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Hemostatic System as a Risk Factor for Cardiovascular Disease in Women with Subclinical Hypothyroidism

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Hypothyroidism has been associated with atherosclerosis. The mechanisms of atherosclerosis in patients with thyroid failure remain controversial. Hypofibrinolysis might be a risk factor for thromboembolic disease in subclinical hypothyroidism (SH). We measured fibrinolytic activity in patients with SH before and after levothyroxine (LT_4) treatment and compared it to those of controls. We prospectively included 35 patients with SH and 30 healthy controls. We treated patients with LT_4 until almost 6 months after the euthyroid state has been achieved. We measured fibrinogen, D-dimer, antithrombin III (ATIII), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) activity, and factor VII. Clinical and anthropometric variables were recorded for both groups. We found increased levels of fibrinogen, PAI-1, and factor VII and decreased levels of ATIII activity in patients compared to control ($p < 0.001$ and $p < 0.05$). Decrease of tPA was not significant ($p > 0.05$). At the end of the LT_4 treatment, significant decreases were determined in PAI-1 and factor VII ($p < 0.05$). In conclusion, our data suggest an important role of hypofibrinolytic and hypercoagulable state on the development of atherosclerosis in patients with SH and beneficial effects of LT_4 treatment for decreasing the risk of atherosclerosis.

Introduction

The development of a sensitive assay for thyrotropin (TSH) has led to the discovery that many patients have abnormal TSH levels without other alterations in serum thyroid hormone levels, a condition termed as subclinical hypothyroidism (SH) (1). Subclinical thyroid failure is often asymptomatic; however, nearly 30% of patients with this condition may have symptoms that are suggestive of thyroid hormone deficiency (2–4). As in overt hypothyroidism, patients with SH may be also shown to be at high risk for atherosclerosis and cardiovascular disease (5,6). It has been argued that many factors were responsible for the development of cardiovascular impairment, such as direct effects of thyroid hormone on myocardium and arteries, lipids, homocysteine levels, and modification of circulating coagulation proteins and impaired fibrinolytic system (7–11). Previous studies suggested that plasma D-dimer, fibrinogen, and plasminogen activator inhibitor type 1 (PAI-1) were altered in patients with moderate or overt hypothyroidism (12,13). Published data analyzed fibrinolytic system in patients with subclinical to overt hypothyroidism are still controversial (11,14). However, surprisingly, there is not a previous study that has analyzed effects of treatment of SH on the hemostatic system.

We undertook this study to evaluate whether subclinical hypothyroidism would affect fibrinolytic system and whether treatment of SH with levothyroxine (LT_4) may improve alterations in fibrinolytic activity.

Materials and Methods

We prospectively included 35 women with SH, defined by normal free thyroxine (FT_4) and elevated TSH and 30 healthy women recruited from among patients who attended our outpatient clinic. Control subjects were defined by normal serum FT_4 and TSH levels. Control cases were matched for age and other characteristics with cases with SH. The study was approved by the Ethical Committee of Kocaeli University. All participants including cases and controls gave a written informed consent to participate this study. The diagnosis of SH was established by at least two determinations of serum thyroid hormones and TSH levels. The causes of SH were autoimmune thyroiditis, surgery because of thyroid diseases, or idiopathic. Any of cases had never received LT_4 replacement therapy. None of the cases had previous history

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of external radiation, radioiodine treatment, and/or drug therapy that would cause SH. Persons with severe obesity, alcohol consumers, patients receiving drugs such as diuretics and β-blockers, and patients with diabetes mellitus, impaired glucose tolerance, coronary hearth disease, familial or secondary dyslipidemia, and hepatic, renal, or other systemic diseases were excluded from the study. Menopausal status was confirmed by measuring follicle-stimulating hormone (FSH), and estradiol-17β serum levels. Patient with SH were given 25 μg LT_4 therapy, and the doses were increased incrementally until TSH and thyroid hormone became normal. Twenty-six of 35 patients completed LT_4 treatment. At the beginning and end of approximately a 6-month period after euthyroidism was achieved, the degree of clinical hypothyroidism was evaluated using the score developed by Zulewski et al. (3) Fourteen symptoms and signs of hypothyroidism, defined by Zulewski et al. (3), were evaluated by a physician who did not know the laboratory data of the patients and controls. They were quantified by a simple and convenient system 1 point = present and 0 point = absent. The value of the total score is given as the sum of the symptoms and signs present (euthyroidism is indicated by a score of 0–1; borderline hypothyroidism, 2–5; and clinical hypothyroidism more than 5). The purpose of using this score is to assess the severity of tissue hypothyroidism, to evaluate patients with discordant laboratory results and to monitor the effect of treatment in SH.

