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Fibrinogen and D-dimers levels in patients with hyperthyroidism before and after radioiodine therapy

Stężenie fibrogenu i D-dimerów u chorych z nadczynnością tarczycy przed i po leczeniu ^{131}I

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Abstract

Background: Various abnormalities of haemostasis have been described in patients with hyperthyroidism. The results of different studies point to the underlying thyroid disease, especially severity of hyperthyroidism and autoimmune processes, as important factors contributing to coagulation-fibrinolytic balance. The objective of this study was to investigate the association between hyperthyroidism (concerning severity of thyroid dysfunction and anti-thyroid perioxidase antibodies level) and plasma fibrinogen and D-dimers levels before and after radioiodine therapy.

Material and methods: The study included 35 non-smoking, postmenopausal women, aged 51–69, with subclinical or overt hyperthyroidism treated with radioiodine. Analysis comprised serum TSH (thyroid stimulating hormone), fT4 (free thyroxine), fT3 (free triiodothyronine), TPO antibodies (anti-thyroid perioxidase) levels, and plasma D-dimers and fibrinogen levels before and 12-16 weeks and 24–28 weeks after radioiodine therapy.

Results: Elevated fibrinogen (3.82 g/L ± 0.75, reference range 2–4.5 g/L) and D-dimers (674.26 ng/mL ± 652.71, reference range 70–490 ng/mL) levels were observed in subjects with hyperthyroidism. They decreased after radioiodine therapy. A negative correlation between plasma fibrinogen and D-dimers levels and anti-thyroid perioxidase antibodies level was found. TSH, fT4 and fT3 correlated with D-dimers level in overt hyperthyroidism.

Conclusions: Hyperthyroidism is associated with a tendency toward hypercoagulation and hyperfibrinolysis. The changes observed in plasma fibrinogen and D-dimers levels are reversible. Fibrinogen level decreases within reference range and D-dimers level decreases almost to the upper reference range. They depend on severity and autoimmunity of the underlying thyroid disease and may be modified by restoring euthyroidism. **(Pol J Endocrinol 2011; 62 (5): 409–415)**

Key words: *hyperthyroidism, fibrinogen, D-dimers, autoimmune thyroid disease*

Streszczenie

Wstęp: U pacjentów z nadczynnością tarczycy opisano różne zaburzenia hemostazy. Wyniki publikowanych dotychczas prac sugerują, że najważniejszymi czynnikami, od których zależy równowaga procesów koagulacji i fibrynolizy, są stopień nasilenia choroby tarczycy oraz procesy autoimmunologiczne. Celem prezentowanej pracy jest ocena stężeń fibrynogenu i D-dimerów w nadczynności tarczycy przed leczeniem i po podaniu ^{131}I w zależności od nasilenia choroby i braku lub obecności przeciwciał przeciw tyreoperoksydazie.

Materiał i metody: Do badania włączono 35 niepalących kobiet po menopauzie, w wieku 51–69 lat, z subkliniczną lub jawną klinicznie nadczynnością tarczycy, leczonych ^{131}I. Badano stężenia tyreotropiny (TSH), wolnej tyroksyny (fT4), wolnej trójjodotyroniny (fT3), przeciwciał przeciw tyreoperoksydazie (anty-TPO) oraz fibrynogenu i D-dimerów przed leczeniem oraz 12–16 tygodni i 24–28 tygodni po podaniu ^{131}I.

Wyniki: U kobiet z nadczynnością tarczycy obserwowano podwyższone stężenie fibrynogenu (3,82 g/L ± 0,75, norma 2–4,5 g/L) i D-dimerów (674,26 ng/mL ± 652,71, norma 70–490 ng/mL), które obniżały się po leczeniu ^{131}I. Stwierdzono ujemną korelację pomiędzy stężeniem fibrynogenu i D-dimerów a stężeniem przeciwciał anty-TPO. U pacjentek z jawną klinicznie nadczynnością tarczycy uzyskano dodatnią korelację pomiędzy stężeniem TSH, fT4, fT3 a stężeniem D-dimerów.

Wnioski: Nadczynność tarczycy wiąże się z większą skłonnością do koagulacji i fibrynolizy. Stężenie fibrynogenu zmniejsza się w zakresie wartości referencyjnych, natomiast D-dimerów zmniejszając się, osiąga górny zakres wartości referencyjnych. Zmiany obserwowane w stężeniu fibrynogenu i D-dimerów są odwracalne. Zależą od stopnia nasilenia nadczynności tarczycy oraz procesów autoimmunologicznych, a także podlegają modyfikacji po przywróceniu prawidłowej funkcji tarczycy.

