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Plasma Total Homocysteine Levels during Short-Term Iatrogenic Hypothyroidism*

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ABSTRACT

Hypothyroidism is associated with increased cardiovascular morbidity, which cannot be fully explained by the atherogenic lipid profile observed in these patients. We have previously found elevated levels of the cardiovascular risk factor, plasma total homocysteine (tHcy), in hypothyroidism.

We conducted a longitudinal study on 17 patients who had undergone total thyroidectomy for thyroid cancer. During 6 weeks of discontinued T_4 substitution before radioscintigraphy (phase I), they attained a hypothyroid state, which was reversed by resupplementation (phase II). Plasma tHcy, serum creatinine, serum and red blood cell folate, serum cobalamin, and serum cholesterol were determined at 2-week intervals throughout phases I and II.

There was a progressive and parallel increase in tHcy (mean, 27%), serum creatinine (37%), and serum cholesterol (100%) during phase I, and these values returned to the original level within 4–6 weeks after reinitiating T_4 therapy. Serum and red blood cell folate levels showed only minor, but statistically significant, changes. In a bivariate model, serum creatinine and serum cholesterol were strongly associated with the changes observed in tHcy during short term hypothyroidism.

In conclusion, we found a transient increase in both plasma tHcy and serum cholesterol during short term iatrogenic hypothyroidism, and the tHcy response is probably mainly explained by concurrent changes in renal function. The increase in both plasma tHcy and serum cholesterol may confer increased cardiovascular risk in hypothyroid patients. (*J Clin Endocrinol Metab* **85:** 1049–1053, 2000)

AUTOPSY STUDIES (1) as well as animal experiments (2, 3) have demonstrated accelerated atherogenesis in hypothyroidism, whereas hyperthyroidism or thyroid hormone supplementation has a protective effect. Progression of angiographically verified coronary artery stenosis is related to serum T_3 levels in euthyroid subjects (4) and seems to be prevented by adequate thyroid hormone replacement in hypothyroid patients (5). Thus, there is compelling evidence that thyroid status affects the progression of atherosclerosis, but the mechanism is not fully understood.

Hypothyroidism is associated with high cholesterol and lipoprotein levels, which are normalized after thyroid hormone replacement (6–8). The atherogenic lipid profile in particular, but also other abnormalities (9–11), have been suggested to be responsible for the increased cardiovascular morbidity in hypothyroid patients (6–8).

Total homocysteine (tHcy) in plasma has recently been proposed as an independent risk factor for occlusive cardiovascular disease (12, 13). The plasma level is affected by several life-style and physiological factors and is elevated under conditions of impaired folate and cobalamin status and in renal failure (12).

We recently reported that plasma tHcy is influenced by thyroid status. Hypothyroid patients had higher plasma tHcy levels than healthy controls and hyperthyroid patients, but a tendency toward low tHcy in hyperthyroidism did not reach statistical significance (14). The heterogeneity of the study population with respect to age, vitamin status, and severity of disease (14) probably reduced the power of this cross-sectional investigation.

In the present work we further investigated the effect of thyroid status on alterations in plasma tHcy levels. We carried out a longitudinal investigation of patients who had undergone total thyroidectomy for thyroid cancer, and who attained an acute iatrogenic hypothyroid state during a transient stop of T_4 supplementation before diagnostic ^{131}I scintigraphy.

Subjects and Methods

Patients and protocol

The patients included had undergone total thyroidectomy due to thyroid cancer. Seventeen consecutive patients who discontinued thyroid hormone supplementation before diagnostic ^{131}I scintigraphy were included. Their mean age was 49 yr (range, 28–78 yr), and 35% were males (Table 1). T_4 supplementation was stopped for 5–6 weeks and was resumed 2 days after ^{131}I scintigraphy, with a dose escalation over 2–3 weeks. All patients gave their informed consent to participate in the study. Fasting blood samples were drawn immediately before discontinuing supplementation (designated time point −6 weeks) and thereafter at 2-week intervals (−4 and −2 weeks) until scintigraphy was carried out (time zero). This period, from −6 to 0 weeks, is referred to as phase I. After resumption of T_4 supplementation, fasting blood samples were drawn at 2-week intervals (2, 4, 6, and 8 to 10 weeks) for up to 10 weeks. The period from 0 to 10 weeks is referred to as phase II. We did not obtain complete blood sampling from all patients. Nine patients

