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A longitudinal observational study on activated partial thromboplastin time in hypothyroidism and effect of thyroxine supplementation

JAYACHANDRA B *, ANAND NANASAHEB PATIL and AMEEQ AHAMED

Department of General Medicine, Al-Ameen Medical College and Hospital, Vijayapura, Karnataka, India.

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Abstract

Background: Hypothyroidism is a common condition characterized by thyroid hormone deficiency, which, if untreated, can lead to severe health consequences and even death. Due to the wide range of clinical presentations and non-specific symptoms, hypothyroidism is primarily diagnosed biochemically. It can result from congenital thyroid abnormalities or iodine deficiency.

Aims and objectives: Aim: To evaluate the correlation between hypothyroidism and Activated Partial Thromboplastin Time (aPTT) and assess the effect of thyroxine supplementation.

Objective: To study the impact of levothyroxine supplementation on aPTT in hypothyroid patients.

Materials and methods: This observational study was conducted at the General Medicine outpatient clinic and inpatient wards at Al-Ameen Medical College and Hospital, Vijayapura, from September 2022 to March 2024. A total of 80 hypothyroid patients of both sexes were included. TSH, Free T4, and aPTT levels were measured with appropriate aseptic precautions.

Results: The majority of subjects were females (90%), with the highest proportion (31.3%) aged 26-35 years. The mean ± SD of pre-thyroxine TSH was 25.453 ± 19.9073, which significantly decreased to 4.299 ± 0.6738 post-thyroxine. aPTT values also decreased significantly post-treatment. A positive correlation was found between TSH and aPTT, while aPTT had a negative correlation with T3 and T4 levels.

Conclusion: aPTT is significantly elevated in hypothyroid patients and shows a positive correlation with TSH levels. Regular monitoring of aPTT should be included in the follow-up of hypothyroid patients.

Keywords: Hypothyroidism; aPTT; TSH; Levothyoxine supplementation; Pre-thyroxine and Post thyroxine-aPTT

1. Introduction

Thyroid hormones are known to be the key regulators of metabolism. Thyroxine (T4) and triiodothyronine (T3) are both produced by the thyroid gland. T4 is the main product and is converted in the periphery by deiodination to T3 which is the main biologically active thyroid hormone. Thyroid dysfunction leads to hypo and hyperthyroidism[1].

Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. If untreated, it can lead to serious adverse health effects and ultimately death. Because of the large variation in clinical presentation and general absence of symptom specificity, the definition of hypothyroidism is pre-dominantly biochemical. Overt or clinical

* Corresponding author: JAYACHANDRA B

primary hypothyroidism is defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range[2].

Hypothyroidism is one of the commonest chronic disorders in Western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000.1 During 2006 12 million prescriptions for levothyroxine (50 μg or 100 μg tablets) were dispensed in England, equivalent to about 1.6 million people taking long term thyroid replacement therapy, about 3% of the population[3].

The prevalence of hypothyroidism in India is 11%, compared with only 2%–4.6% in the Western population. Inland states have a higher prevalence of hypothyroidism compared to coastal states (11.7% vs. 9.5%), probably due to iodine deficiency.

Several disorders of coagulation and fibrinolysis have been widely reported in patients with thyroid dysfunctions. From a clinical standpoint, it is important to note that these coagulation-fibrinolytic disorders usually range from mild to moderate and rarely to severe laboratory abnormalities. Moreover, because they are rapidly reversible after pharmacologic treatment of the hormonal dysfunction, they would appear to be usually of limited importance in clinical practice, provided the underlying disorder is recognized quickly and treated appropriately[3,4].

The link between the hemostatic system and thyroid diseases has been known since the beginning of the past century. The first clinical association was described in 1913, when kaliebe reported an episode of cerebral vein thrombosis in a thyrotoxic patient. Several elements of the process of thrombus formation may be involved. Both thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary hemostasis and lead to bleeding or thrombosis[5].

