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Platelet Function in Overt Hypothyroidism

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Abstract:

BACKGROUND: Hypothyroidism is associated with a shift of the hemostatic system to a hypocoagulable state and inhibited platelet function. However, previous studies did not consider the different degrees of response to thyroxine treatment and its effect on platelet function. This raises the need for further studies to clarify the effect of different degrees of responses to treatment on platelet function in hypothyroid disease.

OBJECTIVES: To characterize the abnormalities in the primary hemostasis (platelet adhesion and aggregation) in patients with overt hypothyroidism on L-thyroxine therapy and to study the effect of variation of the responses to treatment on platelet function.

MATERIALS AND METHODS: This cross-sectional study includes 64 patients with overt hypothyroidism on L-Thyroxine treatment. The patients were divided into three groups according to their response to treatment. Group-I: euthyroid patients (ET) (*n* = 25): (normal thyroid-stimulating hormone [TSH] and free T4), Group II: subclinical hypothyroid (SH) (*n* = 22): (high TSH and normal free T4), and Group III: inadequately treated hypothyroid (IH) (*n* = 17) (high TSH and low T4). Platelet function was assessed by light transmissiom aggregation response to adenosine diphosphate (ADP), arachidonic acid (AA), epinephrine (EPN), collagen, and ristocetin and by the platelet function analyzer (PFA-100) closure times (CTs).

RESULTS: Platelet aggregation responses showed a significant reduction to ADP in ET patients (42.9 ± 20.7), SH patients (41.8 ± 24.2), and IH patients (46.9 ± 20.1) and to risocetin in ET patients (62.9 ± 22.8), SH patients (62.6 ± 21.2), and IH patients (61.3 ± 14.6) as compared to the controls (59.1 ± 9.5) and (75.3 ± 6.9), respectively. There is a significant prolongation of C/EPN: (175.6 ± 82.5) in the IH patients as compared to the controls (141.6 ± 26.8). Significant prolongation of C/ADP CT (132.2 ± 72.5) in IH patients as compared to the controls (100.7 ± 24.1) was found with normalization of both CT in ET patients.

CONCLUSIONS: In overt hypothyroidism using two different tests of platelet function, we confirmed that the existence of a hypocoagulable state is due in part to a defect in primary hemostasis. Moreover, the defect varies according to the degree of response to L-Thyroxine treatment; it is more pronounced in inadequately treated hypothyroid patients and less in the subclinical hypothyroid.

Keywords:

Adenosine diphosphate, hypothyroidism, platelet function analyzer-100, platelet aggregation, platelet function tests, ristocetin

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Introduction

The thyroid gland is responsible for the secretion of the thyroxine hormones, T3 and T4. At the tissue level, T4 becomes activated into the more physiologically active triiodothyronine (T3). T3 regulates metabolism, growth, development, and body temperature. The thyroid activity is controlled by the pituatry hormone thyroid-stimulating hormone [TSH].[1] Thyroid disorders have variable clinical presentations including hypothyroidism, hyperthyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism. Hypothyroidism is failure of thyroid gland to produce thyroid

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hormone. The biochemical profile of overt primary hypothyroidism is elevated TSH, low free T4, and low free T3 levels, while in subclinical hypothyroidism, there is high TSH with normal level of free T4 and T3.[2]

Thyroid diseases such as subclinical or overt thyroid dysfunctions are associated with disturbances of the major components of the hemostatic system: coagulation, fibrinolysis and platelet function.[3] In hypothyroidism, the low levels of thyroid hormones result in a shift of the hemostatic system to a hypocoagulable and hyperfibrinolytic state[4] and hemostatic disturbances ranging from deranged hemostatic laboratory tests to clinically manifested haemorrhagic features.[5]

Attempts to unreveal the pathophysiological mechanism of these hemostatic abnormalities generated many diverse findings. Some authors reported drop in the blood levels of FVII, FVIII, FIX, FX, FXI, and FXII,[5-7] while others found hemostastatic abnormality resembling acquired von Willebrand disease as being the most frequent coagulation disorder in hypothyroidism.[8] This would explain why most patients with hypothyroidism are at increased risk of bleeding ranging from mild mucocutaneous bleeding (e.g., nose or gingival bleeding, menorrhagia, and easy bruising) to a severe posttraumatic or postsurgical bleeding.[3]

Platelet aggregation is a central process in primary hemostasis. Nonetheless, platelet function abnormalities in hypoyhroidism have not yet been well characterized. A few previous studies reported decreased platelet aggregation and agglutination in hypothyroidism;[9,10] however, these results remain inconclusive and await confirmation.