Blood was collected in the morning between 8 and 9 hours after an overnight fast. Samples were centrifuged within 30 minutes at 3000g for 5 minutes. Plasma and serum were separated and stored at -80°C until assays for determination of tissue plasminogen activator levels (tPA), PAI-1, D-dimer, antithrombin III (ATIII), and factor VII could be performed. TSH, FT_4, and free triiodothyronine (FT_3) levels were immediately measured before and every 4 weeks after the initiation of treatment until the euthyroid stage was reached. Thyroid antibodies were measured by an enzyme-linked immunoabsorbent assay. Thyroid antibody levels such as antithyroglobulin and antithyroid peroxidase were considered negative when they were below 0.6 and 100 IU/mL, respectively. At baseline, fibrinogen, prothrombin time (PT), and partial thromboplastin time (PTT) were determined immediately. Serum FT_4 (normal range, 0.85–1.78 ng/dL) and FT_3 (normal range, 1.57–4.71 pg/mL) levels were determined by chemiluminescence immunoassay method with Immulite 2000 (DPC, Los Angeles, CA) kits. DDI (normal range, 0–0.05 μg/mL), ATIII (normal range, 80–120%), and factor VII activity measurements were performed by a STA compact autoanalyzer with use of Diagnostica Stago (Parsippany, NJ) kits. Measurements of tPA activity (normal range, 1–12 ng/mL) were performed by Diagnostica Stago Asserachrom tPA kits. PAI-1 (normal range, <10 AU/mL) levels were measured by Shimadzu CL 770 spectrophotometer (Kyoto, Japan) with synthetic chromogenic substrates methods (Diagnostica Stago Stachrom PAI-1 kits). Fibrinogen measurement (normal range, 200–400 mg/dL) was immediately performed by STA compact auto analyzer with Clauss clotting methods.

Data are presented as mean $\pm$ standard deviation (SD). Statistical analysis was performed by an IBM computer with the use of SPSS, version 9.0 (SPSS, Inc., Chicago, IL). Student's t test or Mann-Whitney U test in the case of nonparametric distribution was used to identify variables showing differences between SH group and controls. Differences of frequencies were tested with the χ^2 test or Fisher's exact test, as appropriate for repeated measures. Treatment effects were compared for value of group with SH before and after treatment by paired t test (two-sided) for normally distribution data and Wilcoxon signed rank test for nonparametric distribution. The level of significance was set at $p < 0.05$. Pearson's correlation analysis was carried out between fibrinolytic parameters and thyroid hormone and TSH levels. Primary study variables were hemostatic parameters that are risk factors for atherosclerotic vascular diseases. Power analysis of this study was performed by using of Power and Sample Size Calculation (*PS*) version 1.0.13. It has been accepted as more valid than 0.8.

Results

The study population included 65 female subjects. Thirty of these had normal thyroid hormones and TSH levels, 35 had normal FT_4 levels and increased TSH levels (SH). Patients had FT_4 levels within the normal range and statistically significant higher TSH levels than the control group. At baseline, control and subclinical hypothyroid groups were similar with respect to age, body mass index, smoking habits, and using of estrogen pills. Smoking habits, mean blood systolic and diastolic pressure were not different between controls and SH group before LT_4 treatment. (Table 1).

There were no significant differences between controls and patients with SH for symptoms ($p > 0.05$) except weight gain and fatigue ($p < 0.05$). Significant improvement of questionnaire for Zulewski score was found in LT_4-treated patients, in contrast to that of patients before treatment. The mean score of patients before and after treatment are, respectively, 3.4 ± 2.5 and 0.19 ± 0.40 ($p < 0.001$). Analyzing subsets of patients, an improvement in symptom score was not noted in those LT_4-treated patients with pretreatment TSH levels greater than 10 μIU/mL. On the other hand, mean symptom score of patients with TSH levels less than 10 μIU/mL was significantly improved with LT_4 treatment ($p < 0.001$).