Thus, hyperthyroidism has predominantly been associated with a hypercoagulant state and a higher risk of venous thromboembolic events, whereas hypothyroidism has been associated with a hypocoagulant state and a higher risk of bleeding episodes. Concerning hypothyroidism and the impact of low levels of thyroid hormones, original investigations have mainly described prolonged activated partial thromboplastin time (APTT) along with a decrease in the level of coagulation factor VIII and von Willebrand factor (vWF)[6].

The influence of thyroid hormone on the coagulation fibrinolytic system is mainly mediated by the interaction between the hormone and its receptors. Various abnormalities have been described, ranging from subclinical laboratory abnormalities to major hemorrhages or fatal thromboembolic events[7]. The relationship between thyroid hormones and the coagulation system is, however, often ignored. One of the reasons could be that, although several *in vivo* abnormalities have been reported in patients with hypothyroidism and hyperthyroidism, most published studies focus on laboratory measurements[8].

In individuals with decreased levels of thyroxine, an increased bleeding time was seen together with a prolonged activated partial thromboplastin time and prothrombin time (PT) and decreased levels of factor VIII, von Willebrand factor, and fibrinogen[9]. However, the reports from previous literature are still controversial in hypothyroidism. Some of the literature data have suggested hypothyroidism produces a hypocoagulable state. However, more recent data evidenced the contradictory fact. Patients with hypothyroidism are at increased risk of developing bleeding complications, which could be relevant in patients undergoing invasive procedures[10].

The clinical implications of the effects of thyroid hormone on the hemostatic system, however, have received relatively little attention.

Thus, the present study, has been undertaken to evaluate activated partial thromboplastin time in hypothyroidism and effect of thyroxine supplementation.

Aims

To evaluate CO-RRELATION between hypothyroidism and Activated Partial Thromboplastin Time and to identify the effect of thyroxine supplementation.

Objective

To study levothyroxine supplement on Activated Partial Thromboplastin Time in hypothyroid patients.

2. Material and methods

2.1. Study design

Longitudinal observational study

2.2. Source of data

Patients with Hypothyroidism attending the General Medicine outpatient clinic and inpatients at AL-AMEEN MEDICAL COLLEGE AND HOSPITAL VIJAYAPUR from SEPTEMBER 2022 TO MARCH 2024, will be taken for the study considering the inclusion and exclusion criteria.

2.3. Inclusion criteria

- All newly diagnosed clinical or subclinical cases of hypothyroidism
- Age >18years
- Both male and female, who were willing to give consent

2.4. Exclusion criteria

Those diagnosed with

- Hemophilia
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjogren's Syndrome
- Malignancies
- Pregnant patients
- Patients on any type of anticoagulant therapy
- Chronic liver disease
- Sepsis

SAMPLE SIZE: 80

2.5. Method of collection of data

80 patients of both sexes with hypothyroidism attending the outpatient clinic and inpatients at AL-AMEEN MEDICAL COLLEGE AND HOSPITAL VIJAYAPUR from SEPTEMBER 2022 TO MARCH 2024, will be taken for the study.

After obtaining Institutional ethical clearance, an informed written consent was taken from all patients before the inclusion to the study. A detailed history of all individuals was taken by using a predesigned proforma. The proforma considered the general symptoms of hypothyroidism such as fatigue, constipation, weight gain, menstrual irregularities, hair loss, apathy, shortness of breath, dry skin and lower limb swelling. Patients were also examined for any signs of hypothyroidism including thyroid swelling and pallor.

2.6. Method of test

2.6.1. Biochemical assay

TSH, Free T4 and aPTT levels are checked after taking adequate amount of blood with strict aseptic precautions.

- Assessment of thyroid function in these patients was carried out.
- Thyroid stimulating hormone (TSH) was measured using immunometric assays.
- Free serum thyroxin level (FT4) was measured using solid-phase chemiluminescent competitive immunoassay method for the quantitative determination of FT4 in serum.
- Reference values were 0.2 - 5 mIU/ml for TSH and 9 - 20 pmol /L for FT4.

