L-Thyroxine Therapy Attenuates the Decline in Serum Triiodothyronine in Nonthyroidal Illness Induced by Hysterectomy

Helen J. Karga, Peter D. Papapetrou, Sakellaris E. Karpathios, Fotini E. Papandroulaki, Constantinos N. Tsompos, Garyphallia P. Papaioannou, Kyriakos P. Aloumanis, and Panayotis L. Papaioannou

It is controversial whether the administration of thyroid hormone to patients with nonthyroidal illness has any beneficial effect. Two groups of patients undergoing abdominal hysterectomy under the same general anesthesia were studied. Group A consisted of 15 women taking chronically L-thyroxine therapy (1.8 μg/kg daily), and group B (control) consisted of 16 apparently healthy euthyroid women taking placebo. Thyroid hormones, cortisol, and interleukin (IL)-6 were measured 1 day before and 1, 2, 3, and 6 days after surgery. Total triiodothyronine (TT_3) decreased to a significantly greater degree ($P < .05$) and for a longer period of time in group B than in group A. The significant increase of reverse T_3 (rT_3) noted early in group B failed to reach the baseline levels until the end of the study, whereas in group A, rT_3 returned to the preoperative values by day 2. Both groups had similar free thyroxine (FT_4) at baseline. FT_4 increased significantly at day 1 and remained significantly elevated throughout the postoperative period in group B only. Serum TT_4, thyroid-stimulating hormone (TSH), and cortisol did not change significantly in either group. In all patients, IL-6 increased significantly to a peak value at day 1, showing a slow decrease thereafter. A stronger negative correlation was found between T_3 and IL-6 in group B than in group A ($r = -.66$, $P < .0001$ *v* $r = -.38$, $P < .001$, respectively) and a strong positive correlation was observed between rT_3 and IL-6 in group B only ($r = .57$, $P < .001$). The long-term treatment with T_4 seems to attenuate the decrease of serum T_3, which occurs during the development of nonthyroidal illness postoperatively. The elevation of IL-6 accounted for a greater proportion of the variations of the T_3 and rT_3 in the control group B than in the T_4-treated group A.

ALTERATIONS IN serum thyroid function tests under severe illness or stressful conditions, in the absence of concurrent hypothalamic-pituitary-thyroid disease, are referred to as nonthyroidal illness, which represents the net effect of more than one disturbance. The inhibition of the 5′-monodeiodinase activity (that leads to the decreased conversion of thyroxine [T_4] to triiodothyronine [T_3] in peripheral tissues), the impairment of T_4 binding to proteins, the decrease in thyroid-stimulating hormone (TSH) production, the decrease of T_4 uptake into tissues, or the changes in the hormone clearance and degradation rates are some of the pathophysiologic mechanisms proposed as underlying cause of this disorder.[1] Major surgical procedures may be associated with a number of endocrine alterations, including those of nonthyroidal illness, which reflect the hormone response to stress and trauma.[2-4] Compared with preoperative values, a transient, significant decrease in T_3, total T_4 (TT_4), free T_4 (FT_4), and TSH concentrations occurs within 24 hours after surgery, and these parameters normalize during convalescence.[2] Several cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-6) are also implicated as causative factors,[5] although an early decrease of T_3 may appear within 30 minutes after the induction of anesthesia before skin incision independently of IL-6 or TNF-α changes.[6]

The response to treatment with thyroid hormones has been studied little during severe nonthyroidal illness, and the question if replacement therapy would be beneficial in such patients still remains unanswered.[5,7] Intravenous administration of L-T_4 to patients admitted into an intensive care unit increased serum TT_4 and FT_4 levels within 3 days, but did not normalize serum T_3 over a period of 10 days.[8] On the other hand,T_3 administration to normal men prevented the decrease in serum T_3 during fasting and maintained the serum T_3 within the normal range.[9] Infusion of T_3 for 6 hours in patients immediately after coronary bypass surgery increased T_3 to supranormal levels and improved postoperative cardiac performance, although it did not change the outcome compared with the control group.[10] To investigate the influence of preceding chronic T_4 therapy on the appearance of nonthyroidal illness after major surgery, several indexes of thyroid function were evaluated postoperatively in 15 women on T_4 replacement therapy and 16 control healthy euthyroid women who underwent abdominal hysterectomy. In addition, cortisol and IL-6 were measured as markers of postoperative systemic reaction to surgery and inflammation.[11,12]) A significantly less pronounced decrease of T_3 and for a shorter period of time was observed in the T_4-treated women than in the control group. The postoperative increase of IL-6 could explain a significant proportion of the variation of T_3 only in the control group.

