DOI: https://doi.org/10.53350/pjmhs2216440

ORIGINAL ARTICLE

Correlations of Plasma Thyroxine with Activated Partial Thromboplastin Time and Fibrinogen Levels in Hyperthyroid Patients

AYESHA IMTIAZ MALIK[1], FARHEEN ZEHRA[2], AYESHA SHAFQAT[3], SAIMA TABASSUM[4], NAJMA QURESHI[5], NIDA TOSIF[6]
[1,2,6]*Department of Pathology, Niazi Medical & Dental College, Sargodha*
[3]*Department of Physiology, Mohi-ud-Din Islamic Medical College, Mirpur, AJK*
[4]*Department of Physiology, Niazi Medical & Dental College, Sargodha*
[5]*Department of Pathology, Mohi-ud-Din Islamic Medical College, Mirpur, AJK*
Correspondence to Dr. ayesha Imtiaz Malik, Email: drmalikayesha@gmail.com, cell: 0321-3997799

ABSTRACT

Background: A complex pattern of hypercoagulability is associated with hyperthyroidism which is attributed to the actions mediated by boosting up of platelet activation, release of pro-coagulatory cytokines and chemokines, and probable interactions of activated platelets and endothelial cells that may lead to increased risk for intravascular thrombosis. Hyperthyroidism is linked to higher levels of fibrinogen, vWF and factor VIII, lower levels of plasminogen and plasminogen activator, decrease in PT and activated partial thromboplastin time (aPTT) levels and non-significant changes in PAI and antiplasmin levels.
Aim: To assess the hypercoagulability and determine the correlation of plasma T4 with aPTT and fibrinogen levels in hyperthyroid patients. M**ethods:** It was an observational prospective study carried out at Niazi Medical College and teaching hospital, Sargodha from January to November 2021. 118 patients with diagnosed hyperthyroidism and above 15 years were recruited in the study that did not have history of coagulability of blood such as hemophilia, immune disorders, cancers, pregnancy, clinically known hypercoagulable state, and on any type of anticoagulant therapy. Levels of thyroid hormones (TSH, T3 and T4), aPTT and fibrinogen were measured in the laboratory. Data was analyzed using SPSS version 20. Frequencies, percentages and range were calculated for categorical variables. Spearman's correlation was used to determine the correlation between plasma T4 levels and aPTT and plasma T4 and fibrinogen in all patients.
Results: Cumulative results showed that 34 (29%) patients had T4 level between 11– 16µg/dl, 45(38%) between 17- 21µg/dl and 39(33%) had T4 levels > 21 µg/dl. Spearman's correlation's results to determine association between plasma T4 and aPTT revealed that a strong negative correlation (rs= -.67, p< .001) exists between plasma levels of Thyroxine (M = 18.49, SD= 3.78) and aPTT (M=23.70, SD=1.70). A moderate positive correlation (rs= .37, p < .001) is evident between plasma thyroxine (M = 18.49, SD = 3.78) and fibrinogen (M = 4.27, SD = 0.43) levels.
Conclusion: High levels of thyroxine (T4) lead to a hypercoagulable state due to shortened aPTT and higher fibrinogen levels and there is a strong negative correlation between plasma thyroxine (T4) and aPTT and fibrinogen levels in hyperthyroid patients.
Keywords: Hyperthyroidism, hypercoagulability, thyroxine (T4), activated partial thromboplastin time (aPTT).

INTRODUCTION

Globally, disorders of thyroid gland and diabetes mellitus are the most common endocrine disorders regardless of age and gender.[1,2] Thyroid gland ailments usually range from subclinical symptoms to overt hyper-or hypothyroidism. As highlighted by the American Thyroid Association, 20 million Americans are reported to experience any form of thyroid abnormality and out of these, 12% will develop a thyroid disease eventually during their lifetime. [3] In Pakistan, it is stated that the prevalence of hyperthyroidism is around 5.1% and 5.8% in males and females respectively whereas that of hypothyroidism is around 4.1 and 5.4% respectively[4]**.** It is evident that the incidence of hyperthyroidism is lower as compare to hypothyroidism in general population of Pakistan as is also indicated by another study[5]**.**

