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Significance of laboratory hemostasis findings in women with thyroid diseases in Saudi Arabia

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Abstract

Diagnostic utility of coagulation profiles in thyroid patients has z hot topic despite rarity of original researches in the topic. During our routine check-up we noticed that some evidences of abnormal hemostasis among patients with thyroid diseases especially women because the frequency of thyroid abnormalities is higher compared to men. What encouraged us to do this research the high significance of hemostasis findings especially when a higher quality control applied to automated devices in the clinical laboratory. Therefore the main goal of the study is to find out the importance of integration of hemostasis profiles as important and routine tests in women patients with thyroid diseases. This is a prospective study aimed to highlight the most significant hemostasis findings essential in 101 patients with thyroid

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disease in Saudi Arabia women. All participants were females at Alsamrya Medical Complex in Jeddah, Saudi Arabia, from December 2017 until July 2019. Participants age range from 16 to 50 years with average age 35 years. Blood samples were obtained and the following tests such as platelets count, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, fibrinogen were performed. In the other hand, thyroid profiles such as Thyroid Stimulating Hormone (TSH), FT3, FT4 were estimated. Samples were run using automated STA Compact Max® for assessment of hemostasis with the fore mentioned parameters. And the mini VIDAS® was used for thyroid profiles. And finally, statistical analysis was performed with and analyzed by using statistical package for social science (SPSS). Chi-square, and other parameters were applied to state the significance of results. The following results were obtained as there was a significant association found between TSH level with platelets count (p value = 0.0029), bleeding time (p value = 0.0414), PT (p value = 0.0154), APTT (p value = 0.0489), and with Fibrinogen (p value = 0.0161). A significant association found between FT3 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value < 0.001), and with Fibrinogen (p value < 0.001). A significant association found between FT4 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value = 0.005), and with Fibrinogen (p value < 0.001). in conclusion hemostasis findings are crucial for management of patients with thyroid diseases and it is important for the clinicians to integrate these findings for routine management of those group of patients.

Key words: Thyroid, patients, bleeding, coagulation, platelets, findings, clotting

INTRODUCTION:

Hemostasis profiles by nature are difficult to predict in relation to many diseases. However in accurate interpretation may lead to catastrophic complications to patients increasing morbidity and mortality. Also may result in negative image created to clinicians and patients without accurate interpretation of these findings. In relation to thyroid diseases, these findings are even more complicated. This

study focused on defining what are the most critical and important findings provide significant result to clinicians treating patients. Thyroid disease is a common medial problem of all ages, the effect of the function of the thyroid gland and the symptoms of thyroid disease vary depending on the type. These include four general types such as hypothyroidism, hyperthyroidism, structural abnormalities such goiter, benign and malignant tumors. Beside there may be abnormal thyroid function tests without any clinical symptoms (sub clinical thyroiditis) and inflammatory diseases as well. Goiter (swelling of a part of the neck) describes both hypothyroidism and hyperthyroidism (1).

The importance of laboratory testing involving Partial Thromboplastin Time (PTT) or Prothrombin Time (PT)/ international normalized ratio (INR) can be divided by the physiological mechanisms into categories as disorders exclusively effecting primary hemostasis do not affect the PT/INR or PTT, they only increase bleeding time, disorders that affect the extrinsic pathway of secondary hemostasis affect the PT/INR and Disorders that affect the intrinsic pathway of secondary hemostasis affect the PTT and metabolic disorders such thyroid dysfunction **(2).**

Clotting mechanism involves both, firstly; cellular components of the clotting mechanism include platelets, endothelial cells, and a series of proteins, enzymes, and ions. And secondly this mechanism involves organ and systems involved which are the circulatory system which includes the lineage of blood cells and blood vessels. The clotting mechanism passes through two and broad mechanisms, these are primary hemostasis: Formation of a weak platelet plug and secondary hemostasis: Stabilizing the weak platelet plug into a clot by the fibrin network. With further details, primary hemostasis is the formation of a weak platelet plug which is achieved in four phases: vasoconstriction, platelet adhesion, platelet activation, and platelet aggregation. In our laboratory practice we continue deal with samples request from clinicians investigating pregnant women with common thyroid problems to interpret whether they suffer from bleeding tendency or hyper coagulation. In study done here in Saudi Arabia, authors reported that there is a significantly decrease in PT was observed in hypothyroid patients, and hyperthyroid patients compared to the control group. Activated thromboplastin time was significantly decreased only in hyperthyroid patients, compared to the

control group **(**3**).** Moreover, fibrinogen level was significantly increased in hyperthyroid patients compared to hypothyroid patients and severe hypothyroidism is associated with significant changes of factor VIII activity and factor von Willebrand. These studies supported our objective **(4 et al, 2010).**

