Effects of levothyroxine treatment on biochemical and hemostasis parameters in patients with hypothyroidism

Sevim Gullu, Hasan Sav and Nuri Kamel
Ankara University, School of Medicine, Department of Endocrinology and Metabolic Diseases, Ibn-i Sina Hospital, Sihhiye 06 100, Ankara, Turkey
(Correspondence should be addressed to S Gullu; Email: sevim.gullu@temd.org.tr)

Abstract

Objective: The aims of the study were to evaluate the disturbances in the coagulation system in patients with overt hypothyroidism (OH), to assess the effects of levothyroxine (LT4) on the coagulation parameters, and to determine whether subclinical hypothyroidism (SH) affects concentrations of coagulation markers and several biochemical parameters, thereby supporting early substitution.

Design: The study included 15 patients with SH (TSH levels 5–10 mU/l), 15 patients with OH and 15 euthyroid controls.

Methods: Blood urea nitrogen, creatinine, creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, total-cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol and triglyceride levels, and bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT), factor VIII activity, von Willebrand factor activity (vWF), platelet count and clotting time were evaluated just before and three months after the maintenance of euthyroidism with LT4 treatment.

Results: Factor VIII and vWF activities were lower in patients with SH than in controls (\( P < 0.01 \)). Increased bleeding time, PT, APTT and clotting time and decreased factor VIII activity and vWF activity were observed in patients with OH when compared with controls. Bleeding time, PT, APTT and clotting time decreased and factor VIII activity, vWF and platelet count increased after LT4 in patients with OH. Increases in factor VIII activity and vWF (\( P < 0.01 \)) were detected also in the SH group with treatment.

Conclusions: OH is associated with significant abnormalities in clotting parameters which are reversed by LT4. In contrast, SH is associated with minor changes in factor VIII activity and vWF which are reversible by LT4. Serum lipids and other measured parameters are not improved by LT4 in patients with TSH < 10 mU/l and these data fail to demonstrate a need to treat such patients.

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Introduction

Thyroid dysfunction, mostly hypothyroidism, is a frequent disorder in the general population, especially among women. Hypothyroid patients may have several hemostatic abnormalities such as modification of the coagulation proteins and bleeding tendency (1–14). A coagulation disorder resembling von Willebrand’s disease has been reported in patients with overt hypothyroidism (OH) (3–8). But the influence of hypothyroidism on hemostasis remains controversial since, in addition to these hypocoagulable states, hypercoagulable states have also been reported (10–15). The mechanisms relating to the alterations in the coagulation system in hypothyroidism are not very well established but direct effects of thyroid hormones have been proposed (10, 11, 16).

Subclinical hypothyroidism (SH) is characterized by increased serum thyrotropin (TSH) levels with normal serum free thyroxine (FT4) and free triiodothyronine (FT3) concentrations. The clinical presentation is non-specific and symptoms are usually subtle (17–19). Although elevated serum cholesterol concentrations and high risk of atherosclerosis and cardiovascular diseases have been reported in some studies, others have failed to demonstrate those findings in patients with mild thyroid failure (17–22).

Changes in muscle and renal functions and alterations in hemostasis have also been reported in patients with SH (13, 23–27). Although increased factor VII activity, higher fibrinogen and plasminogen activator inhibitor (PAI-1) levels and decreased fibrinolytic activity have been observed in mild and moderate hypothyroidism in previous studies, the influence of SH on hemostasis is not very well known.

Although there is no doubt about the treatment of patients with OH, the decision to treat SH patients with levothyroxine (LT4) is controversial. The efficacy
of replacement therapy, especially on the lipid parameters, has shown conflicting results in the English literature (17, 28–37). This discrepancy about treatment seems to have resulted from variations in the TSH levels of the selected populations.

The aims of this study were to evaluate the potential association between OH and disturbances in the coagulation system and to determine whether concentrations of serum lipids, muscle enzymes, renal functions and markers of coagulation are affected in patients with a TSH level between 5 and 10 mIU/l. The effects of levothyroxine replacement on these parameters were also evaluated.