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Słowa kluczowe: *nadczynność tarczycy, fibrynogen, D-dimery, autoimmunologiczna choroba tarczycy*

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Introduction

Thyroid dysfunction may cause mild changes in primary and secondary haemostasis or lead to clinically important thrombosis or haemorrhage. It has been suggested that hyperthyroidism is associated with hypercoagulability and hypofibrinolysis but there is as yet little data on subclinical hyperthyroidism [1]. The direct and indirect effects of excessive thyroid hormones on thrombocytes, coagulation factors and blood viscosity are responsible for disturbances in coagulation and fibrinolytic system [1]. Some authors suggest thyroid-related autoimmune processes may be involved [2–4] while others argue that the haemostatic balance is rarely affected by such mechanisms [5].

Thrombocytopenia in hyperthyroidism is considered to be a metabolic consequence of thyroid hormone elevation [6] (i.e. thyrotoxicosis may increase the phagocytic activity of the reticuloendothelial system) [7, 8]. However, the relationship between autoimmune thrombocytopenic purpura and hyperthyroidism has also been described [9, 10].

Hypercoagulability results from the following biological mechanisms [2, 11–13]: an increased hepatic protein synthesis [14], an increased acute phase reactants synthesis [14–16], an excessive production of tissue factor [17], an increased thrombin and plasmin activity [14] and an increased level of the indicators of endothelial damage (i.e. thrombomodulin and von Willebrand factor) [13–15, 18].

An excess fluid loss (due to an increased metabolism) and an increase in blood volume (due to an increase in red blood cell level) also contribute to hypercoagulability.

Thyroid hormones exert effect on haemostasis through nuclear receptor by altering gene expression of many proteins originating from the liver and endothelium [15, 19, 20].

Hyperthyroidism, overt and subclinical, alters the coagulation-fibrinolytic balance. Various changes have been described in patients with hyperthyroidism [5]. Several reports have demonstrated high plasma

fibrinogen level in hyperthyroid states [13, 14, 21, 22]. The relation of subclinical hyperthyroidism to the blood coagulation system has not been extensively studied. It is suggested that these abnormalities are independent of the underlying pathophysiology of thyroid disease [5]. Changes are reported to return to normal after treatment. Hyperthyroidism is associated with higher thromboembolic potential [13, 22]. Another study confirmed the hypercoagulable state in subclinical hyperthyroidism [20].

The purpose of this study is to evaluate the association between type of hyperthyroidism (degree of thyroid dysfunction and thyroid autoimmunity), haemostatic parameters (fibrinogen and D-dimers) and radioiodine therapy.

Material and methods

35 non-smoking, postmenopausal women aged 51–69 were involved. The mean age was 59 years. We chose postmenopausal and non-smoking women in order to include a homogenous group of patients and to exclude the influence of smoking and effect of oestrogen on coagulation–fibrinolytic balance. All patients were hyperthyroid (21 with toxic goitre, six with autonomous functioning thyroid nodule, seven with Graves' disease, and one with toxic goitre and Graves' disease). They were divided into subgroups according to severity of disease. 20 of them presented with subclinical hyperthyroidism (defined as TSH < 0.4 uIU/mL and fT4 < 20 pmol/L) and 15 presented with overt hyperthyroidism (defined as TSH < 0.4 uIU/mL and fT4 > 20 pmol/L). Patients were also divided into two categories according to level of anti-thyroid peroxidase antibodies. Anti-TPO antibodies refer to undergoing autoimmune processes. As there is very little data on the type of antibodies and their usefulness in investigating haemostasis balance in thyroid dysfunction [8], we chose these antibodies because they are commonly measured in clinical practice: 27 patients had antibodies within the norm (< 35 IU/mL) and in eight the level of antibodies was elevated (> 35 IU/mL). None of the patients had a history of concomitant disease that could have influenced the coagulation-fibrinolytic balance. The study protocol was approved by the Ethics Committee for Human Studies of Wroclaw Medical University. Informed written consent was obtained from all subjects after explanation of the nature, purpose and potential risk of the study.