There were significant differences for thyroid hormones among control and SH groups before and after LT_4 treatment ($p > 0.05$). On the other hand, there were significant changes between TSH levels of controls and patients before and after LT_4 treatment ($p < 0.001$). If patients with SH were stratified according to TSH levels such as less than 10 μIU/mL or more than 10 μIU/mL, there were no significant differences for any of parameters evaluated here.

A significant increase in mean fibrinogen level of subclinical hypothyroid patients was observed ($p < 0.01$). Compared to controls, patients with normal FT_4 levels and increased TSH levels had insignificantly higher DDI levels, significantly higher PAI-1 and factor VII activity ($p < 0.001$). We also determined insignificant decrease of tPA levels ($p > 0.05$) and a significant decrease of ATIII activity in the subclinical hypothyroid group before LT_4 treatment ($p < 0.05$). Platelet count, PTT, and PT were not different among control and SH groups (Table 2). PAI-1 and factor VII activity in patients with LT_4 treatment significantly decreased when compared with those of patients before treatment ($p < 0.05$ (Figs. 1 and 2). TPA activity also increased with treatment

Table 1. Characteristics of Patients with Subclinical Hypothyroidism Before and After LT_4 Therapy and Controls

	Control group	*SH group (before treatment)*	*SH group (after treatment)*
Age (years)	44.3 ± 6.7	42.2 ± 11.6	
TSH (μIU/mL)	1.47 ± 1.04	8.69 ± 5.40[a]	1.97 ± 1.51[b]
FT_4 (ng/dL)	1.16 ± 0.15	1.19 ± 0.54	1.31 ± 0.21
FT_3 (pg/mL)	3.05 ± 0.45	2.75 ± 0.85	2.89 ± 0.56
BMI (kg/m^2)	26.2 ± 4.3	28.1 ± 5.1	26.2 ± 6.9
Systolic blood pressure (mm Hg)	128.2 ± 15.1	126.9 ± 25.3	123.1 ± 17.2
Diastolic blood pressure (mm Hg)	77.0 ± 7.8	79.4 ± 12.0	77.9 ± 6.7

[a]Comparison of control group and SH group before treatment.
[b]Comparison of SH groups before and after treatment.
$p < 0.0001$
LT_4, levothyroxine; TSH, thyrotropin; SH, subclinical hypothyroidism; FT_4, free thyroxine; FT_3, free triiodothyronine; BMI, body mass index.

but it was not significant ($p > 0.05$). Exclusion of women treated with estrogen replacement therapy did not change the differences found between controls and patients with SH before and after treatment.

When smokers were excluded, a significant increase in mean fibrinogen levels was observed in patients with SH before treatment ($p < 0.05$) but it did not change with LT_4 treatment. Similar results were determined for pretreatment PAI-1 activity compared to controls ($p < 0.001$). On the other hand, factor VII activity significantly increased in the SH group before treatment compared to that of controls ($p < 0.001$). It is also insignificantly decreased after treatment in the SH group ($p > 0.05$). With exclusion of premenopausal controls and cases, there were significant increase in fibrinogen levels, PAI-1 and factor VII activity in SH group before treatment compared to those of controls ($p < 0.001$). They insignificantly decreased with LT_4 treatment in SH group ($p > 0.05$).

In the subclinical hypothyroid group before treatment, a significant positive correlation was found between TSH and Zulewski score ($r = 0.382$). On the other hand, there was not any correlation between symptoms score and TSH levels after treatment. We did not determine any significant correlation between hemostatic parameters and Zulewski score. There was also no correlation between hemostatic parameters and TSH levels and antithyroid antibody titers. There were no significant correlation among lipoprotein (a) [Lp(a)] levels, PAI-1, tPA, factor VII activities, fibrinogen, DDI, and ATIII levels ($p > 0.05$).

