Review Article

INFLUENCE OF THYROID HORMONES ON HAEMOSTASIS

ABSTRACT:

AIM

The aim of this research study is to investigate the association and impact of thyroid disorders on haemostasis, specifically focusing on the clotting and bleeding tendencies in patients with thyroid function disorders.

Globally, thyroid gland disorders are a common cause of illness. Increased thyroid gland hormones can result in a variety of disorders, ranging in severity from minor symptoms to fatal diseases. Here, we go over how thyroid hormone can influence the hemostatic system and the danger of bleeding and venous thromboembolism that goes along with it. Hypothyroid people are more likely to experience bleeding issues, which may be important for patients undergoing invasive operations. Physicians should also be mindful of the probability of hyperthyroidism as risk factor for venous thromboembolism, particularly in instances with no apparent cause. To learn more about the relevance of these findings for general practice, clinical investigations are required.

There have been instances of both hypercoagulable and hypocoagulable conditions, which raises concerns about how subclinical hypothyroidism (SCH) affects hemostasis. Therefore, the goal of our study is to examine the importance of clinical trials in this setting.

Keywords: hyperthyroidism; hypothyroidism; blood coagulation; fibrinolysis; bleeding; venous thrombosis.

Abbreviations:T4- Thyroxine,T3 - Triidothyronine,TRH:Thyrotropin releasing hormone,TSH:Thyroid -Stimulating hormone.,SCH:Subclinical Hypothyroidism,LT4:Levothyroxine,vWF: Ag-Von Willebrand Factor Antigen,PTT:Partial thromboplastin Time,VT:Venous Thrombosis PT:ProthrombinTime,VTE:Venousthromboembolism,DVT:Deep Vein Thrombosis,PE:Pulmonaryembolism,PAI- Plasminogen activator inhibitor,AT III- Antithrombin III,CVT:Cerebral venous thrombosis,TFPI:Tissue factor pathway Inhibitor

INTRODUCTION

Thyroid dysfunction is a group of disorders that affect the thyroid. Some of them have a companion change in structure and function, others have no effect.[1]The thyroid gland is situated in the front of neck just above trachea in the adult human which is butterfly in shape. The well developed thyroid gland in a human weighs approximately 15 gram to 20 gram and is attached by the isthmus which synthesizes and secretes T3 and T4 hormones .[2].Thyroid hormones are important mediators of many physiological and metabolic processes, including blood coagulation and their abnormalities can adversely affect various steps in the coagulation process. [3]Thyroid hormone is required for the

normal functioning of numerous tissues in the body. In healthy individuals, the thyroid gland predominantly secretes thyroxine (T4), which is converted into triiodothyronine (T3). T3 binds to the thyroid hormone receptor in the nucleus of cells, where it stimulates the turning on of genes and the production of specific proteins [4]

HYPOTHYROIDISM

Thyrotropin-releasing hormone (TRH) is produced by the brain and stimulates the pituitary gland to create thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to produce and secrete mainly T4 and, while smaller quantities of T3 are possible, alteration in the structure and function of this organ or pathways can result in hypothyroidism [5].Hypothyroidism is defined as a low free T4 level with normal or high TSH, which is one of the most common disorders of the thyroid gland. Hypothyroidism can be categorized into primary, secondary, or tertiary disease, depending on the location of defect. Subclinical Hypothyroidism (SCH) is defined as a serum Thyroid-Stimulating Hormone (TSH) level above the upper limit of normal where levels of serum free thyroxin is normal. Typical symptoms are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as Levothyroxine (LT4) is preferred[6] .Hypothyroidism and endemic goitre are most commonly caused by a lack of iodine. In places around the glob where dietary iodine is sufficient, the autoimmune disease Hashimoto's thyroiditis is the prevalent cause of hypothyroidism (chronic autoimmune thyroiditis).[7]

