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The Effects of Experimental Hyperthyroidism on Hemorheology and Plasma Fibrinogen Concentration

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The present study in female rats determined the effects of experimental hyperthyroidsm on hemorheological parameters and fibrinogen concentration. To induce experimental hyperthyroidism L-thyroxine (0.4 mg/100 g fodder) was added to the fodder of the experimental group rats for 20 d. After experimental duration, T_3, T_4, and TSH levels, plasma and blood viscosity, hematocrit, erythrocyte rigidity index, and plasma fibrinogen concentration values of both the control and the experimental group animals were determined and evaluated. In the experimental group, T_3 and T_4 levels were higher and TSH levels lower than that of the control rats (respectively, $p < 0.01$, $p < 0.001$, $p < 0.001$). Plasma viscosity and fibrinogen concentration of hyperthyroid group were found significantly higher than controls ($p < 0.01$). However there was no significant difference found in blood viscosity, hematocrit, and erythrocyte rigidity index between control and experimental groups. Thus, hyperthyroidism induced increased fibrinogen concentration can alter the rheological structure of blood by inducing increase in plasma viscosity.

Key Words: Hyperthyroidism; blood viscosity; erythrocyte rigidity; fibrinogen.

Introduction

The most common types of endocrinological disease appear as a result of thyroid gland dysfunction *(1)*. The thyroid hormones play a critical role in growth, maturation, and metabolism needed for the normal function of almost all the tissues in the body *(2,3)*. The alteration in the blood levels of the thyroid hormones lead to many pathological states in the organism. The effects of thyroid hormones on hematological parameters and the cardiovascular system are known *(4, 5)*. For example, in thyroid diseases such as Graves' disease or Hashimoto thyroiditis, idiopathic thrombocytopenic purpura (ITP) and reduction in thrombocyte aggregation are seen *(6)*. It is also noted that anemia occurs in hypothyroidism and hyperthyroidism. There are considerable differences between coagulation and fibrinolytic activity *(7)*. Different researchers have reported that the vascular endothelium dysfunction rises and the fibrinolytic activity in the blood is decreased in hyperthyroid patients *(8,9)*. Therefore, this situation in hyperthyroidism might be a risk for thromboembolic events. The thyroid hormones also have either direct or indirect influence on the cardiovascular system *(6)*. These influences on hemorheological parameters are fibrinogen concentration, blood viscosity, plasma viscosity, erythrocyte aggregation, and erythrocyte deformability (erythrocyte rigidity).

Therefore, this study has been planned to study the changes in hemorheological parameters and fibrinogen concentration that are known to be effective parameters in hemorheology in experimental hyperthyroidism.

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Results

The results of both groups from all measured parameters are given in Table 1. Statistically significant increases in serum T_3, T_4 levels were seen in the experimental group compared to the controls ($p < 0.01$, $p < 0.001$). The TSH level was found significantly lower in experimental group than that of the controls ($p < 0.001$). Plasma viscosity and plasma fibrinogen concentrations were found to be higher in hyperthyroid group than control group animals ($p < 0.01$). Blood viscosity values were at original hematocrit and standard hematocrit values and has showed no significant difference between control and experimental groups. RBC rigidity index and hematocrit values also did not change in both groups.

Discussion

In this study after L-thyroxin application to the experimental rats, hyperthyroidism occurred. Production of the hyperthyroidism has been proved by the measurement of the T_3, T_4, and TSH levels of the experimental and the control groups. Statistically significant increased T_3, T_4 and decreased TSH values in the experimental group were taken as the indicator of the hyperthyroidism (Table 1). The fac-

Table 1
Rheological Parameters and Fibrinogen Concentrations of Control and Hyperthyroid Groups Rats

Parameter	Control ($n = 9$)	Hyperthyroid ($n = 8$)
T_3 (ng/100 mL)	68.9 ± 14.8	93.2 ± 16.3**
T_4 (μg/100 mL)	5.40 ± 0.64	6.57 ± 0.64***
TSH (IU/mL)	0.02 ± 0.005	0.01 ± 0.002***
Hematocrit (%)	40.0 ± 4.41	37.0 ± 3.98
Fibrinogen (mg/100 mL)	185.5 ± 22.8	217.7 ± 18.9**
Plasma viscosity (mPa·s)	1.03 ± 0.04	1.11 ± 0.06**
Blood viscosity (mPa·s) (original hematocrit)	2.71 ± 0.29	2.71 ± 0.17
Blood viscosity (mPa·s) (standard hematocrit Hct = 40%)	2.90 ± 0.38	2.89 ± 0.29
Rigidity index (standard hematocrit Hct = 40%)	2.89 ± 0.34	2.62 ± 0.33

Data are the means ± SD. **$p < 0.01$, ***$p < 0.001$.

