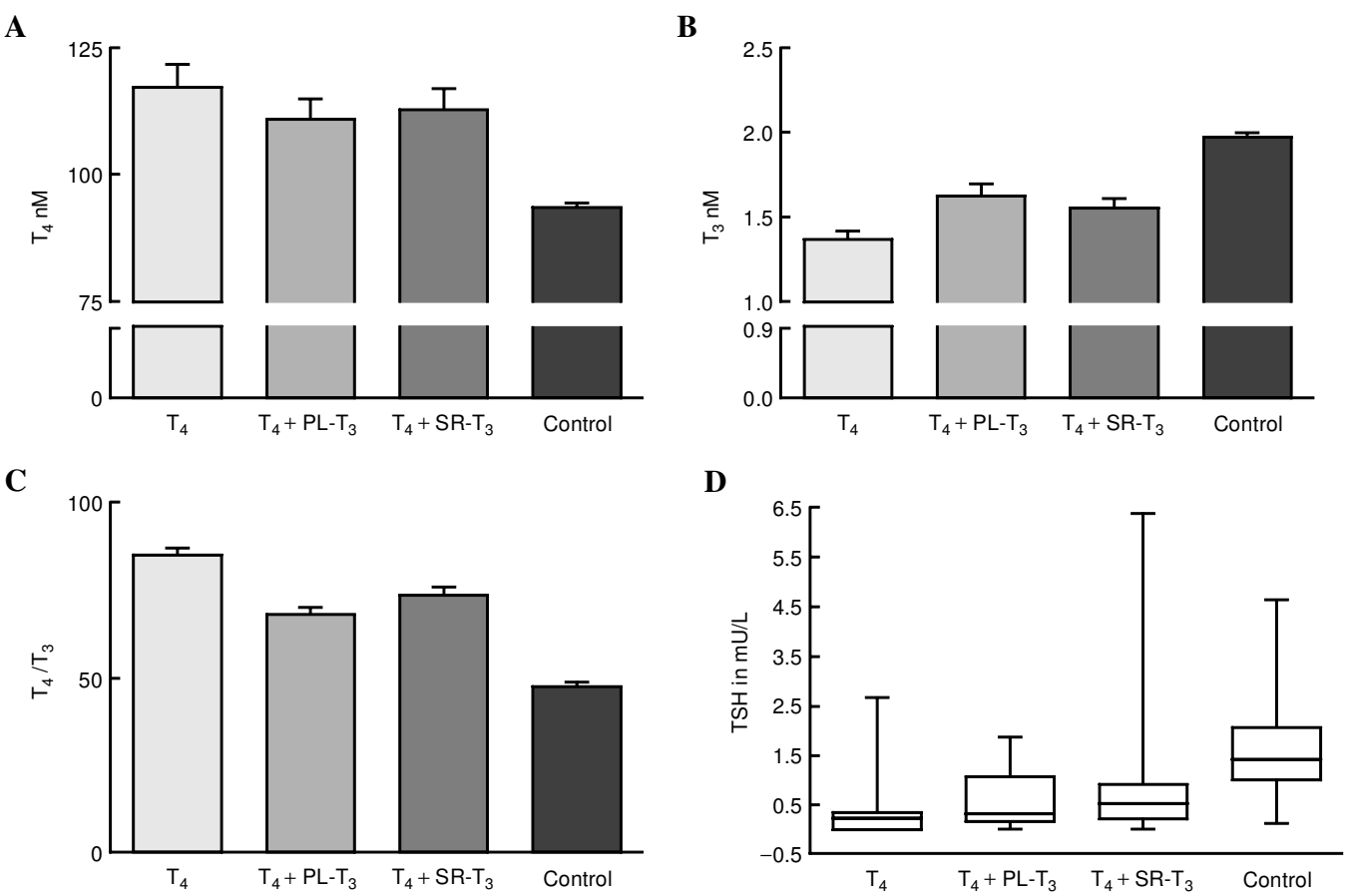

FIG. 1. Mean ± standard error of the mean (SEM) values of serum thyroxine (T_4) (**A**), triiodothyronine (T_3) (**B**), and T_4/T_3 (**C**) ratio and the median ± SEM of thyro-tropin (TSH) (**D**) during substitution with T_4, T_4 plus PL-T_3 or T_4 plus SR-T_3 and in controls.

