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ORIGINAL ARTICLE

Evaluation of Platelet Functions in Patients with Hashimoto's Thyroiditis Versus Healthy Controls: a Cross-Sectional Analysis

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SUMMARY

Background: **To evaluate platelet functions in patients with Hashimoto's thyroiditis (HT) versus healthy controls.**
Methods: **Seventy-five patients with HT and 29 healthy controls were included in this study. Age, serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), anti-thyroglobulin (anti-Tg) antibody and anti-thyroid peroxidase (anti-TPO) antibody, platelet count, *in vitro* platelet aggregation and ATP release reaction tests were recorded and compared between HT and control groups.**
Results: **Median (IQR) serum levels for TSH (p = 0.001), anti-TPO (p = 0.001), and anti-Tg (p = 0.001) antibodies were significantly higher, while FT4 levels (p = 0.005) were significantly lower in patients with HT than in controls. Patients had lower levels of ADP-induced platelet aggregation (p = 0.05) and lower ristocetin-induced ATP release activity (p = 0.05) compared to controls. Platelet count was positively correlated with serum FT4 levels (r = 0.27, p < 0.05).**
Conclusıons: **We found decreased ADP-induced platelet aggregation and ristocetin-induced platelet release activity as well as a positive correlation of platelet count with FT4 levels in patients with HT. Our findings support the role of thyroid hormone status and autoimmunity in the association between HT and platelet aggregation and secretion functions.**
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INTRODUCTION

Hashimoto's thyroiditis (HT) is the most common cause of primary hypothyroidism. Although more frequently accompanied with euthyroid status or mild hypothyroidism, it can also be associated with thyroid failure in up to 10% of cases.
Thyroid dysfunction, excessive or deficient thyroid hormones and thyroid autoimmunity, has been suggested to affect hemostasis [1,2]. Hypothyroidism has generally

been known to be associated with a tendency to bleeding, although hemostatic profile has been suggested to change from bleeding to thromboembolism depending on the severity of the disease. Research concerning the association of thyroid dysfunction and hemostasis has mainly been focused on the coagulation and fibrinolytic systems rather than primary hemostasis [3].

Platelets are to stop bleeding by clumping and clotting blood vessel injuries. Their main function is to provide primary hemostasis. They gather around interrupted endothelium, attach to substances outside and plug the hole: adhesion. They change shape, turn on receptors and secrete the contents of their dense granules: activation. They connect to each other through receptor bridges: aggregation. Platelet functions are interpreted with platelet aggregation and ATP release (secretion) tests by inducing agonists such as collagen, epinephrine, arachidonic acid (AA), adenosine diphosphate (ADP), thrombin, and ristocetin. These agonists are classified as strong (collagen, AA, thrombin, etc.) or weak (ADP, epinephrine, etc.). All directly stimulate platelet aggregation while strong agonists directly induce platelet granule secretion. Generally, platelet function testing is requested in the clinical evaluation of patients with hereditary bleeding problems. Also, these tests help to follow up antiplatelet medication and platelet hyperactivity for research purpose [4,5]. Platelet function defects have been considered to be associated with impaired intracellular signaling pathways and platelet secretion secondary to a number of medical conditions rather than classic platelet function disorders in most of the patients with acquired platelet dysfunctions [6].

Direct action of thyroid hormones on human platelet aggregation was confirmed *in vitro* via inhibition of the phosphorylation of a 20-kd protein and competitive inhibition of myosin light-chain kinase [7-9]. Nonetheless, use of platelet function tests in diseases, except hereditary hematologic diseases, is a fairly recent application. There is limited data available on the relationship between the platelet dysfunction and thyroid diseases. The present study was designed to evaluate *in vitro* platelet functions in patients with HT versus controls.

MATERIALS AND METHODS

Overall, 75 patients with HT (n = 46, 39.6 ± 11.9 years) and controls (n = 29, 36.2 ± 10.8 years) were included in this cross-sectional single-visit study. Receiving thyroid hormone replacement therapy, anti-thyroid medication or any medication likely to affect hemostasis (acetylsalicylic acid, dypridamole, ticlopidine, etc.), and having a history of thromboembolic disease, familial hyperlipidemia, severe systemic diseases, and autoimmune hematologic disease (thrombocytopenia, hemolytic anemia, etc.) were the exclusion criteria of the study. The study protocol was approved by the local ethics committee. All patients gave informed consent before participation.

