The influence of thyroid functional parameters on thromboembolic events: a retrospective analysis

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THE INFLUENCE OF THYROID FUNCTIONAL PARAMETERS ON THROMBOEMBOLIC EVENTS: A RETROSPECTIVE ANALYSIS

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List of abbreviations

T_3 – triiodothyronine

T_4 – thyroxine

TSH – thyroid stimulating hormone

TRH – thyrotropin-releasing hormone

TG – thyroglobulin

MIT – monoiodotyrosine

DIT – diiodotyrosine

H_2O_2 – hydrogen peroxide

DI01 / DI02 / DI03 – deodinase type 1 / 2 / 3

CNS – central nervous system

HPT-axis – hypothalamus-pituitary-thyroid axis

AMP – adenosine monophosphate

cAMP – cyclic adenosine monophosphate

IP3 – inositol triphosphate

TH – thyroid hormone(s)

TR – thyroid receptor(s)

LDL – low-density lipoprotein

UCP1 – uncoupling protein 1 / thermogenin

AMPK – AMP-kinase

BAT – brown adipose tissue

CVS – cardiovascular system

PI3-K/Akt – phosphoinositide-3-kinase-protein kinase B/Akt pathway

NO – nitric oxide

vWF – von Willebrand factor

GP – glycoprotein

PK – prekallikrein

TF – tissue factor

PT – prothrombin time

INR – international normalized ratio

aPTT – activated partial thromboplastin time

DOAK – direct oral anticoagulant

VKA – vitamin K antagonist

MELD – model for end-stage liver disease

DIC – disseminated intravascular coagulation

t-PA – tissue-plasminogen activator

PAI-1 – plasminogen activator inhibitor-1

1. INTRODUCTION

1.1 The thyroid gland and its hormones

1.1.1 Overview of the thyroid gland

Although the thyroid gland is rather a small organ compared to the other ones, its hormones play important roles in various functions of the body. The gland itself is located anterior and inferior to the larynx and behind it lying the trachea (1). This location arises in early embryonic life where the thyroid gland originates from foregut endoderm which is an protrusion of the pharyngeal epithelium that later migrates towards the foramen cecum and base of the tongue to its general location in the anterior neck (1,2). The gland is usually found in the visceral compartment of the neck, where it wraps around the cricoid cartilage, lying posterior to sternothyroid and sternohyoid muscles and inferior to the laryngeal thyroid cartilage (3).

It is described as a smooth and firm gland that consists of two lobes that are connected by a central isthmus and is overall surrounded by a fibrous capsule that further divides the gland into many small lobules by its multiple fibrous projections into the gland structure (4). The normal thyroid volumes range from 10-15ml for females and 12-18ml for males with thyroid lobe dimensions of 40-60mm longitudinal and 13-18mm AP diameter, although physiological measurements can vary in the population (5). Thyroglobin is the iodinated precursor protein of active thyroid hormones and is stored in numerous follicles that lie inside of thyroid lobules (1). After the release of thyroid-stimulating hormone (TSH) by the anterior pituitary gland and binding to its receptors, thyroid follicular epithelial cells convert thyroglobulin to thyroxine (T_4) and triiodothyronine (T_3) (1). TSH release, on the other hand, is mediated by the release of thyrotropin-releasing hormone (TRH) by the hypothalamus (6).

1.1.2 Production and secretion of hormones

The production and secretion of thyroid hormones is a multistep process that involves many physiological processes and pathways. In the beginning, thyroid follicles produce thyroglobulin (TG) by the rough endoplasmic reticulum in thyrocytes, where then the Golgi apparatus packs them into vesicles, which finally enter the follicular lumen by the use of exocytosis (6).

After the oral ingestion of iodine, the sodium-iodine symporter at the thyrocyte basolateral membrane, mediates the transport and concentration of iodine into the cells for

further movement to the colloid via the pendrin transporter (6,7). Iodine is oxidized into its iodinating form and tied to tyrosyl residues in Tg, accompanied by organification where monoiodotyrosine (MIT) and diiodotyrosine (DIT) are formed (6,7). After that, a coupling reaction occurs in which two molecules of DIT combine to build T4 and one molecule of DIT fused with one molecule of MIT and create T_3 (8,9). This coupling process requires the iodine receptor protein, iodine, H_2O_2 and the presence of the thyroid peroxidase (TPO) that is released in the presence of TSH (7,8).

Endocytosis of colloid from the follicular lumen releases T_4 and T_3 into the bloodstream, after the endocytotic vesicles fuse with lysosomes and thyroglobulin is degraded (6). In normal physiological states, the prohormone T_4 is mainly produced and a smaller amount of the bioactive form T_3 is made (10).

Secreted T_4 and T_3 are almost entirely attached to proteins while they are streaming in the blood, where the major binding protein is thyroxine-binding globulin (TBG) and minor portions account for transthyretin (TTR), albumin and lipoproteins (8). Only about 0.3% of the total plasma T_3 exists in a free form that is metabolically active and has effects on peripheral tissues, whereas approximately 0.03% of the total plasma T_4 is unbound and converted to T_3 by the target tissues (8,9). This conversion is mediated by deodinases, which remove an iodine atom from T_4 to form T_3 and this process is mostly achieved by DI01 activity that is produced from the thyroid, liver and kidney (10,11). There are additionally DI02 produced by the CNS, brown adipose tissue, skeletal muscle and heart, as well as DI03 formed by CNS, skin and placenta, although DI03 only produces an inactive form of T_3 (rT3) (11).

1.1.3 Regulation of hormone secretion

Generally, the regulation of thyroid hormone secretion is mediated by the hypothalamic-pituitary-thyroid (HPT) axis. TRH is produced in the paraventricular nucleus of the hypothalamus and is drained into the anterior pituitary gland through the long portal veins at the median eminence (12). After that, TRH binds to its receptor and stimulates the thyrotrophs of the anterior pituitary to release the peptide hormone TSH (13). TSH is able to induce thyroid gland growth and hormone synthesis through a cyclic adenosine monophosphate second messenger system which converts AMP to cAMP and the activation of IP3 signaling pathway (14). In addition to being involved in most parts of thyroid hormone synthesis, storage and release, TSH also enhances the regulation of thyroidal uptake of small

nutrients and molecules and intracellular transport of thyrocyte-specific proteins (15). TRH and TSH act in form of a positive- feedback loop on the thyroid hormone release, when their levels are increased, more hormones are produced and the other way around.

On the other hand, the free form of thyroid hormones have an influence on the negative-feedback loop of the homeostasis in the hypothalamus-pituitary-thyroid axis, in which a low concentration of T_3 and T_4 generate an increased secretion of TRH and TSH causing a rise in thyroid hormones, which then suppresses the release of TRH and TSH (1). Because the HPT-axis aims to maintain the serum thyroid hormone concentrations at a fixed set point during physiological conditions, TSH measurement for diagnostic purposes in thyroid disease is often possible (16,17). However, several conditions can cause alterations of the HPT-axis, including systemic illness, strenuous exercise, starvation, pregnancy and psychiatric diseases (16).

1.2 Influence of thyroid hormones on the body

1.2.1 Metabolism

Thyroid hormones exert effects on multiple organs and physiological systems, therefore their regulation has an important role in human health. Their presence or absence mostly has a quiet opposite consequence on the physiology of the body. Thyroid hormones show numerous contributions to the metabolism due to their regulation of metabolic processes, as well as growth and development through actions in brain, fat tissue, skeletal muscle, liver and pancreas (18).

