Changes in Biochemical Parameters During Complete Thyroid Hormone Deficiency of Short Duration in Athyreotic Patients

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The effect of withdrawal of suppressive therapy with thyroid hormones (200 μg L-thyroxine/day) on serum biochemical profiles and blood cell counts were studied in ten athyreotic thyroid carcinoma patients. After 14 days off therapy, all patients but one were still clinically and biochemically euthyroid. Twenty-eight days without thyroid hormones resulted in severe clinical and biochemical (TT_4, TSH) hypothyroidism. At that time, the following parameters changed significantly: CPK activities increased (in five of ten patients above normal) as well as activities of SGOT, SGPT, and LDH (means and s.d.s within the respective normal ranges). Total cholesterol and triglycerides increased within the normal range. There were minimal but significant increases of serum creatinine and of mean corpuscular volume of erythrocytes as well as decreases of serum sodium and calcium. Our study underlines the importance of further investigation if pathologic biochemical or hematologic parameters are obtained in athyreotic patients after 4 wk withdrawal of thyroid hormone therapy.

J Nucl Med 27:1528–1532, 1986

A patient with differentiated papillary or follicular thyroid carcinoma who is athyroid after surgery and consecutive radioiodine treatment may be either euthyroid or, eventually, hyperthyroid when he is on thyroxine replacement (suppression) therapy. On the other hand, he may be in various stages of thyroid hormone deficiency during the course of follow-up studies for iodine concentrating tissue.

Apart from characteristic clinical signs and symptoms hypothyroidism may present with abnormalities in biochemical parameters, as for example elevations of serum cholesterol (*1*), creatine phosphokinase (*2*), serum transaminases (*3*), lactic dehydrogenases (*4*), uric acid (*5*) and in hematologic parameters (*6*)—changes generally related to the degree of thyroid hormone deficiency (*7*).

Data on biochemical changes following thyroid deficiency have, in the past, usually been obtained in patients presenting with long-standing and gradually developing hypothyroidism. It would, therefore, be of interest (in principle and because of possible misinterpretation of results) to know how the above parameters change in the case of our athyroid follow-up patients during the period beginning from the point when they are taken off thyroid hormone therapy to the point when the examinations for tumor recurrence or/and metastases are carried out.

Received Oct. 2, 1984; revision accepted Mar. 31, 1986.

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PATIENTS AND METHODS

We selected ten patients for the study (eight females, two males; age 37–68 yr, mean 52.5 yr). All patients had differentiated papillary (n = 7) or follicular (n = 3) carcinoma. None of the patients had thyroid tissue left—neither normal nor malignant—and no detectable metastases at the time of examination. All patients had had total thyroidectomy (at least 12 mo before the study was performed) and at least one (ablative) therapeutic dose of radioiodine. All studies were carried out on the patients during their regular follow-up examinations. Details of our follow-up strategy for patients with differentiated thyroid carcinoma have been presented elsewhere (*8*). All patients were on suppressive doses of L-thyroxine (L-T_4), suppression of thyrotropine (TSH) secretion was indicated by the lack of response of TSH to an i.v. dose of 200 μg of thyrotropine-releasing hormone (TRH). TSH suppression was usually achieved with 150–200 μg L-T_4 p.o. daily. In the ten

patients under study, the suppressive dose of L-T_4 amounted to 200 μg per day.

Blood was taken for determination of biochemical parameters after an overnight fast and weighing of the patients; first on the last day of L-T_4 medication and then again after 14 and 28 days without L-T_4.

Routine blood chemical profiles were obtained by well-established, fully automated methods using an American Monitor Parallel System. Blood cell pictures were also obtained by automated methods*. Commercial kits were used for the determination of total T_4†, effective T_4 ratio (ETR) and TSH.

Specifically, follow-up investigations were carried out from Day 25 to 28, including 72-hr retention of a tracer dose of iodine-131 by whole-body counting with a shadowshield whole-body counter. All patients retained <3.5% of the applied dose, thus indicating a complete athyreotic state (*9*). Standard statistical methods were used to calculate means and standard deviations (s.d.s). Data were analyzed by two-tailed paired Student's t-test.