**Subjects and methods**

**Patients**

We prospectively included 15 patients with SH (all female; mean age 47.6 years, range 21–68 years) and 15 patients with OH (all female; mean age 52.8 years, range 30–65 years) from Endocrinology and Metabolic Diseases outpatient clinics and 15 healthy individuals (all female; mean age 49.2 years, range 25–61 years) who served as controls. The study groups were selected among a group of patients who had Hashimoto’s disease with primary SH or OH. Hashimoto’s disease diagnosis was based on antithyroid peroxidase antibody (TPOAb) positivity and hypoechoic-heterogenous pattern on ultrasonography in the presence of firm goiter and hypothyroidism. SH was defined as grossly elevated TSH levels (TSH >20 mU/l) with low FT4 and FT3 levels with clinical signs and symptoms of hypothyroidism. Controls were defined by normal serum FT3, FT4 and TSH levels which are defined by normal serum FT3, FT4 and TSH levels measured at least two times with a three-month interval, and OH was defined as elevated TSH levels (5–10 mU/l) with low FT4 and FT3 levels with clinical signs and symptoms of hypothyroidism. Controls were evaluated twice in a period of 24 h (before and after treatment) and the results of the two measurements were averaged for the statistical analysis. Serum FT3, FT4 and TSH levels were measured by commercially available automated chemiluminescence system kits (ACS: 180, Chiron Diagnostics, East Walpole, MA, USA). Sensitivity for the TSH assay was 0.002 mU/l, the intra-assay coefficient of variation (CV) was 0.3–1.4% and the inter-assay CV was 0.5–1.9%; all were determined in our laboratory.

BUN (ThermoDMA, East Arlington, TX, USA), creatinine (DMA Inc., East Arlington, TX, USA), CPK, LDH and AST (ThermoDMA), total-cholesterol (Total Diagnostics, Exton, PA, USA), HDL-cholesterol (Sigma Diagnostics, Poole, Dorset, UK) and triglyceride (Thermo DMA) were measured by automated systems. LDL-cholesterol was calculated by the Friedwald formula (LDL-cholesterol = total-cholesterol – (HDL-cholesterol plus; triglyceride (TG)/5)). Whole blood analyses were made using an autoanalyzer (Coulter LH 500). Factor VIII activity was measured by coagulometric assay (Dade Behring Marburg GmbH, Marburg, Germany). Von Willebrand factor ristocetin cofactor activity was determined by the platelet agglutination method (Dade Behring Marburg GmbH). PT and APTT were measured by coagulation analyzers using kits from Dade Behring Marburg GmbH. The intra-assay coefficients of variation were as follows: factor VIII 1.2–3.9%, vWF 1.4–3.1%, PT 0.9–1.4%, APTT 0.8–1.5% and the inter-assay coefficients of variation were as follows: factor VIII 1.9–4.7%, vWF
1.6–4.4%, PT 1.8–2.6%, APTT 0.7–3.8%, all determined in our laboratory.

**Statistical analysis**

Results are expressed as the means±S.D. or as the median. ANOVA test-Sheffe’s F test were used for the comparison of groups. Tukey test or Bonferroni corrections were used for post-hoc analysis. Mann–Whitney U test with Bonferroni corrections were used for the comparison of three groups for the data which were not normally distributed. Paired t-test (two sided) for normally distributed data and Mann–Whitney U test for non-parametric distributions were used to evaluate differences in the same group. Significance was defined as P < 0.05. Data were analyzed using SPSS for windows (version 10.0, SPSS, Chicago, IL, USA).

**Results**

**Controls and patients: clinical description**

Clinical parameters of the patients and controls are presented in Table 1. There were no significant differences between the groups for gender, mean age, BMI and for systolic and diastolic blood pressures.

**Baseline thyroid functions and hemostatic parameters in the study groups**

Data are given in Table 2. In patients with OH the mean FT3 level was 3.12 pmol/l, the mean FT4 level was 4.7 pmol/l and the mean TSH level was 63.3 mU/l. In patients with SH the mean FT3 level was 4.4 pmol/l, the mean FT4 level was 14.8 pmol/l and the mean TSH level was 7.1 mU/l. In the controls the mean FT3 level was 5.2 pmol/l, the mean FT4 level was 16.4 pmol/l and the mean TSH level was 1.27 mU/l.

