Plasma Total Homocysteine in Hyper- and Hypothyroid Patients before and during 12 Months of Treatment, Bjørn G. Nedrebo,* Ottar Nygård, Per M. Ueland, and Ernst A. Lien (LOCUS for Homocysteine and Related Vitamins, University of Bergen, 5021 Bergen, Norway; * address correspondence to this author at: Department of Internal Medicine, Haukeland University Hospital, N-5021 Bergen, Norway; fax 47-55975814, e-mail bjoern.gunnar.nedreboe@haukeland.no)

There are consistent reports demonstrating that thyroid status is an important determinant of the plasma/serum concentration of total homocysteine (tHcy) (1–7), which has been established as an independent risk factor of vascular occlusive disease (8). In previous studies, we showed that plasma tHcy was higher in hypothyroid than in hyperthyroid patients (1, 2). Prospective studies have demonstrated normalization of tHcy after thyroid hormone replacement therapy in hypothyroid patients (3, 4), and we recently observed a transient increase in tHcy during short-term iatrogenic hypothyroidism in thyroidectomized patients (5).

To our knowledge, there has been no longitudinal study on tHcy in hyper- and hypothyroid patients across normalization of their thyroid status during treatment. In the present study, we investigated such patients before and during the first 12 months of treatment.

Forty consecutive patients with hyperthyroidism and 12 with hypothyroidism were enrolled. The study protocol was approved by the ethics committee of Haukeland University Hospital, and informed consent was obtained from all participants.

The diagnosis of hyperthyroidism was based on basal serum thyrotropin (TSH) values <0.3 mIU/L, and hypothyroidism on TSH >15 mIU/L. All hyperthyroid patients except one were diagnosed with Graves disease.

Thirty-one of the patients with hyperthyroidism were treated with carbimazole or propylthiouracil. Nine of the patients with hyperthyroidism received radioiodine treatment as primary treatment. All patients with hypothyroidism received thyroxine as the only thyroid hormone replacement therapy.

Blood specimens were collected at inclusion and 1, 6, and 12 months after initiation of treatment. Fasting EDTA-blood samples for tHcy determination were centrifuged within 30 min. The EDTA-plasma was stored at −20 °C until analysis. Plasma tHcy, serum cobalamin, folate, creatinine, and cholesterol were determined according to established methods (5, 9). TSH and free thyroxine (FT4) in serum were measured with the AutoDELFIA hTSH Ultra reagent set and the AutoDELFIA FT4 reagent set from Wallac Oy. Thyroid receptor antibodys (TRAbs) were determined by radioimmunoassay from DLD Diagnostika GMBH.

Baseline characteristics of the hyper- and hypothyroid patient groups were compared by Mann–Whitney U-test. To investigate changes in analyte concentrations within each group, we applied analyses of covariance using an unbalanced repeated-measure design (5V module in BMDP) (10). The covariance between any pairs of repeated measurements was assumed to be equal (compound symmetry). In case of missing data in the response variable (unbalanced data), the program computes and substitutes for the missing value an imputed value that is predicted from the covariate information. In the present study, missing values in the response variables varied from 0% at baseline up to 32% for tHcy in hyperthyroid patients at 12 months. The maximum likelihood of regression and covariance parameters were calculated.

The change in parameters over time was represented by a linear trend model. The time trend was coded as 0, 1, 2, and 3. Thus, the regression coefficients for time trend represent the change relative to the previous visit and are not a function of the length of follow-up. The intercept in this model represents the estimated concentration before treatment, which is close to the mean concentration at baseline. Analyses or graphic presentations based on log-transformed data, percentage of change from baseline, median values, or individual raw data gave similar results and are not presented. Essentially the same results were obtained when the analyses were restricted to patients with complete data sets (25 hyperthyroid, 9 hypothyroid). We also investigated the change in tHcy by treatment after adjustment for sex, age (years), and one additional covariate.

For patients with hyperthyroidism (n = 40) and hypothyroidism (n = 12), the median ages were, respectively, 44 years (range, 19–89 years) and 55 years (range, 35–78 years). In both groups, 75% of the patients were women. In patients with hyperthyroidism, median FT4 was 57.4 pmol/L (24.2 to >77 pmol/L), and except for one patient with a TSH value of 0.1 mIU/L, all remaining patients had TSH <0.05 mIU/L. In hypothyroid patients, median FT4 was 5.4 pmol/L (<5 to 8.6 pmol/L). Three hypothyroid patients had TSH values of 21.0, 28.2, and 33.5 mIU/L, respectively; all remaining patients had TSH >50 mIU/L.

At baseline, tHcy in plasma and folate, total cholesterol, HDL-cholesterol, and creatinine in serum were significantly higher in patients with hyperthyroidism than in patients with hypothyroidism, whereas cobalamin and triglycerides did not differ between the patient groups (data not shown).