Discussion

In this study, most important findings are that patients with SH have low ATIII levels and elevated levels of fibrinogen, factor VII, and PAI-1 which play a role on atherosclerotic disorders, and that factor VII and PAI-1 improve with thyroid replacement treatment. Although moderate or overt thyroid failure must be considered as one of the atherosclerotic risk factors (5,11), there are several studies that have reported a controversial association between SH and atherosclerosis (20–22). Furthermore, a recent study has provided evidence that SH itself may be an independent risk

Table 2. Some Parameters of Hemostatic System in Patients with Subclinical Hypothyroidism Before and After LT_4 Treatment and in Controls

	Control group	*SH group (before treatment)*	*SH group (after treatment)*
PT (INR)	1.03 ± 0.061	1.13 ± 0.41	1.10 ± 0.40
PTT (sec)	28.3 ± 1.8	29.6 ± 3.4	28.8 ± 3.7
Platelet/mm^3	285733 ± 49990	289346 ± 101863	265461 ± 56882
Fibrinogen (mg/dL)	314.5 ± 27.1	329.0 ± 51.2*	320.2 ± 50.8
t-PA (ng/mL)	4.05 ± 1.76	3.60 ± 1.70	3.84 ± 1.50
PAI-1 (AU/mL)	10.18 ± 3.61	19.78 ± 6.20†	15.08 ± 9.42‡
D-dimer (μg/mL)	0.39 ± 0.27	0.52 ± 0.75	0.38 ± 0.43
ATIII (%)	106.2 ± 11.8	101.8 ± 6.4**	101.7 ± 6.5
Factor VII (%)	92.4 ± 13.8	117.2 ± 15.8†	110.3 ± 7.2‡
Lp(a) (g/L)	0.16 ± 0.09	0.27 ± 0.29**	0.30 ± 0.29

Comparison of control group and SH group before treatment (*$p < 0.01$; **$p < 0.05$; †$p < 0.001$).
Comparison of SH groups before and after treatment ‡$p < 0.05$.
LT_4, levothyroxine; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; t-PA tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; ATIII, antithrombin III; Lp(a), lipoprotein (a).

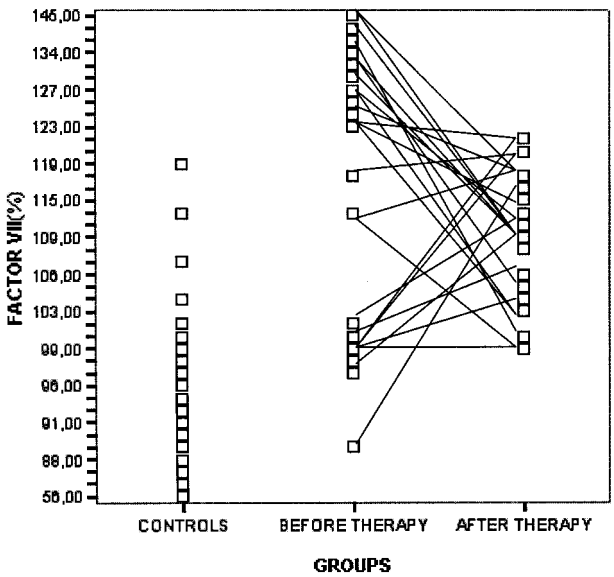


FIG. 1. Distribution of factor VII activity value in control group and case groups.

factor for atherosclerosis and myocardial infarction in elderly women (5). However, these findings were not confirmed by other investigations (20–22). There are several mechanisms involved in the association between mild thyroid failure and cardiovascular disease such as a hypercoagulable state, collagen-induced platelet aggregation, hyperlipidemia, or relaxation of vascular smooth muscle (8). Although the decision to treat patients with SH is usually based on the fact that some symptoms may be reversed by LT_4 treatment and that therapy prevents progression to the overt stage of hypothyroidism, the beneficial role of treatment on hemostatic parameters that play a role on the atherosclerotic changes in patients with SH must be considered for the decision of treatment (15–19).