In all patients, levels of TSH, fT4, fT3, TPO antibodies, fibrinogen and D-dimers were measured using commercial methods (Siemens Immulite 2000 Systems TSH 3rd Generation, Siemens Immulite 2000 Systems ST4, Siemens Immulite 2000 Systems ST3, Siemens 2000 Systems ATA for TPO antibodies, Siemens Multifibrin for fibrinogen and Biomerie Ups. Vidas D-dimer exclusion). The measurements were taken three times: once before administration of radioiodine, once between 12 and 16 weeks after radioiodine therapy, and again between 24 and 28 weeks after radioiodine therapy. Reference ranges were 0.4–4 uIU/mL for TSH, 9–20 pmol/L for fT4, 4–8.3 pmol/L for fT3 and 0–35 IU/mL for TPO antibodies. Reference ranges for haemostatic parameters were 2–4.5 g/L for fibrinogen and 70–490 ng/mL for D-dimers.

Statistical analysis

Results are expressed as mean ± standard deviation. Statistical comparisons for study group before and after treatment were made by Student's t-test. Differences were considered statistically significant when $p < 0.05$ was obtained.

Results

The mean plasma fibrinogen and D-dimers levels in hyperthyroid women are shown in Figures 1 and 2.

Analysis revealed no association between TSH, fT4 and fT3 and fibrinogen and D-dimers. Plasma fibrinogen level measured 12 -16 weeks after treatment was inversely correlated with TPO antibodies levels measured at the same time ($r = –0.19$, $p < 0.001$).

Plasma D-dimers level measured 24-28 weeks after treatment was inversely correlated with antibodies level measured at the same time ($r = –0.244$, $p < 0.001$).

To determine if the severity of hyperthyroidism influenced the coagulation-fibrinolytic system, the 35 hyperthyroid women were divided into two groups: subclinical (20) and overt (15) hyperthyroidism. The mean plasma fibrinogen and D-dimers levels in 20 women with subclinical hyperthyroidism are shown in Figures 3 and 4.

Analysis revealed no association between TSH, fT4, fT3 and fibrinogen and D-dimers.

Plasma fibrinogen level was not associated with TPO antibodies level.

Plasma D-dimers level measured 12–16 and 24–28 weeks after treatment was negatively correlated with

