Hormone Replacement after Thyroidectomy for Cancer: Effects of Thyroxine alone *versus* Thyroxine plus Triiodothyronine on Antioxidant Activity and Lipid Peroxidation

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Objective. Examined was the influence of thyroid replacement with thyroxine (T_4) alone in comparison to T_4 triiodothyronine (T_3) combination on lipid peroxidation and antioxidant activity in hypothyroid patients with thyroid cancer.

Methods. Seventeen patients with thyroidectomy and subsequent radioiodine therapy for cancer are the subject of this report. Patients received thyroid replacement of T_4 alone or T_4 plus T_3 for five weeks. The study was performed in double-blinded cross-over design.

Results. An increase in thyroid stimulating hormone (TSH) concentration was small but statistically significant, and an increase in the concentration of sex hormone-binding globulin, though within the normal range, was substantial after combined hormone treatment. An increase in concentration of vitamin E, though small, was statistically significant. Changes in T_3 concentration were correlated positively with changes in vitamin A concentration ($r = 0.64$; $p = 0.006$). Changes in cholesterol levels were correlated positively with vitamin E and malondialdehyde concentrations ($r = 0.83$, $p < 0.001$ and $r = 0.54$, $p = 0.03$, respectively).

Conclusion. Combined replacement with T_4 plus T_3 stimulates both lipid peroxidation and antioxidant activity, in comparison to treatment with T_4 alone in hypothyroidism due to thyroid cancer.

Key words: thyroid cancer, hypothyroidism, thyroxine, triiodothyronine, lipid peroxidation, antioxidants, malondialdehyde, vitamin A, vitamin E, cholesterol

INTRODUCTION

Recently our group has described the results of treating 33 hypothyroid patients with thyroxine (T_4) alone or with a reduced amount of T4 combined with a small amount of triiodothyronine (T_3) (1). Although combined hormone treatment caused an increase in the concentration of the sex hormone-binding globulin (SH-BG); most of the other metabolic effects and biochemical effects were expected. However, many improvements in psychological function

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occurred after combined treatment. In a more detailed analysis of these improvements, we reported that patients who needed hormone replacement because of thyroidectomy for thyroid cancer profited more from the addition of T_3 than did patients who were being treated for autoimmune thyroiditis (2). Some measures of mental improvement were correlated positively with changes in the concentration of thyroid stimulating hormone (TSH); some were correlated negatively with changes in free T_4.

The present brief report maintains the focus on thyroid cancer patients. It presents findings of changes in antioxidant activity and lipid peroxidation that may be of special relevance to such patients (3).

SUBJECTS AND METHODS

Seventeen patients (15 women and two men) with thyroidectomy and subsequent radioiodine therapy for cancer are the subject of this report. The mean age of the group was 45 years. Supressive therapy consisted of a mean dose of 196 ug T_4 per day. The study protocol was approved by the Ethical Committee of the Kaunas Medical University, and all patients gave informed consent.

Each patient took his or her usual dose of T_4 up to and including the first day of the study. On this day each patient was assigned, according to a prearranged randomized schedule, to receive T_4 (L-Thyroxin Berlin-Chemie) alone for five weeks or to receive T_4 plus T_3 (Triiodthyronin Berlin-Chemie) for five weeks. After five weeks the other treatment was given. Each patient's regimen was based on his or her usual dose of T_4. Most of the T_4 dose was given in usual tablet form. However, some capsules contained 50 ug of T_4, while other capsules of identical appearance contained 12.5 ug of T_3. If a patient, for example, had been treated with 150 ug of T_4 per day, that patient was instructed to take 100 ug of the usual T_4 tablets plus one capsule. Patients took medications once daily, half an hour before breakfast.

At the end of each of the two treatment periods blood was taken from an antecubital vein. Serum was prepared and deep frozen for the later assessment of the variables shown in the table. For a given variable the samples for all the patients were analyzed at the same laboratory session.