Age, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), anti-thyroglobulin antibody (anti-Tg) and anti-thyroid peroxidase antibody (anti-TPO), platelet count, platelet aggregation, and ATP release reaction tests were recorded in all participants and compared between HT and controls. HT were further analyzed with respect to thyroid status, euthyroid (TSH, FT3, FT4 were in normal range) and subclinical hypothyroidism (TSH ≥ 5 mIU/mL, FT3, FT4 were in normal range).

Diagnosis of HT was based on increased serum anti-TPO and/or anti-Tg antibodies and hypo-echogenic pattern on thyroid ultrasonography.

Venous blood samples were collected in the morning after an overnight fast. Serum levels for FT3, FT4, TSH, anti-TPO, and anti-Tg were determined using a chemiluminescence assay method (Beckmann-Coulter DXI system, USA). Platelet count was calculated using the automatic hemocytometer machine (LH-780, Beckman Coulter, USA).

For the platelet aggregation test, 9 mL venous blood was transferred into two standard tubes, each containing 1 mL of a 0.109 M trisodium citrate solution. The aggregometer (Chrono-Log Corporation, Havertown, PA, USA) was used to measure platelet aggregation. The platelet agonist reagents used in this study included collagen (2 μg/mL), epinephrine (5 μM), arachidonic acid (AA, 0.5 mM), adenosine diphosphate (ADP, 5 μM), thrombin (30 μL), and ristocetin (1.25 mg/mL).

During the same analysis, blood samples were also analyzed for the ATP release reaction from platelet dense granules via lumi-aggregometer (Chromolume, Chrono-Log Corporation) following the addition of the same platelet agonist reagents used in the aggregation test. Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk and Levene tests were used to determine distribution and homogeneity of variables. The differences between control and patient groups were compared by Student's *t*-test or Mann Whitney *U* tests. The differences in means among groups were analysed by using one-way ANOVA or Kruskal-Wallis tests. Pearson's correlation test was used for correlation analysis. Data were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR). $p < 0.05$ was considered statistically significant.

RESULTS

Serum TSH [3.71 (6.32) mIU/mL vs. 1.40 (1.26) mIU/mL, p = 0.001], anti-TPO [1,300.0 (1,071.9) U/mL vs. 43.5 (13.0) U/mL, p = 0.001] and anti-Tg [188.0 (197.4) U/mL vs. 25.4 (15.9) U/mL, p = 0.001] were significantly higher, while FT4 levels (0.91 ± 0.20 ng/dL vs. 1.03 ± 0.17 ng/dL, p = 0.005) were significantly lower in HT patients than in controls. No significant difference was noted between patients and controls in terms of age and platelet count (Table 1).

Table 1. Data on age, platelet count, and thyroid function tests in study groups.

	Hashimoto's thyroiditis			Controls (n = 29)	p-value all patients vs. control	p-value hypothyroid vs. euthyroid vs. control
	Subclinical hypothyroidism (n = 21)	Euthyroid (n = 25)	All (n = 46)			
Age (year)	42.0 ± 14.5	37.7 ± 9.1	39.6 ± 11.9	36.2 ± 10.8	0.213 [a]	0.211 [a]
Platelet (x 10^3/L)	245.4 ± 57.7	249.3 ± 55.8	247.5 ± 56.1	249.6 ± 48.0	0.870 [a]	0.957 [b]
TSH (0.35 - 5.0 mIU/mL)	8.35 (7.55)	2.10 (1.35) [*]	3.71 (6.32)	1.40 (1.26) [*]	0.001 [b]	0.001 [b]
FT_3 (2.3 - 4.2 pg/mL)	3.00 (0.69)	3.21 (0.35)	3.20 (0.51)	3.20 (0.58)	0.366 [b]	0.291 [b]
FT_4 (0.7 - 1.76 ng/dL)	0.82 ± 0.22	0.97 ± 0.16 [*]	0.91 ± 0.20	1.03 ± 0.17 [*]	0.005 [a]	0.001 [a]
Anti-TPO (0 - 60 U/mL)	1,300.9 (1,048.7) [+]	706.9 (1,082.7) [+]	1,300.0 (1,071.9)	43.5 (13.0)	0.001 [b]	0.001 [b]
Anti-Tg (0 - 60 U/mL)	190.1 (341.3) [+]	177.1 (197.6) [+]	188.0 (197.4)	25.4 (15.9)	0.001 [b]	0.001 [b]