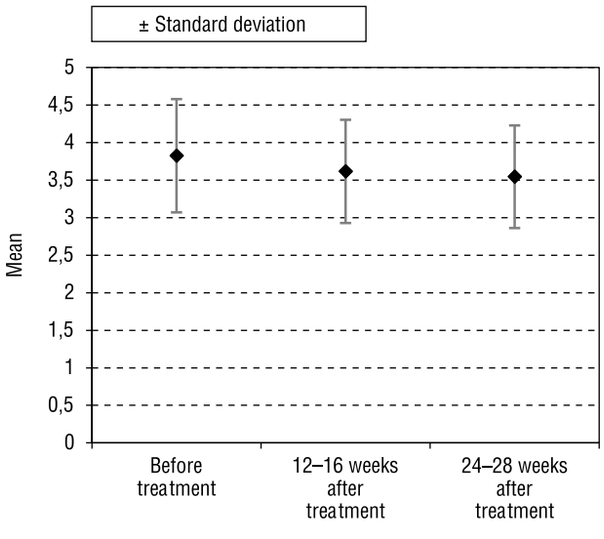

Figure 1. *Fibrinogen [g/L] in hyperthyroidism*

Rycina 1. *Fibrynogen [g/L] w nadczynności tarczycy*

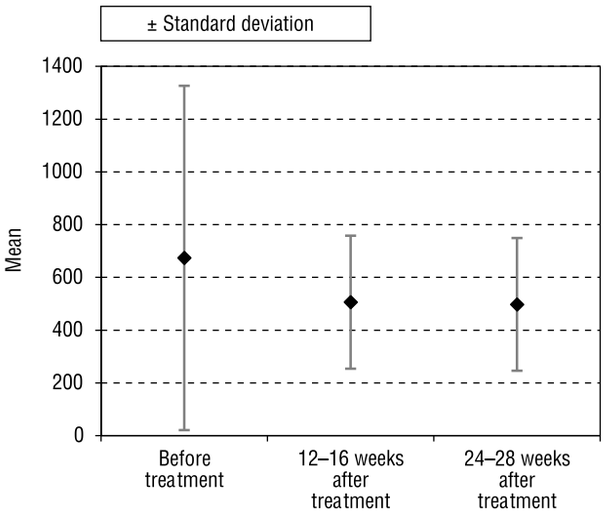

Figure 2. *D-dimers [ng/mL] in hyperthyroidism*

Rycina 2. *D-dimery [ng/mL] w nadczynności tarczycy*

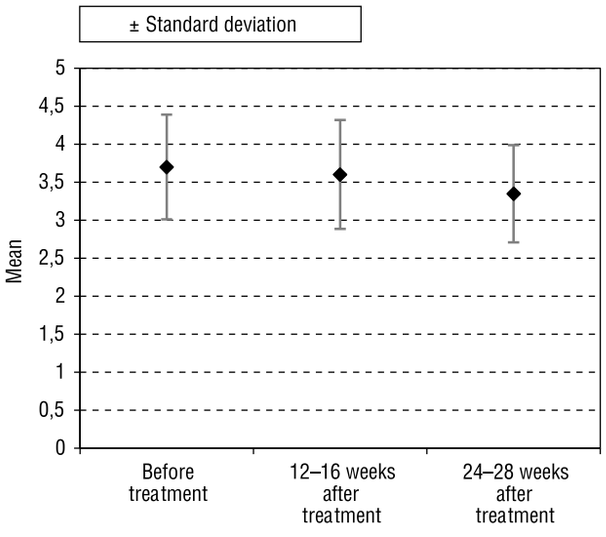

Figure 3. *Fibrinogen [g/L] in subclinical hyperthyroidism*

Rycina 3. *Fibrynogen [g/L] w subklinicznej nadczynności tarczycy*

TPO antibodies level measured at the same time ($r = –0.19$, $p < 0.01$; $r = –0.2$, $p < 0.01$).

The mean plasma fibrinogen and D-dimers levels in 15 women with overt hyperthyroidism are presented in Figures 5 and 6.

Analysis revealed no association between TSH, fT4, fT3 and fibrinogen.

D-dimers plasma level before radioiodine therapy was inversely correlated with TSH level ($r = –0.13$, $p < 0.01$), positively correlated with fT4 level ($r = 0.4$, $p < 0.01$) and did not correlate with fT3 level ($r = 0.09$,

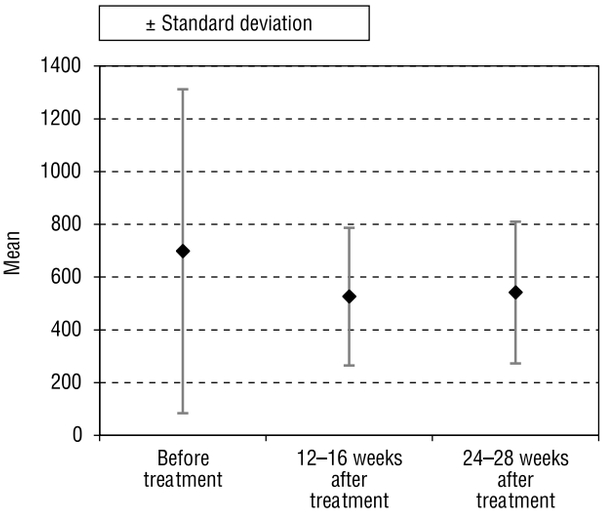

Figure 4. *D-dimers [ng/mL] in subclinical hyperthyroidism*

Rycina 4. *D-dimery [ng/mL] w subklinicznej nadczynności tarczycy*

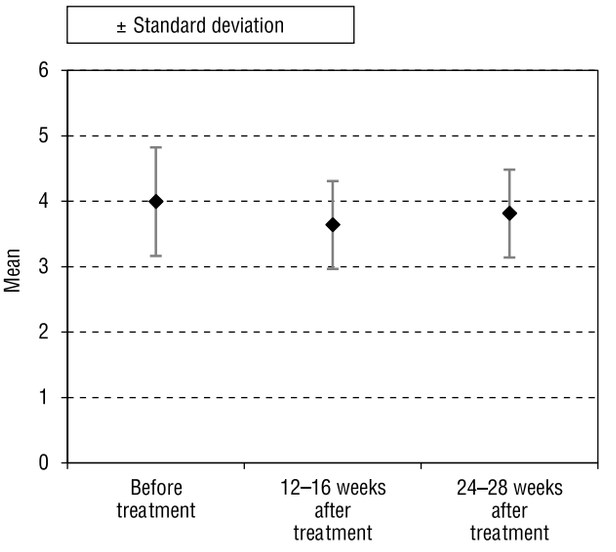

Figure 5. *Fibrinogen [g/L] in overt hyperthyroidism*

Rycina 5. *Fibrynogen [g/L] w jawnej klinicznie nadczynności tarczycy*

$p < 0.01$). Both plasma fibrinogen and D-dimers levels were correlated with TPO antibodies level (Tables I, II).