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TABLE 1. Demography, observation period, and blood indices immediately before T_4 resupplementation (time zero)

Patient no.	Sex (M/F)	Age (yr)	Observation period (weeks)[a]	Plasma tHcy (μmol/L)	Serum creatinine (μmol/L)	Serum cholesterol (mmol/L)	Serum folate (nmol/L)	RBC folate (nmol/L)	Serum cobalamin (pmol/L)
1	F	78	−6 to +6	12.9	93	12.2	9.6	307	299
2	F	49	0 to +8	13.1	98	9.3	13.5	494	627
3	F	55	−2 to +8	14.3	124	13.4	7.9	309	498
4	M	28	0 to +4	9.8	129	8.1	11.0	293	626
5	F	49	0 to +6	13.3	91	8.8	6.3	182	257
6	M	42	−6 to +10	21.8	133	9.8	5.1	298	570
7	F	78	−6 to +10	10.2	98	11.7	12.0	288	635
8	F	32	−4 to +10	22.5	108	9.4	4.2	187	278
9	M	53	−4 to +10	9.7	108	7.8	8.2	428	507
10	F	44	−4 to +10	12.8	100	11.7	10.6	433	578
11	F	45	0 to +8	14.3	127	8.6	8.0	306	329
12	F	38	−6 to +10	40.7	130	10.2	6.2	503	274
13	F	32	−6 to +8	10.0	101	5.0	13.3	359	339
14	M	40	−6 to +0	13.0	117	7.7	6.8	416	597
15	F	66	0 to +10	18.5	110	12.9	9.8	523	382
16	M	50	−6 to +8	13.1	128	9.9	9.0	352	414
17	M	71	−6 to +8	13.0	111	9.5	9.7	325	518
Median		49		13.1	110	9.5	9.0	325	498
(10–90th percentile)		32–74		9.9–22.0	96–129	7.8–12.5	5.8–12.5	248–498	276–626

[a] Given in weeks before (−) and after (+) start (at time zero) of T_4 resupplementation.

were included from the time the supplementation was discontinued, whereas 16 of the patients participated from the time of restart of T_4 replacement therapy (Table 1).

Biochemical methods

The blood samples for tHcy determination [10 mL in ethylenediamine tetraacetate Vacutainer tubes (Becton Dickinson Vacutainer Systems Europe, Meylan, France)] were centrifuged within 30 min at 3000 × *g* for 5 min before analysis. Plasma tHcy levels were determined by a method based on high pressure liquid chromatography and fluorescence detection (15). The between-day precision (coefficient of variation) of the method is less than 3%.

Serum cobalamin was determined with a microparticle enzyme intrinsic factor assay run on an IMx system from Abbott Laboratories (Abbott Park, IL). Serum and red blood cell (RBC) folate were assayed using the Quantaphase folate radioassay produced by Bio-Rad Laboratories, Inc. (Hercules, CA). Cholesterol and creatinine were determined using the Technicon Chem 1 system (Technicon Instruments Corp., Tarrytown, NY).

TSH and T_3 in serum were measured using the AutoDELFIA hTSH Ultra kit and AUTODELFIA T_3 kit from Wallac, Inc. (Turku, Finland). The precision of the TSH assay, expressed as between-assay coefficient of variation, was 4.9% for samples between 0.5–8.3 mIU/L; that for the T_3 assay was below 4.5% for values between 1.0–4.0 nmol/L.