Thermogenesis is mediated through the actions on brown adipocytes and central mechanisms involving the sympathetic nervous system, both of which can be regulated by thyroid hormones (19). The modulation of thermogenesis by TH is enhanced by changing the transcription rate and functionality of UCP1, causing increased metabolic cycling, actions on the sodium-potassium and calcium pump in the skeletal muscle (20). Additionally, the adrenergic-mediated thermogenesis by T_3 causes reduced AMPK phosphorylation, which results in increased lipogenesis and sympathetic output to BAT, therefore increasing the energy expenditure and thermogenesis (18).

The glucose metabolism is another system that is influenced by TH, which occurs by acting directly on the liver through TRβ and centrally through the hypothalamus, both causing a decrease in glycogen synthesis and increase in glucogenolysis and gluconeogenesis (21). T_3

additionally induces beta-cell proliferation due to those cells expressing TRα and THβ isoforms to which the T_3-TR complex is capable to bind and therefore initiating the activation of islet cell transcription factors (22,23).

Consequently, in patients with hyperthyroidism, there is often a resulting peripheral insulin resistance due to the stimulated gluconeogenesis and glycogenolysis, causing glucose intolerance and hyperinsulinemia (22).

Influences of TH on the lipid metabolism include lipolysis and lipogenesis, as well as cholesterol synthesis through the stimulation of transcription of the LDL-R gene which provokes increased cholesterol uptake and enhances its synthesis (18). Therefore, hypothyroidism is commonly linked to increased levels of cholesterol and triglycerides, together with non-alcoholic fatty liver disease (18,24,25).

1.2.2 Cardiovascular system

The cardiovascular effects of thyroid hormones constitute a critical aspect of human health, given that ischemic heart disease and stroke, both components of cardiovascular disease, remain the leading causes of mortality worldwide, and therefore their risk factors and correlations with other diseases have to be investigated (26). TH influence the CVS either directly, by their effects on the cardiomyocytes and vascular smooth muscle cells, or more indirectly, by changing the lipid and carbohydrate metabolism, thus causing an alteration of the risk factors for cardiovascular disease (27,28).

On the genomic level of cardiomyocytes, TH are capable of binding to thyroid nuclear receptors, which further initiate gene transcription of cardiac proteins and cause their upregulation (29,30). Furthermore, T_3 causes a direct modulation of membrane ion channels, and in addition to that, having a strong effect on cardiomyocyte contraction and relaxation, which is highly regulated by the positive effect of T_3 on sarcoplasmic reticulum calcium adenosine triphosphate (SERCA2) and negative effect on phospholamban (PLB) (31).

Therefore, TH have a positive chronotropic and lusitropic effect on the heart, which becomes more clear when we observe the characteristic symptoms of hyperthyroidism, which include tachycardia, palpitations and a widened pulse pressure (30,32). The influence on cardiomyocytes is also mediated by the increased expression of β1-adrenergic receptors by T3, resulting in a larger sensitivity to the action of catecholamines and explains the occurrence of

tachycardia if there is an increased amount of TH (33). In comparison to hyperthyroidism, hypothyroidism is often associated with the opposite effects on the heart. One of the most commonly described issues is the decreased ability of cardiomyocytes to relax, which causes diastolic dysfunction and impaired cardiac contractility, potentially leading to the development of heart failure (29,30,33). When observing the conduction system, hypothyroidism can lead to sinus bradycardia, QT-interval prolongation and the induction of heart blocks (30).

Effects of TH on the vasculature are also regulated on genomic and non-genomic level. Genomically, the gene expression is mediated by the activation of nuclear receptors, which bind gene promoters containing TH response elements (34). Generally, TH cause vascular relaxation by many mechanisms and one of them is the downregulation of angiotensin II type 1 receptor (AT1R) in vascular smooth muscle cells, further increasing the expression of angiotensinogen (34,35). Another way of decreased vascular resistance is the non-genomically T3-mediated nitric oxide production by the activation of the PI3-K/Akt regulated endothelial NO-synthase signaling pathway, resulting in increased bioavailability of NO (35). Those vasodilatory effects result in a decreased renal perfusion and therefore an activation of the renin-angiotensin-aldosterone (RAAS) system occurs which affects an increase in total blood volume by water retention and antidiuretic hormone secretion (30). Although hyperthyroidism can increase systolic blood pressure, a balance between increased cardiac output and decreased systemic vascular resistance can appear and therefore their relation influences the net effect (31).

1.3 Blood coagulation

1.3.1 Primary hemostasis

Blood coagulation, or hemostasis, is a complex process that involves many sequences of events and is generally divided into primary and secondary hemostasis. Primary hemostasis begins with the formation of a platelet plug, a process that heavily depends on the interactions between platelets, adhesive proteins, and the vessel wall. (36). Platelets are anucleate cells that derive from megakaryocytes and in order to facilitate hemostasis by undergoing a change and shape and release granules, they have to be activated (37).

Once vessel wall injury occurred, collagen and von Willebrand factor are released from the injured endothelium, which further bind to platelets, causing them to change into an

irregular surface, forming numerous pseudopods and thereby increasing the surface area (36,37). The binding of vWF to platelets occurs via the glycoprotein Ib receptor, while collagen binding is facilitated by the glycoprotein Ia/IIa receptor, and both processes play an important role in the platelet adhesion process. (38,39).

Those binding processes cause platelet activation by the mobilization of intraplatelet calcium stores by an intracellular signaling pathway that activates multiple kinases, activates phospholipase C (PLC), generates inositol triphosphate (IP3) which bind to their specific receptors (37). The activated platelets then release hemostatic mediators from their granules, including adenosine diphosphate (ADP) which induces the expression of GPIIb/IIIa receptor and serotonin, either causing platelet aggregation and further vasoconstriction (40). Furthermore, after the GPIIb/IIIa receptor is available, the ligands fibrin, vWF, fibronectin, and vitronectin can bind to it, triggering additional platelet activation and forming a hemostatic mass with stabilized clot structure (41). The activated platelets additionally stimulate the production of arachidonic acid which is by cyclooxygenase 1 (COX-1) and Tx-synthase converted to thromboxane A2 and while it is being released from platelets, it can also bind to them and provoke platelet shape change, granule release and platelet aggregation (42).

1.3.2 Secondary hemostasis

The secondary hemostasis is important for further stabilization of the previously formed platelet plug via primary hemostasis and largely relies on the action of so called coagulation or clotting factors (43). While most of the factors have a common name, they are often named by Roman numbers and the suffix -a is added, when the inactive precursor of the proteolytic enzyme, or zymogen, is activated (36). The origin of coagulation factors is mostly denoted to the liver, where factors XIII, XII, XI, X, IX, VII, V, II, and I are produced from hepatocytes, whereas factors VIII and III originate from endothelial cells, factor IV is freely available in plasma and factor V production is also assisted by platelets (44). Clotting factors can be classified into three groups, which are fibrinogen family including fibrinogen, factor V, VIII, XIII, vitamin K-dependent factors meaning factor II, VII, IX, X and the contact family consisting of factor XI, XII, HMWK and prekallikrein (36). The coagulation cascade is typically segmented into distinct phases: the extrinsic pathway, the intrinsic pathway, and the common pathway. (36, 43-47).

The intrinsic pathway is initiated when endothelial wall damage occurs and collagen is exposed, which automatically activates factor XII to factor XIIa, that in turn acts on high-molecular-weight kininogen (HK) and plasma prekallikrein (PK) (43,46). PK is converted to kallikrein and, in a positive-feedback loop, results in further factor XIIa production, which causes factor XI to be transformed to factor aXI (46). That activation of factor XI changes factor IX to IXa (45). While factor IXa activates factor VIII, they combine to form the intrinsic tenase (Xase) complex on activated platelet surfaces and catalyze the formation of factor Xa, which is then part of the common pathway (48).