Another widely used test of platelet function is the platelet function analyzer (PFA-100), which has replaced the bleeding time as a test of primary hemostasis.[11] Its use to asses primary hemostasis in hypothyroidism was scarce and only few reports were spotted on its use in patients with abnormal thyroid function. Homenick *et al*.[12] who evaluated the PFA 100 closure times (CTs) in patients with overt hypothyroidism, subclinical hypothyroidism, and overt hyperthyroidism found prolonged collagen-epinephrine (C/EPI) CT in hypothyroidism and shortened C/epinephrine (EPN) in hyperthyroidism. The second larger study in overt hypothyroidism revealed 56% and 50% prolongation of C/EPI and collagen/adenosine diphosphate (C/ADP) CT, s respectively, which were reversed by levothyroxine therapy.[13]

Other than the wide disagreements in the literature on platelet function in hypothyroidism, there was also hetrogenisity in the selection of patients and total disregard to the different degrees of response to thyroxine treatment of overt hypothyroidism and the possible effect of this phenomenon on platelet function. This opens the door for further studies to clarify the effect of different degrees of responses to treatment on platelet dysfunction in hypothyroid disease. Therefore, our objectives were (1) to characterize the abnormalities in the primary hemostasis (i.e., platelet adhesion and aggregation) in patients with overt hypothyroidism on replacement therapy with L-thyroxine and to find out the effect of different degrees of response to treatment on platelet function.

Materials and Methods

Patients

The study group consists of 64 patients with hypothyroidism; all were on L-thyroxine therapy. The patients were randomly selected from the Outpatient Endocrinology Clinic at King Khalid University Hospital, Riyadh, Saudi Arabi. The underlying cause of the hypothyroidism was Hashimotos disease. Eighty-eight age- and sex-matched euthyroid individuals served as controls. Patients were split into three groups according to their response to therapy, as follows:

- Group I: Euthyroid patients (n = 25): In these patients, TSH and T4 blood levels normalized after treatment with L-thyroxine and they were still on treatment
- Group II: Subclinical hypothyroid (n = 22): After treatment with L-thyroxine, these patients continued to show persistent elevation in TSH level with normal free T4 level while on treatment
- Group III: Inadequately treated hypothyroid (n = 17): This group is on treatment with L-thyroxine but still have abnormal thyroid function tests with an elevated levels of TSH and low free T4.

The exclusion criteria for entry into the study were cardiac, renal, hepatic, and other systemic diseases. None of the patients had a history of bleeding or blood coagulation disorders or had received anticoagulants. Body mass index was calculated as weight divided by height squared meter. The study protocol was approved by the Institutional Review Board (IRB) and written informed consent was obtained from all the subjects.

Laboratory analysis

Platelet aggregation studies

Venous blood samples were collected, directly into vacutainer tubes containing Sodium Citrate (0.129M) to give a blood: Citrate ratio of 9:1. Proper mixing of blood and anticoagulant was attained by gentle inversion and the samples were transported without delay (within 2 h of collection) to the Coagulation Laboratory, College of Medicine. The blood samples were centrifuged at 1000 rpm for 7 min to separate platelet-rich plasma (PRP), which was used for the platelet aggregation studies.

Aggregation was measured in response to ADP (20 µmol/l), collagen (0.19 g/l), AA (1.64 mmol/l), adrenaline (100 µmol/l), and ristocetin (1.5 g/l) (Bio/Data Corp. USA), as detailed before.[14] All these concentrations of agonists represent the final concentrations obtained by adding 20 µl of the aggregating agent to 180 µl of PRP. Aggregation was recorded in an Aggregation Profiler (PAP4, Bio/Data, USA), which registers the results of the aggregation responses as maximum aggregation (MA%) as well as slopes (S) of the aggregation curves.