SUBJECTS AND METHODS

The study population consisted of 2 groups of patients undergoing total abdominal hysterectomy for fibromas under general anesthesia. Group A comprised 15 women with a mean age of 49 years (range, 44 to 56 years) who were taking for at least 1 year T_4 replacement therapy, (sodium levothyroxine, average 1.8 μg/ kg, by mouth daily) for iatrogenic hypothyroidism (posthyroidectomy or after treatment with radioiodine). Control group B comprised 16 healthy, euthyroid women matched for age (mean age, 50; range, 43 to 57 years) who had similar initial thyroid status to the patients of group A. Matching criteria for the thyroid status included the baseline levels of serum TSH, serum TT_4, and T_3. The patients were admitted to the hospital 1 day before surgery. Women with known or suspected other diseases or receiving other therapies were excluded. The operation was started the next morning

From the Second Division of Endocrinology and the Department of Obstetrics and Gynecology, Alexandra Hospital, Athens, Greece.
Submitted December 9, 2002; accepted April 16, 2003.
Address reprint requests to Helen J. Karga, MD, Second Division of Endocrinology, Alexandra Hospital, Vas. Sofias and Lourou St, Athens 115 28, Greece.

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Table 1. Profiles of the Various Parameters Measured at Baseline and During the Postoperative Period in Both Groups

	Preoperatively	Postoperatively			
	Day −1	Day 1	Day 2	Day 3	Day 6
Group A (n = 15)					
TT_4 (nmol/L)	164 ± 19	142 ± 29	153 ± 26	144 ± 31	183 ± 34
FT_4 (pmol/L)	18 ± 3	17 ± 2	18 ± 2	19 ± 4	20 ± 3
T_3 (nmol/L)	1.8 ± 0.5	1.4 ± 0.4†	1.5 ± 0.4†	1.6 ± 0.4†	1.8 ± 0.4
rT_3 (nmol/L)	0.8 ± 0.1	1.2 ± 0.4*	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.3
TSH (mIU/L)	0.8 ± 0.5	1.4 ± 0.9	1.4 ± 0.9	1.5 ± 0.8	1.6 ± 0.5
Cortisol (nmol/L)	497 ± 32	521 ± 21	527 ± 28	485 ± 24	549 ± 19
IL-6 (pg/mL)	2.7 ± 0.9	12 ± 0.6*	11.5 ± 1.11*	10.8 ± 1.3*	8.5 ± 1.2*
Group B (n = 16)					
TT_4 (nmol/L)	145 ± 30	124 ± 25	139 ± 24	155 ± 26	165 ± 36
FT_4 (pmol/L)	17 ± 2	19 ± 2*	20 ± 3*	20 ± 3*	20 ± 2*
T_3 (nmol/L)	1.9 ± 0.5	0.9 ± 0.3*†	1.0 ± 0.4*†	1.2 ± 0.4*†	1.5 ± 0.5*
rT_3 (nmol/L)	0.7 ± 0.1	1.1 ± 0.3*	1.0 ± 0.1*	1.0 ± 0.1*	0.8 ± 0.9*
TSH (mIU/L)	1.1 ± 0.4	1.4 ± 0.4	1.4 ± 0.6	1.0 ± 0.5	1.3 ± 0.6
Cortisol (nmol/L)	523 ± 45	521 ± 15	525 ± 29	485 ± 25	549 ± 35
IL-6 (pg/mL)	2.7 ± 1.8	13.7 ± 2.1*	14.0 ± 2.5*	12.2 ± 2.5*	8.9 ± 2.7*

NOTE. Values shown are means ± SD.