Thyroid hormones are shown to be effective mediators of several physiological processes, one of them is coagulation, therefore, their irregularities can drastically impact the coagulation cascade[6-8]**.** Thyroid problems can cause a variety of hemostatic complications, extending from minor laboratory abnormalities to substantial clinically evident hemostatic dysfunctions, even serious bleeding and thromboembolism[9-10]**.** Hypothyroid patients are vulnerable of bleeding, while those with hyperthyroidism are more likely to have thromboembolic problems (8–40%) including major emboli, accounting for 18% of deaths associated with thyrotoxicosis[10]**.**

There is substantial evidence showing that coagulation factors are altered due to raised circulating thyroid hormone levels[11-13]**.** Although the mechanisms appear to be more complex, it is hypothesized that the actions are mediated by triggering activation of platelets, release of pro-coagulatory cytokines and chemokines and activated platelets and endothelial cells' interactions that may lead to increased risk for intravascular thrombosis.[13] Recent studies have established a genomic relation too between thyroid hormone and nuclear thyroid hormone receptor (TR), TRb. [14-15] Hyperthyroidism usually causes hypercoagulability and hypofibrinolysis,[12-16] and is linked to higher levels of fibrinogen, vWF and factor VIII,[17-18] lower levels of plasminogen and plasminogen activator, and minor changes in PAI and antiplasmin levels.[17] A significant decrease in PT and aPTT levels have also been reported.[19] All above factors point towards hypercoagulable state putting patients at risk of thromboembolism.

This study was not only aimed to evaluate the potential risk of disturbances in the coagulation system in hyperthyroid patients as indicated by altered aPTT and fibrinogen levels but also to define the association between these hemostatic markers and thyroid hormones. Very limited data is available to highlight the association of serum thyroid hormones and coagulation indices (aPTT and fibrinogen) and no study has yet been reported in South Asia. Therefore, to our knowledge this study is the first to describe such association.

The objective of the study was to observe the hypercoagulability by measuring levels of aPTT and fibrinogen in hyperthyroid patents and to determine the association between plasma thyroxine (T4) levels and aPTT and fibrinogen levels in hyperthyroid patients.

MATERIALS AND METHODS

It was a prospective observational cohort study which was carried out at the pathology laboratory of Niazi Medical College and Teaching hospital, Sargodha from January to November 2021 after permission from International Ethical Review Board. 118 (sample size calculated from open Epi3 with confidence interval of 98%) patients with diagnosed hyperthyroidism were recruited from medical OPD, endocrinology OPD, and medical wards that were referred for testing of aPTT and fibrinogen levels.

Inclusion Criteria: All diagnosed cases of hyperthyroidism (treatment naïve or uncontrolled with medication), more than 15 years of age, of both genders who willingly gave consent and assent were included in the study.
Exclusion Criteria: Patients with any other diseases which could alteraPTT and fibrinogen levels, or coagulability of blood such as hemophilia, immune disorders like systemic lupus erythematosus, rheumatoid arthritis etc, cancers, pregnancy, clinically known hypercoagulable state, and on any type of anticoagulant therapy were excluded from the study.

METHODOLOGY

Levels of thyroid hormones (TSH, T3 and T4), aPTT and fibrinogen were measured in the laboratory. Reference range of aPTT was taken to be 26-40 seconds while that of fibrinogen is 1.8 – 3.6 g/l[20] The level of TSH was taken to be 0.35 – 5.5mIU/L, and T4 is 4.9 – 11.7µg/dl. Throughout the study period the quality of test results was validated by regular internal quality control (IQC) procedures. 10 ml of venous sample was drawn using venipuncture. TSH, T4, aPTT and fibrinogen level were measured by commercially available automated analyzer. Statistical analyses were performed using the statistical package SPSS version 20 and the level of statistical significance was set at P value < 0.05. Frequencies, percentages and range were calculated for categorical variables. Spearman's correlation was used to determine the correlation between plasma T4 levels and aPTT and plasma T4 and fibrinogen in all patients.