However many physicians still ignore the existing relationship between thyroid hormones and the coagulation system. It is important for clinicians to realize that hemostaic balance can be affected by thyroid dysfunction, as well as hepatic, renal, and other systemic diseases **(5,6).**

Other studies such as this supported our objectives has concluded that minor coagulation abnormalities were observed in both subclinical hypo- and hyperthyroidism compared to clinical hypo- and hyperthyroidism. Platelets count was also slightly decreased in both types of the disease. There was no significant effect of the treatment and age of such patients on the measured parameters. The study recommended screening female patients with hypo- and hyperthyroidism for coagulation defect, to avoid the risk of such complications **(5,6).**

In addition, a large number of studies have important methodological drawbacks, such as lack of a control group, small study size, heterogeneity of cause and severity of thyroid dysfunction, and different laboratory assays **(7).**

Therefore, the purpose of this review is to summarize systematically the effects of excess or deficiency of thyroid hormone on the coagulation-fibrinolytic system in vivo, to generate well-founded hypotheses, and to give direction for future basic and clinical research on this topic. In study done by Mohamed-Ali and Ahmed RO assessed coagulation profiles in hypothyroid and hyperthyroid female patients in Sudan, this study was published in Saudi Medical Journal in 2008. The study concluded that minor coagulation abnormalities were observed in both subclinical hypo- and hyperthyroidism compared to clinical hypo- and hyperthyroidism. Platelets count was also slightly decreased in both types of the disease. The study recommended screening female patients with hypo- and hyperthyroidism for coagulation defect, to avoid the risk of such complications **(8).**

In a study done by Gao et al published in Ann Clin Lab Sci 2017 which assessed Alteration of Hemostatic Parameters in Patients with Different Levels of Subclinical Hypothyroidism and

the Effect of L-thyroxine Treatment, concluded with correlation of thyroid diseases resulted in abnormal haemostasis **(9).**

Chang et al studied the Spectrum of Coagulation Abnormalities in Thyroid Disorders and concluded with increasing evidence indicates that several haemostatic abnormalities occur in patients with both hyperthyroidism and hypothyroidism. Although a wide inter-patient heterogeneity exists, it can be roughly generalized that thyroid disease will be analyzed **(10).**

Ordookhani and Burman studied Hemostasisin Hypothyroidismand Autoimmune Thyroid Disorders they concluded that overt hypothyroidism is associated with a hypocoagulable state and subclinical hypothyroidism and autoimmune thyroid disorders may induce a prothrombotic state **(11).**

MATERIALS AND METHODS

This is a prospective study aimed to highlight the most significant hemostasis findings essential in 101 patients with thyroid disease in Saudi Arabia women. All participants were females at Alsamrya Medical Complex in Jeddah, Saudi Arabia, from December 2017 until July 2019. Participants age range from 16 to 50 years with average age 35 years.

Sampling:

Blood samples were obtained and the following tests such as platelets count, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time (APTT), fibrinogen were performed. In the other hand, thyroid profiles such as Thyroid Stimulating Hormone (TSH), FT3, FT4 were estimated. Samples were run using automated STA Compact Max® for assessment of hemostasis with the fore mentioned parameters. And the mini VIDAS® was used for thyroid profiles. And finally, statistical analysis was performed with and analyzed by using statistical package for social science (SPSS). Chi-square, and other parameters were applied to state the significance of results.

RESULT:

Concerning the results of the investigation done, our study found that among cases laboratory finding were as following; **Coagulation findings were as the following:** platelets count 291.3 ± 84.1 $x10^3$, bleeding time 3.7± 1.1 seconds, clotting time 6 ± 1.3 seconds, PT 14.6 ± 2 seconds, APTT 37 ± 6.2 seconds and fibrinogen 308 ± 105.3 (mg/dl). **The thyroid function tests findings were as the following:** TSH 8.7 ± 8.2 (uIU/ml), FT3 5.1 ± 4.5 (Pmol/l) and FT4 14.4 ± 8.6 (Pmol/l) as detailed in table 1: Among the **cases** group, cross tabulation was done to assess the relation between the coagulation findings and the thyroid function tests using chi square statistical test. The analysis found the following: A significant association found between TSH level with platelets count (p value = 0.0029), bleeding time (p value = 0.0414), PT (p value = 0.0154), APTT (p value = 0.0489), and with Fibrinogen (p value = 0.0161) as detailed in table 2. A significant association found between FT3 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value < 0.001), and with Fibrinogen (p value < 0.001) as detailed in table 3. A significant association found between FT4 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value = 0.005), and with Fibrinogen (p value < 0.001) as detailed in table 4.