Clinical hypothyroidism is defined on the basis of the criteria of thyroid abnormalities as defined by the Dutch National Healthcare Consensus Committee.

Subclinical hypothyroidism: it is indicated by increased serum TSH in the presence of a normal serum FT4 level.

Clinical hypothyroidism: it is indicated by increased serum TSH with decreased serum FT4 level, at which stage most patients have symptoms and benefit from treatment.

aPTT was done in all patients biochemically diagnosed with hypothyroidism.

2.6.2. Reference value (Test / Control): 30 - 40 sec / 32 sec.

Patients with TSH > 10 was taken for the study as Levothyroxine therapy has been recommended for patients with TSH persistently > 10 mIU/1 (156). Severity scoring was done as per the study done by Thoyyib et al). Patients were then started on treatment with levothyroxine. Patients were followed up until they attained an euthyroid state, usually after 6 weeks of initiation of treatment. TSH, Free T4 and aPTT were repeated, within 1 week of attaining euthyroid state. The association between TSH and aPTT was evaluated and the alteration in after attaining euthyroid state was noted.

2.6.3. Outcome

TSH, Free T4 and aPTT levels after levothyroxine supplementation.

2.7. Statistical analysis

Data was entered in Microsoft excel and was analyzed using statistical software. The association between activated partial thromboplastin time and TSH levels was done using student paired t test. The degree of association between TSH and aPTT, also between their delta values was determined using Spearman's correlation coefficient

3. Results

Table 1 Distribution of age

Age	Frequency	Percentage
15-25 years	17	21.3
26-35 years	25	31.3
36- 45 years	20	25.0
46-55 years	10	12.5
56- 65 years	6	7.5
>65 years	2	2.5
Total	80	100.0

Inference: Among the subjects, maximum 25(31.3%) subjects were from 26-35 years followed by 20(25%) were from 36-45 years, 17(21.3%) were from 15-25 years, 10(12.5%) were from 46-55 years, 6(7.5%) were from 56-65 years and only 2(2.5%) were from >65 years.

Table 2 Distribution of gender

Gender	Frequency	Percentage
Male	8	10.0
Female	72	90.0
Total	80	100.0

Among the subjects, male were 8(10%) and maximum females were 72(90%).

Table 3 Distribution of symptoms

Symptoms	Frequency	Percentage
Yes	49	61.2
No	31	38.8
Total	80	100.0

INFERENCE: Among the subjects, symptoms were present in 49(61.2%) and absent in 31(38.8%).

Table 4 Comparison of TSH pre thyroxine and TSH post thyroxine

Group	Mean± SD	Mean diff	t value	P value
TSH pre thyroxine	25.453± 19.9073	21.1538	9.484	<0.001***
TSH post thyroxine	4.299± .6738			

Test used- paired t test, p<0.001*** highly significant

INFERENCE: Mean ±SD of TSH pre thyroxine and TSH post thyroxine were 25.453± 19.9073 and 4.299± .6738 respectively. Results were found to be highly statistically significant on comparing TSH pre thyroxine and TSH post thyroxine. It was clear in graph that TSH pre thyroxine was maximum and reduced in TSH post thyroxine.

Table 5 Comparison of t4 pre-thyroxine and t4 post thyroxine

Group	Mean± SD	Mean diff	t value	P value
T4 pre thyroxine	8.087± 4.5232	-6.8562	-11.008	<0.001***
T4 post thyroxine	14.944± 3.3380			

Test used- paired t test, p<0.001*** highly significant

INFERENCE: Mean ±SD of T4 pre thyroxine and T4 post thyroxine were 8.087± 4.5232 and 14.944± 3.3380 respectively. Results were found to be highly statistically significant on comparing T4 pre thyroxine and T4 post thyroxine. It was clear in graph that T4 post thyroxine was maximum in compare to T4 pre thyroxine.