Although our knowledge of the effect of hypothyroidism on the hemostatic system is based mainly on previous studies performed in patients with overt hypothyroidism, the influence of thyroid insufficiency on hemostatic system is still controversial (14,23–25). Despite the known association of cardiovascular disease and coagulation cascade, there is no report about the association between the hemostatic system and atherosclerotic complications of SH except the study of Müller et al. (14). Although patients with SH have been shown to be at high risk for atherosclerosis, the pathogenesis of this association still remains unclear. As is known, the active form of factor VII, factor VIIa, prompts neointimal hyperplasia (26). High factor VII has been shown to be a risk factor for cardiovascular events. A longitudinal analysis in atherosclerotic patients suggested that increased cardiovascular risk factors were associated with higher levels of factor VII activity (27,28). In a previous study, a significant increase of factor VII activity in patients with SH was reported (14). There are conflicting results for factor VII levels in overt hypothyroidism (23,29,30). Although our findings were not similar to data of patients with overt hypothyroidism (23), indicating a prethrombotic potential in patients with SH, our findings correlate with results of a previous study performed on patients with SH (14) and with the study by Chadarevian et al. (30), which recently found increased factor VII activity in cases with overt hypothyroidism. Hypercoagulable state in patients with SH might add to the risk for atherosclerotic vascular disease. It can be stated that increased factor VII activity might theoretically add to this risk (14). In the present study, our findings suggest that increased factor VII activity in patients with SH represents a potential hypercoagulable state, which might augment the already existing risk for atherosclerotic complications. There is no previous study that evaluates the role of LT_4 treatment on factor VII activity in SH. Although no previous report is known to us, observing a decrease of factor VII activity with thyroxine replacement seems important. With regard to this, LT_4 treatment in patients with SH may have more importance if there are any additional atherosclerotic vascular risk factors. The effect of estrogen replacement therapy on the risk for cardiovascular disease is conflicting. Some studies showed significant reduction of risk, others, however, have not found the same favorable effect (14). What is known is that patients with SH are at risk for atherosclerotic vascular disease. Although estrogen replacement therapy could account for an increase in factor VII, we determined an increased factor VII activity with or without estrogen replacement therapy (31).

The main finding of this study is that before treatment patients with SH display an increased PAI-1 level compared to that of controls and a decreased level with LT_4 treatment. A recent study found high PAI-1 antigen levels in moderate hypothyroidism and low levels in severe hypothyroidism (11). Although Müller et al. (14) reported that there were no significant differences of PAI-1 levels in cases with SH, we found increased PAI-1 levels in patients with SH despite exclusion of smokers and users of estrogen-containing drugs compared to controls. With exclusion of smokers, we did not determine any significant change between PAI-1 levels of patients with SH before and after LT_4 treatment. After LT_4 treat-

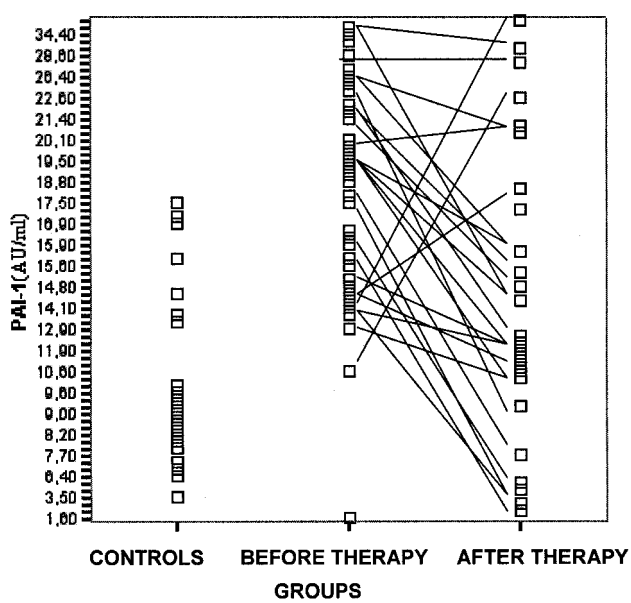


FIG. 2. Distribution of plasminogen activator inhibitor type 1 (PAI-1) levels in control group and case groups.

ment, PAI-1 levels decreased in patients who are not taking estrogen replacement therapy. Smoking is associated with increased prevalence of hypothyroidism and impaired endogenous fibrinolysis (32,33). A previous study suggested that there was not any effect of smoking on fibrinolytic activity (11). In this study, the number of cases in this subgroup is not enough to compare with results of previous studies. Menopause is an independent risk factor for atherosclerotic disease (34). We also found a significant increase of PAI-1 and factor VII levels in postmenopausal subgroup of patients when compared with controls, but decreased levels of these parameters after treatment is not significant. The insignificance of improvement with treatment may be due to small study population and short treatment period or menopause, which causes hypercoagulable state and hypofibrinolysis.