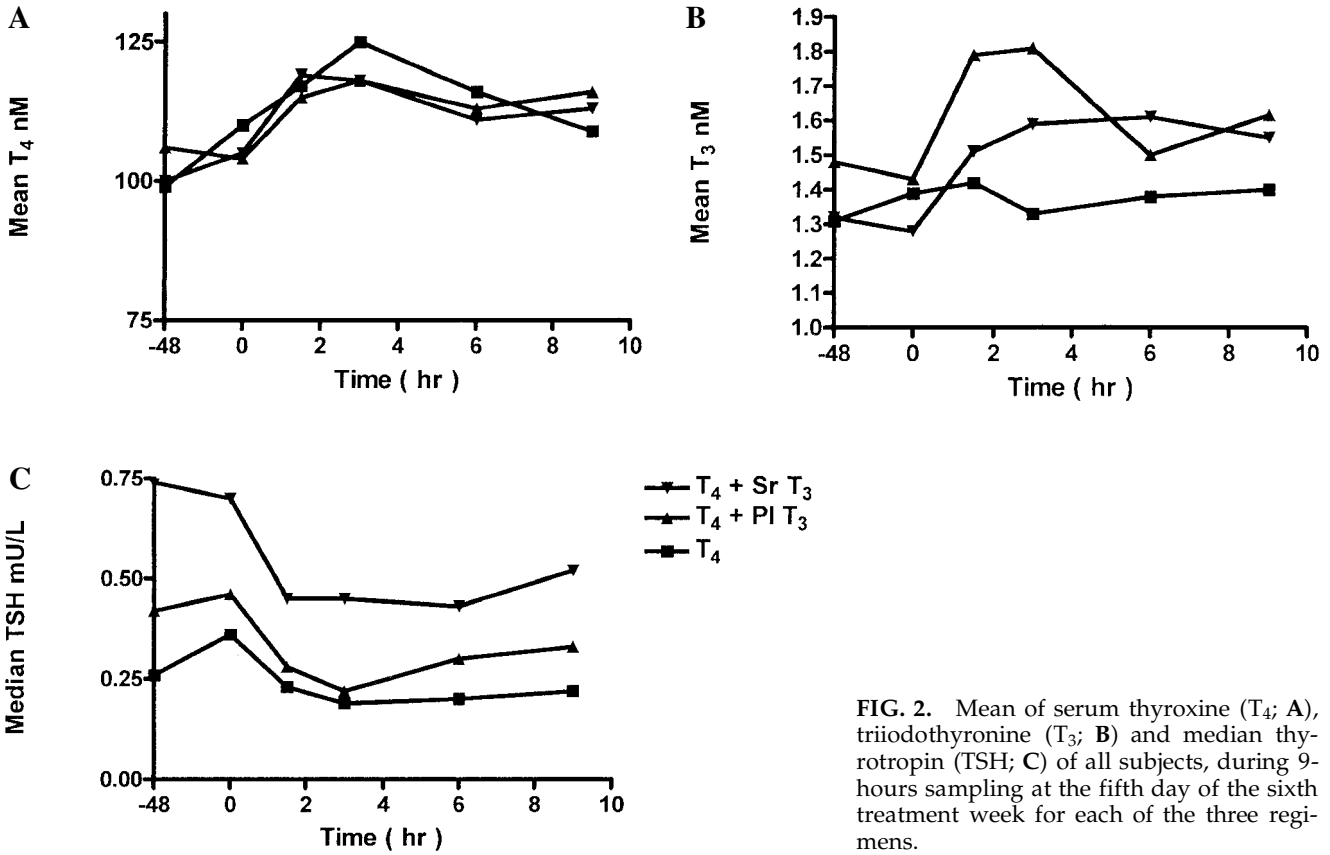

FIG. 2. Mean of serum thyroxine (T_4; **A**), triiodothyronine (T_3; **B**) and median thyrotropin (TSH; **C**) of all subjects, during 9-hours sampling at the fifth day of the sixth treatment week for each of the three regimens.

Results

The values of serum T_4, T_3, T_4/T_3 ratio, and TSH, during the different regimens, are depicted in Figure 1A–D. In Figure 1A, the mean value of T_4 during T_4-only substitution was not significantly different from the mean T_4 during T_4 + PL-T_3 ($p = 0.14$), but significantly higher during T_4 + SR-T_3 ($p = 0.025$) and in controls ($p < 0.0001$). The values of the combination treatments were not significantly different ($p = 0.67$). In Figure 1B, the mean serum T_3 during T_4-only treatment was significantly lower than during T_4 plus PL-T_3 ($p = 0.0016$), T_4 plus SR-T_3 ($p = 0.026$) and in controls ($p < 0.0001$). The mean serum T_3 during T_4 plus PL-T_3 was not significantly different from T_4 plus SR-T_3 ($p = 0.23$). Figure 1C shows the mean serum T_4/T_3 ratio that was significantly higher on T_4-only than on T_4 plus PL-T_3 ($p < 0.0001$), T_4 plus SR-T_3 ($p < 0.0001$) and in controls ($p < 0.0001$), while the T_4/T_3 ratio on T_4 plus PL-T_3 was significantly lower than on T_4 plus SR-T_3 ($p = 0.026$). In Figure 1D, the median serum TSH on T_4-only treatment was not significantly lower than on T_4 plus PL-T_3 ($p = 0.11$), but significantly lower than on T_4 plus SR-T_3 ($p = 0.033$) and than in controls ($p < 0.0001$), while no significant difference was present between the two combination preparations ($p = 0.14$). TSH concentrations during treatment with T_4 plus PL-T_3 and T_4 plus SRT_3 were significantly lower than in controls (both $p < 0.0001$).