Platelet function analyser-100 test

PFA-100 is a device that simulates an injured blood vessel, involving the formation of a thrombus under constant high shear rates (5000–6000/s). Citrated whole blood (800 µl) is aspirated through disposable test cartridges by the application of a constant vacuum. The PFA-100 tests were performed according to the instructions provided by the manufacturer (Dade-Behring Inc., Miami, Fl, USA). A microscopic (147 µ) aperture in the machine is fitted with replaceable disposable collagen-ADP (C/ADP) or collagen-epinephrine (C/EPI) coated cartridges. When blood comes in contact with the membrane, platelets are activated, adhere to the collagen in the cartridge, aggregate and form a plug. The formed platelet plug occludes the aperture, resulting in cessation of the blood flow. The instrument measures the time from the start of the test until the aperture is completely occluded and then registers the end point as the CT in seconds.

Biochemical tests including TSH, free T4, complete blood count (CBC), white blood cell (WBC), and lipid profile were obtained from patient medical records.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp., USA. Numerical data were presented as mean and standard deviation. One-Way ANOVA was used to compare laboratory parameters, platelet aggregation tests, and CTs between study groups. Tukey correction was used for multiple pairwise comparisons. A test with a $P < 0.05$ was considered statistically significant.

Results

Baseline clinical and demographic data of the 64 subjects [Table 1] did not show any significant differences for age and body mass index between the three study groups; euthyroid group, partially treated hypothyroidism (subclinical), and inadequately treated hypothyroidism for age and mean body mass index. However, for gender, females are more than males in all the groups. Thyroid function tests (TSH, free T4) are summarized in Table 2. Hemostatic parameters including CBC, WBC, lipid profile with normal reference ranges are given in Table 3.

Aggregation tests

Platelet aggregation responses to different agonists showed a significant reduction in platelet aggregation response to ADP in euthyroid group (42.9 ± 20.7), subclinical hypothyroidism (41.8 ± 24.2), and inadequately treated hypothyroidism (46.9 ± 20.1) as compared to the controls (59.1 ± 9.5); $P \leq 05$ [Figure 1]. Similarly, there is a statistically significant reduction in Ristocetin-induced platelet aggregation in euthyroid group (62.9 ± 22.8), subclinical hypothyroidism (62.6 ± 21.2), and inadequately treated hypothyroidism (61.3 ± 14.6) as compared to the controls (75.3 ± 6.9); P value ≤0.05 [Figure 2]. EPN-induced aggregation response decreased significantly (41.9 ± 20.2) in the inadequately treated hypothyroid patients as compared to the controls (59.4 ± 11.4); $P \leq 0.05$ [Figure 3]. Aggregation responses to other agonists were reduced as compared to the controls, but this reduction was not statistically significant [Figures 4 and 5]. Table 4 summarizes the aggregation responses to different agonists.

Platelet function analyzer closure time

In the inadequately treated hypothyroid group, there is a significant prolongation of both C/EPN (175.6 ± 82.5 s) and C/ADP CT (132.2 ± 72.5 s) as compared to the control group (141.6 ± 26.8 s for C/EPN CT) [Figure 6] and (100.7 ± 24.1 s for C/ADP CT) [Figure 7 and Table 5]. In contrast, a shortening was noted in both the C/EPN CT (132.4 ± 63.2, 121.2 ± 47.9 s) and C/ADP CT (99.0 ± 33.4, 93.8 ± 39.3 s) in the euthyroid and subclinical hypothyroid groups, respectively, as compared to the control group. However, this reduction was not statistically significant.