HYPERTHYROIDISM

Thyrotoxicosis is a clinical indication of excessive thyroid hormone activity at the tissue level caused by unusually high thyroid hormone concentrations in the blood. Hyperthyroidism, a subtype of thyrotoxicosis, is defined as excessive thyroid hormone production and secretion by the thyroid gland.[8].Hyperthyroidism is characterised by an abnormally high concentration of thyroid hormones in tissues as a result of rise in thyroid hormone synthesis, increased release of preformed thyroid hormones, or an endogenous or exogenous extrathyroidal source. Gravesdisease(Caused by autoantibodies targeting TSH receptors), toxic multinodular goitre, and toxic adenoma are the most common causes of an excess of thyroid hormones.[9]. Hyperthyroidism is usually characterised by a hypermetabolic condition caused by elevated T4 or T3 levels[10].Based on biochemical manifestations, hyperthyroidism can be classified in to overt or subclinical . Overt hyperthyroidism can be identified by low blood thyroid-stimulating hormone (TSH) concentrations and elevated serum concentrations of thyroid hormones thyroxine (T4), triiodothyronine (T3), or both. Subclinical hyperthyroidism can be diagnosed by low serum TSH levels but normal serum T4 and T3 levels[11]

Based on clinical and biochemical manifestations

-Most of the patients shows clinical and biochemical symptoms of disease

-Other people have fewer and less obvious clinical signs, yet biochemical hyperthyroidism exists. Others have little or no clinical hyperthyroidism and their only biochemical abnormality is a low blood thyroid-stimulating hormone (TSH) concentration.[12]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[13]

HAEMOSTASIS

Haemotasis is a host defence mechanism that protects the integrity of the vascular system after tissue injury. The mechanism has several important functions. It helps to maintain blood in a liquid state while it remains circulating within the vascular system, to arrest bleeding at the site of injury / bleeding by formation of a hemostatic plug and to ensure eventual removal of plug when healing is

complete.[14].The relationship between thyroid diseases especially those related to hormones, may have extreme effect on hemostasis directly or indirectly.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. There are so many other agents and we believe that among those factors metabolisms are important and the thyroid serves as the key organ in that process. Therefore thyroid diseases in general and especially with hormonal dysfunction affect hemostasis[15][16][17]It has been documented that there is influence of thyroid hormone on the coagulation and 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. [18]

REVIEW OF LITERATURE.

D D W Kim et al have done a study in hyperthyroid patients and their study points at a moderate relationship between VT and acute hyperthyroidism. Furthermore, the results imply that hyperthyroidism is frequently an additional risk factor for VT but is rarely the main risk factor.[19]

Khalid Abdelsamea et al conducted a study in hypothyroid patients to find out the changes in their coagulation profile,performed PT and PTT and have found that except for PTT, the degree of hypothyroidism had no impact on the coagulation markers.The PTT results revealed a substantial inverse relationship between TSH, T4, and T3 levels. TSH, T4, and T3 levels revealed a negligible negative correlation between PT and INR.[20]

In the study by Basma Awni et al it is found that Thyroid dysfunction and abnormal coagulation have a close relationship.[21]

Aseel Awad studied the link between hyperthyroidism and thromboembolism and they suggest that elevated thyroid hormone levels must be taken into consideration as a risk factor for the development of VTE.[23]

Another study by erem et al have found thatvascular endothelial dysfunction and reduced blood fibrinolytic activity may occur in hyperthyroid individuals. This endothelial activation can be a sign of a more thromboembolic-prone circumstances.[24]N R Farid et al have conducted a study on blood coagulation and fibrinolytic activity in thyroid patients have found that the reciprocal of thyroid antibody titres and fibrinolysis showed a significant association[25]

In another study by C Erem et al in hypothyroid patients,they have monitored the coagulation as well as the fibrinolytic activity and discovered a hypofibrinolytic condition in hypothyroid individuals.Their findings imply that patients with hypothyroidism may be at higher risk of thrombosis and ultimately myocardial infarction.[26]Another study by the same author on lipid profile, bleeding, and fibrinolytic activity in subclinical thyroidsm and their data suggested that subclinical hyperthyroidism may present a hypercoagulable state, which could increase the risk of atherosclerotic problems which are already existing[27]

Coagulation patterns in Sudanese female patients with thyroid dysfunctions was studied by Mohamed S et al and they found that when compared to clinical hypo- and hyperthyroidism, modest coagulation abnormalities were seen in both subclinical hypo- and hyperthyroidism.[28]