[a] - Student's *t*-test and [b] Mann-Whitney *U*-test for "patient vs. control" analysis.
[a] - ANOVA test and [b] Kruskal-Wallis test for "hypothyroid vs. euthyroid vs. control" analysis.
Values are expressed as mean ± SD or median (interquartile range).
[*] - $p < 0.001$; compared to subclinical hypothyroidism.
[+] - $p < 0.001$; compared to control.

Table 2. Agonist-induced platelet aggregation in study groups.

	Hashimoto's thyroiditis			Controls (n = 29)	p-value all patients vs. control	p-value hypothyroid vs. euthyroid vs. control
	Subclinical hypothyroidism (n = 21)	Euthyroid (n = 25)	All (n = 46)			
Arachidonic acid (0.5 mM)	71.00 (7.50)	76.00	74.50	75.00	0.836 [b]	0.104 [b]
Adenosine diphosphate (5 µM)	68.00 (12.50)	65.00	66.00	73.00	0.012 [b]	0.030 [b]
Epinephrine (5 µM)	65.00 (44.00)	64.00	65.00	71.00	0.175 [b]	0.345 [b]
Collagen (2 µg/mL)	75.00 (14.00)	76.00	75.00	75.00	0.254 [b]	0.414 [b]
Thrombin (30 µL)	87.71 ± 7.36	88.60 ±	88.20 ±	88.45 ±	0.851 [a]	0.855 [a]
Ristocetin (1.25 mg/mL)	88.00 (10.50)	88.00	88.00	91.00	0.200 [b]	0.425 [b]

[a] - Student *t*-test and [b] Mann-Whitney *U*-test for "patient vs. control" analysis.
[a] - ANOVA test and [b] Kruskal-Wallis test for "hypothyroid vs. euthyroid vs. control" analysis.
Values are expressed as mean ± SD or median (interquartile range).
[*] - $p < 0.01$; compared to control.

Except for significantly lower level of ADP-induced platelet aggregation [66.00 (21.25%) vs. 73.00 (21.00%), $p < 0.05$] in HT patients than in controls, no significant difference was noted between the two groups in terms of agonist induced platelet aggregation. ADP-induced platelet aggregation was significantly lower in euthyroid HT patients [65.00 (23.00%) vs. 73.0 (21.0%), $p < 0.01$] but not in the subclinical hypothyroid group as compared with controls, while no significant difference was noted in ADP-induced aggregation with respect to thyroid status (Table 2).

Based on the significantly lower ristocetin-induced ATP

Table 3. Agonist-induced platelet ATP release activity in study groups.

	Hashimoto's thyroiditis			Controls (n = 29)	p-value all patients vs. control	p-value hypothyroid vs. euthyroid vs. control
	Subclinical hypothyroidism (n = 21)	Euthyroid (n = 25)	All (n = 46)			
Arachidonic acid (nmol)	1.12 (1.02)	1.01	1.06	0.88	0.107 [b]	0.259 [b]
Adenosine diphosphate (nmol)	0.51 (0.98)	0.48	0.50	0.93	0.078 [b]	0.169 [b]
Epinephrine (nmol)	0.53 (0.79)	0.69	0.59	0.75	0.139 [b]	0.165 [b]
Collagen (nmol)	1.15 (0.79)	1.12	1.14	1.15	0.736 [b]	0.934 [b]
Thrombin (nmol)	0.88 ± 0.49	1.04 ±	0.99 ±	0.92 ±	0.679 [a]	0.515 [a]
Ristocetin (nmol)	0.43 (0.80) **	0.61	0.54	1.23	0.006 [b]	0.018 [b]

[a] - Student's *t*-test and [b] Mann-Whitney *U*-test for "patient vs. control" analysis.
[a] - ANOVA test and [b] Kruskal-Wallis test for "hypothyroid vs. euthyroid vs. control" analysis.
Values are expressed as mean ± SD or median (interquartile range).
* - $p < 0.05$ and ** - $p < 0.01$; compared to control.

