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## Evaluation of new biomarkers as a predictor for thrombosis in patients with thyroid dysfunction

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### Abstract:

**Introduction:** Thyroid hormone has a significant impact on every cell in the body by altering the rate of growth, cellular progression and differentiation, and the change in the levels of micronutrients, hormone stages, protein synthesis, lipids, and CHO. The connection between thyroid problems and blood coagulation systems was first mentioned scientifically at the beginning of the previous century. In patients with thyroid dysfunction, numerous acquired coagulation-fibrinolytic system abnormalities were studied. These deviations can range from minor lab anomalies to serious medical hemostatic dysfunction.

**Aim of the study:** To evaluate novel biomarkers as thrombosis predictors in thyroid dysfunction patients.

**Subjects and Methods:** This case-control study included 60 participants as follows; 20 patients in Group A, who have hyperthyroidism, have elevated thyroid functions, Group B contains 20 patients with hypothyroidism who have decreased thyroid function, and Group C consists of 20 individuals with normal thyroid function (the euthyroid group). Methods included taking a complete medical history (including OCPS use), age, gender, smoking, history of cancer, thromboembolic events, bleeding disorders, and thorough clinical examination. For lab tests and measurements of the CBC, PT, PTT, PC, TSH, FT4, D-dimer, and p-selectin level.

**Results:** The study groups did not differ significantly from one another regarding the PT-INR, PTT, and D-dimer levels, as well as the CBC components. Additionally, PTT and PLT count levels were significant predictors of p-selectin levels.

**Conclusion:** It can be concluded that there was no significant variance among study groups concerning CBC components, PT-INR, PTT, and D-dimer level.

**Key words:** thyroid diseases; thrombosis; hemostasis; p-selectin.

## 1. Introduction

The thyroid weighs about 20 grammes and is the most significant endocrine organ in the body. The right lobe is typically bigger than the left. At the age of 15, a person reaches full size. A small isthmus located just below the cricoid cartilage connects the two lateral lobes, which are located anterior to the cricoid cartilage. Intrathyroidal factors, commonly the quantity of iodide within the thyroid cell, and extrathyroidal factors, such as the thyroid-stimulating immunoglobulin in Graves' disease, both affect the synthesis of thyroid hormone [1].

The extrathyroidal 5-deiodination of T4 yields the majority of T3, which can be altered without affecting thyroid function. Two types of 5-deiodinases convert T4 into T3 in this process. The adhesion of T3 to nuclear thyroid hormone-specific receptors mediates the majority of thyroid hormone effects. The greater biologic activity of T3 is due to its ten-fold higher specificity for this receptor complex compared to T4 [2]

Through the vasculature, blood moves as a liquid under pressure. The process that causes

a blood vessel to stop bleeding is known as hemostasis. The blood vessels' endothelium preserves an antithrombotic outer layer that keeps the blood in a fluid state [3].

Hemolysis is not formally defined by any single authority. The simplest definition is the "cessation of bleeding," but since death ultimately causes the bleeding to stop, it is not a good illustration of hemostasis. The control of bleeding without the induction of pathologic thrombotic events like coronary artery disease, cerebrovascular disease, arterial thrombosis, or peripheral arterial disease is a more precise clinical definition of hemostasis [4].

At the start of the previous century, the clinical connection between thyroid disorders & the blood coagulation system had first been established. In cases of thyroid dysfunction, multiple newly discovered defects of the coagulation-fibrinolytic process have been documented. These deviations can be anything from mild laboratory anomalies to serious hemostasis disorders [5].

## 2. Subjects and methods

### 2.1. Subjects

The sample size was calculated using G-Power© software version 3.1.7 (Institute of

Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). A minimal sample size of patients was 20 patients in each

group. Effect size 0.39 Depending on previous research results. Two-sided (two tails) type I error 0.05 and power of 80%.

### ***Inclusion criteria***

All cases with thyroid issues over the age of 18 are being monitored at the Fayoum University Hospital's Internal Medicine Outpatient Clinics. Participants in the control group had healthy thyroid function.

### ***Exclusion criteria***

Patients who exhibited the traits listed below were ineligible:

- Age > 70.
- A history of cancer.
- Previous thromboembolic incidents or bleeding issues.
- Patients taking OCPS or oral anticoagulants.
- Pregnancy.
- Thyroiditis.

