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Assessment of the relationship between thyroid diseases involvement and effect on hemostasis; a prospective analysis of hemostasis profiles in women with control group in Saudi Arabia

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Abstract

As it has been well documented that bleeding or coagulations disorders are common and especially in patients with thyroid disease, we conducted this case control study covered 153 study participants whom divided into two study groups; the first group who diagnosed

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with thyroid gland abnormalities (cases group) and healthy group (control group). Blood samples for Thyroid Function Tests and Hemostasis and coagulations investigations were carried out. All participants were selected under informed consent and especially for the control group otherwise healthy (18). However all cases were know by physicians as patients with thyroid diseases. Investigation of coagulation and bleeding disorders in relation to thyroid is a hot topic, but requires intensive research.

The study was aimed to study of coagulation parameters among ladies with hypo and hyper thyroid diseases in Saudi Arabia and to investigate the role of Stago Coagulation analyzer for assessment of abnormal hemostasis in thyroid diseases, to estimate abnormal hematological findings in women with hypo thyroid diseases or thyroidectomy patients as well as hyperthyroid patients. We used the following techniques including, Complete Blood Count and coagulation parameters sucha as Prothrombin Time (PTT) / Fibrinogen/Activated Partial Thromboplastin Time (APTT), Platelets Count using Stago cogulation analyzer while for the thyroid function using the VIDAS® for Thyroid Stimulating Hormone (TSH), FT4 and FT3 assays. 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 and 12 to 54 years average 30.9 years for cases and the control age group respectively. Nearly two thirds of them were classified in cases group (66%) while (34%) were in the control group as displayed in table 1 and figure 1. 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 and 12 to 54 years average 30.9 years for cases and the control age group respectively.

We found a significant increasing in bleeding time (difference of 0.5 seconds, p value 0.002), clotting time (difference of 0.7 seconds, p value < 0.001), PT (difference of 0.6 seconds, p value 0.001), and APTT (difference of 0.2 seconds, p value 0.046) and the result in platelets count (difference of 8.9 $x10^3$, p value 0.506) and fibrinogen level (difference of 0.8 (mg/dl), p value 0.830) between the two study groups.

In conclusion, our study is one of very rare studies and our result showed excellent and extreme significant compared to literature.

We were able to link effects on coagulation factors synthesis or on platelet function and metabolism, fibrinolytic system with support of advance understanding of the mechanism of action of thyroid hormone at the cellular level and may provide insight into the functioning and regulation of the hemostatic system itself therefore we recommend that these test should be included routinely for any patients with thyroid disease especially those undergoing surgery.

Key words: Thyroid, coagulation abnormalities, bleeding, clotting, hypothyroidism, hyperthyroidism, thrombosis

INTRODUCTION:

Indeed it is well documented scientifically and historically, hemostasis is a process by which the human body protects against loss of blood through the clotting mechanism and against bleeding as well this process involves many factors such nutritional, pathological, hormonal and genetic abnormities and involves many in-between factors as well **(1. 2, 3, 4).**

The relationship between thyroid diseases and especially those related to hormones may have extremely effect on hemostasis directly or indirectly. It is well understood that thyroid disease are common and not yet clearly linked to abnormal hemostasis or hemostasis effect related. Despite there are many disease related to primary hemostasis which is defined as abnormality in primary hemostasis exactly involves clotting factors, bleeding factors and platelets and vascular factors with other agents involved hemostasis. Other agents are many and we believe that on these essentials is metabolism and the thyroid serves as the key organ in that process. Therefore thyroid diseases in general and especially with hormonal dysfunction affect hemostasis. Interestingly and related to our topic we include disorders related metabolism and the basal metabolic rate (BMR) and the most essential organ related is the thyroid gland which involved directly and indirectly lacking and sufficiency of coagulation factors and related to vascular and cardiovascular disorders including thrombosis and embolism and related coagulation

disorders with direct impact on hemostasis and laboratory findings **(5, 6, 7).**

There has been strong relationship between abnormal hemostatis and thyroid diseases for long time and have been known since the beginning of the past century **(8).** With the first clinical link has been described in 1913, when Kaliebe reported cases of cerebral vein thrombosis in a hyperthyroidism patient **(8).** However, thyroid dysfunction and autoimmune disease may affect physiological pathways in hemostasis and lead to bleeding or thrombosis. It has been documented that there is influence of thyroid hormone on the coagulation fibrinolytic system is mainly due to interaction between the hormone and its receptors or in another way affecting coagulation and other essential factors due to the low or insufficiency in the basal metabolic rate. These lead to significance in the laboratory results ranging from subclinical laboratory abnormalities to major bleeding or fatal thrombosis.