Multiple comparisons for the hemostatic variables between the three groups showed no significant

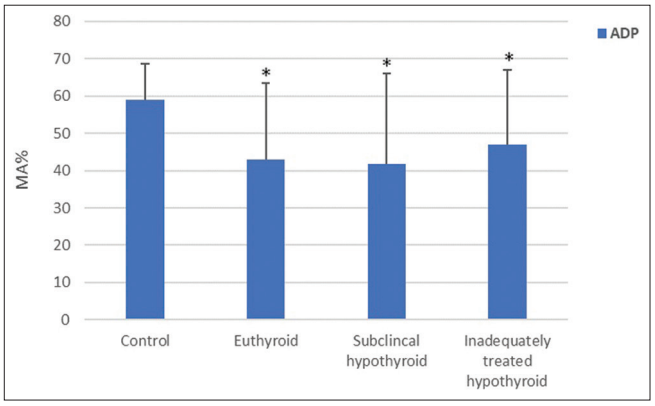

Figure 1: Adenosine diphosphate-induced platelet aggregation of the study groups expressed as the maximum aggregation percentage. *P* value are obtained by comparison with controls (*Designates statistical significance as compared to the control response)

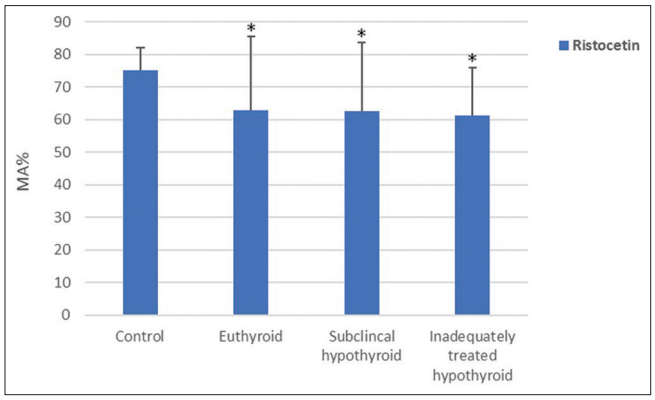

Figure 2: Ristocetin-induced platelet aggregation of the study groups expressed as the maximum aggregation percentage. *P* value are obtained by comparison with controls (*Designates statistical significance as compared to the control response)

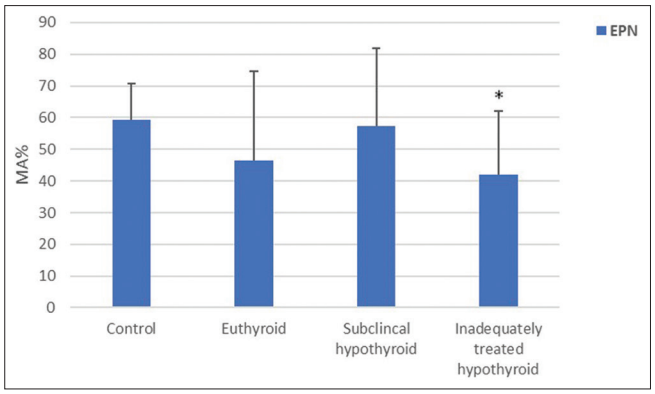

Figure 3: Epinephrine-induced platelet aggregations of the study groups expressed as the maximum aggregation percentage. *P* value are obtained by comparison with controls (*Designates statistical significance as compared to the control response)

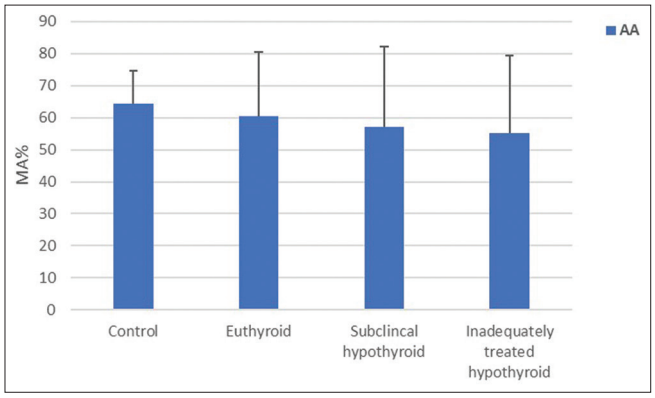

Figure 4: Arachidonic acid-induced platelet aggregations of the study groups expressed as the maximum aggregation percentage. Results are expressed as mean value ± standard deviation. *P* value are obtained by comparison with controls. No significant differences were found between variables