### ***2.2. Study design***

The following information was acquired on 60 people between February 2021 and October 2021 from the Fayoum University Hospitals in the Fayoum Governorate. The patients were divided into three groups:

1. Group A: 20 patients with hyperthyroidism on TT and have an increased thyroid function.
2. Group B: 20 people with thyroid dysfunction (hypothyroidism group, on TT).
3. Group C: 20 people had normal thyroid function (the euthyroid group).

### ***2.3. Methods***

Laboratory examinations were performed on a sample of venous blood, including:

- TSH, FT4; CBC; PT, PTT, and PC (prothrombin concentration).
- D-dimer.
- P-selectin level: To assess human p-selectin in cell culture supernates, serum & plasma, the Quantikine® Human P-Selectin/CD62P Test is a 1.25-hour solid-phase ELISA. It includes antibodies produced in response to the recombinant factor and recombinant human p-selectin.

### ***2.4. Statistical Analysis***

Complete medical history taking, including age, sex, smoking, blood disorders or thromboembolic events, usage of drugs, including OCPS, and clinical assessment were performed on every patient.

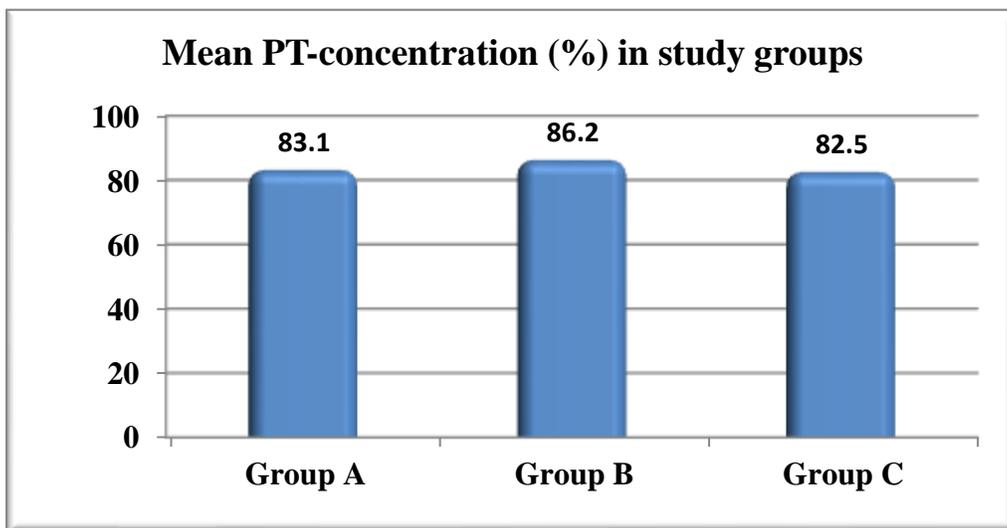
### 3. Results

Regarding PT-INR titer and categories and PT-concentration level, there was no statistically significant distinction among study groups ( $p>0.05$ ), indicating that thyroid dysfunction had no impact on PT-INR level,

PT-time titer, or PT-concentration level. Also, there was no statistically significant variance ( $p >0.05$ ) amongst study groups concerning PTT titer (**Table 1, Figure 1**).

**Table 1:** Comparison between study groups regarding PT profile.

Variables		Group A (N=20)	Group B (N=20)	Group C (N=20)	P-value
PT-time (sec)	Mean ± SD	12.26±0.87	12.04±0.91	12.27±0.69	0.61
	High	0 (0%)	0 (0%)	0 (0%)	
	Normal	20 (100%)	20 (100%)	20 (100%)	
PTT titer	Mean ± SD	34.5±4.3	34.4±5.4	34.5±3.8	0.99
	High	0 (0%)	0 (0%)	0 (0%)	
	Normal	20 (100%)	20 (100%)	20 (100%)	



**Figure 1:** Mean PT concentration in study groups.

The average HB level for groups A, B, and C is 12.2, 12.6, and 12.4, respectively. Groups A, B, and C all have mean PLT levels of 252; 261; and 247, respectively. Groups A, B, and C all have mean TLC levels of 7.4, 7.7, and 7.3, respectively. There was no statistically significant variance in the results of the