All hormone measurements were assayed by commercial kits (Orion Diagnostica, Kauniainen, Finland). Serum TSH was estimated by means of ultrasensitive immunoradiometric assay. Intraasay variability was 5.8% at 0.05–0.5 μU/ml and 1.9% at 0.5–50.0 μU/ml, lowest detectable values, 0.05 μU/ml. Free T_4 (FT_4), total T_4 and total T_3 were assayed by radioimmunoassay kits. Intrassay variations were 7.0%, 4.0% and 4.5%, lowest detectable values 0.08 ng/dl, 1.2 μg/dl and 6.7 ng/dl, respectively.

Serum total triglycerides and cholesterol were measured by enzymatic colorimetric methods (Sera-Pak Triglycerides Fast Color kit, Bayer Corporation, Tarrtown, NY). SH-BG was measured with immunoenzymometric kits (Medix Biochemica, Kauniainen, Finland).

Serum vitamin E concentration, serum vitamin A concentration and serum malondialdehyde (MDA) concentration were assessed by spectrofluorimetrical method (4, 5).

Paired *t* tests were used to compare paired data from the two treatment periods. Probability values were based on two-sided interpretation of test results. Pearason's product–moment correlation coefficient (*r*) was used to examine relationships among selected measurements. Absolute values were expressed as mean ± standard deviation.

RESULTS

The results of the study are shown in Table. The values for the four thyroid axis variables and for the first three of the six metabolic variables listed have previously been published (2). They are included here to provide the needed context for the values of the three metabolic variables that have not previously been reported – vitamin A, vitamin E, and MDA. The thyroid axis variables need only brief comment, because the only effect of combined hormone treatment that was not expected was an increase in concentration of TSH. With the concentration remaining very low, the increase in TSH was small but statistically significant. Changes in the concentration of triglycerides and cholesterol were trivial. The increase in the concentration of SH-BG, though within the normal range, was substantial after combined hormone treatment.

After combined hormone treatment the concentration of vitamin A showed a trivial increase. An increase in the concentration of vitamin E, though small, was statistically significant. An increase in the concentration of MDA approached statistical significance.

Among 45 tests for correlations between biochemical variables, only three were statistically significant. Changes in T3 concentration correlated positively with changes in vitamin A concentration ($r = 0.64$; $p = 0.006$). Changes in cholesterol levels correlated positively with vitamin E and MDA concentrations ($r = 0.83$, $p < 0.001$ and $r = 0.54$, $p = 0.03$, respectively).

Table. **Biochemical findings in serum after treatment with Thyroxine (T_4) and after T_4 plus Triiodothyronine (T_3) combination (n = 17) (mean ± S.D.)**

	T_4 treatment	T_4 plus T_3 treatment	p, paired t test	Normal range
Thyroid axis variables				
Thyroid stimulating Hormone (μU/ml)	0.06 ± 0.02	0.09 ± 0.06	0.04	0.3–0.5
Free T_4 (ng/dl)	2.47 ± 0.71	1.95 ± 0.59	0.000	0.7–2.1
Total T_4 (μg/dl)	16.4 ± 3.0	12.7 ± 2.6	0.000	4–11
Total T_3 (μg/dl)	83.3 ± 35.3	105.3 ± 40.7	0.001	75–125
Metabolic variables				
Triglycerides (mg/dl)	131.0 ± 61.9	135.5 ± 64.6	0.80	47–228
Cholesterol (mg/dl)	196.2 ± 30.8	203.8 ± 38.5	0.15	152–268
Sex-hormone binding globulin (μg/dl)	2.64 ± 1.48	3.39 ± 1.77	0.02	0.4–3.5
Vitamin A (μg/dl)	61.8 ± 12.6	64.6 ± 12	0.14	>55
Vitamin E (mg/dl)	0.85 ± 0.15	0.93 ± 0.20	0.05	>0.86
Malondialdehyde (μg /ml)	34.6 ± 5.6	38.9 ± 7.2	0.06	<36

DISCUSSION

As noted above, the increase in TSH after combined hormone treatment was not expected. Indeed, it did not occur in patients with autoimmune thyroiditis, as discussed in our earlier report (2). It is interesting to note that Ridgway et al. (6) reported that T_3 treatment of hypothyroid patients increased TSH response to thyrotropin-releasing hormone infusion.