RESULTS

Changes in serum T_4, ETR, and TSH concentrations in patients while on suppressive L-T_4 medication, and 14 and 28 days following withdrawal of L-T_4 are given in Fig. 1. During L-T_4 treatment, all patients but one (Patient 5) had ETR and total T_4 serum concentrations above our normal range. This is in accordance with complete suppression of TSH secretion as observed in all patients. Fourteen days without L-T_4 resulted in a significant decrease of ETR ($p < 0.001$) and total T_4 ($p < 0.001$). However, only one patient (Patient 5) had an ETR and three patients (Patients 5, 7, 8) total T_4 levels below the normal range. The mean values of total T_4 (5.1 ± 1.2 μg/dl) and ETR (0.91 ± 0.04) were within the normal range. The increase of the mean values of TSH serum concentrations 14 days after withdrawal of L-T_4 (from 0.5 ± 0.4 to 2.7 ± 5.8 μU/ml) was not significant, and only Patient 5 had a serum TSH above normal (0–6 μU/ml) at that time. After 28 days without thyroid hormone supplementation, all mean and individual values for total T_4 (1.9 ± 0.7) and ETR (0.80 ± 0.04) were below, and TSH (55.2 ± 24.0 μU/ml) values above normal range.

Six of our ten patients were overweight prior to and during L-T_4 treatment. The mean weight gain after 14 days without L-T_4 (1.0 ± 1.0 kg or + 1.3 ± 1.7%) was not significant. There was, however, a significant increase ($p < 0.001$) of weight after 4 wk without L-T_4 (mean weight gain 2.3 ± 1.4 kg or + 3.1 ± 1.9%).

Creatine phosphokinase (CPK) serum activities also did not change significantly after 14 days off L-T_4 treatment; all values were within the normal range (0–70 U/l) (Fig. 1). However, a significant increase

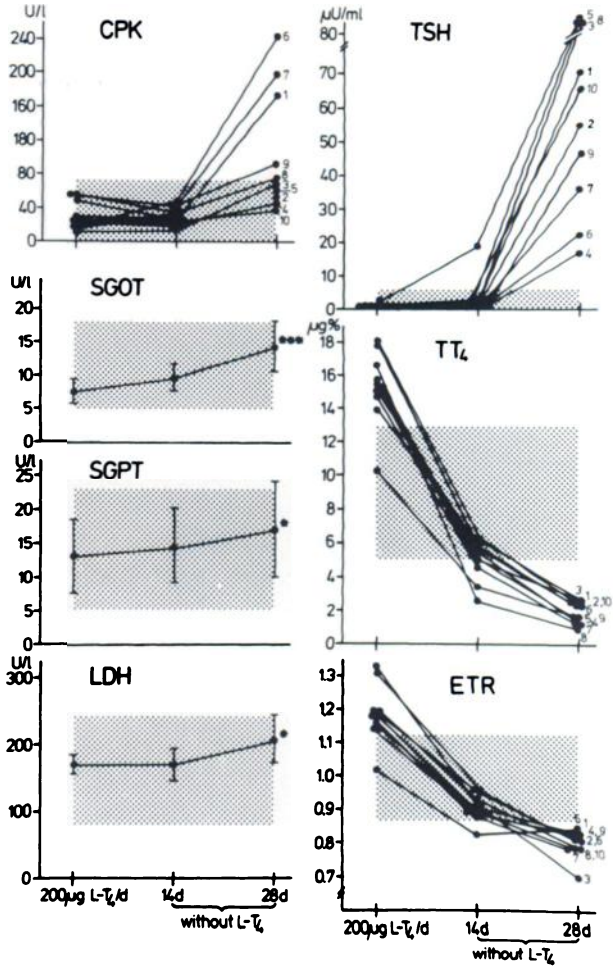

FIGURE 1
Individual curves with numbers of patients (as referred to in text) of serum thyroid hormone concentrations and CPK before and after withdrawal of suppressive therapy with L-T_4 (200 μg daily for at least 3 mo) in athyreotic disease-free thyroid carcinoma patients. On left lower side mean values ± s.d.s of serum activities of muscle related enzymes SGOT, SGPT, and LDH are given. Hatched areas represent respective normal ranges

($p < 0.01$) occurred after 28 days without L-T_4 (mean 106 ± 72 U/l); the highest observed value was 242 U/l. There was, moreover, a significant increase in the other muscle related enzymes—serum glutamic oxalacetic (SGOT), glutamic pyruvic transaminases (SGPT), and lactic dehydrogenase (LDH) after 28 days off L-T_4. The mean values and s.d.s of these enzymes remained, however, within their normal ranges throughout the entire observation period (Fig. 1).