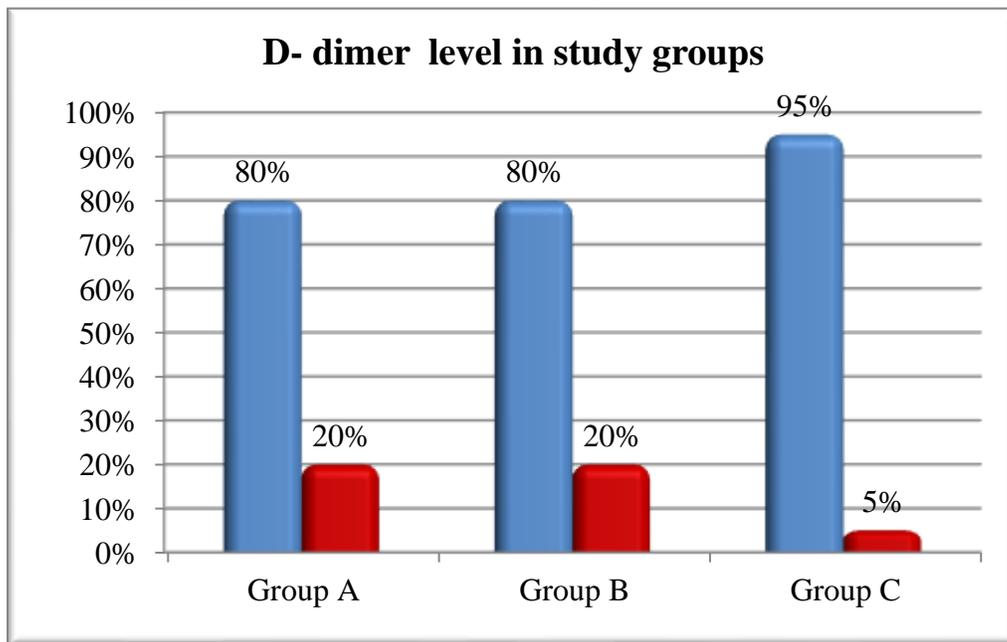
complete blood count investigations (HB, PLT count, and TLC) among the study group ( $p >0.05$ ) (Table 2).

Regarding D-dimer, there was no statistically significant variance among study groups concerning D-dimer level or D-dimer titer (Figure 2).

**Table 2:** Comparison between study group as regards CBC component.

Variables	Group A (N=20)	Group B (N=20)	Group C (N=20)	P-value
HB	12.2±1.7	12.6±1.4	12.4±1.7	0.74
PLT	252±84.7	261.9±92	247.4±75.7	0.85
TLC	7.4±2.5	7.7±2.8	7.3±2.3	0.87

HB: Hemoglobin; PLT: Platelets; TLC: Total leucocytes count



**Figure 2:** D-dimer level in study group.

The multivariate linear regression model analysis was performed to explore the explanatory power of variant investigation on the p-selectin level. It demonstrated statistically significant predictors of PTT and PLT count levels ( $p = 0.008$  and  $0.01$ , respectively) with no prediction power to other investigations.

**Table 3:** Multivariate linear regression analysis to assess the prediction power of different investigation to p-selectin level.

Variables	B	SE	Beta	Sig
Constant	-195.6-	527.52		0.71
PT-INR	-15.8-	90.24	-0.052-	0.86
PT Time	11.7	28.68	0.26	0.68
PT Conc	-0.57-	2.41	-0.15-	0.81
PTT	2.79	1.01	0.34	0.008
TSH	-.487-	0.63	-0.08-	0.44
FT4	1.05	1.13	0.10	0.35
HB	4.54	2.69	0.19	0.09
PLT	0.13	0.052	0.32	0.01
TLC	1.54	1.53	0.11	0.32
D- dimer	-16.268-	12.39	-.015-	0.19

#### 4. Discussion

In the early part of the previous century, a clinical association between thyroid diseases and the hemostatic system was established for the first time. Thyroid dysfunction patients have been found to have several different acquired disorders of the coagulation-fibrinolytic system. Subclinical laboratory abnormalities to clinically significant hemostasis disorders may

fall within this category. As regards CBC components: our study revealed that there was no statistically significant variance among study groups as regards (HB level, PLT count and TLC).

This agreed with Jafarzadeh et al., 2010 and Dorgalaleh et al., 2013, which included 102 patients with hypothyroid, 84 with hyperthyroid

and 118 healthy individuals as a control groups, as it showed that no statistically significant variances among these groups of patients, as regard PLT and TLC [6, 7]. This study also goes hand in hand with Ibrahim, (2020) and Ahmed and Mohammed, 2020 who showed that Thyroid function has less impact on platelets [8, 9]. On the other hand, this study disagreed with Modala Modala et al., 2017, and Iddah et al., 2013, studies showing that low platelet counts were seen in hypothyroid states [10, 11]. I also disagreed with Shetty and Vijaya (2019), which showed that the lowest counts of TLC were discovered in the hypothyroid group, where they were significantly decreased in comparison to the hyperthyroid group but not reduced when contrasted with the euthyroid groups [12].