The extrinsic pathway, on the other hand, is largely relying on tissue factor (factor III), which is abundant in extravascular cells and especially in adventitial cells surrounding blood vessels, explaining the activation of this pathway by endothelial injury from outside (39). Additionally, there are polyphosphates released from the platelets during primary hemostasis, which are able to transform factor VII to VIIa, that can now combine with TF to form a complex (49). The TF-factor VIIa complex is now, with the aid of calcium ions, capable of activating factor X to Xa, which is an important part of the common pathway (44).

As it is shown in Figure 1, both pathways combine at the point, where factor X is transformed to Xa. This mechanism is initiated by tenase, which is existing in two forms: one is formed by factor VIIIa, IXa, calcium ions and a phospholipid in the intrinsic pathway and the other form is made up of factor VIIa, activated TF and calcium ions from the extrinsic pathway (45). The activated factor X, together with its cofactor (factor V), tissue phospholipids, platelet phospholipids and calcium ions, stabilizes and forms the prothrombinase complex (36,45). This complex is now able to convert prothrombin (FII) to thrombin (FIIa) by cleaving it at R271 on platelet surfaces via the prothrombin-2 pathway and on non-platelet surfaces at R320 via the meizothrombin pathway (51). Finally, fibrinogen needs to be converted to fibrin with the aid of the thrombin-mediated proteolytic cleavage that produces intermediate protofibrils, which are then remodeled to mature fibers that induce stabilization of the already formed blood clot (52).

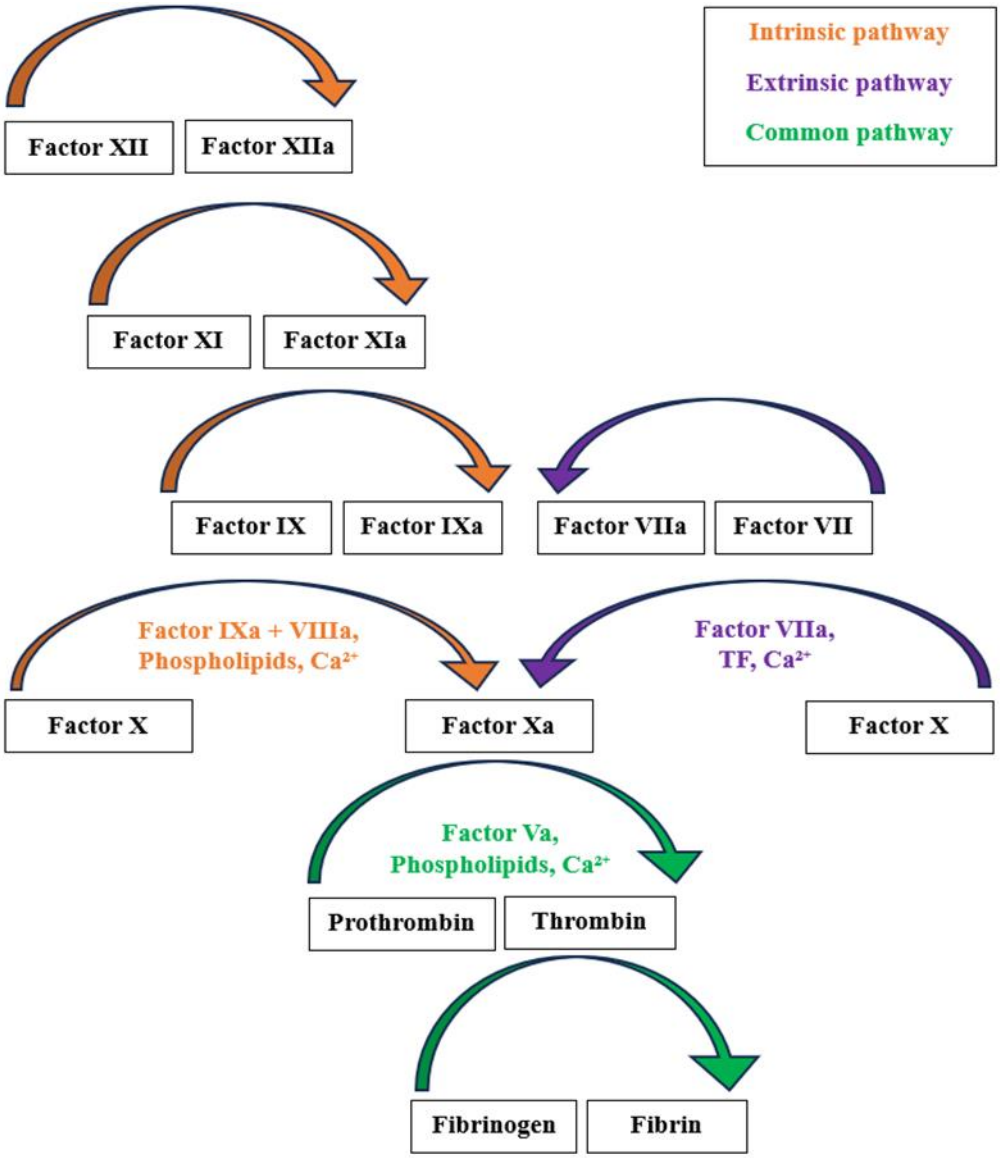

Figure 1. The coagulation cascade

Source: Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014;5:515-23.

1.3.3 Measurement of blood coagulation

In order to have an overview of the functioning of coagulation, there must be ways to measure this process. The measurement of coagulation can be helpful for the evaluation of coagulation factors, but also for the detection of any pathophysiological processes that are connected with increased or decreased production or functioning of those factors. The most commonly requested and performed coagulation tests include prothrombin time (PT),

international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen and thrombin time (TT) (53).

Starting with the prothrombin time, which is commonly used to evaluate the extrinsic and common pathway of coagulation, therefore helping to detect deficiencies or decreased function of factors II, V, VII, X and low fibrinogen concentrations (54). Because these factors are also vitamin K-dependent, PT measurement can be used for the monitoring of anticoagulants that act as vitamin K antagonists, such as warfarin (55). Although DOAK activity often not requires a routine measurement, their action could also be measured by PT, which especially pertains to dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor (53,56). The PT is commonly expressed by either the Quick method or the Owren method, with the difference being the sample volume in the reaction mixture, even though it is recommended to express the oral anticoagulation therapy by using the INR (57).

To standardize PT values, the INR was developed and is achieved by dividing the patient´s PT value by a mean normal or control PT value, which is sometimes further adjusted by adding correction factor called the international sensitivity index (ISI) (58). In addition to monitor patients on VKAs, other indications for obtaining the INR are baseline sample assessment before coagulation therapy, calculation of MELD score, diagnosis of DIC and bleeding diathesis in patients with extrinsic or common pathway coagulation factor deficiency (59).

In order to evaluate the intrinsic and common coagulation pathways, the aPPT is commonly used, and therefore the test is abnormal in the presence of reduced quantities of factors XII, XI, IX, VIII, X, V, prothrombin and fibrinogen (60). During the therapy with unfractionated heparin, aPPT can be used for controlling its action, which relies on the action of heparin by binding to antithrombin and thus inhibiting thrombin and the conversion of fibrinogen to fibrin (53,61). As already mentioned for PT, DOAKs do not commonly require routine measurement, but for the action of dabigatran and edoxaban, aPPT values can be helpful for estimating the function of those drugs (56). Other indications for the use of aPPT include inherited coagulation factor deficiencies, like Hemophilia A (factor VIII deficiency), Hemophilia B (factor IX deficiency), von Willebrand disease, vitamin K deficiency and the diagnosis of DIC (62).