The presence of hypofibrinolysis is indicated by a reduction of tPA activity and an increase of PAI activity. It has been anticipated that high plasma tPA levels should protect against subsequent coronary events (32). In epidemiologic studies of patients with ischemic heart disease and in a healthy male population, total plasma tPA concentrations positively predict future coronary events (11,14,35). Although there is no previous study that evaluated tPA activity in patients with SH, in a study performed on patients with moderate and severe hypothyroidism, tPA antigen levels decreased in the moderate hypothyroid group and increased in the severe hypothyroid group (11). Müller et al. (14) reported that tPA did not differentiate in patients with SH. In this study, we determined insignificant decreased tPA activity in patients with SH.

Multiple prospective studies have identified an association between plasma fibrinogen concentrations and coronary heart disease (36–38). There are several potential mechanisms by which fibrinogen can promote the development of atherosclerosis and thrombosis. A number of factors affect fibrinogen levels such as gender, smoking, etc. (39–42). An insignificant decrease of fibrinogen levels in patients with moderate and severe hypothyroidism was previously reported (43). In a recent study performed in patients with SH, fibrinogen was found to be elevated compared to controls (11). We also determined an increase in patients with SH compared to controls. Elevated levels of fibrinogen have consistently been shown as independent predictors of initial and recurrent cardiovascular events (14). The mechanisms by which fibrinogen may promote atherosclerosis are not fully understood. It affects the hemostatic system and is the major determinant of plasma viscosity. Fibrinogen is an acute-phase reactant and could therefore also be a marker for increased inflammatory activity (44). In this study, a significant increase of fibrinogen level despite exclusion of smokers and those treated with estrogen replacement therapy suggests that subclinical hypothyroidism is an independent risk factor. We also determined significantly high concentrations of fibrinogen in patients with the postmenopausal subclinical hypothyroid subgroup. This study has shown that there was no significant beneficial effect of LT_4 treatment to fibrinogen levels in patients with subclinical hypothyroidism. This result may be because of the number of study population and relatively short period of treatment.

ATIII is an important inhibitor of thrombin and several other coagulation enzymes. Inherited isolated deficiency of ATIII is a rare autosomal-dominant disorder that is associated with recurrent deep vein thrombosis and pulmonary emboli (45). Müller et al. (14) reported that ATIII levels did not change in the SH group compared to controls. However, we determined a significant decrease in patients with SH compared to controls. This result suggests presence of hypercoagulopathy in SH. On the other hand, ATIII level did not significantly increase with LT_4 treatment.

Increased PAI-1 levels with or without high serum triglyceride, total cholesterol, and other risk factors were suggested as an independent risk factor (46). Whereas increased PAI-1 and tPA antigen with decreased fibrinolytic activity have been demonstrated in patients with coronary heart disease in many cross-sectional studies (47), there was no consensus on the prognostic value of these fibrinolytic variables. While clot lysis time and tPA antigen have been shown to be predictive of cardiovascular events and mortality, conflicting results have been obtained for PAI-1 determination, PAI-1 being predictive in some reports but not in others (35,47–49). Fibrinolytic parameters are strongly related to atherosclerotic risk factors such as insulin resistance parameters, lipid, and inflammation markers (46,50). Recent epidemiologic studies support the concept that subclinical hypothyroidism is an independent atherosclerotic risk factor. A previous study suggested a hypofibrinolytic state in patients with moderate hypothyroidism. Their results also suggest that the risk of developing thrombosis and myocardial infarction because of high PAI-1 levels might be increased (51,52).

The mechanisms by which thyroid hormone status affects fibrinolysis still remain unclear. The suggested hypotheses are as follows: direct effect of thyroid hormones on either synthesis and catabolism of proteins; reduction of catecholamine receptor density in hypothyroidism, leading to an increase in PAI-1 level; consequences of atherosclerosis and endothelial dysfunction, a condition associated with reduced release of hemostatic factors and indirect effect through autoimmunity (14), but our study population is too small to draw such a comment.

Finally, in patients with SH, which is an independent risk factor for atherosclerosis, high PAI-1 levels (a marker of hypofibrinolysis and increased factor VII activity, one of the components of hypercoagulopathy) together with increased lipids indicate the necessity of diagnosis and treatment of SH to prevent the development of atherosclerotic complications. Improvement of PAI-1 and factor VII together with improvement of lipids as a result of LT_4 treatment significantly decreases atherosclerotic risk in patients with SH. Further research on hemostatic factors could improve our knowledge of the pathogenesis of atherosclerosis and its complications in patients with SH. It may also help us better understand the effects of LT_4 treatment and find new ways to prevent atherosclerotic diseases.

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