Table (1) summary statistics for investigation results for CASES group (n = 101)

Automated Technology	Investigation	Observations	Mean	Standard deviation	Minimum	Maximum
Sysmex KX21	Platelets count $x10^3$	101	291.3	84.1	132.0	599.0
	Bleeding Time (min)	101	3.7	1.1	2.0	6.8
	Clotting Time (min)	101	6.0	1.3	3.0	10.2
STAGO Full Automated	PT (Sec)	101	14.6	2.0	10.0	22.0
	APTT (Sec)	101	37.0	6.2	24.0	50.0
	Fibrinogen (mg/dl)	101	308.0	105.3	123.0	677.0
Minividas full automated	TSH (uIU/ml)	101	8.7	8.2	0.1	58.2
	FT3 (Pmol/l)	101	5.1	4.5	0.8	36.6
	FT4 (Pmol/l)	101	14.4	8.6	1.3	82.6

Table (2) the relation between TSH with coagulation findings among cases group (n = 101)

Investigations		TSH						Total		P value
		Low		Normal		High				
Platelets count (x10³)	Low	1	2.9	0	0.0	1	1.5	2	2.0	0.0029
	Normal	32	91.4	1	100.0	61	93.8	94	93.0	
	High	2	5.7	0	0.0	3	4.6	5	5.0	
Bleeding Time (min)	Low	4	11.4	0	0.0	0	0.0	4	4.0	0.0414
	Normal	30	85.7	1	100.0	57	87.7	88	87.1	
	High	1	2.9	0	0.0	8	12.3	9	8.9	
Clotting Time (min)	Low	0	0.0	0	0.0	0	0.0	0	0.0	-
	Normal	34	97.1	1	100.0	55	84.6	90	89.1	
	High	1	2.9	0	0.0	10	15.4	11	10.9	
PT (Sec)	Low	6	17.1	0	0.0	0	0.0	6	5.9	0.0154
	Normal	24	68.6	1	100.0	48	73.8	73	72.3	
	High	5	14.3	0	0.0	17	26.2	22	21.7	
APTT (Sec)	Low	12	34.3	0	0.0	7	10.8	19	18.8	0.0489
	Normal	17	48.6	1	100.0	38	58.5	56	55.4	
	High	6	17.1	0	0.0	20	30.8	26	25.8	
Fibrinogen (mg/dl)	Low	4	11.4	0	0.0	13	20.0	17	16.8	0.0161
	Normal	20	57.1	1	100.0	48	73.8	69	68.3	
	High	11	31.4	0	0.0	4	6.2	15	14.9	

Table (3) the relation between FT3 with coagulation findings among CASES group (n = 101)

Investigations		FT3						Total		P value
		Low (n = 51)		Normal (n = 36)		High (n = 14)				
Platelets count (x10³)	Low	1	2.0	1	2.8	0	0.0	2	2.0	0.9867
	Normal	49	96.1	32	88.9	13	92.9	94	93.0	
	High	1	2.0	3	8.3	1	7.1	5	5.0	
Bleeding Time (min)	Low	0	0.0	0	0.0	4	28.6	4	4.0	< 0.001
	Normal	43	84.3	36	100.0	9	64.3	88	87.1	
	High	8	15.7	0	0.0	1	7.1	9	8.9	
Clotting Time (min)	Low	0	0.0	0	0.0	0	0.0	0	0.0	-
	Normal	41	80.4	35	97.2	14	100.0	90	89.1	
	High	10	19.6	1	2.8	0	0.0	11	10.9	
PT (Sec)	Low	0	0.0	0	0.0	6	42.9	6	5.9	< 0.001
	Normal	33	64.7	34	94.4	6	42.9	73	72.3	
	High	18	35.3	2	5.6	2	14.3	22	21.7	
APTT (Sec)	Low	7	13.7	3	8.3	9	64.3	19	18.8	< 0.001
	Normal	25	49.0	28	77.8	3	21.4	56	55.4	
	High	19	37.3	5	13.9	2	14.3	26	25.8	
Fibrinogen (mg/dl)	Low	14	27.5	2	5.6	1	7.1	17	16.8	< 0.001
	Normal	35	68.6	31	86.1	3	21.4	69	68.3	
	High	2	3.9	3	8.3	10	71.4	15	14.9	

Table (4) the relation between FT4 with coagulation findings among cases group (n = 101)