Statistical analyses

To investigate the various determinants of plasma tHcy as well as the change in the tHcy level during the study period, analyses of covariance using an unbalanced repeated measure design allowing for missing values, were used (5V module in BMDP) (16). Analyses were performed separately for phase I and phase II, with time zero being the last time point of phase I and the first time point of phase II.

The change in tHcy over time was represented by a linear time trend, coded as 0, 1, 2, and 3 in phase I and 0, 1, 2, 3, 4, and 5 in phase II; thus, the estimated coefficients represent the change in tHcy relative to that at the previous visit. A quadratic or curve-linear term was also tested in some models. Because it did not improve the models, it is not included in the data presented.

In the various models, several structural forms of the within-subject covariance matrix were tested. Because the results showed minor variation with different covariance structures, and compound symmetry tended to be the most appropriate according to Akaike's information criterion (17), the latter structure was applied in all of the models presented. The default Newton-Raphson algorithm was used to compute maximum likelihood, because other algorithms gave similar results.

Results

Thyroid hormone status

After discontinuation of T_4 supplementation for 6 weeks, all 17 subjects attained a hypothyroid state, as evidenced by a TSH level higher than 50 mIU/L and low T_3 levels (Fig. 1).

Total plasma homocysteine

Plasma tHcy increased gradually from a median concentration of 10.9 to 13.1 μmol/L (mean, 27%) during 6 weeks of discontinued T_4 supplementation, *i.e.* phase I. After T_4 administration was resumed, tHcy slowly declined and reached the original level within 4–6 weeks (Fig. 2). The changes both during phases I and II were highly significant ($P < 0.001$; Table 2).

Vitamin status, creatinine, and cholesterol

There was a moderate decrease in serum and RBC folate after T_4 supplementation was discontinued (phase I), which reached statistical significance for RBC folate ($P < 0.02$). After restart of T_4 supplementation (phase II), both RBC and serum folate increased ($P < 0.01$). The serum cobalamin showed a different response characterized by stable levels during phase I and a significant ($P < 0.001$) decrease during phase II (Fig. 2 and Table 2).

Both serum creatinine and total cholesterol increased during phase I ($P < 0.001$) and decreased during phase II ($P < 0.001$). Notably, the patterns of these changes closely followed those in plasma tHcy (Fig. 2 and Table 2).

Covariations

The changes in tHcy over time during phases I and II were assessed before and after adjustment for potential covariates,

which include creatinine, vitamins, and serum cholesterol. Adjustment for creatinine abolished the change in tHcy in phase I ($P = 0.92$), whereas it was only attenuated in phase II ($P = 0.001$). After adjustment for RBC or serum folates or cobalamin in bivariate models, the tHcy changes were still highly significant in phases I and II ($P \leq 0.005$). In contrast, adjustment for cholesterol had strong effects in both phases ($P = 0.13$ and 0.14, respectively). These data are in accordance with a strong association between the values for tHcy and creatinine in phases I and II ($P = 0.001$) and between tHcy and cholesterol, particularly in phase II ($P = 0.001$). Only weak associations between tHcy and the vitamins ($P \geq 0.06$) were observed.

Discussion

The short term, transient hypothyroid state obtained when discontinuing the T_4 supplementation before diagnostic scintigraphy represents a unique model for studying the metabolic effects of thyroid hormone in man. The longitudinal design ensures high statistical power, because the interindividual variations are minimized. The data are somewhat weakened by incomplete sample series due to logistic problems.