Rita Chandarevian et al studied in their study revealed that people with mild hypothyroidism had a hypofibrinolytic condition.Patients with severe hypothyroidism, on the other hand, shows tendency to bleed in addition to having low levels of von Willebrand factor.[29]Liviu G et al studied the link between venous thromboembolism in thyroid dysfunction and they revealed that patients with hypothyroidism but not those with hyperthyroidism showed an elevated risk of PE, DVT, and VTE. [30]

A study was conducted by Muller et al to find out whether the haemostatic profile can be used as a risk factor for vascular or thrombotic disease in hypothyroid patients,and they found

hypercoagulable state, which could explain why hypothyroid patients have been observed to have a higher prevalence of coronary heart disease.[31]Bregje van Zaane et al done a study on increasing free thyroxine levels as a risk factor for developing a first venous thrombosis and their data indicated that lower FT4 levels are protective of VT while higher FT4 levels are associated with a risk for the condition. [32]

J.Debeji et al conducted a study on the coagulation system's response to variations in thyroxine and thyroid-stimulating hormone levels and they suggested that a rise in thyroxine levels is linked to rising levels of FVIII, FIX, VWF, and fibrinogen, and that this change is not largely brought on by high TSH levels.[33]

A study done by Arash Ordookhani et al in overt and subclinical hyperthyroidism have revealed that an elevated thyroid hormone level concentrations causes the haemostatic balance to move towards a hypercoagulable, hypofibrinolytic condition. Because of this, even modest cases of thyrotoxicosis are associated with an elevated risk of cardiovascular morbidity and mortality.[34]

Roberta Lupoli noted that subclinical hypothyroidism is linked to a prothrombotic condition as shown by changes in primary and secondary hemostasis.[35]Chadarevian et al have studied the association between thyroid hormones and fibrinogen and they found out that patients with normal-low FT4 levels tend to be more coagulable than those with normal-high FT4 levels.[36]

A study conducted by Muhammed Thoyyib et al had found that moderate to severe hypothyroidism was discovered to be a hypocoagulable state, while hyperthyroidism and mild hypothyroidism presents hypercoagulable states. [37]

Sibel guldiken conducted a study in patients with subclinical hypothyroidism to find out the fibrinolytic capacity in such patients and their data suggested that women with SH frequently experience hypercoagulability.The risk of thromboembolic problems in SH may increase when fibrinolytic activity declines.[38]

Another study on fibrinolytic activity in thyroid patients was done by hume et al and the results showed that compared to the hyperthyroid and euthyroid groups, the hypothyroid patients exhibited significantly higher fibrinolytic activity. In one incidence of hypothyroidism, observations showed that thyroid medication could reduce fibrinolytic activity.[39]

A. R. Peralta et al studied the association between hypothyroidism and venous thromboembolism and they found that hypothyroidism has been demonstrated to influence a variety of haemostatic and fibrinolytic parameters, indicating that it may play a role in cerebral venous thrombosis.They advocate including thyroid function in the routine workup of CVT patients.[40]

MCuianu et al conducted a study to find out the vWf levels in hyperthyroid individual and the data suggested that In individuals with hyperthyroidism, it was discovered that the von Willebrand factor antigen and activity assessed as a ristocetin cofactor were both elevated.This is the cause of the thrombotic propensity.[41]

Mehmet Ali et al Compared to the control group and subclinically hypothyroid patients, free TFPI levels were considerably greater in hyperthyroid patients, but not in hypothyroid patients. [42]John yango et al conducted a study in patients who underwent thyroidectomy to find out the effect on thyroid hormones on coagulation parameters and they suggested that in individuals with severe hypothyroidism compared to patients in the euthyroid condition, FVIII:C, VWF:Ag, were dramatically lowered, whereas APTT was significantly elevated which leads to bleeding. Patients receiving therapy did not experience any modifications in their clotting characteristics.[43]