*Significant differences of the mean value of each day from baseline (day before the operation) (Wilcoxon paired test).

†Significant differences between corresponding days of the 2 groups.

after an overnight 12-hour fast. Oral feeding restarted 48 hours after surgery, and in the meantime, parenteral food was administered with appropriate proportions of carbohydrates, fat, protein, and energy content to prevent malnutrition. An identical diet was given during the subsequent inpatient evaluation, and it was designed to maintain a stable nutritional status. The 2 groups underwent a similar surgical procedure under identical routine anesthesia and were monitored in an identical fashion during the study period. Anesthesia was induced by intravenous (IV) administration of fentanyl and propofol and was maintained with a combination of IV fentanyl and isoflurane and inhaled O_2 /N_2O. Pancuronium was administered for relaxation. During the time of the study, the patients of group A were receiving regularly their T_4 tablets every morning fasting (including the day of the operation), while the patients of group B were receiving placebo tablets. The placebo started on day −1 and stopped on day 6. Before T_4 or placebo tablets were given, fasting blood samples were drawn at 7:30 AM 1 day before (−1 day) and 1, 2, 3, and 6 days after surgery. The day of the operation is day 0. After the separation, the sera were kept frozen (−20°C) until the day of the assay. All patients gave informed consent to participate in this study, which was approved by the Scientific Committee of the hospital.

Measurement of Hormones and IL-6

All samples were run in duplicate, and the mean value of the results is reported. The samples of an individual subject were run in the same assay to minimize the interassay variation. Serum TT_4 and T_3 were determined using competitive radioimmunoassay (RIA) kits, and serum FT_4 was measured by a solid phase RIA as has been described previously.[13] Reverse T_3 (rT_3) was measured by RIA, (RADIM, S.p.A., Roma, Italy) with normal range (NR) 0.36 to 0.77 nmol/L and coefficient of variation (CV) 7.1% at 0.66 nmol/L. For the TSH determination, a third generation 2-site chemiluminescence immunoassay was used (Nichols Institute Diagnostics, Nijmegen, The Netherlands) with NR 0.40 to 4.00 μU/mL and CV 4.8% for a TSH level of 1.28 μU/mL. Cortisol was measured by a solid phase RIA (Coat-A-Count; Diagnostic Products, Los Angeles, CA) with NR 138 to 690 nmol/L and CV 4% for the values of 331 nmol/L. Serum IL-6 was measured by an ultrasensitive solid phase "sandwich" enzyme immunoassay technique (Quantikine HS, High Sensitive; R&D Systems, Minneapolis, MN). The NR was 0.38 to 10.10 pg/mL, with CV 5.9 for the value of 2.73 pg/mL.

Statistical Analysis

All variables are presented as mean ± SD. The Wilcoxon signed rank sum test for paired groups was used to compare the longitudinal changes of the variables over time within each group. Differences of the means of the variables between the 2 groups were evaluated by the *t* test. Differences were considered statistically significant at $P < .05$. Correlation relationships were determined by simple linear regression analysis and multiple linear regression analysis.

RESULTS

The mean age of the women of group A (49 ± 2 years) did not differ significantly from group B (50 ± 3 years). Mean serum TT_4, T_3, FT_4, and TSH at day −1 were not different between the 2 groups as a result of matching. Body weight was maintained constant in all patients, and none of them experienced any important postoperative complications. Consequently, the patients were discharged from the hospital on the sixth day after the operation. The results of the various parameters measured in the 2 groups are summarized in Table 1. Figure 1 displays the time course (means ± SD) of several parameters of thyroid function, serum cortisol, and IL-6 levels 1 day before the operation (day −1) and at 1, 2, 3, and 6 days postoperatively. On the day of the admission (day −1), all patients were euthyroid.