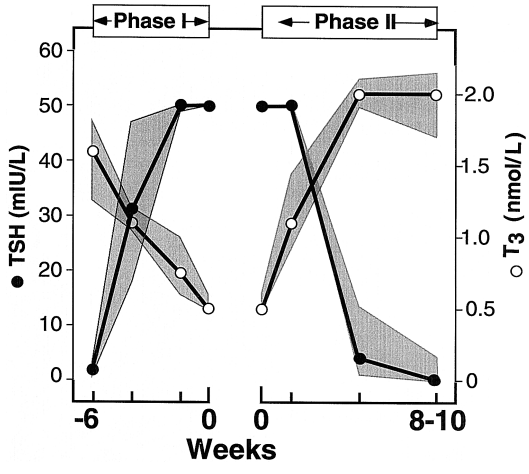

FIG. 1. Thyroid hormone status during iatrogenic hypothyroidism. Levels of TSH (*closed circles*) and T_3 (*open circles*) were recorded during discontinuation of T_4 supplementation (phase I) and after restart of T_4 therapy (phase II). The times on the *x*-axis are −6, −4, −2 to −1, 0, 1 to 2, 4 to 6, and 8 to 10 weeks. Data are given as medians, and the *shaded areas* indicate 25th and 75th percentiles.

The main finding is a gradual increase in plasma tHcy during development of the hypothyroid state and a return of the tHcy level when T_4 supplementation was resumed. Notably, the increase (phase I) and decrease (phase II) take place over weeks. A similar time course was observed for serum creatinine and total cholesterol. The kinetics of these changes might reflect the turnover rate of T_4, which has a half-life of about 7 days in humans (18). This is supported by comparing tHcy and thyroid hormone kinetics during phases I and II (Figs. 1 and 2).

The results of the present study are in accordance with the recent observation that plasma tHcy is high in hypothyroid patients and tends to be low in hyperthyroid patients (14). The apparent close relation between the plasma tHcy and thyroid hormone levels during phases I and II indicates a hormone effect on homocysteine metabolism, distribution, or clearance. A similar argument can be made for the creatinine and cholesterol responses.

Reversible elevation of serum creatinine has previously

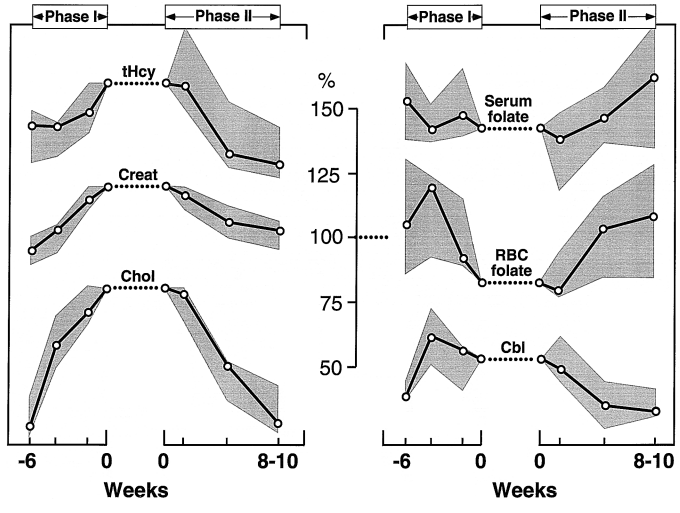

FIG. 2. Changes in tHcy and other blood indices during iatrogenic hypothyroidism. The concentrations of tHcy, serum creatinine (Creat), serum total cholesterol (Chol), serum folate, RBC folate, and serum cobalamin (Cbl) were determined during discontinuation of T_4 supplementation (phase I) and after restarting T_4 therapy (phase II). The levels are calculated as a percentage of the individual values determined at the time of resumption of T_4 therapy, which is set as 100%. The times on the *x*-axis are −6, −4, −2 to −1, 0, 1 to 2, 4 to 6, and 8 to 10 weeks. Data are given as medians, and the *shaded areas* indicate 25th and 75th percentiles.