Table 4. Correlation between platelet count and thyroid function parameters.

	Platelet count	
	r	p
TSH (mIU/mL)	-0.154	0.186
FT_3 (pg/mL)	0.002	0.985
FT_4 (ng/dL)	0.270	0.019
Anti TPO (U/mL)	0.005	0.966
Anti Tg (U/mL)	0.014	0.904

r - correlation coefficient, Pearson's correlation analysis.

release activity [0.54 (0.67) nmol vs. 1.23 (1.51) nmol, $p < 0.05$] in HT patients compared to controls, no significant difference was noted between study groups in point of agonist induced platelet release activity. Ristocetin-induced ATP release was significantly lower in both hypothyroid and euthyroid HT patients compared to the control group [0.43 (0.80) nmol vs. 0.61 (0.60) nmol vs. 1.23 (1.51) nmol; $p < 0.05$ and $p < 0.01$, respectively]. It was similar between hypothyroid and euthyroid patients ($p = 0.018$) (Table 3).

Platelet count was positively correlated with serum FT4 levels ($r = 0.27$, $p = 0.019$), while no significant correlation of platelet count was noted with TSH, FT3, anti-TPO or anti-Tg levels (Table 4).

DISCUSSION

Platelets are basic factors of primary hemostasis. Although platelet count is a routine test, platelet function tests are not commonly used in clinical practice. In this study, we showed that platelet count was unchanged, but ADP-induced platelet aggregation and ristocetin-induced platelet release activity were impaired in HT. Alteration in platelet count in thyroid disorders is associated with metabolic state resulting from excess or deficient thyroid hormone. Hyperthyroidism results in accelerated platelet turnover and shortened platelet survival, whereas severe hypothyroidism causes bone marrow myxedema associated megakaryocytopoiesis resulting in low platelet count [2]. In literature, decreased, increased or unaffected platelet counts were detected in hypothyroid status [10].

Thyroid autoimmune disorders have also been associated with decreased platelet count within the context of autoimmune polyendocrinopathies. Increased peripheral platelet consumption mediated by autoimmune factors leads to bleeding disorders [11,12]. Autoimmune derived platelet dysfunction is more frequently observed in Graves' disease, while hypothyroidism is associated with acquired reduction in von Willebrand factor protein synthesis due to insufficient thyroxine levels, which is reversible after thyroid hormone replacement therapy [12,13].

Our study expressed significant differences in FT4, TSH, and thyroid antibodies between HT and control groups. Although TSH levels were significantly higher and FT4 levels were significantly lower in patients with HT than in controls, thyroid hormones in patients were still within normal ranges. Therefore, the patient group is relatively hypothyroid compared to control. Our findings indicate no abnormality in platelet count in patients compared to control subjects, supporting the generally accepted notion that platelet count remains unaffected and within the normal range in hypothyroidism and HT [2,10,14,15].

We found a positive correlation of platelet count with FT4 levels in the correlation analysis. The association between immune trombocytopenia and autoimmune thyroid disease has been described in various case reports and research. A low platelet count may also develop into hypothyroidism due to autoimmune peripheral platelet consumption and inhibited megakaryocytopoiesis [16,17]. Our findings emphasize the likelihood of decreased platelet counts in cases of overt hypothyroidism and thus the risk of bleeding disorders in patients with HT.