The relationship between thyroid hormones and the coagulation system is, however, often ignored by many practitioners. One of the reasons could be that, although there strong scientific hypothesis to relate bleeding abnormalities with hypothyroidism and hyperthyroidism or vice versa, many but scientific research data on the topic is lacking. One study published in the Europian Journal of Endocrinology in 2011 the authors concluded that hypothyroid patients were more prone to develop mild to moderate bleeding **(9)**. Other study has also indicated that there is a close relation between hyperthyroidism and causing an increased sensitivity to the anticoagulant effects of warfarin which is important to monitor patients with hyperthyroidism and warfarin treatment **(10).** Also it is important to note that subclinical hyperthyroidism causes an increase in circulating clotting factor X. Hypothyroidism can cause increased fibrinogen, factor VII, increased plasminogen activator inhibitor, and decreased antithrombin III; all of these lead to a prothrombotic state[7]. Other studies such as this meta-analysis showed consistent evidence of a hypercoagulable and hypofibrinolytic state in thyrotoxicosis. And however recommended that well-designed studies with clinical and laboratory outcomes are needed to provide more definitive data **(11).** There is also a correlation that hypo coagulable state in overt hypothyroidism and a prothrombotic state **(12).**

Stuijve et al found that thyrotoxicosis shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state with a rise in factors VIII and IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1. This was observed in endogenous and exogenous thyrotoxicosis, and in subclinical as well as overt hyperthyroidism. They conclude that both subclinical and overt hyperthyroidism induce a prothrombotic state, which is therefore likely to be a risk factor for venous thrombosis **(11).** Extensive data reported in the literature indicate that abnormal hemostasis is a common phenomenon in patients suffering from thyroid dysfunction. It has been decanted that these abnormalities may do not harbor frank abnormal laboratory findings that can used to convince physicians to start treatment, although many recent studies including our study has shown abnormalities if not current but may involved future coagulopathies and, major hemorrhagic or thromboembolic complications to patients. There is a general trend that generally agreed that patients with hypothyroid disease are more prone to bleeding tendency, equally but opposite to them patients with hyperthyroidism are at a higher risk of thrombosis or embolism **(13**). Other literature reports data have convinced that the interaction between thyroid disorders and hemostasis is more complex and may require extensive molecular and other tools research. The complexity of this interaction is has been explained in a review published by Franchini in 2006, in that review he focused on particular on the different factors involved in the pathogenesis of relevant hemostatic abnormalities associated with thyroid dysfunctions clinically.

The objective of this study was to find the significance of laboratory findings in this group of patients. This led us to conduct this research to contribute solving this problem. There was only scant laboratory or investigative research on the topic internationally and locally in Saudi Arabia.

MATERIALS AND METHODS

This is a case control study focuses on the relation of abnormal hemostasis in women with thyroid problem compared with healthy ladies in Saudi Arabia. These patients are selected following referred by clinicians so their demographic, clinical and other data will be

available. 101 cases participated in the study with control of samples 52 participants. 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 and 12 to 54 years average 30.9 years for cases and the control age group respectively. All data was collected from anonymized participants were explored using informed consent and patient's Samples were obtained for and the following investigations were performed include, platelets count, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, fibrinogen assessment for hemostasis. And thyroid profiles such as Thyroid Stimulating Hormone, FT3, FT4 were estimated. Technology used for hemostasis testes is STA Compact Max® which is a fully automated benchtop analyzer built on the most reliable platform in the industry. With an expansive test menu, the Compact Max is a robust, highefficiency analyzer with enhanced throughput making it the perfect system offering for mid-sized laboratories available from the company website. And the mini VIDAS® Industry system is an immunodiagnostic system intended to be used by trained and qualified laboratory professionals, for veterinary and industrial applications. The mini VIDAS® Industry system is intended to execute an immunoassay protocol and to release results according to the package insert of the VIDAS® assay kits. 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:

This is a case control study covered 153 (101 cases with 52 cases Control group) study participants whom divided into two study groups; the first group who diagnosed with thyroid gland abnormalities (cases group) and healthy group (control group). Nearly two thirds of them were classified in cases group (66%) while (34%) were in the control group as displayed in table 1 and figure 1: In this study the difference between the coagulation findings had been assessed to realize the effect of thyroid abnormalities on the coagulation parameters using t statistical test to assess the difference

between unpaired means. The analysis found the following; we found a significant increasing in bleeding time (difference of 0.5 seconds, p value 0.002), clotting time (difference of 0.7 seconds, p value < 0.001), PT (difference of 0.6 seconds, p value 0.001), and APTT (difference of 0.2 seconds, p value 0.046) as displayed in table 22 and figures 3 – 6. Our study did not able to detect any significant difference in platelets count (difference of 8.9 $x10^3$, p value 0.506) or fibrinogen level (difference of 0.8 (mg/dl), p value 0.830) between the two study groups as showed in table 3 and figures 2 and 7. Regarding the interpretation of the coagulation findings among CASES group, our study found that; HIGH results were obtained as following; Platelets count (5%), Bleeding Time (8.9%), Clotting Time (10.9%), PT (21.8%), APTT (25.7%), and Fibrinogen (14.9%). In CONTROL group, all coagulation findings were normal except (3.8%) of them who had high results in PT as showed in table 3. Regarding the interpretation of the thyroid function tests results findings among CASES group, the study found that (63.4%) of them had high results in TSH, (13.9%) in FT3, and (17.8%) in FT4 results. All TFTs were normal among CONTROL group as detailed in table 4.

Table (1) the distribution of the study participants according to their study groups (n = 153, 101 cases + 52 controls)

Study groups	Frequency	Percent
Cases	101	66.0
Controls	52	34.0
Total	153	100.0

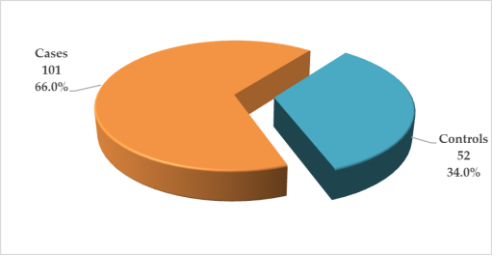

Figure (1) the distribution of the study participants according to their study groups (n = 153, 101 cases + 52 controls)

Table (2) the deference in the coagulation findings between the study groups (n = 153, 101 cases + 52 controls)

Automated Technology	Investigation	Study group		Difference	95% CI	P value
		Cases (Mean)	Controls (Mean)			
Sysmex KX21	Platelets count (x10³)	291.3	300.2	8.9	-17.44 to 35.24	0.506
	Bleeding Time (min)	3.7	3.2	-0.5	-0.81 to -0.18	0.002
	Clotting Time (min)	6.0	5.3	-0.7	-1.08 to -0.31	< 0.001
STAGO Full Automated	PT (Sec)	14.6	14.0	-0.6	-1.08 to -0.31	0.001
	APTT (Sec)	37.0	36.8	-0.2	-1.18 to -0.01	0.046
	Fibrinogen (mg/dl)	308.0	308.8	0.8	-2.04 to 1.64	0.830

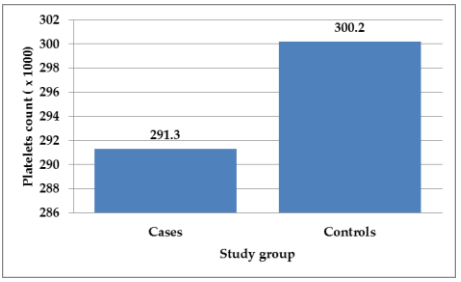

Figure (2) the deference in the Platelets count between the study groups (n = 153, 101 cases + 52 controls)

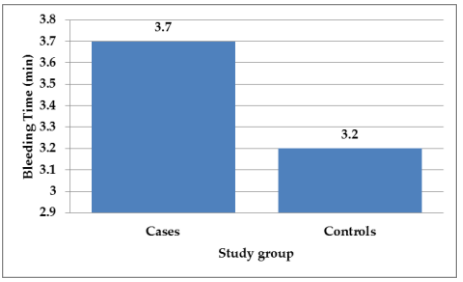

Figure (3) the deference in the Bleeding Time between the study groups (n = 153, 101 cases + 52 controls)