The difference in plasma fibrinogen and D-dimers levels between women with hyperthyroidism, subclinical hyperthyroidism and overt hyperthyroidism was statistically non-significant. Analysis revealed no correlation between fibrinogen, D-dimers level and dose of radioiodine.

Discussion

The aim of our study was to investigate changes in coagulation and fibrinolysis in various types of hyperthyroidism. Our data showed plasma fibrinogen level in the upper laboratory range in subjects before treatment, which was in agreement with previous studies. The same results were obtained by Burggraaf et al. [14]. In their study on endothelial function in patients with hyperthyroidism, they found that fibronectin and fibrinogen levels were increased. Erem et al. investigated

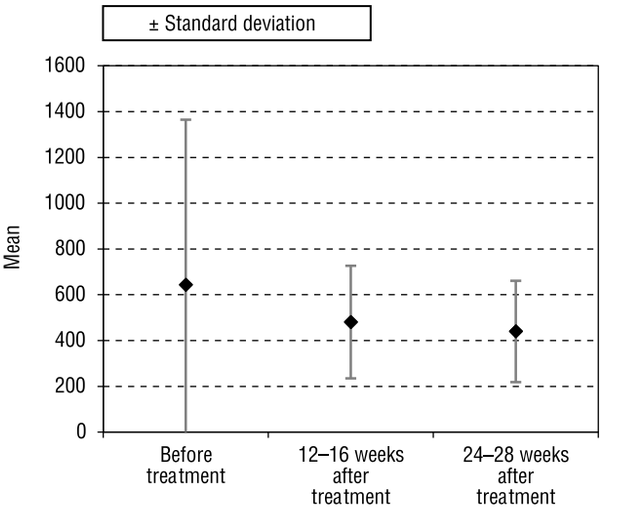

Figure 6. *D-dimers [ng/mL] in overt hyperthyroidism*

Rycina 6. *D-dimery [ng/mL] w jawnej klinicznie nadczynności tarczycy*

Table I. ***Correlation between fibrinogen and anti-TPO in overt hyperthyroidism***

Tabela I. ***Korelacja pomiędzy fibrynogenem a anty-TPO w jawnej klinicznie nadczynności tarczycy***

	TPO antibodies 1	TPO antibodies 2	TPO antibodies 3
FIBRINOGEN 1	r = 0.007, p = 0.01	No calculation	No calculation
FIBRINOGEN 2	r = –0.29, p = 0.05	r = –0.25, p = 0.001	No calculation
FIBEINOGEN 3	r = –0.02, p = 0.05	No calculation	r = 0.29, p = 0.05

Table II. *Correlation between D-dimers and anti-TPO in overt hyperthyroidism*
Tabela II. *Korelacja pomiędzy D-dimerami a anty-TPO w jawnej klinicznie nadczynności tarczycy*

	TPO antibodies 1	TPO antibodies 2	TPO antibodies 3
D–DIMERS 1	$r = -0.24$, $p < 0.05$	No calculation	No calculation
D-DIMERS 2	$r = -0.18$, $p < 0.01$	$r = 0.08$, $p < 0.001$	No calculation
D-DIMERS 3	$r = -0.25$, $p < 0.05$	No calculation	$r = -0.34$, $p < 0.05$

coagulation and fibrinolysis and proved significantly increased fibrinogen in hyperthyroid patients compared to euthyroid controls [13]. Lippi et al. found high fibrinogen values in outpatients with hyperthyroidism [23]. Dörr et al. revealed elevated plasma fibrinogen levels in subjects with decreased serum TSH [24].