In Figure 2, the mean serum T_4 (Fig. 2A) and T_3 (Fig. 2B) and median TSH (Fig. 2C) are depicted for all subjects for each of the three regimens during the 9-hour sampling on the fifth day of the sixth study week. It can be seen that serum T_4 shows a limited but steady rise during sampling in all three treatments without any significant difference between them. During T_4 plus PL-T_3, serum T_3 shows a considerable peak between 0 and 6 hours, whereas during T_4 plus SR-T_3 no peak is present but a slight rise similar to T_4. No substantial change in T_3 concentrations is seen during T_4-only treatment. The pharmacokinetics of T_3 during both combination treatments are depicted in the Table 1. The data show that the AUC_{0-24} of T_3 during both treatments are virtually

TABLE 1. PHARMACOKINETIC PARAMETERS OF TRIIODOTHYRONINE (MEAN ± SEM)

Parameter	*T_4 + PLT_3*	*T_4 + SRT_3*	p *value*
C_{max} (nmol/L)	1.83 ± 0.06	1.67 ± 0.06	0.038
T_{max} (h)	3.2 ± 0.56	4.97 ± 0.75	0.032
$AUC_{0-24\ h}$ (nmol.h/L)	37.97 ± 1.49	36.65 ± 1.43	0.43

T_4, thyroxine; PL-T_3, plain triiodothyronine; SR-T_3, slow-release triiodothyronine; C_{max}, maximal concentration; AUC_{0-24}, area under the curve from 0–24 hours; T_{max}, time point of C_{max}.

the same, while C_{max} and T_{max} of T_3 during the SR-T_3 regimen are significantly lower and later, respectively, than during PL-T_3.

Discussion

Substitution of thyroid function with LT_4 in patients with primary hypothyroidism, when titrated to normalize serum T_4, results in a mean serum T_3 level that is lower than normal. However, when T_4 is administered in amounts to normalize serum T_3, T_4 parameters will rise to supranormal concentrations (11,12). The reason for this is that the thyroidal contribution to serum T_3, which is approximately 20% of total serum T_3 (13), is lacking in patients with absent thyroid function. Thus, in this situation all plasma T_3 is derived from T_4. Hence, in T_4 substitution, more T_4 has to reach the plasma compartment than under normal conditions to ensure normal plasma T_3. Consequently, whatever dose of T_4 is substituted, the serum T_4/T_3 ratio will always be abnormal, that is, elevated. It has been established in rats that the extent to which nuclear receptor-bound T_3 is derived from plasma T_3 and from local T_3 production from T_4 varies among tissues. Thus, for instance, nuclear T_3 in cerebral cortex is derived for approximately 80% from local conversion of T_4, in pituitary for approximately 50%, in skeletal muscle for approximately 40%, and in liver for only approximately 5% (14,15). When rats are infused with T_4 in combination with T_3 in the same ratio in which they are normally secreted, the euthyroid state in all of the many tissues studied is ensured. Any variation of this ratio leads to tissue hypothyroidism or hyperthyroidism in various organs (16).

Although the exact contribution of the different sources of nuclear T_3 in human tissues is unknown, there are many similarities regarding thyroid hormone production and metabolism between rat and humans (17). Therefore, it would not be surprising if a similar situation with regard to the negative tissue effects of an abnormal plasma T_4/T_3 ratio would exist in humans as well. For instance, when T_4 is administered in a dose such that serum T_3 is normal, serum T_4 parameters will be increased and serum TSH will be suppressed (18) because thyrotropic nuclear T_3 occupancy is importantly dependent on plasma T_4.

The ratio that we used in this study was based on data of thyroid hormone secretion and intestinal absorption in humans (19,20). The pharmacokinetics of T_3 show that the slow-release preparation is indeed slowly releasing T_3 *in vivo* as the T_{max} occurs significantly later and the C_{max} is significantly lower than in the case of plain T_3. The total amount absorbed (see AUC) is the same for both preparations. Despite the fact that thyroid function parameters and the T_4/T_3 ratios improved substantially in the combination regimens, they were still not normal (Fig. 1). The combination treatment with slow-release T_3 did not result in a serum T_3 peak but only in a slow rise of T_3 after intake, comparable to that of T_4 (Fig. 2a and 2b). The relative variation of TSH in the three regimens is not different and one could wonder why during T_4 plus PL-T_3 serum TSH fluctuation is not at variance with that in the other two treatments. However, it should be realized that TSH secretion is importantly dependent on serum T_4 (14,15), that may dilute any effect of serum T_3 variations.

From this study it is apparent that using a slow-release T_3 preparation, nonphysiologic T_3 peaks are avoided. We suggest that in future studies on the effects of T_4 plus T_3, only sustained release T_3 preparations are being used.

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