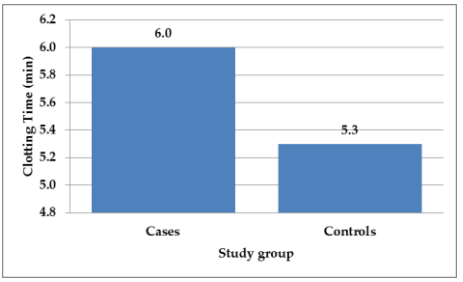

Figure (4) the deference in the Clotting Time between the study groups (n = 153, 101 cases + 52 controls)

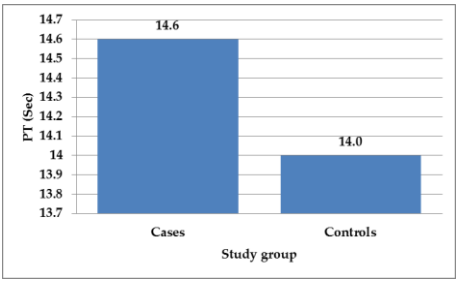

Figure (5) the deference in the PT between the study groups (n = 153, 101 cases + 52 controls)

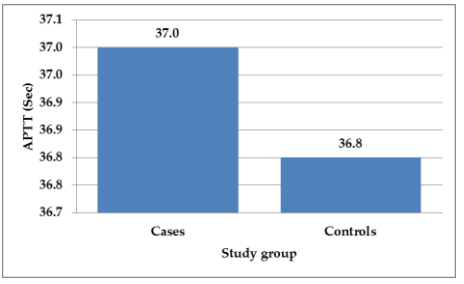

Figure (6) the deference in the APTT between the study groups (n = 153, 101 cases + 52 controls)

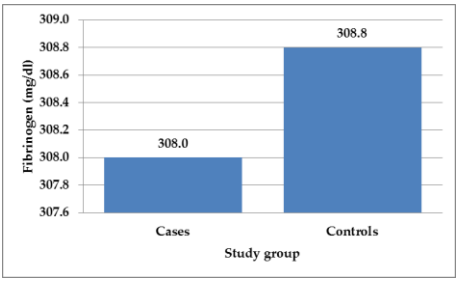

Figure (7) the deference in the Fibrinogen between the study groups (n = 153, 101 cases + 52 controls)

Table (3) the interpretation of Coagulation investigations between the study groups (n = 153, 101 cases + 52 controls)

Coagulation investigations		Cases (n =101)		Controls (n = 52)	
		Freq.	Percent	Freq.	Percent
Platelets count (x10^3)	Low	2	2.0	0	0.0
	Normal	94	93.0	52	100.0
	High	5	5.0	0	0.0
Bleeding Time (min)	Low	4	4.0	0	0.0

	Normal	88	87.1	52	100.0
	High	9	8.9	0	0.0
Clotting Time (min)	**Low**	0	0.0	0	0.0
	Normal	90	89.1	52	100.0
	High	11	10.9	0	0.0
PT (Sec)	**Low**	6	5.9	0	0.0
	Normal	73	72.3	50	96.2
	High	22	21.8	2	3.8
APTT (Sec)	**Low**	19	18.8	0	0.0
	Normal	56	55.4	52	100.0
	High	26	25.7	0	0.0
Fibrinogen (mg/dl)	**Low**	17	16.8	0	0.0
	Normal	69	68.3	52	100.0
	High	15	14.9	0	0.0

Table (4) the interpretation of Thyroid function tests between the study groups (n = 153, 101 cases + 52 controls)

Thyroid function tests		**Cases (n =101)**		**Controls (n = 52)**	
		Freq.	**Percent**	**Freq.**	**Percent**
TSH	**Low**	35	34.7	0	0.0
	Normal	1	1.0	52	100.0
	High	65	64.4	0	0.0
FT3	**Low**	51	50.5	0	0.0
	Normal	36	35.6	52	100.0
	High	14	13.9	0	0.0
FT4	**Low**	28	27.7	0	0.0
	Normal	55	54.5	52	100.0
	High	18	17.8	0	0.0