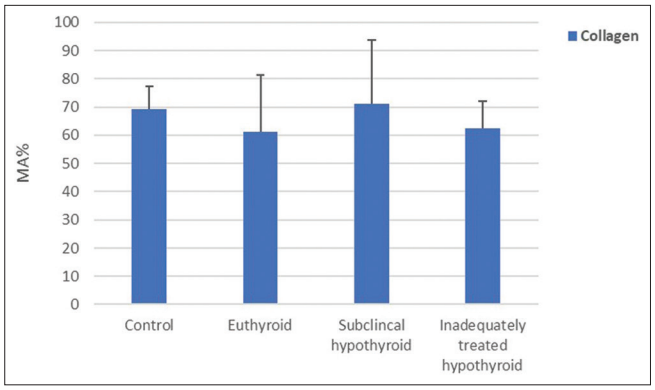

Figure 5: Collagen-induced platelet aggregation of the study groups expressed as the maximum aggregation percentage. Results are expressed as mean value ± standard deviation. *P* value are obtained by comparison with controls. No significant differences were found between variables

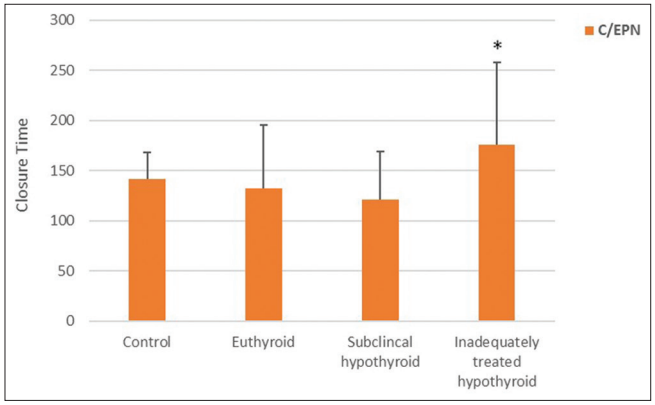

Figure 6: Collagen epinephrin closure time of the study groups expressed as mean ± standard deviation. *P* value are obtained by comparison with controls (*Designates statistical significance as compared to the control response)

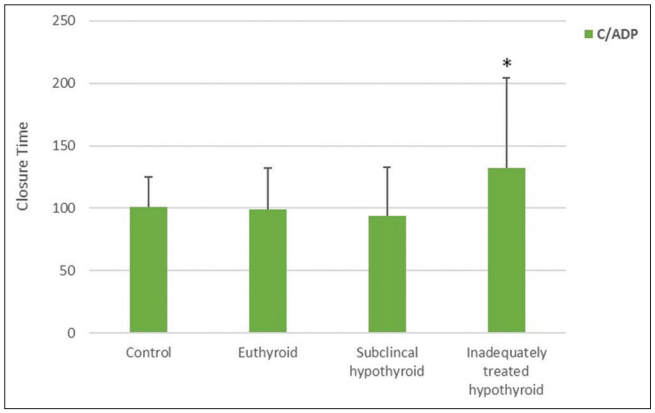

Figure 7: Collagen adenosine diphosphate closure time of the study groups expressed as mean ± standard deviation. *P* value are obtained by comparison with controls (*Designates statistical significance as compared to the control response)

variations except in HCT and WBC. The average HCT in the euthyroid group as well as in the inadequately treated hypothyroid group were significantly lower than in the subclinical hypothyroid group; $P \leq 05$. Significant decrease was also observed in the average WBC count in euthyroid group as compared to inadequately treated hypothyroidism patients; $P \leq 05$. No significant change was noted in lipid profile between groups [Table 3].

No correlation was found between the aggregation tests, C/ADP and C/EPN, and either TSH or free T4 levels.