Fibrinogen measurement occurs mainly by the Clauss method and is indicated in patients experiencing high amounts of blood loss, as fibrinogen appears to be one the most

vulnerable coagulation proteins (63,64). TT describes the formation of fibrin from fibrinogen in the presence of thrombin and together with fibrinogen evaluation, it can be helpful in the detection of inherited or acquired qualitative and quantitative fibrinogen deficiencies (47,60,63).

In addition to that, platelet count and bleeding time are fundamental assessments in evaluating primary coagulation (47). Platelet count provides quantitative insight into platelet availability, while bleeding time measures the functional integrity of primary hemostasis, crucial for diagnosing bleeding disorders and thrombotic tendencies (36,47).

1.3.4 Dysfunctional coagulation – thrombus formation

For many reasons, the process of coagulation can be dysfunctional, which can either result in decreased coagulation, which causes bleeding, or the opposite, in increased coagulation, causing thrombus formation. Due to the purpose of this study, we will focus on the process of thrombus formation, especially ischemic strokes as cerebrovascular aspects.

When the process of blood coagulation is accelerated, the formation of a blood clot or thrombus in arterial or venous blood vessels can occur, which we then refer to as thrombosis (65). Although arterial and venous thrombosis have a distinct pathophysiology and their treatment differs, they commonly share the same risk factors that can be categorized into modifiable and non-modifiable or inherited risk factors (66,67). Modifiable risk factors include a history of hypertension, obesity, smoking, diabetes mellitus, waist-to-hip ratio, unhealthy diet, alcohol intake or psychosocial stress, while non-modifiable risk factors are age, gender, ethnicity, hereditary blood disorders or the natural aging process of the cardiovascular system (68). According to the Acute Stroke Treatment (TOAST) classification, ischemic strokes can be further divided into subgroups regarding their etiology, which are stroke from cardioembolic origin, large vessel atherosclerosis, small vessel occlusion, stroke of indefinable etiology and stroke of other determined origin (69,70).

Atherosclerosis is considered to be the major cause of stroke development, because in large vessel atherosclerosis a chronic inflammatory process occurs, in which lipid accumulation at the arterial intimal wall causes the formation of fibrous plaques that are able to rupture and cause thrombosis (71). In small cerebral arteries, atherosclerosis also induces ischemic symptoms by the formation of stenoses, while diabetes and hypertension are mainly

associated with those lacunar strokes (72). Although atherosclerosis accounts for the major reason for the development of a stroke, about 20% of all ischemic strokes is caused by the occurrence of thromboembolism due to cardiac rhythm abnormalities, in which atrial fibrillation accounts for the major risk factor (68). Stroke of other determined etiology comprises causes of stroke that are more uncommon, including hypercoagulable states or arterial dissections, therefore not fitting into the previous categories (73). The last group of strokes, which are those of undetermined origin, have the features of reversible cause, inadequate investigation of a cause or unknown causes and include a persistent foramen ovale, paroxysmal atrial fibrillation, vasculitis, hypercoagulability or vasoconstriction (74,75).

There is also evidence that blood coagulability has an impact on cerebral arterial thrombosis, due to the discovery of almost all coagulation proteins near or even inside atherosclerotic lesions (70,76). The occurrence of stroke in younger patients may suggest an inherited predisposition to coagulation disorders, such as Factor V Leiden mutation, antithrombin deficiency, protein C deficiency, or protein S deficiency and while these conditions alone may not solely cause a stroke, they can significantly increase the overall risk when combined with other risk factors. (77,78).

1.4 The thyroid gland and coagulation

1.4.1 Induction of hypo- and hypercoagulable states

Thyroid hormones are known to have an influence on various functions of the body. As described earlier in this study, both increased or decreased amounts of thyroid hormone can act as risk factors for the development of thromboembolic events. Known risk factors include the increased occurrence of atrial fibrillation in patients with hyperthyroidism and the altered lipid metabolism causing hyperlipidemia in patients with hypothyroidism (79).

Their influence on the cardiovascular and cerebrovascular system in terms of coagulation and thrombus formation is less commonly discussed, although it is already known that overt or subclinical hyperthyroidism and hypothyroidism alter the coagulation-fibrinolytic balance (80). Those alterations seem to be quiet opposite for the most part. It has been demonstrated that low levels of thyroid hormone lead to a hypocoagulable state, which can even promote bleeding and high levels of thyroid hormones may provoke thromboembolisms due to an induced hypercoagulable state (81). One exception is described for subclinical

hypothyroidism, in which platelet hyperreactivity is associated with a prothrombotic state and therefore an increased risk of cardiovascular and cerebrovascular disease (82).

1.4.2 Effect on platelet function and coagulation factors

The influence on blood coagulation is mediated by the effects of thyroid hormone on platelet function and coagulation factors. Platelet activation is mainly initiated by binding of thyroid hormone at a specific receptor which is expressed by platelets in form of integrin αvβ3, resulting in the release of adenosine triphosphate and aggregation (83,84). By those mechanisms and the fact, that thyroid hormones cause increased vWF activation, platelet activation and aggregation are enhanced, which could significantly increase the risk of cerebrovascular events (85). On the other hand, patients experiencing hypothyroidism seem to have a lower vWF activity, that could be explained be decreased protein synthesis and therefore a greater bleeding tendency (85,86).

Additionally, the increased risk of thrombus formation and the development of embolism is described for the effect of thyroid hormones on coagulation factors. A rise in serum-free T4 correlated with an increase of the coagulation factors FXIII B subunit, FIX, an inhibitor of activated protein C, SERPIN A5, and α2-antiplasmin (87,88). By observing the coagulation factors of hyperthyroid patients, some previous research suggest that there is an elevated turnover of coagulation factors II, VII and X, as well as increased levels of factor VIII in the serum (89,90). Other studies showed that patients with hyperthyroidism tend to have a higher plasma level of fibrinogen and elevated values of t-PA and PAI-1, causing decreased fibrinolysis and therefore a greater risk of thrombus formation (91,92). As stated earlier, the effect of hypothyroidism on the factors of coagulation is varying, depending the degree of hypothyroidism. For moderate hypothyroidism (TSH, 10-50 mU/L), many patients also show a decreased fibrinolytic activity by higher levels of fibrinogen, α2-antiplasmin, t-PA and PAI-1 (93,94). In contrast to that, patients with severe hypothyroidism (TSH, >50 mU/L), exhibit lower α2-antiplasmin, t-PA and PAI-1 levels, suggesting a greater risk for bleeding (93).

Most of the previous studies clearly focus on the association of serum-free T_4, T_3, TSH and anti-TPO levels with the risk of venous thrombosis. Due to various studies indicating that high levels of T_4 favor a prothrombotic state, the strongest correlation between thyroid hormones and thromboembolisms seems to be mediated by FT_4 (95,96,97). This association is less clear for FT_3 levels because they rise in a non-linear manner with increasing risk of venous

thrombosis (96). Even the opposite is described in some studies, which means that patients with a poor prognosis in acute ischemic stroke show elevated values of T_4 but decreased values of T_3, indicating a reverse relationship (98). Neither for high nor for low levels of anti-TPO an effect on the development of thrombosis was found (95,96). Serum TSH levels of patients suffering from venous thrombosis compared to not affected participants did not differ significantly, although there was a somewhat increased risk for lower TSH levels found (95,96).