Research by Giuseppe Lippi et al confirms that hyperthyroidism may be linked to hypercoagulability as a result of shortened APTT and elevated fibrinogen levels. Considering ways to prevent thrombotic problems in hyperthyroid patients should be taken into account if these findings are validated.[44]A study by J S Rogers et al revealed that Blood loss and thrombi formation occur simultaneously as a

result of decreased plasma factor VIII coagulant activity in hypothyroid individuals and enhanced coagulant activity in hyperthyroid patients.[45]
In another study by J A Rennie et al in hypothyroid individuals found that fibrinolytic activity and plasminogen levels were dramatically decreased. Significantly more fibrinolytic activity was seen in hypothyroid patients. [46]

DISCUSSION

According to the study of Franchini ,Ford HC, Carter ,Erem C, Kavgaci [47][48][24], hypothyroidism is the thyroid illness most usually connected with a bleeding propensity.Myrup and colleagues studied primary hemostasis in hyperthyroid and hypothyroid patients and, among the parameters ,they found a significantly longer bleeding time in untreated hypothyroid patients than in normal controls. Moreover, the authors found that the levels of von Willebrand factor antigen (VWF:Ag) in plasma from hypothyroid patients were less than the values recorded in hyperthyroid patients.[29] Similar results were reported by Rogers and colleagues [45] and Gullu and colleagues [49] However, diagnosing this related coagulopathy is challenging since it is seldom found by normal laboratory testing, and hypothyroidism frequently has a gradual start with mild clinical signs and symptoms. As a result, the right diagnosis is sometimes delayed until the bleeding propensity manifests itself as significant hemorrhage following trauma or surgery.However, the majority of the studies report that acquired VWD associated with hypothyroidism resolves completely after thyroid hormone therapy [50].Hypothyroidism is associated with depression of a variety of coagulation factors was first observed by Egeberg [51] and Simone [52], who found a significant decrease of factor VIII, IX and XI levels in hypothyroid patients, Other studies confirmed these findings and also described low levels of plasma coagulation factors VII, X and XII [2,53].As regards the bleeding tendency in hyperthyroid patients, some authors observed significant platelet changes in patients with hyperthyroidism [54][55][56].In fact, Mu¨ller and colleagues done a study in 42 women with subclinical hypothyroidism and the results suggested that the presence of a hypercoagulable state [30], rather than a bleeding tendency, in patients with thyroid failure, thus supporting the observation by Hak and colleagues [57] of an increased risk of cardiovascular events in patients with subclinical hypothyroidism. These findings confirmed the previous results of Chadarevian et al. [58], who found an increased factor VII activity and D-dimer levels in overt hypothyroidism, which are both high risk factors for thromboembolic events . However, in a subsequent study by the same authors found a altered pattern of fibrinolytic activity according to the severity of hypothyroidism, thus updating the previous findings of a generalized increased fibrinolytic activity in hypothyroidism. When compared with controls, patients with moderate hypothyroidism had a higher risk of developing cardiovascular diseases due to a decreased fibrinolytic activity.Various abnormalities of coagulation parameters predisposing to a hypercoagulable state have also been reported in hyperthyroid patients, including elevated anticardiolipin antibody titers[59][60].

CONCLUSION

In conclusion, clinically overt hypothyroidism and hyperthyroidism modify the hemostatic balance in opposite directions. This supports the assumption that thyroid hormone excess and deficit are the main mechanisms of a hypercoagulable and hypocoagulable state, respectively.Patients with moderate hypothyroidism who have been proven to be at high risk for cardiovascular disease have lower fibrinolytic activity. Subjects with severe hypothyroidism will have a increased fibrinolytic activity. Increased factor X activity in patients with subclinical hyperthyroidism represent a potential hypercoagulable state, which might augment the already existing risk for atherosclerotic complications. Also thyroid hormones may play a role at different levels of the complex haemostatic system in

subclinical thyroid disease likewise hyperthyroidism is usually an additional risk factor but rarely the sole risk factor for VT.

The therapy and age of these individuals had no influence on the assessed values. More studies are needed to widen our knowledge on this topic and to assess whether the implementation and monitoring of these risk factors in practice will lead to improving our ability to prevent and manage VTE by reducing its risks.It is important for clinicians to realize that haemostatic balance can be affected by thyroid dysfunction, as well as hepatic, renal, and other systemic diseases.

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