Table 6 comparison of APTT pre thyroxine test group and APTT post thyroxine test group

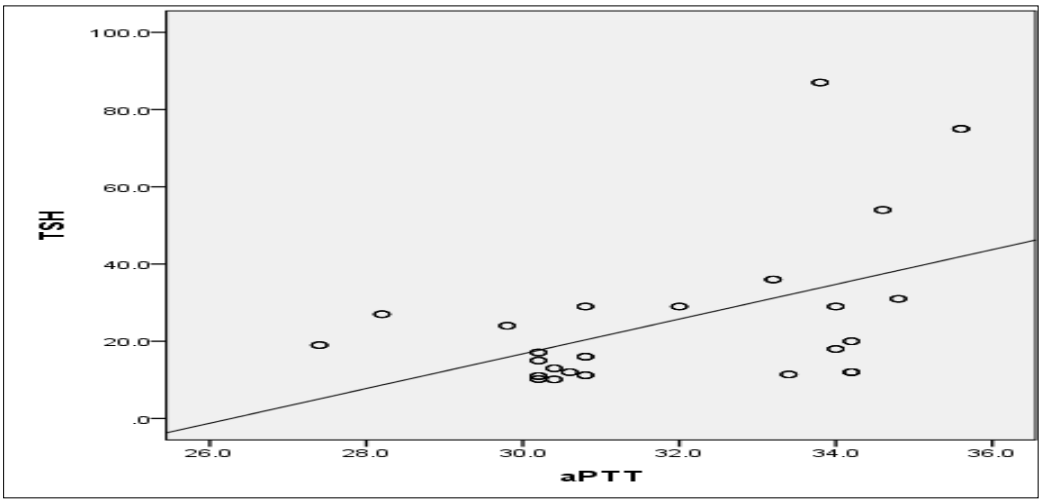
Group (TEST)	Mean± SD	Mean diff	t value	P value
aPTT pre thyroxine	36.005± 1.6541	4.0725	17.413	<0.001***
aPTT post thyroxine	31.933± 2.2068			

Test used- paired t test, p<0.001*** highly significant

Mean ±SD of aPTT pre thyroxine and aPTT post thyroxine were 36.005± 1.6541and 31.933± 2.2068 respectively. Results were found to be highly statistically significant on comparing aPTT pre thyroxine and aPTT post thyroxine. It was clear in graph that aPTT pre thyroxine was maximum and reduced in aPTT post thyroxine.

Table 7 Correlation between TSH and aPTT

GROUP VARIABLE	GROUP VARIABLES	CORRELATION COEFFICIENT ®	P-VALUE
TSH	aPTT	0.380**	0.001**



Test used = Pearson correlation, , **p=0.001= highly statistically significant

Figure 1 Graphical Correlation between TSH and aPTT

Inference: When comparing group variable, TSH and aPTT result were found to be highly significant and Pearson correlation was positive (correlation coefficient is 0.380).

4. Discussion

Several disorders of coagulation and fibrinolysis have been widely reported in patients with thyroid dysfunctions. From a clinical standpoint, it is important to note that these coagulation, fibrinolytic disorders usually range from mild to moderate and rarely to severe laboratory abnormalities.

Many factors are responsible for maintaining the hemostatic balance, and, among them, hormones directly influence both primary and secondary hemostasis. In particular, a bleeding tendency is often observed in hypothyroid patients, and a possible increased risk of sinus and cerebral vein thrombosis has been reported in clinically overt hyperthyroidism.

Thus, based on this the present has been conducted in the dept of General Medicine at AL-AMEEN MEDICAL COLLEGE AND HOSPITAL VIJAYAPUR. All the hypothyroidism diagnosed patients from outpatient dept were selected for the study with study period from SEPTEMBER 2022 TO MARCH 2024. All the patients were selected for the study were above 18 with some exclusion criteria.