Investigations		FT4						Total (n = 101)		P value
		Low (n = 28)		Normal (n = 55)		High (n = 18)				
Platelets count (x10³)	Low	0	0.0	2	3.6	0	0.0	2	2.0	0.4901
	Normal	27	96.4	51	92.7	16	88.9	94	93.0	
	High	1	3.6	2	3.7	2	11.1	5	5.0	
Bleeding Time (min)	Low	0	0.0	0	0.0	4	22.2	4	4.0	< 0.001
	Normal	21	75.0	54	98.2	13	72.2	88	87.1	
	High	7	25.0	1	1.8	1	5.6	9	8.9	
Clotting Time (min)	Low	0	0.0	0	0.0	0	0.0	0	0.0	-
	Normal	20	71.4	52	94.5	18	100.0	90	89.1	
	High	8	28.6	3	5.5	0	0.0	11	10.9	
PT (Sec)	Low	0	0.0	0	0.0	6	33.3	6	5.9	< 0.001
	Normal	18	64.3	47	85.5	8	44.4	73	72.3	
	High	10	35.7	8	14.5	4	22.2	22	21.7	
APTT (Sec)	Low	4	14.3	6	10.9	9	50.0	19	18.8	0.0005
	Normal	12	42.9	38	69.1	6	33.3	56	55.4	
	High	12	42.9	11	20.0	3	16.7	26	25.8	
Fibrinogen (mg/dl)	Low	10	35.7	6	10.9	1	5.6	17	16.8	< 0.001
	Normal	18	64.3	45	81.8	6	33.3	69	68.3	
	High	0	0.0	4	7.3	11	61.1	15	14.9	

DISCUSSION:

Based on these findings we found that there was a significant association found between TSH level with platelets count (p value = 0.0029), bleeding time (p value = 0.0414), PT (p value = 0.0154), APTT (p value = 0.0489), and with Fibrinogen (p value = 0.0161). A significant association found between FT3 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value < 0.001), and with Fibrinogen (p value < 0.001). A significant association found between FT4 level with bleeding time (p value = < 0.001), PT (p value < 0.001), APTT (p value = 0.005), and with Fibrinogen (p value < 0.001). Although there were scant data of the relationship between thyroid hormonal disturbances and disease and hemostasis changes, this is study is one of few studies covered this topic extensively. Therefore compared to many previous studies, our study showed great promises to link between thyroid disorders and their impact on hemostasis (12.13).

Our statistics in this study supported the importance of laboratory diagnosis of blood coagulation changes in patients with thyroid diseases (5,6,13).

We are perfectly aware that many attempts in literature to justify the importance of these laboratory findings in patients with thyroid diseases, but our study has shown great promises in the

impact of abnormal or changes in hemostasis process in patients with thyroid diseases. All these documentations, made this study as a genuine and original, we stated that there were few data related topic compared to other studies still the topic is interesting and further expansion is required. One of the problems stated however, and most of studies contradicting the hemostatic findings such as PT, PTT, etc we documented that there is lack of clinical implications and many physicians do not rely on these findings especially surgeons (12,13, 14).

This study again support that more dialogue with physicians to relay on hemostasis findings in patients with thyroid disease. It is important to note that thyroid diseases presented with a complicated pathobiology, especially those related to hormones abnormality and other proliferative and inflammatory disorders (12,13).

Important fact to consider that bleeding disorders and specially clotting abnormalities such as stroke with be presented at late stage, this study supports that hemostasis findings may serve as screening or predicting investigations to patients with thyroid disease both bleeding and thrombosis with all consequences and the danger may be in stroke and thrombotic like consequences therefore absolutely lab findings play a major role for patient management. Variability and inaccuracy of automation used and quality measures affect laboratory findings, in this study the machines selected to run samples were perfectly calibrated and quality tested, providing these significant findings.

CONCLUSION:

It is important for clinicians to realize that hemostaic balance can be affected by thyroid dysfunction, equally to the hepatic, renal, and other systemic diseases. Introduction of routine, screening or prediction of hemostatic investigations for all patients with thyroid diseases especially those undergoing or candidates for surgery. Further study focus on flowcytometry of platelets morphology and markers if there are any changes in patients with thyroid disease and normal platelets count. Lack of data and insignificance of result of platelets count and fibrinogen support deep assessment of these findings in large data as well. Discussion with physicians about the impotence of laboratory findings in the existing relationship between

thyroid hormones and the coagulation system has to be considered. Application of proteomics for molecular assessment of the interaction between thyroid hormones and hemostatic mechanisms should be considered for further evaluation in original researches.

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