Table 1: Demographic data of the study groups

Parameters	All hypothyroid patients (*n*=64)	Euthyroid (*n*=25)	Subclinical hypothyroid (*n*=22)	Inadequately treated hypothyroid (*n*=17)
Age (years)	41.5±15.8	45±16	39.1±13	41±18
Sex (female:male)	54:10	24:1	15:7	16:1
BMI (kg/m^2)	30.7±11.4	29.7±29.7	32.7±15.8	29.7±10.2

BMI=Body mass index

Table 2: Thyroid function tests in the study groups

Parameters	Euthyroid (*n*=25)	Subclinical hypothyroid (*n*=22)	Inadequately treated hypothyroid (*n*=17)	Reference range
TSH (m IU/L)	2±1.5	8.6±4.2	14.4±8.6	0.25-5.0
Free T4 (pmol/L)	16.7±3	14.8±2.1	6.4±4.3	11.5-22.7

TSH=Thyroid stimulating hormone; T4=Thyroxine hormone

Table 3: Laboratory parameters of the study groups expressed as mean±standard deviation with normal reference range

Variable	Euthyroid (*n*=25)	Subclinical hypothyroid (*n*=22)	Inadequately treated hypothyroid (*n*=17)	Reference range
RBC (10×e^{12}/L)	4.5±0.3	4.8±1.3	4.4±0.7	4.2-5.5
HB (g/L)	114.9±33.3	129.1±34.5	107±41.5	120-160
HCT (%)	36.3±3.5	40.7±5.2	35.1±5.7	37-47
MCV (fl)	81.7±6.8	80.8±8.2	79.4±9.4	80-94
MCH (pg)	27.1±2.8	26.2±3.6	25.7±3.9	27-32
MCHC (g/L)	333.7±9.1	332±17	316.9±76.7	320-360
Platelet (10×e^9/L)	296±89	275±81	303.8±86.2	140-450
MPV (fl)	8.7±1.3	8.5±0.9	8.8±0.9	7.2-11.1
WBC (10×e^9/L)	6.3±2	7.5±2	7.9±1.9	4-11
Cholesterol (mmol/L)	4.9±0.9	4.9±0.9	4.5±0.9	3.2-5.2
LDL (mmol/L)	2.9±0.9	2.8±0.8	2.5±1	1.48-4.25
HDL (mmol/L)	1.6±0.4	1.3±0.24	1.5±0.9	0.96-2.15
TG (mmol/L)	1.1±0.6	1.6±1	1.3±0.7	1-1.48

RBC=Red blood cell; HB=Haemoglobin; HCT=Haematocrit; MCV=Mean cell volume; MCH=Mean cell volume; MCHC=Mean cell haemoglobin concentration; MPV=Mean platelet volume; WBC=White blood cells; LDL=Low density lipoprotein; HDL=High density lipoprotein; TG=Triglyceride

Table 4: Platelet aggregation of the study groups expressed as the maximum aggregation percentage

Parameters	Euthyroid (*n*=25)	*P*	Subclinical hypothyroid (*n*=22)	*P*	Inadequately treated hypothyroid (*n*=17)	*P*	Control group
ADP (µmol/l)	42.9±20.7*	0.003	41.8.9±24.2*	0.006	46.9±20.1*	0.086	59.1±9.5
AA (µmol/l)	60.4±20.1	NS	57.1±25.1	NS	55.1±24.3	NS	64.4±10.3
EPN (µmol/l)	46.5±28.0	0.142	57.4±24.4	0.991	41.9±20.2*	0.054	59.4±11.4
Collagen (g/l)	61.2±20.1	NS	71.2±22.5	NS	62.5±9.6	NS	69.3±8.1
Ristocetin (g/l)	62.9±22.8*	0.031	62.6±21.2*	0.068	61.3±14.6*	0.035	75.3±6.9

*That the mean difference is statistically significant at the 0.05 level. *P* value are obtained by comparison with controls. ADP=Adinosine diphosphate; AA=Arachedonic acid; EPN=Epinephrine; NS=Not significant

Table 5: Platelet function analyser of the study groups expressed as mean±standard deviation

Parameters (closure time)	Euthyroid (*n*=25)	*P*	Subclinical hypothyroid (*n*=22)	*P*	Inadequately treated hypothyroid (*n*=17)	*P*	Control (*n*=88)
C/EPN	132.4±63.2	0.829	121.2±47.9	0.259	175.6±82.5	0.049*	141.6±26.8
C/ADP	99.0±33.4	0.997	93.8±39.3	0.861	132.2±72.5	0.017*	100.7±24.1

*That the mean difference is statistically significant at the 0.05 level. *P* value are obtained by comparison with controls. C/EPN=Collagen epinephrine cartridge; ADP=Adinosine diphosphate; C/ADP=Collagen-ADP cartridge