DISCUSSION:

As a case control study covered 153 participants, these study participants has been divided into two study groups; while the first group who diagnosed with thyroid gland abnormalities (cases group) the other was a healthy group (control group). As overall estimation, nearly two thirds of them were classified in cases group (66%) while (34%) were in the control group. We have noted that in our study the difference between the coagulation findings had been assessed to realize the effect of thyroid abnormalities on the coagulation parameters using t statistical test to assess the difference between unpaired means. The analysis found the following. The significant increasing in bleeding time, clotting time (difference of 0.7 seconds, p value < 0.001), PT, p value 0.001, and APTT, p value 0.046. These justifies there is strong relation between thyroid dysfunction which

harboured coagulation abnormality. Also our study did not able to detect any significant difference in platelets count with p value 0.506 or fibrinogen level p value 0.830 between the two study groups. The possible reason and based on coagulation pathways which were complicated and it seemed that both platelets and fibrinogen will be affected when true coagulation or clotting process is triggered as the platelets came initially and fibrinogen significance is late or end product, Regarding the interpretation of the coagulation findings among case group, our study found that; higher results were obtained as follows; Platelets count (5%), Bleeding Time (8.9%), Clotting Time (10.9%), PT (21.8%), APTT (25.7%), and Fibrinogen (14.9%). In control group, all coagulation findings were normal except (3.8%) of them who had high results in PT. Regarding the interpretation of the thyroid function tests results findings among cases group, the study found that (63.4%) of them had high results in TSH, (13.9%) in FT3, and (17.8%) in FT4 results (17). All TFTs were normal among control group. 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. Referring to Squizzato et al, we can also conclude that, this research approved that thyroid dysfunctional diseases, hypothyroidism and hyperthyroidism, and subclinical, affect hemostasis. However, the overall coagulation and fibrinolytic effect has been documented in this study. Hypothyroidism and hyperthyroidism affect coagulation-fibrinolytic tests and in fact it affects hemostasis and reports should be considered by physicians (16). The effect is consistent among participants in this study and in the control group justifies the support the increased risk of bleeding in hypothyroidism and an increased risk of thrombosis in hyperthyroidism. Even if some results are discordant and not matched with other findings especially in platelets and fibrinolytic system but may be indirectly **(8)**.

Based on Squizzato et al, there were no definitive data available for the assessment the degree of the hypocoagulable and hypercoagulable state in overt hypothyroidism and hyperthyroidism, respectively. Published case reports suggest a clinical relevance, but prospective clinical studies are absolutely lacking **(7,8)**.

Hypothyroidism and hyperthyroidism affect the hemostatic balance and this supports the idea that thyroid hormone excess and

deficit are the main mechanisms of a hypercoagulable and hypocoagulable state, respectively especially for hypermetabolic and hypometabolic states. The complex hemostatic balance is influenced by autoimmune mechanisms, including idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome, or acquired hemophilia, and other underline genetic disorders albeit indirectly. The hypercoagulable and hypocoagulable states are probably independent of the underlying pathophysiology of thyroid disease which is complicated by nutritional, endocrine and other pathologies. In the past, other hypotheses have been postulated to explain coagulation abnormalities in thyroid patients, such as endogenous arginine vasopressin and adrenergic system imbalance, but these have never been proven (14).

Other studies however, support the concept of a hypercoagulable state in subclinical hypothyroidism which is supported in our study. Once again this study with this few data and short term of study was significant, we attribute these result to the objective of the study, good SOPs, quality of machines, sample handling, reagents and selection of patients. In literature, there were few coagulation test abnormalities have been described in subclinical hyperthyroidism and hypothyroidism. Our study was also supported by one study, investigated for coagulation-fibrinolytic abnormalities in subclinical hyperthyroidism **(15)**.

CONCLUSION:

From a research point of view, study of the effects of thyroid hormone and its impact on certain components of the hemostatic system, for example effects on coagulation factors synthesis or on platelet function and metabolism, fibrinolytic system with support of advance understanding of the mechanism of action of thyroid hormone at the cellular level and may provide insight into the functioning and regulation of the hemostatic system itself therefore we recommend that further studies in team involving laboratory professionals and endocrinologists is important for reaching the correct consensus for integrating hemostasis laboratory findings for better management of patients with thyroid diseases.

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