4.1. Age

In the present study (table 1) distribution of age shows out of 80 patients maximum 25(31.3%) subjects were from 26-35 years followed by 20(25%) were from 36-45 years, 17(21.3%) were from 15-25 years, 10(12.5%) were from 46-55 years, 6(7.5%) were from 56-65 years and only 2(2.5%) were from >65 years.

In study done by Thoyyib, *et al*[11,12] *found that* the mean age for hyperthyroidism is found to have 37.5 years.

According to studies the mean age of the hypothyroidism 46 years, 42.5 years. This could be due to regional bias.

4.2. Gender

In this study (table 2) shows gender distribution and we found that maximum were females 72(90%) and male were 8(10%) in our study. According to the previous studies hypothyroidism and anemia more commonly seen in the females. Probably this could be the reason for the maximum females in our study.

4.3. Symptoms

In the current study, out of 80 subjects only in 49(61.2%) presented symptoms (table 3). Among the subjects weight gain were seen in 22(27.5%), fatigue were seen in 43(53.8%), menstrual irregularities in females were seen in 38(47.5%), hair loss were seen in 38(47.5%), constipation were seen in 29(36.3%), shortness of breath were seen in 23(28.8%) , Apathy were seen in 12(15%), dry skin were seen in 17(21.3%) , LL swelling were seen in 27(33.8%).

On thyroid hormone evaluation in study patients, before and after the treatment, we found significant results. (table 4) shows Mean ±SD of TSH pre thyroxine and TSH post thyroxine were 25.453± 19.9073 and 4.299± .6738 respectively. The comparison of Comparison of T4 pre thyroxine and T4 post thyroxine (table 5) shows significant results with the Mean ±SD of T4 pre thyroxine and T4 post thyroxine as 8.087± 4.5232 and 14.944± 3.3380 respectively. The graph clearly indicates that T4 post thyroxine was maximum in compare to T4 pre thyroxine.

The Comparison of aPTT pre thyroxine TEST group and aPTT post thyroxine TEST group (table 6) shows Mean ±SD of aPTT pre thyroxine and aPTT post thyroxine were 36.005± 1.6541and 31.933± 2.2068 respectively and results were highly significant and on correlation between TSH and aPTT, we observed significant with correlation coefficient is 0.380.

Mohammed Ali *et al*.[13,14] observed a significant decrease in PT in hyperthyroid patients compared to the control group. Activated thromboplastin time was also significantly decreased in hyperthyroid patients, compared to the control group in the same study.

According to Ordookhani A and Burman KD et al[15] Hypothyroidism has been reported to be associated with a decreased-, increased-, or an unaffected platelet count, as well as a decreased platelet aggregation and agglutination. Other platelet indices and function in hypothyroidism, such as decreased adhesiveness, aggregation, platelet factor, heat production, abnormal response to aspirin, and abnormal prostaglandin production are summarized elsewhere.

In a study on 15 overt hypothyroid, 15 subclinical hypothyroid and 15 euthyroid controls, increased bleeding time, prothrombin time (PT), activated partial thromboplastin time (aPTT), and clotting time and decreased FVIII activity (FVIII:C) and vWF activity (vWF:C) were detected in overt hypothyroid compared to control individuals.

Our results are consistent with previous studies conducted by Roger *et al*. and Mouton *et al*. In mild/subclinical hypothyroidism, Muller *et al*. reported a hypercoagulable state, and they found increase in factor VIII and vWF activities. Chadarevian *et al*. and Canturk *et al*. also explained mild/subclinical hypothyroidism as a hypofibrinolytic hypercoagulable state. Egeberg. and Simone also reported the same results. It has been found that the thyroxin increases the factor VIII levels by a heightened direct genetic transcription of coagulation factor VIII or decreased clearance of factor VIII by increased release of vWF.