Discussion

The main drive to the current study is our observation that most of the previuos studies on the hemostatic abnormalities in overt hypothyroidism compared these abnormalities between patints with overt hypothyroidism before replacement therapy and after they became euthyroid. However, it is known from clinical observations that the response to thyroid hormone treatment varies widely among patients; some achieve euthyroid state and others will remain hypothyroid despite being on therapy, either because of inadequate thyroxine dose or because of the variation in the individual human responses to therapy.[15]

Besides, those group of patients, in which their thyroid hormones (T4 and T3) and TSH levels did not normalize after therapy, have not been studied or inadvertently ignored. In addition, although, the data available in the literature showed impaired hemostasis in hypothyroidism, most of these studies assessed only secondary hemostasis (fibrin formation) without providing adequate data on the primary hemostasis (platelet phase). Studies specifically assessing platelet function are currently lacking. Therefore, in the present cross-sectional study, we selected a group of hypothyroid patients in whom the diagnosis of overt hypothyroidism was established and were put on L-thyroxine replacement therapy. During the course of the treatment, they became either euthyroid, subclinical hypothyroid, or remained inadequately treated hypothyroid. Our aim was to determine whether their different responses to treatment will be reflected in differences in platelet function. Our study is different from previous published reports in that we assessed platelet function in hypothyroid patients who were on treatment whether becoming euthyroid or not. In these patients, we specifically assessed platelet adhesion and aggregation, using light transmission aggregometry and the PFA-100 analyzer.

Patients with overt hypothyroidism who were on replacement therapy displayed impaired aggregation responses particularly to ADP and Risocetin, as compared to the healthy controls. According to the response to treatment, the impairment of aggregation responses was more evident in the inadequately treated hypothyroid group.

It is worthwhile adding that, in platelet aggregometry studies, we used five different agonists, ADP, arachidonic acid (AA), EPN, collagen, and ristocetin and the results obtained showed that patients with euthyroid, subclinical hypothyroidism, and those who were inadequately treated displayed significantly decreased responses to ADP and risocetin. On the otherhand, EPN-induced aggregation response decreased in the inadequately treated hypothyroid patients. Although aggregation responses to other agonists were decreased in all groups, the decrease did not reach statistical significance.

Our findings agree with those of Palareti *et al*. who studied 21 patients with acquired hypothyroidism after total thyroidectomy and found impaired platelet reactivity to Ristocetin, collagen, and adrenalin.[16] Another study on primary hemostasis in hyperthyroid and hypothyroid patients found significantly longer bleeding time, and impaired platelet agglutination response to Ristocetin but greater platelet aggregation response to ADP in untreated hypothyroid patients than in normal controls.[17] Interestingly, Myrup *et al*.[17] found that the bleeding time, Ristocetin-induced platelet agglutination, and vWF: Ag normalized during L-thyroxine treatment. This indicates clearly that the observed defects in primary hemostasis in hypothyroidism are a consequence of thyroid hormone deficiency.

In contrast to almost all published observations, Masunaga *et al*.[9] found enhanced platelet aggregation responses to ADP and collagen in patients with primary hypothyroidism and inhibited responses to both agonists in patients with hyperthyroidism (Grave's Disease) and that these responses normalized when the euthyroid status was attained posttreatmnt in both patient groups. Their study was conducted in a small number of hypothyroid patients ($n = 12$) who were recruited before and after receiving treatment;[9] but this alone cannot offer explanation for their anamolous findings. Similarly, Lupoli *et al*.[18] reported an increase in aggregation responses to ADP and AA in subclinical hypothyroid patients. However, their patients were different because they were diagnosed to have subclinical hypothyroid with normal T4 and T3 and elevated TSH levels before treatment, while our patients started as overt hypothyroid and they became subclinical hypothyroid during treatment.