In hyperthyroid patients, tHcy, creatinine, and cholesterol increased during treatment. Serum folate decreased significantly, whereas there was no significant change in cobalamin (Fig. 1 and Table 1). In hypothyroid patients, significant decreases were observed for tHcy, creatinine, and cholesterol. There were no significant changes in cobalamin and folate (Fig. 1 and Table 1). After 12 months...
of treatment, plasma tHcy in the two patient groups approached the same concentrations (Fig. 1).

We determined the time-dependent changes in plasma tHcy in hyper- and hypothyroid patients with and without adjustment for one potential covariate. Inclusion of cholesterol or, to a lesser degree, creatinine in the model almost abolished the change in tHcy. This demonstrates that the changes in tHcy were strongly correlated to cholesterol and creatinine (Table 1).

This study confirms published data that tHcy is increased in hypothyroidism (1–7) and tends to be low in hyperthyroidism (2, 7). In addition, it provides data on the time course for the normalization of tHcy and covariates such as serum cholesterol and creatinine during 12 months of treatment of patients with hypo- and hyperthyroidism, demonstrating that these blood indices gradually approached the same values (Fig. 1).

The strength of this study is the longitudinal, prospective design. Furthermore, because of the large number of hyperthyroid patients included (n = 40), the study allowed assessment of the modest increase in tHcy (median increase, 2.0 μmol/L) that occurred during treatment of these patients. The marked decrease in tHcy in hypothyroid subjects during treatment (median decrease, 5.6 μmol/L) reached significance (Table 1) in spite of the low number of subjects (n = 12).

During treatment of both patient groups, plasma tHcy showed a strong covariation with serum cholesterol and creatinine, whereas there was essentially no relation to serum folate and cobalamin (Table 1). From these observations, one may infer that changes in renal function rather than vitamin status may account for variations in plasma tHcy. This relationship may be attributable to effects of thyroid hormones on renal hemodynamics. Both animal and human studies have demonstrated that hypothyroidism is associated with low and hyperthyroidism with high glomerular filtration rate (11, 12), which in turn is closely related to plasma tHcy (13). Renal homocysteine excretion is negligible (14), but homocysteine metabolism...
The changes in cholesterol showed a time course similar to that of tHcy (Fig. 1 and Table 1). A significant correlation between serum cholesterol and tHcy has also been demonstrated in some epidemiologic studies (20–22). The mechanism behind this covariation has not been clarified (23), but increases in both cholesterol and tHcy in hyperthyroidism may have an interactive effect (24), which may contribute to the high prevalence of arterial occlusive disease in hyperthyroid patients (25). Conversely, low concentrations of both factors in hypothyroid patients may afford protection (26).

In conclusion, tHcy was increased in hyperthyroidism and was decreased in hypothyroidism. During treatment, tHcy gradually approached the same concentration in these patient groups. Parallel changes in serum creatinine, tHcy, and serum cholesterol has important medical implications: (a) increases in both tHcy and cholesterol in hyperthyroidism may increase cardiovascular risk; and (b) TSH should be determined in subjects with unexplained hyperhomocysteinemia and increased cholesterol, as recently suggested by Hussein et al. (3).

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### Table 1. Changes in parameters during treatment of patients with hyper- or hypothyroidism. a

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted values</th>
<th>Hyperthyroidism (n = 40)</th>
<th>Hypothyroidism (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>Regression coefficient</td>
<td>P a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma tHcy, μmol/L</td>
<td>8.4</td>
<td>0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum folate, nmol/L</td>
<td>16.1</td>
<td>-0.82</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum cobalamin, pmol/L</td>
<td>402</td>
<td>-8.09</td>
<td>0.18</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>70.0</td>
<td>8.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>4.7</td>
<td>0.66</td>
<td>&lt;0.001</td>
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<tr>
<td>Plasma tHcy values (μmol/L) adjusted for c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum folate</td>
<td>9.4</td>
<td>0.39</td>
<td>0.002</td>
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<tr>
<td>Serum cobalamin</td>
<td>10.3</td>
<td>0.36</td>
<td>0.003</td>
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<td>Serum creatinine</td>
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<td>0.22</td>
<td>0.22</td>
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<tr>
<td>Serum cholesterol</td>
<td>6.0</td>
<td>0.11</td>
<td>0.44</td>
</tr>
</tbody>
</table>

a The parameters were determined before treatment and after 1, 6, and 12 months of follow-up. The intercept is an estimate of the concentration before treatment, and the coefficient is the estimated change between consecutive measurements.

b Test for linear trend.
c Adjustment for only one covariate.

### References

18. Mason RL, Hunt HM, Huxthall L. Blood cholesterol values in hyperthyroidism