TABLE 2. Changes in tHcy and other blood indexes measured for 6 weeks of discontinuation (phase I) and for 6–8 weeks after resumption of T_4 supplementation (phase II) in 17 patients who had undergone total thyroidectomy for thyroid cancer

Parameter	Phase I			Phase II		
	Intercept	Coefficient	*P* value	Intercept	Coefficient	*P* value
tHcy (μmol/L)	10.3	1.75	<0.001	15.9	−1.57	<0.001
Serum folate (nmol/L)	10.0	−0.33	0.20	8.81	0.40	0.007
RBC folate (nmol/L)	435	−24.5	0.018	365	24.9	<0.001
Cobalamin (pmol/L)	453	5.07	0.62	446	−22.6	<0.001
Creatinine (μmol/L)	80.4	10.6	<0.001	110	−4.87	<0.001
Total cholesterol (mmol/L)	5.23	1.60	<0.001	9.72	−1.11	<0.001

The parameters were measured every second week. The intercept refers to the estimated level at the start of each phase; the coefficient is the estimated change per 2-week interval; the *P* value refers to test for linear trend. Analysis of covariance, using an unbalanced repeated measured design allowing for missing values, was used (16). tHcy, Total homocysteine in plasma.

been reported during discontinuation and resumption of T_4 supplementation (19). We observed a close relation between plasma tHcy and serum creatinine in iatrogenic hypothyroidism. Both the tHcy and creatinine responses can be explained by the hypodynamic circulation in hypothyroidism (20). Thyroid hormones are cardiotonic agents, which increase cardiac output while lowering systemic vascular resistance (21, 22), resulting in increased renal blood flow (20). This, in turn, may increase the glomerular filtration rate, which is related to serum creatinine (23), but also closely associated with plasma tHcy (24, 25). The mechanism behind renal homocysteine clearance is debated (26), but may be explained by an important role of renal metabolism in the overall homocysteine homeostasis (27).

An alternative explanation for the concurrent elevation of plasma tHcy and serum creatinine during iatrogenic hypothyroidism is the formation of homocysteine in conjunction with creatine-creatinine synthesis, which is related to muscle mass (28). However, creatinine formation was not increased in hypothyroid patients in one study (29). Furthermore, significant changes in muscle mass during the short study period are unlikely. Taken together, these data give no support to the idea (14) that increased tHcy during hypothyroidism is due to enhanced homocysteine production.

We observed a moderate transient decline in both serum and RBC folate during discontinuation of T_4 supplementation. This is in agreement with the finding published previously by us (14) and others (30), demonstrating elevated serum folate in hyperthyroidism and low levels in hypothyroidism. The folate response could be related to direct effect of thyroid hormones on folate-metabolizing enzymes, including methylenetetrahydrofolate reductase (31). Folate status has been established as a major determinant of tHcy level (32). However, in the present study the changes in vitamin levels are minor and show only weak, nonsignificant, correlations with tHcy. This suggests that impaired folate status is not responsible for the transient hyperhomocysteinemia during discontinuation of T_4 supplementation.

The mechanism and implication of the significant drop in serum cobalamin during the phase II of the observation period are uncertain. It may reflect cobalamin depletion caused by, but lagging behind, the iatrogenic hypothyroidism due to the long half-life of tissue cobalamin (33). Others have shown that cobalamin levels are reduced (30) or unchanged during hypothyroidism (30, 34).

In line with previous studies (35–37), serum cholesterol levels increased during the development of hypothyroidism and decreased to control values after 6 weeks of replacement therapy. Notably, cholesterol showed covariation with both tHcy and creatinine. This responsiveness suggests that thyroid hormones influence cholesterol metabolism or disposition (38). There is one report on homocysteine effects on cholesterol production and secretion (39). This may contribute to the covariation between cholesterol and homocysteine observed in the present study, but also to the moderate associations observed in some epidemiological studies (40–42).

In conclusion, plasma tHcy increased during well defined, short term hypothyroidism, and there was a concurrent, transient increase in both serum creatinine and serum cholesterol. Increased serum creatinine levels probably reflect a reduced glomerular filtration rate, which, in turn, is linked to impaired renal homocysteine clearance and hyperhomocysteinemia. The medical implication of the concurrent increases in serum cholesterol and tHcy levels is a possible strong interactive effect between these two cardiovascular risk factors (43), which may explain in part the accelerated atherosclerosis in hypothyroid patients.

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