Total cholesterol and triglycerides serum levels were normal during L-T_4 therapy even in our overweight patients (Table 1). There was a significant increase of both lipids without thyroid hormone supplementation after 4 wk; mean values of cholesterol, however, did not exceed the upper limit of normal. Triglycerides varied considerably at this point in time with a mean

TABLE 1
Mean Values ± s.d.s of Biochemical and Hematologic Parameters That Have Changed Significantly After Withdrawal of Thyroid Hormones in Athyreotic Disease-Free Thyroid Carcinoma Patients

	L-T_4 treatment	Off therapy with L-T_4		Normal range
		14 days	28 days	
Total cholesterol (mg/dl)	163 ± 31	195 ± 30	226 ± 33‡	150–250
Triglycerides (mg/dl)	127 ± 58	171 ± 101	196 ± 109†	50–180
Creatinine (mg/dl)	0.8 ± 0.1	0.8 ± 0.2	1.0 ± 0.2†	0.5–1.4
Sodium (mmol/l)	144 ± 3.5	142 ± 2.5	141 ± 3.1†	135–152
Calcium (mg/dl)	10.0 ± 0.3	9.5 ± 0.4*	9.4 ± 0.3†	8.5–10.5
MCV of erythrocytes (fl)	86.7 ± 3.4	86.7 ± 3.4	88.2 ± 3.8*	77–91

*p <0.05.
†p <0.01.
‡p <0.001 (paired Student's t-test).

value above normal. Blood glucose levels were normal and showed a tendency to decrease with decreasing thyroid hormone levels. The differences, however, were not significant and are not presented.

Liver function parameters (total bilirubin, gamma glutamyltransferase, and alkaline phosphatase) as well as total protein concentrations were unaffected by the changes in thyroid hormone levels. All patients while on L-T_4 treatment had normal renal function parameters (serum creatinine, bound urea nitrogen, uric acid) remaining within normal limits throughout the entire observation period with only a minimal yet significant increase in serum creatinine after 28 days without L-T_4 (Table 1). The normal serum electrolytes (sodium, potassium, chlorides) and phosphate concentrations were not altered by the thyroid hormone withdrawal except for the sodium levels that decreased minimally but significantly after 28 days (Table 1). Serum calcium levels were already significantly decreased after 14 days without L-T_4. The significance of the decrease becoming more pronounced after 28 days.

There were no significant changes in the normal red blood cell parameters except for a borderline significant minimal increase of the mean corpuscular volume of erythrocytes after 28 days without L-T_4. Iron serum concentrations as well as white blood cells and thrombocytes were normal and unaffected by changes in thyroid hormones.

DISCUSSION

During therapy with TSH-suppressive doses of L-T_4, mean values and most of the individual values of total T_4 and ETR were above normal in the patients under study but no other biochemical or hematologic abnormalities were observed.

After 14 days without L-T_4 medication, only one patient developed biochemical hypothyroidism with elevated TSH, and total T_4 and ETR values below normal. This indicates that a longer period of L-T_4 withdrawal is necessary for the thyroid hormone depletion required for correct determination of iodine retention in residual thyroid tissue or differentiated metastases. There was, at that point, only one significant difference in nonhormonal parameters in comparison to initial values obtained during L-T_4 treatment; serum calcium levels had significantly decreased while remaining normal. A possible explanation for this phenomenon may be that the patients have relatively high, but still normal, calcium levels in the phase of borderline hyperthyroidism (while on suppressive L-T_4 therapy) and that calcium levels decrease when thyroid hormone is withdrawn since hyperthyroidism has been shown to occur quite frequently with hypercalcemia of a mild degree (*10*). On the other hand, it has been reported that hypothyroidism can induce hypocalcemia (*11*), which would explain the higher degree of significance of the relative decrease after 28 days without L-T_4.