RESULTS

As highlighted in Table 1, number of patients in our study was 118 out of which 43 (36%) were males and 75(64%) were females. 24 males and 62 females were married. Minimum age was 19 while maximum age was 65 years with a mean of 35.54 years. 34(29%) patients had T4 level between 11–16µg/dl, 45(38%) between 17 - 21 µg/dl and 39(33%) had T4 levels > 21µg/dl. aPTT levels range from 17 sec to 28 sec (Mean=23.7 sec, S.D. 1.691) (Fig 1). Fibrinogen levels range from 2.9 to 5.2 g/dl (mean= 4, SD= .432) (Fig 2).To test the association between plasma levels of T4 and aPTT, a Spearman's correlation was conducted (Table 2). The results showed that there is a strong negative correlation (rs = -.67, p < .001) between plasma levels of thyroxine (M = 18.49, SD = 3.78) and aPTT (M = 23.70, SD=1.70). The Spearman's correlation test between plasma levels of thyroxine (M=18.49, SD = 3.78) and fibrinogen (M=4.27, SD=0.43) depicted a moderate positive correlation (rs = .37, p < .001) (Table 3). These results revealed that hyperthyroidism is associated with hypercoagulable state due to shortened aPTT and hypofibrinolysis due to elevated levels of anti-fibrinolytic clotting factors like fibrinogen.

Fig 1:

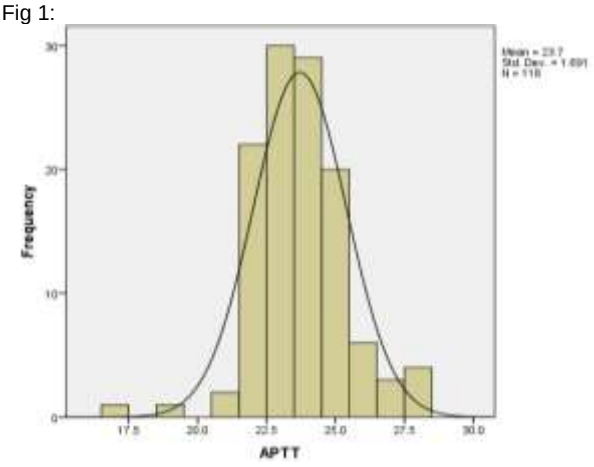

Fig. 2:

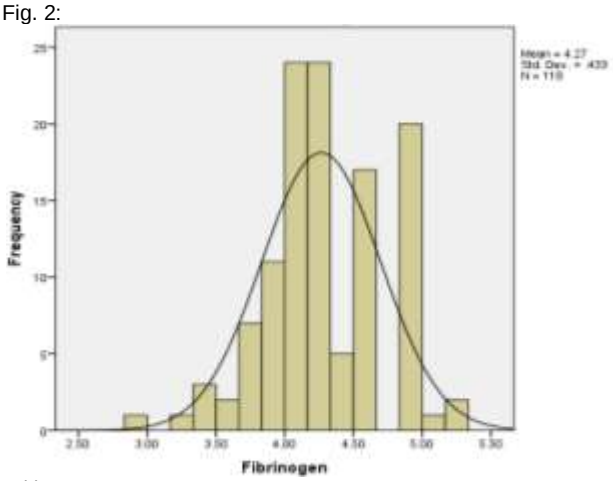

Table 1:

Variable	Frequency (N=118)	%age
Gender		
Males	43	36
Females	75	64
Marital status		
Married	66	56
Unmarried	52	44
Plasma T4 level (µg/dl)		
11- 16	34	28.8
17 - 21	45	38.1
>21	39	33.1

Table 2: Spearman's Correlation Table Showing the Association between Plasma Levels of T4 and aPTT

		T4	Fibrinogen
T4	Correlation Coefficient	T4	Fibrinogen
	Sig (2-tailed)	1.00	.37
	N	-	.000***
Fibrinogen	Correlation Coefficient	118	118
	Sig (2-tailed)	.37	1.00
	N	.000***	-
		118	118

Note. N = 118 hyperthyroid patients. ***,p < .001 level.

Table 3: Spearman's Correlation Table Showing the Association between Plasma Levels of Free T4 and Fibrinogen

		T4	Fibrinogen
T4	Correlation Coefficient	1.00	.37
	Sig (2-tailed)	-	.000***
	N	118	118
Fibrinogen	Correlation Coefficient	.37	1.00
	Sig (2-tailed)	.000***	-
	N	118	118

Note. N = 118 hyperthyroid patients. ***, p < .001 level

DISCUSSION

The strong correlation between the thyroid hormones and the coagulation system has long been cherished in the past[5]**.** Several coagulation and fibrinolytic abnormalities have been extensively described in patients with dysfunctions of thyroid gland. All previous studies point towards the fact that hyperthyroidism is associated with hypercoagulability including the risk of thromboembolism.