2. OBJECTIVES

2.1 Aims of the study

The aim of this study is to investigate a potential connection between abnormal thyroid function parameters and the occurrence of stroke. The study will compare a group of patients who have experienced a stroke as a thromboembolic event with a control group that has not. Laboratory parameters, including FT_3, FT_4, and TSH for thyroid function, as well as PT (Quick) and PTT for coagulation, will be analyzed and compared between the two groups.

2.2 Hypothesis

1. Patients that experienced a stroke show different thyroid functional parameters compared to the patients that did not suffer from stroke.
2. Patients with a stroke have a different relation of FT_3/FT_4 in comparison to the non-stroke group.
3. There exists a disparity in the coagulation parameters between the case and the control group.
4. Thyroid hormones affect coagulation parameters by promoting coagulation through elevated hormone levels.
5. Anticoagulants affect thyroid hormone levels in the blood, whereas thyroid medications impact blood coagulation.

3. MATERIALS AND METHODS

3.1 Study design

This study was conducted in a form of a retrospective study, which means that all variables, laboratory values and information about the patient´s history were already obtained and collected.

For better comparison of laboratory values between patients that developed a stroke and patients that did not, we decided to perform a case-control study. In this way we can analyze the differences between two groups of patients and directly compare them.

3.2 Participants

The represented population of our case group consists of adult (age of 18 and older) female and male patients that were hospitalized and later diagnosed with a neurological thromboembolic event, which is stated in their dismissal letter. The variables included in the case group are a diagnosed thromboembolic event and key laboratory values, notably thyroid functional parameters, blood clotting variables (PT, PTT), and platelet count. Additionally, erythrocyte and leukocyte count, hematocrit, liver function parameters (GOT, GPT, GGT), creatinine and urea are obtained.

Patients who experienced a thromboembolic event without any thyroid functional parameters obtained were excluded from the study. Important is also that the laboratory values are in close relation to the actual event. After CT imaging with contrast agent or after lysis therapy, the values are likely to be influenced by the mentioned procedures, thus the laboratory values shortly after arriving of the patients to the hospital were used.

The entry variables for the control group consist of any other diagnosis, except a thromboembolic event and all laboratory parameters that were already mentioned for the case group.

The exclusion criteria were similar to those in the case group. Patients without obtained thyroid functional or coagulation parameters were excluded from this study.

After that we were left with 134 in the case group and 139 patients in the control group.

3.3 Data sources and reference values

The study focused on the measurement of thyroid functional parameters of patients that were treated in the hospital of Coburg from 2020 to 2023. Those parameters were obtained by taking blood samples and we used TSH, FT_3 and FT_4 as thyroid functional parameters. Additionally, other laboratory values that are in close relation to thromboembolic events are obtained. Those include platelet and erythrocyte count, liver enzymes, creatinine and urea. The values were taken from the operating system ORBIS, which the hospital is using for documentation.

To clarify if thromboembolic events are in relation to thyroid functional parameters, the patient´s history is also important to analyze. Thus we focused especially on thyroid and cardiovascular comorbidities that are already known, as well as on the medication the patient is taking.

Table 1 shows the most important parameters that were used and their reference ranges and units.

Table 1. Laboratory parameters with their reference range and unit

Parameters	Reference range	Unit
Systolic /diastolic blood pressure	120-140 / 70-80	mmHg
Heart rate	60-100	bpm
Erythrocytes	4.44 – 5.61	10^6/µl
Hematocrit	0.40 – 0.49	l/l
Leukocytes	3.91 – 10.9	10^3/µl
Thrombocytes	166 – 308	10^3/µl
FT_3	3.1 – 6.8	pmol/l
FT_4	12 – 22	pmol/l
TSH	0.27 – 4.4	µU/ml
PTT	25.9 – 36.6	sec
Quick	70 – 130	%

3.4 Ethical approval

This study focuses on retrospective laboratory values, which were already obtained when this study started. The patients were also pseudonymized to meet their data protection obligations. Those circumstances enable that patient data cannot be traced. This study was approved by the IRB of the Medical School REGIOMED Coburg on the 15th February 2024.

3.5 Statistical analysis

The initial table formation was done by using Microsoft Excel (2019, Version 2403, Microsoft, Redmond, United States). For statistical analysis, the program JMP Clinical (2022-2023, Version 17.2.0, SAS Institute Inc, Cary, United States) was applied. The tests for normal distribution were Shapiro-Wilk, as well as Anderson-Darling test. For both, a P-value lower than 0.05 indicated that there is no normal distribution and a P-value higher than 0.05 indicated a normal distribution. Due to the not normal distribution of all laboratory parameters, the Mann-Whitney-U test was used for the comparison of the same value in both groups. Furthermore, the influence of one laboratory parameter on another was examined using Spearman's correlation coefficient. For analyzing categorial data, the Chi-square test was applied.

The statistical significance value was set at $P<0.05$.

4. RESULTS

Table 2 presents the primary characteristics and laboratory values of the case and control groups. There are significant differences in both systolic and diastolic blood pressure values between the groups ($P<0.001$). Notably, the systolic and diastolic values in the case group fall outside the reference range, whereas the control group only slightly exceeds the systolic reference range.

There is a statistically significant difference in erythrocyte values between the two groups ($P=0.002$), with both groups showing values below the reference range. Hematocrit values also exhibit significant differences ($P<0.001$), with only the control group displaying values below the reference range.

For thyroid functional parameters, there is a significant difference in FT_3 values ($P=0.033$), with higher values observed in the case group. TSH values are significantly different ($P=0.015$), being lower in the case group compared to the control group. The FT_3/FT_4 ratio also shows a significant difference between the groups ($P=0.043$), with a higher ratio in the case group.

Both coagulation parameters are statistically significant. PTT values are lower in the case group compared to the control group ($P=0.029$), while Quick values are higher in the case group ($P<0.001$).

Additionally, Figure 2 illustrates the FT_3/FT_4 ratio for both the stroke group (A) and the non-stroke group (B). While both groups exhibit nearly identical median values (0.23 and 0.21, respectively), their distributions differ considerably. The non-stroke group displays a greater number of outliers, resulting in a broader interquartile range (IQR) of 0.11, compared to the stroke group's IQR of 0.09.

Table 2. Characteristics of both groups

Parameters	Case group (N = 134)	Control group (N = 139)	*P*
Age	77 (IQR 20.25)	73 (IQR 17)	0.068*
Female sex	65 (48.51)	73 (52.52)	0.464†
Male sex	69 (51.49)	66 (47.48)	0.067†
Systolic blood pressure	**160 (IQR 26)**	**144 (IQR 35)**	**<0.001***
Diastolic blood pressure	**90 (IQR 16)**	80 (IQR 18)	**<0.001***
Heart rate	80 (IQR 20.50)	81 (IQR 26.50)	0.608*
Erythrocytes	**4.42 (IQR 0.92)**	**4.19 (IQR 1.51)**	**0.002***
Hematocrit	0.40 (IQR 0.07)	**0.37 (IQR 0.08)**	**<0.001***
Leukocytes	7.90 (IQR 3.11)	8.59 (IQR 4.26)	0.176*
Thrombocytes	221.5 (IQR 95.5)	225.5 (IQR 106.5)	0.951*
FT_3[a]	3.87 (IQR 1.22)	3.47 (IQR 1.74)	**0.033***
FT_4[b]	16.58 (IQR 4.51)	17.18 (IQR 5.81)	0.272*
FT_3/FT_4 ratio	0.23 (IQR 0.09)	0.21 (IQR 0.11)	**0.043***
TSH[c]	1.08 (IQR 1.40)	1.70 (IQR 5.14)	**0.015***
PTT[d]	29.25 (IQR 5.22)	30.20 (IQR 8.50)	**0.029***
Quick	102 (IQR 17)	89 (IQR 28)	**<0.001***