Serum TSH, FT_4, and T_3 were not different between the 2 groups and were within the concentration observed during the first postoperative day and, although in both groups T_3 decreased significantly, in the control group B, it decreased to a greater degree by approximately 48% (from 1.94 ± 0.44 to 0.94 ± 0.28 nmol/L, $P < .001$) compared with a decrease of 27% in group A (from 1.85 ± 0.45 to 1.38 ± 0.38 nmol/L, $P < .027$), (Table 1, Fig 1A). Analysis of individual values showed that in none of the subjects in group A did serum T_3 decline

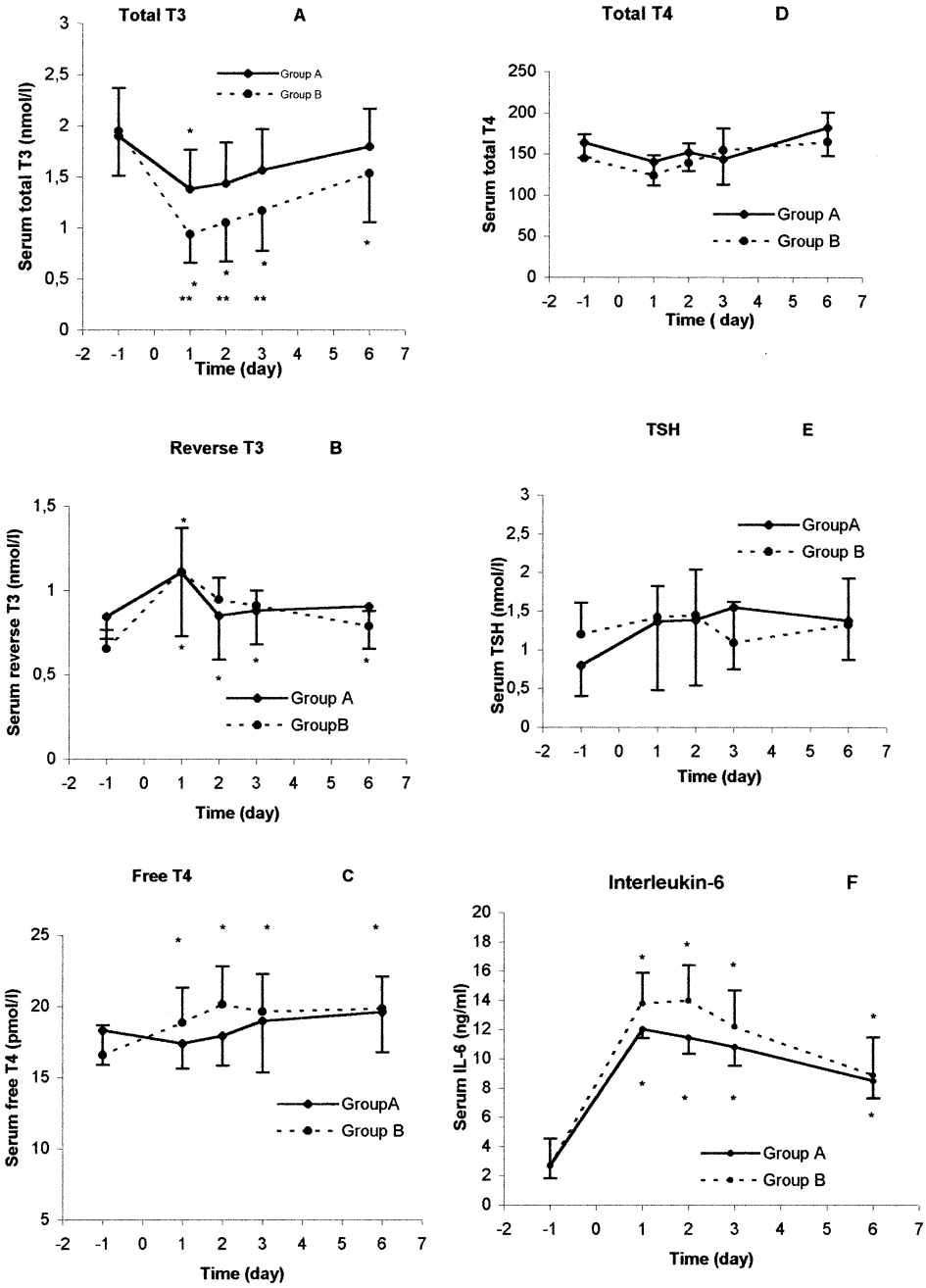

Fig 1. Longitudinal changes of serum T_3, rT_3, FT_4, TT_4, TSH, and IL-6 levels in patients 1 day before (day −1) and at days 1, 2, 3, and 6 after the operation. The day of the operation is day 0. The mean ± SD of the values are shown. *Statistically significant difference from baseline (Wilkoxon paired test). **Differences between corresponding days between the 2 groups (*t* test).