The current study investigated the relationship between thyroid hormones and the coagulation system in hyperthyroid patients with abnormal plasma T4 levels. Our study showed that aPTT was shortened in hyperthyroid patients. This finding was consistent with results of Squizzato et al[6], Lippi at al[21], Mohammed Ali et al[19] and Thoyyib et al[22]**.**

Because the aPTT has been proven to be a risk factor for venous thrombosis regardless of factor VIII and IX activity[23] this finding reflects its meaningfulness clinically. There was a negative association found in current study between plasma thyroxine levels and aPTT in hyperthyroid patients. However, we could not find similar studies to show such association, therefore, it might be the initial study to describe such association. A study conducted by Debeij et al highlighted a negative association between free thyroxine levels and venous thromboembolism[11] Plasma fibrinogen levels were also higher in our study group emphasizing on the procoagulant effect in hyperthyroid patients. A large cross sectional Study conducted in Germany by Dorr M. et al[24] showed elevated plasma fibrinogen in overt hyperthyroidism compared to euthyroids thereby aiding our finding. Similar results were shown in studies of Stuijver et al[12], Squizzato et al[6] and Mohammad- Ali et al[19] Thoyyib et al, on the contrary, reported that their study showed no increase in levels of fibrinogen in hyperthyroidism[22].

This, to our knowledge, is the first study that reports a negative association between plasmaT4 levels and aPTT in hyperthyroid patients. With prevalence of thromboembolism in hyperthyroid patients to be around 8–10%[25] including pulmonary and cerebral thromboembolism[12], this study will provide a foundation for future research in this field and will be beneficial for clinicians in assessing hypercoagulability in hyperthyroid patients prior to any intervention in order to prevent significant morbidity. Although routine measurement of coagulation factors is not indicated in hyperthyroid patients, but in light of the correlation of hypercoagulability with the degree of rise in thyroxine levels as highlighted in current study, it would be useful to conduct large randomized trials to determine systematically limit at which assessment of coagulation is indicated in hyperthyroidism.

CONCLUSION

We conclude that high levels of plasma thyroxine (T4) shift the hemostatic system to a hypercoagulable state (as evident by shortened aPTT and higher fibrinogen levels) and there is a strong negative association between plasma thyroxine (T4) and aPTT and fibrinogen levels stressing that hyperthyroid patients need to be evaluated for hypercoagulable state in order to prevent the risk of thromboembolism.

Conflict of interest: There is no conflict of interest that would prejudice the neutrality of this scientific research.

Limitation: The limitation of our study is the small sample size which does not allow us to randomize our results. Moreover, demographic variables (e.g. smoking, body mass index, hypertension, etc.) other than age, gender and marital status could not be retrieved from our database.