Data are presented as median and interquartile range (IQR) or as frequency N (%)
Values out of the given reference range (see table 1) are marked
P-values of significance (P<0.05) are marked
* Mann-Whitney-U test
† Chi- square test
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

A) Case group B) Control group

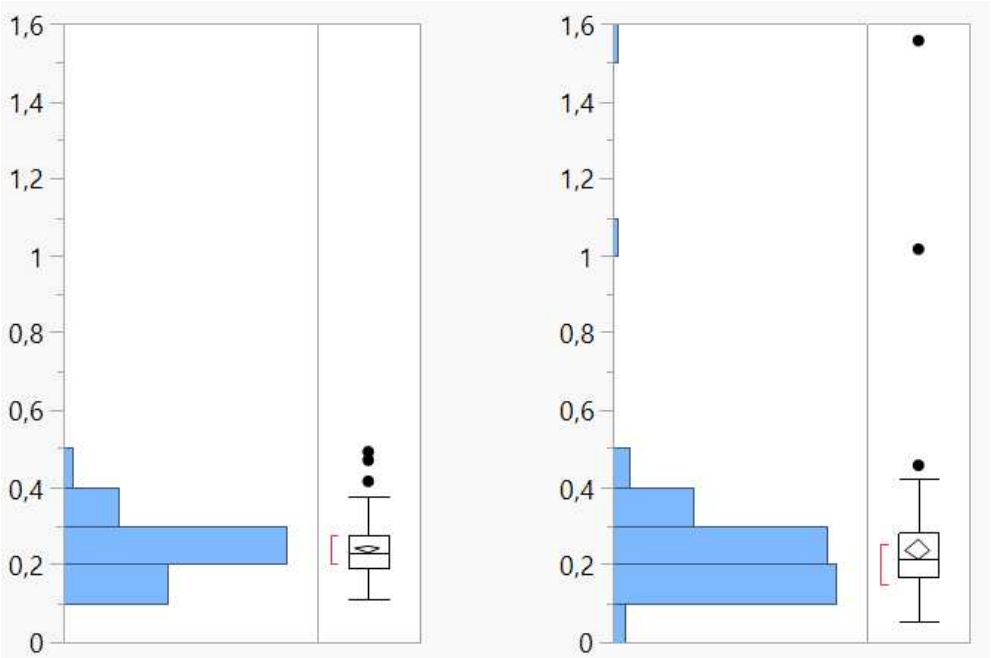

Figure 2. FT_3/FT_4 ratios of the stroke group (A) and the non-stroke group (B)

*Wilcoxon signed-rank test, P=0.043

To examine if there is a relation between FT_3 values of the stroke and the non-stroke group and all other laboratory parameters, a Spearman´s correlation analysis was carried out in Table 3. A significant correlation between FT_3 and erythrocytes was found for both groups (rho=0.371 vs rho=0.339, both P<0.001), which was also shown in the correlation between FT_3 and hematocrit (rho=0.360 vs rho=0.381, both P<0.001). For leukocytes, a weak correlation was indicated with FT_3 for the stroke group (rho=0.217, P=0.012). FT_3 also correlated weakly with FT_4 in both groups (rho=0.208, P=0.016 vs rho=0.236, P=0.005). A very weak but significant correlation was found in the non-stroke group between FT_3 and PTT (rho=-0.197, P=0.021) and between FT_3 and Quick (rho=0.188, P=0.028).

Table 3. Relation of FT_3[a] to other laboratory parameters illustrated via Spearman´s correlation

Laboratory parameters		Case group	Control group
Erythrocytes	*P**	**<0.001**	**<0.001**
	Spearman´s rho	0.371	0.339
Hematocrit	*P**	**<0.001**	**<0.001**
	Spearman´s rho	0.360	0.381
Leukocytes	*P**	**0.012**	0.350
	Spearman´s rho	0.217	-0.080
Thrombocytes	*P**	0.590	0.432
	Spearman´s rho	-0.047	0.067
FT_4[b]	*P**	**0.016**	**0.005**
	Spearman´s rho	0.208	0.236
TSH[c]	*P**	0.645	**0.004**
	Spearman´s rho	0.040	-0.242
PTT[d]	*P**	0.248	**0.021**
	Spearman´s rho	0.102	-0.197
Quick	*P**	0.509	**0.028**
	Spearman´s rho	0.058	0.188

*p-values of significance ($p<0.05$) are marked
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

Table 4 shows the relation between FT_4 and other laboratory values. Here, the only significant correlation was found between the thyroid functional parameters. FT_4 correlated with FT_3 in both groups (rho=0.208, P=0.016 vs rho=0.236, P=0.005), as it is already shown in Table 4. The other correlation is between FT_4 and TSH in the stroke and the non-stroke group (rho=-0.215, P=0.013 vs rho=-0.369, P<0.001).

Table 4. Relation of FT_4[a] to other laboratory parameters illustrated via Spearman´s correlation

Laboratory parameters		Case group	Control group
Erythrocytes	*P**	0.559	0.980
	Spearman´s rho	-0.051	0.002
Hematocrit	*P**	0.382	0.854
	Spearman´s rho	-0.076	-0.016
Leukocytes	*P**	0.206	0.660
	Spearman´s rho	0.110	-0.038
Thrombocytes	*P**	0.227	0.078
	Spearman´s rho	0.105	0.150
FT_3[b]	*P**	**0.016**	**0.005**
	Spearman´s rho	0.208	0.236
TSH[c]	*P**	**0.013**	**<0.001**
	Spearman´s rho	-0.215	-0.369
PTT[d]	*P**	0.482	0.415
	Spearman´s rho	0.061	-0.070
Quick	*P**	0.834	0.372
	Spearman´s rho	-0.022	0.077

*p-values of significance (P<0.05) are marked
[a] thyroxine
[b] triiodothyronine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

Another correlation to observe is the one between TSH and other laboratory values, illustrated in Table 5. Once more, the sole significant correlation identified was between TSH and the other thyroid functional parameters, as previously indicated in Tables 3 and 4.

Table 5. Relation of TSH[a] to other laboratory parameters illustrated via Spearman´s correlation

Laboratory parameters		Case group	Control group
Erythrocytes	*P**	0.135	0.088
	Spearman´s rho	0.130	-0.146
Hematocrit	*P**	0.099	0.225
	Spearman´s rho	0.143	-0.105
Leukocytes	*P**	0.412	0.216
	Spearman´s rho	-0.072	0.106
Thrombocytes	*P**	0.641	0.765
	Spearman´s rho	0.041	0.026
FT_3[b]	*P**	0.645	**0.004**
	Spearman´s rho	0.040	-0.242
FT_4[c]	*P**	**0.013**	**<0.001**
	Spearman´s rho	-0.215	-0.369
PTT[d]	*P**	0.870	0.147
	Spearman´s rho	-0.014	0.125
Quick	*P**	0.450	0.193
	Spearman´s rho	0.089	-0.112

*p-values of significance (p<0.05) are marked
[a] thyroid stimulating hormone
[b] triiodothyronine
[c] thyroxine
[d] partial thromboplastin time

Medication intake in both groups was analyzed using the Chi-square test, as displayed in Table 6. A significantly higher number of patients in the control group are taking thyroid medication (P<0.001). Additionally, there are more patients in the control group taking DOACs (P=0.003).