below the normal range postoperatively, whereas in 5 of 12 patients in group B, serum T_3 decreased below the lower limit of normal (0.90 nmol/L). The lowest mean serum T_3 concentrations occurred on postoperative day 1 in both groups. However, while in the T_4-treated group A, serum T_3 returned to the baseline (preoperative) levels by the third postoperative day, and in group B, it remained lower until the end of the follow-up period (Fig 1A). The comparison of T_3 concentrations between the 2 groups at the different sampling times showed that T_3 levels remained significantly lower in group B versus group A for the 3 days after surgery (day 2, $P = .006$; day 3, $P = .007$) (Table 1, Fig 1A). The increase of rT_3 in the postoperative days was concurrent with the reduction of serum T_3 concentration. In group A, rT_3 increased by 25% 1 day after the operation (from 0.84 ± 0.13 to 1.11 ± 0.38 nmol/L, $P < .05$) and within 48 hours returned to the baseline level, remaining stable thereafter. In contrast, in the patients of group B, rT_3 increased by 59% from the baseline value (from 0.65 ± 0.04 to 1.11 ± 0.1 nmol/L, $P < .001$), but remained significantly elevated until the sixth postoperative day (Fig1B). FT_4 changed slightly (about ± 6%) in group A throughout the study period in comparison with group B in whom FT_4 increased significantly on day 2 and remained elevated thereafter. However, the concentrations of FT_4 at the different sampling times did not

Table 2. Correlations Between Various Serum Parameters in Groups A and B

	Group A	Group B
T_3 *v* IL-6	$r = -.38$	$r = -.66$
	$P < .001$	$P < .0001$
rT_3 *v* IL-6	$r = .03$	$r = .57$
	NS	$P < .0001$
TSH *v* FT_4	$r = -.46$	$r = .18$
	$P < .001$	NS

NOTE. Correlations between the various parameters were tested by linear regression using for each variable all values of the observation period.

Abbreviation: NS, not significant.

differ significantly between the 2 groups (Table 1, Fig 1C). In patients of both groups, serum TT_4 showed a tendency to decrease on day 1 after the operation, started to increase thereafter, but all changes in both groups did not reach statistical significance (Table 1, Fig 1D). Again, the fluctuations in serum TSH were not statistically significant and were similar in both groups (Fig 1E, Table 1).

In both groups, a marked increase in serum IL-6 was observed on day 1 after the operation (peak values in group A 12.03 ± 0.61 pg/mL and in group B 13.67 ± 2.08 pg/mL) followed by a gradual decrease thereafter (Fig 1F). The peak mean serum IL-6 occurred concurrently with the lowest T_3 level and with the peak value of rT_3. The increase of IL-6 was statistically significant, and this cytokine remained significantly higher than the baseline level throughout the study in both groups ($P < .001$, Table 1). The increase of IL-6 was similar in both groups. In both groups, mean serum cortisol levels were within the normal range initially and did not change significantly during the postoperative period (Table 1).