After a 4-wk withdrawal of L-T_4 our patients presented with typical signs and symptoms of hypothyroidism, and clinical impression was substantiated by pathologically low ETR and total T_4 serum levels as well as by high TSH concentrations. Biochemically and clinically overt hypothyroidism, therefore, must have developed between Day 14 and Day 28 after hormone withdrawal. This hypothyroidism of short duration, however, induced several significant alterations in biochemical profiles—CPK activities were pathologically high at Day 28 in five of our ten patients and had increased in all patients in comparison to the values obtained during L-T_4 treatment. CPK has been reported to be elevated in at least 60% of hypothyroid patients (*2*), which is in good agreement with our findings. Our findings that acute onset hypothyroidism of maximally 14 days duration can produce pathologic CPK values is of great clinical interest since angina may be frequently observed in older patients during the withdrawal of thyroid hormones for diagnostic purposes. It has been pointed out only recently that the diagnosis of cardiac disease in myxedematous patients still presents a challenge to cardiologists (*12*). In contrast to studies presented by Fleisher et al. (*4*) and by Graig and Smith (*13*) concerning patients with chronic, gradually developed hypothyroidism we were unable to find a direct correlation between thyroid hormone or TSH levels and the CPK activities in our patients. This discrepancy may be due to the short duration of hypothyroidism in our patients that has not yet allowed equilibrium of CPK and TSH levels.

The significant increase of other muscle-related enzymes like SGOT, SGPT and LDH observed here has already been shown by others (2,4,14,15) to occur in

hypothyroidism. These changes in muscle enzymes are believed to be due either to chronic ongoing muscle damage (unlikely in our patients) or to decreased enzyme clearance rates (*16*). We believe that our observation that these enzymes increase significantly yet remain within the normal range is of clinical interest. Pathologic values of these parameters merit further investigation in athyreotic thyroid cancer patients and cannot be explained by the hypothyroid state alone.

Total cholesterol has been shown to be elevated in hypothyroidism already in 1934 (*1*) and, therefore, the observed significant increase in fasting cholesterol levels was to be expected. It is interesting to note, however, that in only one of our patients a pathologically high serum cholesterol level of 295 mg/dl was measured after 4 wk without L-T_4. This suggests only a gradual development of hypercholesterolemia following acute onset thyroid hormone depletion. Serum triglycerides also increased significantly after 28 days off L-T_4. The wide scatter of concentrations in the hypothyroid state is in good agreement with other reports (*17,18*) and with the observation of a considerable variability of the reaction of triglycerides to treatment with L-T_4 in hypothyroid patients (*19*). The statistical significance of the increase of triglycerides in our patients is surprising since it has been shown by two groups (*18,20*) that even long-standing thyroid failure does not necessarily have an appreciable influence on serum triglyceride concentrations.

Renal function parameters and serum electrolytes were normal during therapy with L-T_4 and remained normal after L-T_4 withdrawal. The minimal but significant increase of serum creatinine probably reflects a fall of the glomerular filtration rate, since it has been shown that the glomerular filtration rate had already decreased considerably 4 days after experimental total thyroidectomy in dogs (*21*). The observed decrease—also minimal but significant—in sodium levels is probably due to a myxedema induced increase in total-body water.

A borderline significant minimal increase in the MCV of erythrocytes was the only change in hematologic parameters. It may be speculated that this increase in corpuscular volume represents the first step in development of myxedema-induced macrocytic anemia, although usually normocytic normochromic anemia occurs in hypothyroidism (*22*). An increase in the mean corpuscular volume, however, has been reported by Horton et al. (*6*) in 29 of 53 hypothyroid patients.

In summary, overt clinical and biochemical hypothyroidism develops 14 to 28 days after acute diagnostic withdrawal of suppressive thyroid hormone replacement in athyroid patients. A broad spectrum of significant changes occurs in this hypothyroidism of short duration. These changes differ in some respects from what is observed in gradually developing longer standing hypothyroidism. For the evaluation of routine blood chemical profiles it is, however, important to note that only CPK activities and in some rare cases triglcyerides concentrations changed beyond normal in our athyroid patients. This underlines the necessity of further investigation of pathologic parameters obtained in such patients at their regular follow-up.

FOOTNOTES

* Coulter Counter Modell S Plus II, Coulter Electronics, Krefeld FRG.

† SPAC-T_4, Mallinckrodt, St. Louis, MO.

‡ ETR-Res-O-mat, Mallinckrodt, St. Louis, MO.

§ TSH-Rea-mat, Mallinckrodt, St. Louis, MO.

ACKNOWLEDGMENT

The skillful technical help of Miss Isabelle Auersperg is gratefully acknowledged by the authors.

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