In our study, we observed that fibrinogen level decreased after radioiodine therapy. We found no association between plasma fibrinogen level and dose of radioiodine, which may suggest that this effect depends on restoring normal thyroid function rather than the dose of radioiodine. Our findings are consistent with Burggraaf et al.'s and Marongiu et al.'s observation. In Burggraaf's study, fibrinogen level returned to normal after treatment with thiamazol [14]. Marongiu et al. investigated fibrinogen levels first in Graves' disease and then in hyperthyroid patients before and after treatment [15, 16]. It was elevated in hyperthyroidism and returned to normal values after restoring euthyroidism.

The severity of thyroid dysfunction may have a significant influence on the haemostatic balance. Hypothyroidism is generally associated with bleeding tendency [5, 25–27]. However, it has been suggested that the risk for thrombosis may be increased in subclinical or moderate hypothyroidism, as is the risk for haemorrhage in overt hypothyroidism [1, 28, 29]. In hyperthyroidism, a tendency toward thrombosis has been observed [1]. Some authors have underlined that there is still little data available on coagulation and fibrinolysis in subclinical hypothyroidism and hyperthyroidism [2].

To evaluate changes in plasma fibrinogen level according to severity of thyroid disease, subjects were divided into two groups: subclinical hyperthyroidism and overt hyperthyroidism. In both groups, plasma fibrinogen levels were elevated. The same conclusions were drawn from systematic review of thyroid dysfunction and effects on coagulation and fibrinolysis by Squizzato et al. and from a brief report on the association between thyrotropin and fibrinogen, in which Dörr et al. focused on subclinical hyperthyroidism [5, 24].

Our data, obtained for subclinical hyperthyroidism, confirmed decreasing plasma fibrinogen after radioiodine therapy during the whole observation. In overt hyperthyroidism, lower plasma fibrinogen level was observed only at first measurement after radioiodine therapy.

We decided to measure fibrinogen and D-dimers levels twice after treatment in order to confirm that observed changes are not transient. In the study by Burgraaf et al., fibrinogen level was measured after one week of treatment with propranolol, and after therapeutic treatment with thiamazol, when it returned to normal [14].We did not find data on repeated D-dimer measurements in other authors. In Squizzato et al.'s article, fibrinogen and D-dimer levels were measured only once after treatment [5].

Our data revealed no association between TSH, fT4, fT3 and fibrinogen. This is inconsistent with Debeij et al.'s and Chadevarian et al.'s results [30, 31]. They reported that increasing fibrinogen level was associated with rising levels of T4 and fT4. However, Yango et al. demonstrated that recombinant human TSH administration had no effect on haemostatic parameters [32].

Plasma D-dimers level was also investigated in these three groups. It was higher before treatment, and then decreased in the hyperthyroidism group. After dividing into groups, results missed statistical significance, what may suggest that severity of thyroid disease is only one of the possible factors contributing to the coagulation-fibrinolytic balance. Our results contradict the findings of Chadevarian et al. [30]. They studied the fibrinolytic system in hypothyroid patients, and obtained different results according to the severity of hypothyroidism: higher levels of D-dimer in overt hypothyroidism and lower levels of D-dimer in moderate hypothyroidism. This issue has not been extensively investigated yet.

In subjects with overt hyperthyroidism, TSH and fT4 correlated with plasma D-dimers level before treatment. There was positive correlation for fT4 and negative for TSH. D-dimers level did not depend on fT3. These results are inconsistent with previous observations. Chadarevian et al. observed a negative correlation between D-dimers and fT4, but they investigated patients with hyperlipidaemia who did not present symptoms of

thyroid disease [33]. Horne et al. found no changes in D-dimers level in thyroid cancer patients on thyroid hormone suppression therapy when they were hypothyroid and hyperthyroid [22].This discrepancy may result from heterogeneity of the investigated groups — the presented studies did not concern D-dimers and fT4 in endogenous hyperthyroidism.

Both abnormal thyroid function and autoimmunity may modify haemostasis [1, 17]. Some concomitant autoimmune disorders involving the coagulation system have been described in thyroid dysfunction of autoimmune pathogenesis [3]. Panzer et al. investigated patients with hyperthyroidism and low platelet count [6]. They found platelet-associated antibodies in three out of 15 subjects and suggested that platelet abnormalities are due to metabolic rather than immunological processes. Petri et al. studied the prevalence of antiphospholipid antibodies in autoimmune thyroid disorders and in healthy individuals [34]. They found the same incidence of these antibodies in both groups. In another study, Marongiu et al. described a factor VIII inhibitor in Graves' disease [35]. The same result was obtained by Sievert et al. [36]. They confirmed an association between autoimmune thyroid disease and other autoimmune disorders. However, Porter et al. suggested that the presence of these antibodies may be the nonspecific mediator of immune system activation [12]. Contradictory results were presented by Cordiano et al. [37]. They reported that in 15 out of 18 patients with hyperthyroidism (Hashimoto's thyroiditis and Graves' disease) and thrombocytopenia, platelet autoantibodies were found. Hofbauer et al. and Suigmoto et al. revealed that restoring euthyroidism by antithyroid drug therapy caused remission of coagulation disorder [38, 39].