Table 6. Medication intake in the case and control group

Medication	Case group (N=134)	Control group (N=139)	*P**
Levothyroxine	33 (24.6)	61 (43.9)	**<0.001**
Platelet inhibitor	49 (36.6)	48 (34.5)	0.726
DOAC[a]	15 (11.2)	35 (25.2)	**0.003**
Vitamin K antagonist	7 (5.2)	9 (6.5)	0.660

Data are presented as number N (%)
P-values of significance (P<0.05) are marked
*Chi-square test
[a] direct oral anticoagulant

Table 7 illustrates the laboratory parameters of the case and control groups receiving anticoagulation. The erythrocyte count in both groups is significantly different (P=0.031) and falls below the reference range. The hematocrit values in the control group are also below the reference range and show a significant difference between the two groups (P=0.012).

Regarding thyroid functional parameters, the FT_3 values are significantly higher in the case group (P=0.046), and TSH values are significantly lower (P<0.001) in the case group compared to the control group.

The PTT is lower in the case group (P=0.002), while the Quick values are significantly lower in the control group (P<0.001).

Table 7. Comparison between case and control group with anticoagulation

Parameters	**Case group (N=71)**	**Control group (N=92)**	***P****
Erythrocytes	**4.34 (IQR 0.85)**	**4.07 (IQR 1.03)**	**0.031**
Hematocrit	0.40 (IQR 0.07)	**0.36 (IQR 0.09)**	**0.012**
Leukocytes	7.68 (IQR 3.09)	8.52 (IQR 4.09)	0.248
Thrombocytes	222 (IQR 88)	224 (IQR 110)	0.708
FT_3[a]	3.76 (IQR 1.27)	3.40 (IQR 1.75)	**0.046**
FT_4[b]	17.05 (IQR 4.23)	17.31 (IQR 4.56)	0.804
TSH[c]	0.85 (IQR 1.14)	1.90 (IQR 4.93)	**<0.001**
PTT[d]	29.50 (IQR 5.70)	32.50 (IQR 9.60)	**0.002**
Quick	102 (IQR 16)	84 (IQR 32)	**<0.001**

Data are presented as median and interquartile range (IQR)
Values out of the given reference range (see table 1) are marked
P-values of significance (P<0.05) are marked
* Mann-Whitney-U test
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

Presented in Table 8 is the relationship of laboratory values between the case and control groups not taking any form of anticoagulation. Only the erythrocyte count and hematocrit value in the control group fall below the reference range, but these values are not significantly different from those in the case group.

The sole parameter showing a significant difference is the Quick value (P=0.047), which is higher in the case group.

Table 8. Comparison between case and control group without anticoagulation

Parameters	**Case group (N=63)**	**Control group (N=47)**	***P****
Erythrocytes	4.50 (IQR 1.00)	**4.38 (IQR 0.71)**	0.071
Hematocrit	0.41 (IQR 0.08)	**0.39 (IQR 0.07)**	0.090
Leukocytes	8.09 (IQR 3.29)	8.81 (IQR 5.48)	0.566
Thrombocytes	221 (IQR 99)	227 (IQR 113)	0.544
FT_3[a]	4.01 (IQR 1.35)	4.06 (IQR 2.19)	0.629
FT_4[b]	16.03 (IQR 3.97)	16.79 (IQR 6.93)	0.098
TSH[c]	1.41 (IQR 1.53)	1.36 (IQR 5.57)	0.961
PTT[d]	28.90 (IQR 4.60)	27.85 (IQR 4.53)	0.186
Quick	103 (IQR 21)	101 (IQR 22.5)	**0.047**

Data are presented as median and interquartile range (IQR)
Values out of the given reference range (see table 1) are marked
P-values of significance (P<0.05) are marked
* Mann-Whitney-U test
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

Table 9 shows the comparison between the case and control groups, focusing exclusively on patients taking thyroid medication. Both the erythrocyte count and hematocrit values in both groups fall below the reference range, yet they do not differ significantly between the groups.

Overall, no laboratory values demonstrated significant differences after accounting for thyroid medication intake.

Table 9. Comparison between case and control group with thyroid medication

Parameters	**Case group (N=33)**	**Control group (N=61)**	***P****
Erythrocytes	**4.27 (IQR 0.92)**	**4.27 (IQR 0.96)**	0.901
Hematocrit	**0.38 (IQR 0.08)**	**0.37 (IQR 0.08)**	0.925
Leukocytes	7.26 (IQR 3.25)	7.81 (IQR 4.64)	0.563
Thrombocytes	226 (IQR 81)	230.5 (IQR 131.8)	0.990
FT_3[a]	3.53 (IQR 1.27)	3.12 (IQR 1.74)	0.256
FT_4[b]	17.05 (IQR 3.97)	18.85 (IQR 7.44)	0.075
TSH[c]	1.00 (IQR 1.54)	1.23 (IQR 5.95)	0.727
PTT[d]	28.30 (IQR 4.55)	29.70 (IQR 8.88)	0.093
Quick	101 (IQR 18)	96.5 (IQR 30.5)	0.056

Data are presented as median and interquartile range (IQR)
Values out of the given reference range (see table 1) are marked
P-values of significance (P<0.05) are marked
* Mann-Whitney-U test
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

Illustrated in Table 10 is the comparison between the case and control groups for patients not taking any form of thyroid medication. The erythrocyte count is significantly higher in the case group compared to the control group (P<0.001), and similar results are observed for the hematocrit value, which is also significantly higher in the case group (P<0.001). Both erythrocyte count and hematocrit are below the given reference range.

Regarding thyroid functional parameters, the TSH value is significantly lower in the case group (P=0.002).

Additionally, the Quick value, one of the coagulation parameters, shows a significant difference (P<0.001), with higher values observed in the case group.

Table 10. Comparison between case and control group without thyroid medication

Parameters	**Case group (N=101)**	**Control group (N=78)**	***P****
Erythrocytes	**4.48 (IQR 0.93)**	**4.10 (IQR 0.98)**	**<0.001**
Hematocrit	**0.41 (IQR 0.07)**	**0.37 (IQR 0.09)**	**<0.001**
Leukocytes	8.03 (IQR 2.92)	8.88 (IQR 4.33)	0.092
Thrombocytes	221 (IQR 98.5)	224 (IQR 99)	0.984
FT_3[a]	4.02 (IQR 1.21)	3.66 (IQR 1.73)	0.183
FT_4[b]	16.15 (IQR 4.42)	15.97 (IQR 4.24)	0.410
TSH[c]	1.24 (IQR 1.36)	1.90 (IQR 4.42)	**0.002**
PTT[d]	29.50 (IQR 5.45)	31.20 (IQR 9.90)	0.062
Quick	102 (IQR 16.5)	84 (IQR 28.5)	**<0.001**

Data are presented as median and interquartile range (IQR)
Values out of the given reference range (see table 1) are marked
P-values of significance (P<0.05) are marked
* Mann-Whitney-U test
[a] triiodothyronine
[b] thyroxine
[c] thyroid stimulating hormone
[d] partial thromboplastin time

5. DISCUSSION

This study examines the comparison between a group of patients who experienced a stroke and another group of patients with various other diagnoses, excluding stroke. General characteristics such as age and gender, as well as laboratory values, were analyzed and compared between the two groups.