Linear regression analysis of serum T_3 on serum IL-6 for the entire observation period (preoperative day 1 and postoperative days 1,2, 3, and 6) gave the following results: There was a significant negative linear correlation between T_3 and IL-6 in the control group B ($r = -.66$, $P < .0001$), as well as in the T_4-treated group A ($r = -.38$, $P < .001$) (Table 2). Similar regression of rT_3 on IL-6 showed a significant positive correlation between rT_3 and IL-6 only in group B ($r = .57$, $P < .0001$), while no significant relationship was found in group A (Table 2). Linear regression of TSH on FT_4 for the entire follow-up period showed a significant negative correlation between the 2 indexes for group A ($r = -.46$, $P < .001$), while in group B, TSH was not related to FT_4 ($r = .18$) (Table 2). Multiple linear regression of serum T_3 simultaneously on serum FT_4, serum IL-6, and serum rT_3 showed that in both groups, there was no significant correlation between T_3 and FT_4. The correlation of T_3 with IL-6 and T_3 versus rT_3 was stronger in control group B (standardized coefficient for T_3 *v* IL-6 $= -0.49$, $P < .001$; standardized coefficient for T_3 *v* $rT_3 = -0.28$, $P \sim .07$) than in the T_4-treated group A (standardized coefficient of T_3 *v* IL-6 $= -0.39$, $P = .015$; standardized coefficient for T_3 *v* $rT_3 = -0.10$, $P = .530$). Multiple linear regression of TSH simultaneously on FT_4, T_3, and IL-6 showed again a significant correlation of TSH with FT_4 only in group A (standardized coefficient TSH *v* $FT_4 = -0.46$, $P \sim .005$).

DISCUSSION

The present study demonstrates that in patients who were already on chronic replacement therapy with T_4 the decline of serum T_3 after surgery was manifested in milder form and was of shorter duration compared with euthyroid patients with intact thyroid taking placebo. The significant decrease of serum T_3 and the increase of serum rT_3 appeared rapidly, within the first 24 hours postoperatively in both groups, but in the control group, these changes were more prominent and lasted for as long as 6 days after surgery. In addition, T_4 treatment did not influence the circulating markers of stress and inflammation, because cortisol and IL-6 were changed longitudinally in a similar manner in both groups. Because the clinical outcome, the nutritional status, and the serum cortisol and IL-6 levels were similar in both of our groups before and during the postoperative period, it could be suggested that our patients were expected to develop a nonthyroidal illness of approximately equal severity postoperatively.

In the control group (group B) of the present work, a significant decrease of T_3 and a concurrent increase of rT_3 occurred postoperatively, lasting for at least 6 days after the operation, and this finding is in accordance with most published studies in similar patients.[2,14,15] Wound stress, general anesthesia, postoperative inflammation, and calorie deprivation[12,14,16,17] may coexist in surgical patients, and all are known contributing factors to the decrease of T_3 in nonthyroidal illness. In contrast, in our patients on chronic T_4 therapy, a smaller decrease of serum T_3 occurred 24 hours postoperatively, and this was of a shorter duration. It could be suggested that the daily administration of L-thyroxine protected the patients from the development of a marked decrease of serum T_3 by preserving T_3, FT_4, and rT_3 at more stable levels. In surgical stress, the decrease in T_3 appears within a few hours or even within 10 minutes after the start of the surgical procedure and usually is of more than a week duration and has direct relationship with the patient's recovery process.[2,4,6]

One of the main causes of nonthyroidal illness is the decrease of extrathyroid conversion of T_4 to T_3 because of the reduced 5′-deiodinase tissue activity, which also leads to reduced catabolism of rT_3. We can hypothesize that in our control group the 5′-deiodinase activity was decreased after surgery in a greater degree and remained lower at least until the sixth postoperative day, while in the T_4-treated patients, the enzyme activity was only slightly changed. This is also supported by the fact that a strong negative correlation between T_3 and rT_3 was found only in the control group. It is possible that the long-term administration of T_4 in group A maintained constant and at a higher level the expression of 5′-deiodinase in tissues.[18] It is known that there are T_3 response elements upstream of the human deiodinase gene, and that T_3 induces the deiodinase expression at the transcriptional level.[19] It is also possible the differences in serum T_3 and rT_3 concentrations in the 2 groups could be the result of different amounts of T_4 to the liver, depending on whether the T_4 was secreted by the woman's thyroid gland and reached the liver via systematic circulation or

was swallowed and absorbed into the portal circulation and therefore reached the liver before being more widely distributed.

In both of our groups, significant changes of serum TT_4 and TSH were not found. Thus, the postoperative increase of FT_4 only in the control group is unlikely to represent a tissue resistance to thyroid hormone developing acutely postoperatively. We think that an increase of FT_4 in group A was not observed, because such a phenomenon was masked by the constant supply of exogenous T_4. An additional factor preventing a possible increase of FT_4 in group A, as might have happened somehow in the control group B, was probably the lack of thyroid reserve capable of responding with increased T_4 secretion.