As regards HB level, the study agreed with Shetty and Vijaya, 2019 which showed that the RBCs in the hyper and euthyroid categories were within normal limits [12]. On the other hand, the study disagreed with some previous studies as Dorgalaleh et al., 2013 and Ahmed and Mohammed, 2020 which showed that There was a significant relationship between anemia and thyroid dysfunction ( $P = 0.000$ ), with 31.3% of cases suffering from anemia [6].

As regards PT-INR, these results agreed with Erem et al. (2003), who showed that PT in hyperthyroid patients was not different from the

control subjects [13]. Also, the results agreed with Lippi et al., 2009 who showed that the median values of PT and fibrinogen did not significantly vary among euthyroid cases and those with hypothyroidism [14].

On the other hand, this study disagreed with other previous studies, which showed that the PT value was discovered to be significantly lesser in hypothyroid & hyperthyroid cases when compared with the control group [9, 15]. Furthermore, Thoyyib et al. (2018) showed that PT was found to be significantly lower in the hyperthyroid group than in the control group, but that PT exhibited a little rise at baseline in moderate and severe hypothyroidism, and that PT was shown to be significantly lower in these patients after achieving euthyroid condition on therapy [16].

As regards PTT titer, this study showed no statistically significant difference between study groups, which indicated no effect of thyroid dysfunction on PTT level. This agreed with many other previous studies. Erem et al., (2003) showed that PTT in hyperthyroid patients were not different from the control subjects [13]. Lippi et al. (2009) and Ibrahim (2020) showed that the median values APTT did not significantly distinct among euthyroid cases and those with hypothyroidism [9, 14]. Also, Thoyyib et al. (2018) showed that APTT did not

significantly differ between hypo or hyperthyroidism and the control group [16].

On the other hand, the study disagreed with other previous studies, which revealed the median APTT was lower in hyperthyroid cases and the median fibrinogen level was greater in hyperthyroid cases than in euthyroid individuals [9, 14].

As regards the D-dimer level, our research revealed that there was no statistically significant variance among study groups. This agreed with a previous study by Eiman et al. (2018), who showed that There was no statistically significant distinction among the D-dimer levels of individuals with hypothyroidism and those with hyperthyroidism who were receiving medication [17]. Supported the findings of Mazur et al. (2014), that euthyroid was reached in 91.4% of hyperthyroid and 85.7% of hypothyroid participants following three months of thyroid function achieving medication, and that fibrin clot characteristics improved [18]. That was in agreement with another previous study, in which patients with severe hypothyroidism who took levothyroxine saw improvements in their coagulation problems and hyper-fibrinolytic status [19]. However, further research is needed to determine the therapeutic effects of the

temporary reduction in fibrinolytic activity that occurs when TSH levels return to normal.

On the other hand, the results disagreed with another previous study, which showed that the D-dimer level was statistically significantly greater in cases with hyperthyroidism contrasted with those normal healthy control groups ( $p < 0.001$ ) [20]. Also disagreed with the study conducted by Chadarevian et al. (2001), who showed that patients with severe hypothyroidism display both higher D-dimer levels and slightly lower fibrinogen levels than controls [21].

As regards the analysis to assess the prediction power of various investigations to the p-selectin level: The multivariate linear regression model analysis was performed to explore the explanatory power of various investigations on the p-selectin level. It demonstrated that there were statistically significant predictors of PTT, and PLT count levels with no prediction power to other investigations. That study agreed with Fei et al. (2016), as regards PLT count and its relation to p-selectin but disagreed with the same study as regards D-dimer [22]. The previous study which showed that the level of D-dimer, p-selectin, and platelet count might be promising PVT diagnostic indicators, there is a positive relation between them.

## Conclusion

we can conclude that there was no significant variance among study groups Concerning CBC components, PT-INR, PTT

and D-dimer level. Also, there was a significant predictor of PTT and PLT count level about p-selectin level.

### Ethical consideration and patient consent:

The study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee (Approval no. m 604, number (79), 10/1/2021).

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**Conflicts of Interest:** All authors declare they have no conflicts of interest.

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