The increase in SH-BG noted in the present report in thyroid cancer patients was observed earlier in a group of 33 patients, which was comprised of the present 17 cancer patients and 16 patients with autoimmune thyroiditis. The increase in SH-BG after combined treatment attests to the sensitivity to T3 of the liver enzymes that produce SH-BG. In thyroidectomized rats given thyroxine alone for treatment of hypothyroidism, normal concentration of triiodothyronine could not be achieved in tissues such as liver without the administration of supraphysiologic doses or combined T_4 plus T_3 treatment (7).

It is well known that thyroid hormones exert a wide range of effects on lipid synthesis and degradation and also influence antioxidant activity. Findings in rats indicate that hyperthyroidism, but not hypothyroidism, increases lipid peroxidation in some tissues, though antioxidant capacity is decreased in both conditions (8). Clinical findings replicate experimental data suggesting that vitamin E concentration is decreased in hypothyroid and thyrotoxic patients in comparison to euthyroid controls, and that in thyrotoxic patients an increase in lipid peroxidation is most evident (9).

Antioxidant activity plays an important role in neoplastic disease generally, though little is known about its exact role in thyroid cancer (3). Present data demonstrate that combined replacement with T_4 plus T_3 stimulates both lipid peroxidation and antioxidant activity, in comparison to treatment with T_4 alone. This may constitute an advantagous addition to those described elsewhere (1, 2).

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HIPOTIREOZĖS, KURIĄ SUKĖLĖ TIREOIDEKTOMIJA DĖL SKYDLIAUKĖS VĖŽIO, PAKAITINIO GYDYMO VIEN TIROKSINU ARBA TIROKSINO IR TRIJODOTIRONINO KOMBINACIJA ĮTAKA ANTIOKSIDANTŲ AKTYVUMUI IR LIPIDŲ PEROKSIDACIJAI

S a n t r a u k a

Tikslas. Buvo palygintas pakaitinio hipotireozės gydymo vien tiroksinu (T_4) ir tiroksino bei trijodotironino (T_3) kombinacija poveikis lipidų peroksidacijai ir antioksidantų aktyvumui ligoniams, kuriems po skydliaukės vėžio gydymo prasidėjo hipotireozė.

Tyrimo metodai. Tyrime dalyvavo septyniolika ligonių, kuriems dėl skydliaukės vėžio buvo atlikta tireoidektomija ir taikytas gydymas radioaktyviuoju jodu. Dėl skydliaukės vėžio gydymo atsiradusi hipotireozė studijos metu buvo gydoma arba T_4, arba T_4 ir T_3 kombinacija. Kiekvienas gydymo kursas truko penkias savaites. Tyrimas atliktas dvigubai aklu, kryžminiu metodu.

Rezultatai. Gydant hormonų kombinacija, statistiškai patikimai padidėjo tireotropinio hormono ir lytinius hormonus surišančio proteino koncentracija. Buvo nustatytas nedidelis, tačiau statistiškai reikšmingas vitamino E koncentracijos padidėjimas. T_3 koncentracijos pokyčiai teigiamai koreliavo su vitamino A koncentracijos pokyčiais ($r = 0,64$, $p = 0,006$), o cholesterolio koncentracijos pokyčiai – su vitamino E ir malondialdehido koncentracijos pokyčiais (atitinkamai, $r = 0,83$, $p < 0,001$ ir $r = 0,54$, $p = 0,03$).

Išvada. Kombinuota T_4 ir T_3 pakaitinė hipotireozės terapija, palyginti su gydymu vien T_4, stimuliuoja tiek lipidų peroksidaciją, tiek antioksidantų aktyvumą.

Raktažodžiai: skydliaukės vėžys, hipotireozė, tiroksinas, trijodotironinas, lipidų peroksidacija, malondialdehidas, vitaminas A, vitaminas E, cholestrolis