In Thoyyib, *et al study,* 8 out of 10 cases of mild hypothyroidism were those who were taking thyroxin for more than 3 months but their TSH level was not in the normal range at the time of recruitment. This could be the reason for the high factor VIII levels in mild hypothyroidism in our study. Significant elevations of factor VIII have been reported to occur in conditions such as strenuous exercise, epinephrine infusions, fever induction, pregnancy, and intravascular hemolysis, treatment with progestational agents, renal failure, hyperglobulinemia, and treatment with prednisone. However, all these confounding factors were excluded in our study.

In study done by Thoyyib, *et al*[11] moderate and severe hypothyroidism, factor VIII levels were notably low at the baseline with mean values 105.89% and 89.87%, respectively. The factor VIII levels decreased with increase in the severity of hypothyroidism suggesting hypothyroidism to be a hypocoagulable state. After supplementation with thyroid hormones, these patients attained euthyroid state, and factor VIII levels increased to 143.92% and 147.06%, respectively. This increase was statistically significant with P = 0.044 and 0.001, respectively. These findings were consistent with observations of Chadarevian *et al*[15] and Cantürk *et al*[16].

Hypothyroidism has also been associated with a decrease in factor VIII activity, vWF Antigen, vWF activity, vWF ristocetin, fibrinogen, ristocetin agglutination, factor IX, XI, decrease in plasminogen activator inhibitor, factor VIII:C,

vWF:C. A recent study done by Yango J et al observed in hypothyroidectomized patients with severe short-term hypothyroidism before and after receiving either levothyroxine revealed that hypothyroidism is associated with significant decrease in FVIII activity, vWF antigen, vWF activity and increased aPTT compared to the time that the patient becomes euthyroid after receiving thyroid hormone replacement therapy. Administration of recombinant human TSH (rhTSH) has no effect on coagulation factors, which suggests alteration in coagulation factors is due to thyroid hormone deficiency rather than elevation in TSH.

Compared with pretreatment values in hypothyroid patients, significant increases were noted in plasma concentrations of vWF, fibronectin and plasma arginine vasopressin (AVP) levels after levothyroxine therapy.

A study of 20 patients with overt hypothyroidism before and after therapy with thyroid hormones revealed a less compact fibrin structure with enhanced fibrinolysis consistent with a bleeding tendency, in hypothyroidism versus euthyroidism in the same patient. Fibrin clot structure/function has been shown to predict predisposition to thrombotic events, as clots with compact structure and resistance to fibrinolysis are associated with premature and more severe atherothrombotic disease.

It was the isolated finding of a prolonged APTT that was unexplained and subsequently led to the assessment of thyroid function. The abnormalities observed in specific coagulation parameters in our case are in line with the findings reported in the literature and seem to support a hypocoagulant state in hypothyroid individuals. More evidence is needed to inform the debate on any routine assessment of thyroid function in relation to coagulation disorders and vice versa. However, the combined evidence from the literature and our report may favor the assessment of thyroid function in cases of unexplained biochemical coagulation abnormalities, in particular the assessment of TSH in the case of prolonged APTT of unknown origin.

4.4. Strength of the study

We found significant correction between the PTT and the TSH levels and PTT was significantly higher in the study participants indicating hypothyroidism.

The study participants responded to the treatment of thyroxine.

Since the endpoints of the study were laboratory values of coagulation and fibrinolytic parameters, these are not likely to be biased by not having performed a double blinded study.

5. Conclusion

The study concluded that PTT was significantly higher in patients with hypothyroidism. There was correlation established between PTT and TSH levels. Our study forms the basis for future studies for the comprehensive assessment of coagulation abnormalities in thyroid disorders.

Limitations

Our study was restricted to the PTT and the TSH levels. The study did not observe the hematological and biochemical parameters.

Our study was not designed to further look into the proposed pathophysiological mechanisms underlying the relation between thyroid hormone and hemostasis. Our results may be limited due to the relatively small sample size.

Compliance with ethical standards

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Disclosure of conflict of interest

None declared.

Statement of ethical approval

The study was approved by the Institutional Ethical Committee.

Statement of informed consent

Informed consent was obtained from all individual participants who were included in the study.

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