A few experimental studies have shown that adhesion and aggregation functions of platelets were affected from thyroid hormone status. Depression of platelet aggregability has been reported in hypothyroid rats. Also, Gardikas et al. observed that hypothyroid subjects have weak platelet aggregation in the presence of ADP, epinephrine, and a connective tissue extract [10,18]. Masunaga et al. investigated platelet aggregation tests with ADP and collagen reagents in 14 patients with Graves' disease, 12 with HT and 3 with idiopatic hypothyroidism. They noted that ADP-induced platelet aggregation was lower in patients with untreated Graves' disease, while comparatively increased in patients with untreated primary severe hypothyroidism. Authors also reported a significant inverse correlation between the extent of platelet aggregation and plasma levels of thyroid hormones, which became normal on achievement of euthyroid status after administration of anti-thyroid drugs or thyroid hormone [7]. Myrup et al. reported significantly longer bleeding time and decreased agglutination response to ristocetin in untreated hypothyroid patients [19]. In another study, ristocetin, as well as collagen and epinephrine induced platelet reactivity was reported to be impaired in patients with acquired hypothyroidism after a total thyroidectomy and was normalized during L-thyroxine treatment [20].

Platelets play a role not only in hemostasis-thrombosis events but also in intercellular communication, inflammation, and immunomodulatory activity. Impaired platelet functions may contribute to the pathogenesis of different diseases such as cardiac, pulmonary, cerebral ones. Currently, research studies were conducted on this subject. On the basis of these results it is suggested that platelet function tests may increasingly be used for monitoring efficacy of antiplatelet therapy, predicting the adverse effect of therapy, and following symptoms of diseases [21-23]. Additionally, association between autoimmune thyroid diseases and platelet function has been known to be dependent on the status of thyroid hormones along with a change in hemostatic profile from bleeding to thromboembolism in hypothyroidism, and this state depends on the severity of the disease [24]. The point that needs to be explained is which step and how the hemostasis is affected in thyroid dysfunction.

In this study, we found ADP-induced platelet aggregation was lower in HT patients compared to control groups and similar in the subclinical hypothyroid subgroup and control groups. The platelet aggregation tests induced by agonists other than ADP were similar between patients and control groups. It also revealed lower ristocetin-induced ATP release reactions in patients with HT. The reduction was not noted in platelet release activity induced by agonists other than ristocetin. We did not observe a significant reduction in ristocetin-induced ATP release activity in between subclinical hypothyroid and euthyroid sub-groups. Our findings emphasize that euthyroid and without severe hormone deficiency hypothyroid status appear to have different effects on platelet aggregation and secretion functions in primary hemostasis. Data in our paper support the notions that platelets have more sensitive and more remarkable correlation coefficients to aggregation induced by ADP and ristocetin-induced ATP release reactions in HT. Besides, as previously mentioned, TSH levels of our patients with HT were subclinical and comparatively hypothyroid compared to control group. If there was a more severe hypothyroid group in our study, platelet function tests with other reagents could show significant differences. We hope that these findings may throw light on hemostasis in autoimmune HT. Although a tendency to bleeding is well-known to be associated with overt hypothyroidism, a limited number of studies show *in vitro* platelet function tests in heterogen hypothyroid groups (post-operative, idiopathic) [23, 25]. We did not find any specific research about the relationship between ATP release reaction and HT in the literature. Our study is one of a few on this topic. Also, the advantage of the present study compared to others is that the subject group was larger and we used more reagents (6 vs. 2).

On the other hand, the present study has some limitations. It could be that the high sample size might prevent us from achieving statistical significance concern-

ing agonist-induced platelet function in HT and to reveal the exact role of thyroid status in assessment of primary hemostasis. Also, we did not evaluate platelet aggregation and ATP release activity tests after thyroxine therapy, which could give additional information about platelet functions. However, our findings might represent a contribution to the literature, because limited data is available on the relationship between HT (euthyroid and/or hypothyroid subgroups) and platelet aggregation and secretion functions tests.

CONCLUSION

Our findings revealed impaired ADP-induced platelet aggregation and ristocetin-induced platelet release activity and positive correlation of platelet count with FT4 levels in patients with HT. These results emphasize the potential effect of different thyroid hormone status and autoimmunity on platelet dysfunction and bleeding tendency in HT. Further larger scale studies are needed to determine the association of platelet dysfunction with thyroid autoimmune disorders and to address the utility of platelet function tests in clinic practice.

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Declaration of Interest:
The authors declared no potential conflicts of interest.

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