tors that determine the rheological properties of the blood are blood viscosity, plasma viscosity, hematocrit, fibrinogen concentration, and erythrocyte deformability. When the considered parameters were examined in the rats that were induced to be hyperthyroid, it was found out that blood viscosity did not show any difference in either the original or the corrected (to 40%) hematocrit levels compare to the control group values. Contrary to our findings, Kossler et al. *(10)* had determined an increase in the blood viscosity in hyperthyroidism, and they explained it by an increase in hematocrit value. At the same time, we have also determined no statistical difference in hematocrit values between both groups (Table 1). The unchanged blood viscosity values in our study may depend on unchanged hematocrit. In addition to unchanged hematocrit according to our results, when the erythrocyte rigidity index is examined, no significant difference was observed in the hyperthyroid group compared to the control group. Therefore, it may be concluded that from the erythrocyte point of view no contribution had been done to the viscosity in hyperthyroidism. Just as a matter of fact, the oxygen demand of the tissues increases in hyperthyroidism due to the increase in metabolism. Because of the increased oxygen demand, erythrocyte production increases and the mass of the erythrocytes also increases. However; as the increase in plasma volume outweighs the increase in erythrocyte mass, a mild anemia is observed *(11)*. Toktamis et al. *(12)* have also similarly found that the hematocrit value did not change in their study, which examined the blood parameters in hyperthyroid rats. In addition, when we look at the erythrocyte rigidity index, which refers to the erythrocyte deformability, no significant difference was observed in the hyperthyroid group compared to the control group. These findings may be another cause for no change in blood viscosity. In our study, plasma viscosity values have been found significantly higher when compared to the control group ($p < 0.01$). The blood viscosity values remaining unchanged while plasma viscosity increases may result from the alteration in the plasma proteins, because it is known that plasma viscosity is affected by plasma protein concentration. The study of Ruggiero et al. covers lipid cholesterol ratio in the cell membrane, and they have detected that there was a cholesterol transport from plasma to eryhtrocyte membrane but no change was found in this ratio in hyperthyroid rats *(13)*. Although Kossler et al. *(10)* found the plasma viscosity and plasma protein values lower in the rats in which they induced hyperthyroidism compared to the control group, Marongiu et al. *(14)* found plasma fibrinogen concentrations higher in hyperthyroidism than in the control group. The researchers claim that, in hyperthyroidism, both the fibrinogen synthesis and fibrin degradation products (Bβ 15–42) increase. But they demonstrated that fibrinogen concentrations and fibrin degradation products decrease when they treat the hyperthyroid patients. Another group of researchers found that, once again in hyperthyroid state, fibrinogen is elevated *(8,15)*. Similarly in our study, the fibrinogen concentration of hyperthyroid rats have been found to be significantly higher compared to the control group ($p < 0.01$). In our study finding plasma viscosity higher in the hyperthyroid group may result from the increase in fibrinogen concentration. According to results of our research, the hemorheological alterations in the experimentally induced hyperthyroid rats only resulted from increase in plasma viscosity. This elevation may be related to the elevation of the plasma fibrinogen concentration. The increase in the thyroid hormones did not affect the hematocrit levels and erythrocyte rigidity. Variations in erythrocyte concentration are the main reason for changes in whole blood viscosity. In our results it may be seen that no change was detected in erythrocyte concentration *(16)*. Therefore, the increased plasma viscosity is based on mainly increased fibrinogen concentration. As a result, it can be said that in experimental hyperthyroidism, plasma viscosity increase is associated with the increase in fibrinogen concentration and this affects the rheology of the blood.

Materials and Methods

In our study Spraque–Dawley type albino female rats weighing 160–200 g were used in both control and experimental group animals. Both control ($n = 9$) and experimental group ($n = 8$) animals were kept in the same physical conditions during the experimental period and were fed with standard fodder and tap water. To constitute hyperthyroidism L-thyroxin (0.4 mg/100 g fodder) was given to experimental group animals for 20 d *(12)*. At the end of 20 d, the animals were sacrificed under anesthesia and blood samples were drawn to measure triiodothyronine (T_3), thyroxine (T_4),

thyroid stimulant hormone (TSH) levels, hematocrit (% Hct), plasma viscosity, blood viscosity, erythrocyte deformability, and plasma fibrinogen concentration. Our protocol and methods were approved by the Animal Care and Use Committee of Laboratory Animal Service of the Istanbul University, Turkei. Serum levels of T_3, T_4, and TSH were determined by the radioimmunoassay (RIA) method (Diagnostic Products Corporation). The coat-A-count procedure is a solid-phase radioimmunoassay where ^{125}I-labeled T_3, T_4, and TSH are in the sample for antibody sites. This reaction takes place in the presence of blocking agents that liberate bound triiodothyronine from carrier proteins; hence, the assay measures total T_3, T_4, and TSH, because both free and protein-bound T_3, T_4, and TSH from the sample are able to compete with radiolabeled T_3, T_4, and TSH for antibody sites. Radioactivity counting was performed in a gamma counter (Searle, Nuclear Chicago Division, model 1185). Hematocrit was measured by the microhematocrit centrifuge technique. Blood viscosity was measured at original and standard hematocrit values. For standardization, plasma of the animal either has been added or removed from the blood and percentage hematocrit was adjusted to 40% *(17)*. Erythrocyte deformability was described as erythrocyte rigidity index (RBC index). The ability of RBCs to deform was represented as a RBC rigidity index, which is the inverse value of the RBC deformability *(18,19)*. Both plasma and blood viscosity were measured in Harkness viscometer (Coulter Electronics Ltd, Ser. No: 6083, England) and evaluated in relation to distilled water at 37°C *(20)*. The plasma fibrinogen concentration was determined according to the Ratnoff and Menzie method in spectrophotometer (UV-160 A, Shimadzu) at 520 nm wavelength *(21)*. Statistical analysis was done by the Mann–Whitney *U* test. The values were expressed as means ± standard deviation. Differences between groups were considered significant at the $p < 0.05$ level.

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