Factor VIII and vWF activities were significantly decreased in the patients with SH compared with the control group (P<0.01). Patients with OH showed significantly elevated bleeding time, prothrombin time, APTT and clotting time, and significantly decreased factor VIII activity, vWF levels and platelet counts compared with the controls. vWF and factor VIII activities were lower and APTT duration was higher in the patients with OH when compared with the patients with SH (Table 2).

**Biochemical parameters in patients with SH**

Data are given in Table 3. BUN, creatinine, AST, CPK, LDH, HDL-cholesterol and triglyceride levels were similar in the patient and control groups. Although total cholesterol and LDL-cholesterol levels were higher in patients with SH than in controls, they were not statistically significant.

**Changes in parameters after levothyroxine treatment**

**Overt hypothyroidism**

Bleeding time, PT, APTT and clotting time decreased significantly (P<0.05 for all) and factor VIII activity, vWF activity and platelet count increased significantly in the OH group after LT4 therapy (P<0.01, P<0.01 and P<0.05 respectively) (Table 4).

**Subclinical hypothyroidism**

Data are depicted in Table 5. Statistically significant increases in factor VIII activity (137±23 vs 111±26%, P<0.01) and vWF activity (133±19 vs 102±22%, P<0.01) were detected in the SH group after LT4 treatment. None of the biochemical parameters nor the other hemostatic parameters changed with the therapy.

**Discussion**

The main finding of the present study is that hypothyroid patients display a distinct pattern of alteration in the coagulation system depending on the severity of the disease. Compared with controls, patients with OH had higher bleeding time, prothrombin time, activated partial thromboplastin time (APTT) and clotting time and lower factor VIII activity, vWF levels and platelet counts.

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**Table 1** Clinical characteristics of control subjects and patients with subclinical and overt hypothyroidism. Results are given as either means±s.d. or median (range).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Subclinical hypothyroidism</th>
<th>Overt hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Gender</td>
<td>All female</td>
<td>All female</td>
<td>All female</td>
</tr>
<tr>
<td>Age (years) (range)</td>
<td>49.2 (25–61)</td>
<td>47.6 (21–68)</td>
<td>52.8 (30–65)</td>
</tr>
<tr>
<td>TSH (mU/l) (range)</td>
<td>1.3 (0.6–1.9)</td>
<td>7.1* (5.2–10)</td>
<td>63.3† (36–124)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4±5.3</td>
<td>26.2±5.4</td>
<td>25.8±6</td>
</tr>
<tr>
<td>Current smoker (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124±13</td>
<td>132±15</td>
<td>128±20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75±8</td>
<td>74±10</td>
<td>72±15</td>
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There were no statistically significant differences for these parameters except for TSH: *P<0.01 compared with controls; †P<0.0001 compared with controls.
platelet counts. Even the study population with SH exhibited lower factor VIII and vWF activities.

The influence of thyroid failure on hemostasis has been studied but is still not very well understood. The effect of hypothyroidism on the coagulation system is based mainly on the studies performed exclusively in patients with OH, presenting conflicting results (1–15). Mostly hypocoagulable states were observed in those studies. Decreased platelet adhesiveness, abnormal bleeding times, decreased levels of factors VIII, IX, XI and XII and a state with low vWF activity, such as acquired von Willebrand disease (vWD) and a bleeding tendency have been described especially in patients with OH (4–9). On the other hand, some recent studies have suggested a hypercoagulable state, as shown by increases in platelet and factor VII activities and decreases in fibrinolytic activity in severe hypothyroidism (10–15). Changes in PAI-1 levels have also been shown in patients with hypothyroidism (12–14). In the present study, hemostatic parameters including bleeding time, PT, APTT, factor VIII activity, vWF activity, platelet count, and clotting time were found to be altered in patients with OH. Although these findings have suggested a hypocoagulable state, i.e., acquired von Willebrand disease, in our patients no clinical bleeding abnormality was observed. Levothyroxine treatment improved all of these parameters in the patient groups. It could be suggested that generalized diminution in protein synthesis in hypothyroidism may also cause decreases in the coagulation factors. A deficiency of other coagulation factors, including factor VII, V, IX, and X, may have contributed to the prolongation of the APTT in the present patient group.