Serum TSH secretion is expected to remain unchanged during surgery, but in some reports, a significant decrease of TSH has been described the first postoperative day or a sharp increase that starts within hours in patients subjected to cholocystetomy.[2,6] Cortisol, which could be implicated as a causative factor for the inhibition of TSH secretion in our patients, was not significantly changed, and a negative correlation between cortisol and TSH was not found. It is possible that an increase of serum cortisol with a simultaneous suppression of serum TSH occurred earlier, within hours, after the operation. In the present work, the postoperative measurements of the thyroid function parameters started 1 day after the operation and, therefore, the possibility that we may have missed a possible such phenomenon cannot be excluded, and we may have observed only the recovery phase characterized by the increasing TSH.[21]

The negative correlation found between TSH and FT_4 in the T_4-treated patients reflects preservation of normal pituitary-thyroid axis responsiveness throughout the follow-up period. This contrasts with a study in which the T_4 therapy inhibited TSH secretion, and this prevented an important factor for normalization of thyroid function during the recovery phase.[8] This discrepancy may be due to the fact that our patients were treated with moderate doses of T_4 (non–TSH-suppressive) and probably they had a milder form of postoperative nothyroidal illness. The greater slope of the TSH versus FT_4 regression line in group A indicates a greater sensitivity of the TSH secretion for the change of FT_4 in this group. This might be due to a relatively decreased activity of deiodinase type 2 in the pituitary induced by the exogenous T_4 in the patients of group A, as happens in hyperthyroidism.[18]

The small, insignificant decrease of total T_4 in the patients of both groups, in contrast to the increase (group B) or no change (group A) of FT_4 may indicate a reduction in the binding of thyroid hormones to plasma proteins. In this study, thyroxine-binding globulin (TBG) or T_3 resin uptake were not measured, but other studies have demonstrated that many proteins, including prealbumin, are decreased in patients with nonthyroidal illness.[2,7] Moreover, a rapid consumption of TBG due to protease cleavage at inflammatory sites of trauma has been proposed as an additional mechanism of serum T_4 decrease during cardiac bypass surgery.[21]

The significant increase of serum IL-6 raises again the issue that cytokines may be one of the causative factors of nonthyroidal illness in our patients. The postoperative elevation of IL-6 is in accordance with other studies, and it has been reported to occur rapidly (within a few hours) in patients after total abdominal hysterectomy.[22] Although the elevation of IL-6 was similar between our 2 groups, the regression analysis of T_3 on IL-6 demonstrated that about 66% of the variation of T_3 could be associated with IL-6 changes in the controls (group B) and only 38% in the T_4-treated group A. Similarly, in group B, IL-6 accounted for 57% of the variation of rT_3, while in the T_4-treated group A, IL-6 had minimal association with the variation of rT_3. In vitro experiments with human thyrocytes or in vivo with rats have shown that several cytokines, including IL-6, inhibit some thyroid cell functions.[23] On the other hand, IL-6 might have reduced, at least in part, the synthesis of TBG.[23] Taken together, it could be suggested that the differences in the correlation between IL-6 and T_3, rT_3, or FT_4 between the 2 groups were probably due to the constant supply of T_4 in group A, which attenuates or masks the peripheral effects of IL-6 in this group compared with the nontreatment group.

In conclusion, we found that in women on long-term T_4 replacement therapy and measurable (not completely suppressed) TSH, the decrease of serum T_3 postoperatively was less pronounced than in the control group and lasted for a shorter period of time. While the increase of IL-6 could explain a significant proportion of the change of T_3 and rT_3 in the control group, this proportion was not observed in the group on T_4 treatment and with low endogenous thyroid reserve. Thus, it seems that long-term treatment with moderate doses of T_4 attenuates the biochemical severity of postoperative low T_3 syndrome. However, the changes we found are rather small, and it is not clear if they have any biologic importance.

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