REFERENCES

1. Zoofishan B, Kabir A, Amir S and Faryal, R. Relationship of symptoms with demographic features in case of thyroid disorders in Pakistani population. Asian J. of Biomedical & Pharmaceutical Sciences.2012; 2(12):37-40.
2. Hage M, Zantout MS, and Azar ST. Thyroid Disorders and Diabetes Mellitus. Journal of Thyroid Research.2011; 2011: 439463.
3. General Information/Press Room [Internet]. American Thyroid Association. [cited 2021, December 22nd]. Available from: https://www.thyroid.org/media-main/press-room/
4. Reza S, Shaukat A, Arain TM, Riaz QS, and Mahmud M. Expression of Osteopontin in Patients with Thyroid Dysfunction. PLoS ONE. 2013; 8 (2):1-7.
5. Shah N, Ursani TJ, Shah NA, Raza HM. Prevalence and Manifestations of Hypothyroidism among Population of Hyderabad, Sindh, Pakistan. Pure and Applied Biology. 2020; 10(3): 668-675.
6. Squizzato A, Romualdi E, Buller HR, Gerdes VE. Clinical review: Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. J Clin Endocrinol Metab. 2007; 92(7):2415–20. doi: 10.1210/jc.2007-0199
7. Vescovi PP, Favaloro EJ, Lippi G, Garofano M, Montagnana M, Manzato F, et al. The spectrum of coagulation abnormalities in thyroid disorders. Semin Thromb Hemost. 2011; 37(1):7–10.
8. Erem C. Coagulation and fibrinolysis in thyroid dysfunction. Endocrine. 2009; 36(1):110–8. doi: 10.1007/s12020-009-9185-z. [PubMed: 19367377].
9. Davis PJ, Mousa SA, and Schechter GP. New Interfaces of Thyroid Hormone Actions with Blood Coagulation and Thrombosis. Clinical and Applied Thrombosis/Hemostasis. 2018; 24(7):1014-1019.
10. Elbers LPB, Fliers E, and Cannegieter SC. The influence of thyroid function on the coagulation system and its clinical consequences. J Thromb Haemost. 2018; 16: 634–45
11. Debeij J, van Zaane B, Dekkers OM, Doggen CJ, Smit JW, van Zanten AP, Brandjes DP, Büller HR, Gerdes VE, Rosendaal FR, and Cannegieter SC. High levels of procoagulant factors mediate the association between free thyroxine and the risk of venous thrombosis: the MEGA study. J Thromb Haemost. 2014;12(6):839-846
12. Stuijver DJF, van Zaane B, Romualdi E, Brandjes DPM, Gerdes VEA, and Squizzato A. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: a systematic review and meta-analysis. Thromb Haemost. 2012; 108(6):1077-1088.
13. Horacek J, Maly J, Svilias I, Smolej L, Cepkova J, Vizda J, Sadilek P, Fatorova I, and Zak P. Prothrombotic changes due to an increase in thyroid hormone levels. Eur J Endocrinol. 2015; 172(5):537-542.
14. Davis JP, Mousa SA, and Schechter GP. New interfaces of thyroid hormone actions with blood coagulation and thrombosis. Clinical and Applied Thrombosis/Hemostasis .2018; 24(7):1014-1019,
15. Elbers LP, Moran C, Gerdes VE, van Zaane B, Meijers J, Endert E, Lyons G, Chatterjee VK, Bisschop PH, Fliers E. The hypercoagulable state in hyperthyroidism is mediated via the thyroid hormone beta receptor pathway. Eur J Endocrinol. 2016;174: 755-762.
16. Franchini M, Montagnana M, Manzato F, Vescovi PP. Thyroid dysfunction and hemostasis: an issue still unresolved. Semin Thromb Hemost.2009; 35(3):288–94.
17. Horacek J, Maly J, Svilias I, Smolej L, Cepkova J, Vizda J, et al. Prothrombotic changes due to an increase in thyroid hormone levels. Eur J Endocrinol. 2015; 172(5):537–42.
18. Poplawska-Kita A, Siewko K, Telejko B, Modzelewska A, Mysliwiec J, Milewski R, et al. The changes in the endothelial function and haemostatic and inflammatory parameters in subclinical and overt hyperthyroidism. Int J Endocrinol. 2013: 981638
19. Mohamed-Ali MS, and Ahmed RO. Coagulation profiles in hypothyroid and hyperthyroid female patients in Sudan. Saudi Med J. 2008; 29(9):1289–93
20. Barbara J. Bain, Imelda Bates, Mike A Laffan. Investigations of hemostasis (chapter 18). Dacie and Lewis Practical Haematology (12th edition) .2017, Elsevier Ltd.
21. Lippi G, Franchini M, Targher G, Montagnana M, Salvagno GL, Guidi GC, et al. Hyperthyroidism is associated with shortened APTT and increased fibrinogen values in a general population of unselected outpatients. J Thromb Thrombolysis. 2009; 28(3):362–5.
22. Thoyyib M, Garg S, Gupta N, Aggarwal S, and Pandit S. Study on coagulation factor VIII and fibrinogen levels in patients with thyroid disorders. Indian J Endocr Metab. 2018; 22:479-84
23. Hron G, Eichinger S, Weltermann A, Quehenberger P, Halbmayer WM, and Kyrle PA. Prediction of recurrent venous thromboembolism by the activated partial thromboplastin time. J Thromb Haemos. 2006; 4:752–756
24. Dorr M, Robinson DM, Wallaschofski H, Schwahn C, John U, Felix SB, and Völzke H. Low serum thyrotropin is associated with high plasma fibrinogen. J Clin Endocrinol Metab. 2006; 91(2):530–34.
25. Erem C. Thyroid disorders and hypercoagulability. Seminars in Thrombosis and Hemostasis. 2011; 3:17–26.