As to vWF and its role in primary hemostasis, vWF interacts with the platelet glycoprotein recptor GPIb and this results in platelet activation and the subsequent platelet aggregation that requires the presence of fibrinogen.[19] Both very low fibrinogen or dysfibrinogenemia can result in a decrease in platelet aggregation and defective hemostasis. Significant reduction in the levels of fibrinogen[10,20] and vWF has been reported in hypothyroidism.[4] In the current study, the response of platelets to activation by various aggregation agonists accounted for by low levels of fibrinogen and vWF in these patients. In addition, deficiency of thyroid hormone can affect the synthesis of components of PG pathway of platelet activation which, in turn, will affect the aggregation response to both AA and ADP.[21]

The aggregation response to ristocetin requires the presence of normal vWF antigen and thus reduced aggregation response to risocetin indicates the existence of acquired vWD.[3,8,13]

The endothelium, the main source of vWF, seems to be an important target for thyroid hormone action,[13] which can nongenomically affect the behavior of endothelial cells[22] and the synthesis of proteins originating from the endothelium.[5] Thus, thyroid dysfunction can result in disturbances of vWF synthesis through its action on endothelial cells.[20] It is noteworthy that, in the current study, we could not find any significant variation in the

aggregation response to ristocetin between the three studied patient groups. Thus, the significant reduction in Risocetin induced aggregation response that we obtained in the three study groups can be attributed to a common cause; abnormality in vWF levels.

Other than agonist-induced aggregometry, we also assessed primary hemostasis using PFA-100 which measures the adhesive function of platelet as well as the platelet aggregation. PFA-100 is currently used as substitution to bleeding time,[11] and the clinical impact of PFA-100 lies in the association between prolonged CTs and increase risk of bleeding.

Our finding of prolongation of both C/ADP and C/EPN CTs particularly in the inadequately treated hypothyroid group reflects a delay in platelet plug formation and a defect in primary hemostasis. This defect can be the consequence of the previously reported low levels of vWF or acquired von Willebrand disease in these hypothyroid patients.[20]

Homoncik *et al*.[12] reported prolongation of C/EPN CT in patients with overt hypothyroidism which shortened after treatment with thyroxine. Interestingly, they also found shortening of the C/EPN CT in patients with hyperthyroidism that increased toward normal after therapy with thiamazole. More recently, Horacek *et al*.[13] reported a significant shortening of the C/EPN and C/ADP CTs in thyroidectomy-induced hypothyroid patients who developed hyperthyroidism 6 weeks after levothyroxine treatment. These observations put together confirm the close interrelationship between thyroid function or specifically the level of circulating thyroid hormone and its significant role in primary hemostasis.

Recently, it has been shown that physiological concentrations of L-thyroxine (T4) activate platelets resulting in degranulation and aggregation. This hormonal action is initiated nongenomically at the thyroid hormone receptor; (avb3) which is expressed on the platelet surface.[22] Thus, low levels of thyroid hormone in hypothyroidism seem to lead to a higher bleeding risk, whereas high levels increase the risk of hypercoagublity and venous thromboembolism.[10]

The clinical impact of these findings lies in the association between inhibited aggregation responses and prolongation of PFA-100 CTs and the increased risk of bleeding. This should be taken into consideration when these patients are prepared for surgical procedures. That no bleeding manifestations were observed in these patients could well be due to the fact that the reduction in the vWF level[23] did not reach a critically low level to trigger bleeding.

One limitation of the present study is the small sample size of patients enrolled in the study. Moreover, simultaneous measurement of fibrinogen and vWF blood levels could have added important information about the pathophysiologal state of the reduced platelet activation in these hypothyroid patients. Further studies are needed in larger sample size to rule out if the platelet dysfunction in hypothyroidism carries a serious risk of a bleeding tendency.

Conclusions

In the present study, using two different tests of platelet function, we attempted to investigate platelet function in overt hypothyroid patients in different stages of response to L-thyroxine. We confirmed the existence of a defect in primary hemostasis particularly in the inadequately treated hypothyroid patients and this disturbance in platelet function varies according to the degree of response to treatment. Increased tendency to bleeding is more pronounced in the hypothyroid patients who were inadequately treated followed by the subclinical hypothyroid group. It will be of interest to consider the grade of responses to thyroid hormone therapy in patients with hypothyroidism when expose to clinical conditions that carry the risk of excessive bleeding such as menorrhagia and surgical operations.

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Conflicts of interest

There are no conflicts of interest.

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