Marongiu et al. confirmed that antiphospholipid antibodies were more common in Graves' disease patients than healthy controls [29]. Another possible mechanism for thrombocytopenia in patients with hyperthyroidism is binding of antibodies (other than TSH receptor antibodies) to proteins located on the thrombocyte membrane [8].The literature data shows an association between autoimmune thyroid diseases and autoimmune coagulation disturbances, although they are more likely to be concomitant disorders rather than caused by autoimmune thyroid disease [3].

However, Erem reported that an excess or a deficiency of thyroid hormones affects the coagulation-fibrinolysis balance [1]. Squizatto et al. suggested that autoimmune mechanisms rarely contribute to this balance [5]. Shih et al. explained the role of thyroid hormone in the synthesis of blood clotting factors [19].They exert their effect through nuclear thyroid hormone receptors in hepatocytes. Erem et al. suggested that the coagulation and fibrinolysis processes in hyperthyroidism are regardless of the aetiology [13]. They observed the same changes in haemostasis despite different pathogenesis of thyroid disease.

In order to determine the role of thyroid autoimmunity in processes of haemostasis, we evaluated the association between fibrinogen, D-dimers and anti-TPO as indicators of underlying autoimmune processes. In a previous study Dörr et al. proposed that autoimmune thyroid disease might be responsible for an elevated level of inflammatory plasma proteins [24]. Erem et al. supplemented the hypothesis that autoimmune processes modify haemostasis [1]. Some reports denied such an association, i.e. Squizzato et al. postulated that the hypercoagulable state does not depend on the underlying pathophysiology of thyroid disease [5].

In subjects with hyperthyroidism, we observed a negative correlation between TPO antibodies level before treatment and plasma fibrinogen level measured at the same time. Similar correlation was found in subclinical and overt hyperthyroidism groups. In addition, the positive correlation between plasma fibrinogen level and TPO antibodies measured the second time after treatment in the overt hyperthyroidism group suggests that the influence of autoimmunity on the coagulation-fibrinolytic system may be modified by other factors such as mode of treatment or severity of disease. Such a relation has not been discussed previously.

When D-dimers were considered in subjects with hyperthyroidism, a negative correlation was found between plasma D-dimers level measured the second time after radioiodine therapy and TPO antibodies measured before treatment. In subclinical and overt hyperthyroidism, a negative correlation was observed for measurements before and after treatment in different combinations. In contrast, no correlation was observed for the first measurement after treatment in the overt hyperthyroidism group, which may also support the hypothesis that other factors also exert an effect on haemostasis. There is no data available to compare with these results. However, the number of patients with autoimmune hyperthyroidism was very small.

Despite statistically important differences between fibrinogen and D-dimer level in patients with hyperthyroidism before and after treatment, the clinical importance of these changes is still being discussed.

Abnormalities of haemostasis range from subclinical laboratory findings to clinically significant disorders of haemostasis and, rarely, major thromboembolism [1, 3]. They are usually of limited consequence in clinical practice [2]. However, major emboli may account for 18% of deaths associated with thyrotoxicosis and

the incidence of arterial thromboembolism is approximately 8–40% [11, 13]. The risk for thrombosis due to hypercoagulability increases in clinical hyperthyroidism [1, 23]. In our study, none of the patients presented with symptoms of thrombotic complications.

Conclusion

Hyperthyroidism exerts an effect on the coagulation-fibrinolytic balance. It affects plasma fibrinogen and D-dimers level. We found fibrinogen in the upper reference range and elevated D-dimers that decreased after treatment. This association depends on autoimmunity and severity of thyroid disease — the strongest relationship is observed in overt hyperthyroidism. However, the number of cases was small, especially after dividing into subgroups. Thus, further studies are needed for a better understanding of these relations and for their quantitative ratio.

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