There are few studies in the English literature covering patients with SH (12, 13, 27). Muller et al. (12) reported a hypercoagulable state in patients with SH and they found no change in factor VIII and vWF activities. Chadarevian et al. (13) observed decreased fibrinolytic activity in patients with TSH levels between 10 and 50 mIU/l. In a recent study, Canturk et al. reported increased fibrinogen, PAI-1 and factor VII and decreased antithrombin III concentrations in a group of patients with SH (27). They also found improvements in these parameters with LT4 treatment, and came to the conclusion that SH is a hypofibrinolytic hypercoagulable state. In contrast to these studies, our patients with SH exhibited a hypocoagulable state.
as shown by decreased factor VIII and vWF activities, and both factors were improved with LT4 treatment.

Several factors may affect coagulation including age, sex, smoking, drugs and other medical conditions. In the present study we only included non-smoking female patients and compared their results with matched healthy controls. Since none of the individuals had any conditions that might alter the evaluated parameters, the only distinct aspect in the study was the thyroid hormone levels. Thus it seems that thyroid hormones have a direct influence on hemostatic factors. The mechanisms by which low thyroid hormones have a direct influence on hemostatic factors are not well established and are conflicting. Chadarevian et al. evaluated the relationship between fibrinogen, D-dimer and FT4 in their two in vitro studies and found a negative and independent relationship between FT4 and the mentioned parameters (10, 11). They concluded that FT4 plays a physiological role in the regulation of the hemostatic equilibrium and that low FT4 levels are associated with a hypercoagulable state. On the other hand, in a very recent in vitro study, a direct stimulatory effect of triiodothyronine on fibrinogen synthesis has been observed (16).

It appears that altered primary hemostasis is a feature of hypothyroidism and levothyroxine replacement therapy resolves these abnormalities in both overt and subclinical hypothyroidism. It is difficult to draw a firm conclusion from our results because of the relatively small number in the study population but we suggest that, although clinically insignificant, this hypocoagulable state should be kept in mind in patients who present with bleeding symptoms and signs.

In the present study, serum total-cholesterol, LDL-cholesterol and HDL-cholesterol levels of patients with SH were not different from the controls. Despite various assessments of the literature, the relationship between SH, serum lipids and atherosclerosis is still ambiguous (17, 20–22). Some cross-sectional studies suggested that serum cholesterol levels are significantly higher as shown by decreased factor VIII and vWF activities, and both factors were improved with LT4 treatment. Although this is a cross-sectional study, it may be suggested that altered primary hemostasis is a feature of hypothyroidism and levothyroxine replacement therapy resolves these abnormalities in both overt and subclinical hypothyroidism. It is difficult to draw a firm conclusion from our results because of the relatively small number in the study population but we suggest that, although clinically insignificant, this hypocoagulable state should be kept in mind in patients who present with bleeding symptoms and signs.

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in individuals with mild thyroid failure but some others did not (17–22). Another debate in patients with SH is the need for replacement treatment with thyroid hormones. Although results of several studies suggest that thyroid hormone substitution therapy reduced total- and LDL-cholesterol levels in patients with SH, this finding has not been confirmed by others (28–37). Several alterations in muscle function, skeletal muscle abnormalities, and renal function abnormalities have been reported in both subclinical and overt hypothyroidism (23–26). We could not find any abnormalities in renal function tests or muscle enzyme levels in SH patients, and no changes were observed after LT4 treatment in this group. None of the biochemical parameters, including the serum lipid levels, changed with LT4 replacement therapy in the patient group with SH in the present study. This may be due to the relatively mildly elevated initial TSH levels of the patients, since the TSH levels were all below 10 mIU/l in our patients. Although it is difficult to make a strong suggestion because of the small number in the study population, regarding all the parameters studied in the patients with SH in the present study, we, like others, also think that treating asymptomatic, otherwise healthy SH patients is not necessary (17, 28).

In conclusion, a tendency to hypocoagulable state can be seen in both subclinical and overt hypothyroidism. This alteration in hemostasis is reversed by LT4 replacement. However, the clinical significance of these changes remains to be elucidated. On the other hand, since patients with a TSH level below 10 mIU/l show no abnormalities regarding serum lipids, muscle enzymes and renal functions and do not benefit from LT4 administration, treatment can be preserved for those patients who have potentially reversible symptoms, hypercholesterolemia or a high risk of progression to OH as revealed by older age.

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