The median age of the stroke group was 77 years, which is significantly higher compared to the age reported in other studies on stroke. For example, Demeco et al. reported a mean age of 58.36 years for stroke patients (99), consistent with a large study by Chen et al., which analyzed 63 trials and found a mean age of 60.36 years (100). However, the median age of the non-stroke group was 73 years, resulting in no significant age difference between the two groups.

Another notable aspect of the general characteristics of both groups is their systolic and diastolic blood pressure values, particularly in the stroke group, which were markedly elevated. The stroke group exhibited a median systolic blood pressure of 160 mmHg, compared to 144 mmHg in the non-stroke group. While both values exceed the reference value of 140 mmHg, the stroke group's mean was significantly higher. Similarly, for diastolic blood pressure, the non-stroke group had values near the cut-off of 80 mmHg, with a median of 80 mmHg, whereas the stroke group had a higher median of 90 mmHg. These findings are particularly relevant given that hypertension is a major risk factor for stroke development (101). Upoyo et al. noted that many stroke patients also suffer from uncontrolled hypertension (102), which corroborates our observation of elevated blood pressure in the stroke group.

When comparing the laboratory parameters of both groups, erythrocyte counts and hematocrit levels were found to be significantly different. Given that elevated red blood cell counts and hemoglobin levels are associated with a higher risk of stroke development (103), and our findings indicate lower values or values at the lower threshold, we concluded that these factors do not contribute to stroke development in our study population. Although it was noted that these parameters were significantly different before categorizing patients based on anticoagulation intake; however, this significance disappeared after the division. Both anticoagulation and thyroid medication appear to influence these values, as they remained significant only in the absence of thyroid medication.

Other laboratory parameters that significantly differed between the two groups included FT_3, TSH, PTT, and Quick. The case group exhibited a slightly higher median FT_3 value compared to the control group, suggesting that patients experiencing a stroke have elevated

levels of the metabolically active FT_3 in their blood. The median TSH value in the stroke group was 1.08 IQR 1.40, compared to 1.70 IQR 5.14 in the non-stroke group, indicating a lower mean TSH in patients who experienced a stroke. The non-stroke group exhibited higher TSH values and a greater number of values outside the normal distribution. Lower TSH values in the stroke group and higher FT_3 values suggest a tendency towards a hyperthyroid state, which could be associated with an increased risk of stroke, even though FT_4 did not significantly differ between the groups. Our findings contrast with those of other studies, which report no significant difference in TSH levels between patients who experienced a thromboembolic event and those who did not, although these studies primarily address venous thromboembolism (95,96). Those studies indicate that venous thromboembolism is mainly associated with high FT_4 levels (95,96); similarly, Lin et al. found the same association for pulmonary embolism (97).

Jiang et al. discovered that patients with poor outcomes from acute ischemic stroke exhibited a decreased FT_3/FT_4 ratio, characterized by lower FT_3 and higher FT_4 values. In our study, the FT_3/FT_4 ratio was significantly different, with the case group exhibiting a slightly higher FT_3/FT_4 ratio. This finding suggests a potential connection between the risk of developing a stroke and thyroid hormone conversion.

Additionally, PTT was lower in the stroke group (29.25 IQR 5.22) compared to the non-stroke group (30.20 IQR 8.50). The median Quick value was higher in the stroke group with 102 IQR 17, compared to 89 IQR 28 in the non-stroke group. As PTT reflects the intrinsic coagulation pathway and the Quick value reflects the extrinsic coagulation pathway, these findings suggest that patients who experienced a stroke have a higher rate of coagulation compared to those in the non-stroke group.

Given that some studies suggest hyperthyroid patients exhibit increased turnover of coagulation factors across the extrinsic, intrinsic, and common coagulation pathways (89,90), we aimed to determine whether thyroid functional parameters influence coagulation parameters. In our study, FT_3 was the thyroid functional parameter with the most correlations among other parameters. According to our statistics, FT_3 influences FT_4 in both the stroke and non-stroke groups, as well as TSH, PTT, and Quick in the non-stroke group. As FT_3 is more metabolically active and has various effects on target organs (8,9), this could explain why FT_3 showed the most correlations among all thyroid parameters in our study. FT_4, on the other hand, only showed correlations with other thyroid functional parameters, specifically with FT_3 and

TSH in both groups, although the correlation was stronger in the non-stroke group. TSH, which differed significantly between the two groups, now shows correlation only with FT_4 in both groups and with FT_3 in the non-stroke group.

Hence that thyroid functional parameters can be influenced by thyroid medication and coagulation parameters can be affected by anticoagulant intake, we also compared both groups after dividing them based on their use of these medications. It showed that there were more patients in the control group taking thyroid medication and DOACs.

When comparing the stroke and non-stroke groups, those taking anticoagulants exhibited significant differences in FT_3, TSH, PTT, and Quick values, mirroring the results prior to dividing patients by anticoagulant intake. FT_3 levels were higher in the stroke group, while TSH levels were lower, indicating a more hyperthyroid state in the case group. Additionally, the case group demonstrated lower PTT and higher Quick values, suggesting a more hypercoagulable state compared to the control group. The comparison of both groups without anticoagulant intake showed significant differences only in Quick values, which remained higher in the stroke group. The lack of significant differences in other laboratory parameters post-division suggests that anticoagulant intake may influence FT_3 and TSH values, as they were previously significant.

Finally, we compared the stroke and non-stroke groups after dividing them based on thyroid medication intake. For patients taking thyroid medication, none of the laboratory values significantly differed between the case and control groups. However, for patients not taking thyroid medication, significant differences were observed in TSH and Quick values, with the case group exhibiting lower TSH and higher Quick values. In contrast to that, previous significant FT_3 and PTT values showed no significance after the division into thyroid medication intake. These findings highlight the established relationship between thyroid medication and FT_3 levels and suggest that thyroid medication may also influence PTT values and, consequently, blood coagulation.

Certainly, this study has several limitations that could potentially affect the overall findings. Firstly, it was conducted retrospectively, which means that not all laboratory data initially collected could be included in the study, resulting in some missing values (105). Despite accounting for anticoagulation and thyroid medication, many patients were also taking numerous other medications that could potentially influence thyroid functional parameters or coagulation parameters. The study focused on values obtained from the first blood sample taken

upon admission to minimize the impact of medications administered in the emergency department or during hospitalization. However, this approach does not eliminate the possibility that patients arriving via emergency services may have received medications during transport. Furthermore, any inflammatory conditions such as infectious diseases or chronic illnesses in patients can alter the coagulation system and thyroid hormone secretion, thereby affecting coagulation and thyroid functional parameters (106). Additionally, other known risk factors affecting various body systems, such as smoking, hypertension, or obesity (67), were not accounted for in this study.

Due to the intricate and multifaceted nature of hormonal regulation in the body and its wide-ranging influences, additional research is necessary to obtain deeper insights into this subject.

6. CONCLUSION

1. It was confirmed that patients that experienced a stroke show higher FT_3 and lower TSH values compared to patients that did not suffer from stroke.
2. Patients with a stroke show a different relation of FT_3/FT_4 in comparison to the non-stroke group.
3. It was verified that patients that suffered from a stroke display lower PTT and higher Quick values than patients that did not experience a stroke.
4. The sole correlation between thyroid function and coagulation parameters was observed with FT_3, which is related to PTT and Quick in the non-stroke group.
5. Anticoagulants seem to influence FT_3 and TSH values in the blood, whereas thyroid medication affects PTT values.

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8. SUMMARY

Objectives: Thyroid hormones are known to have numerous actions on body systems and functions, but their influence on blood coagulation and thrombus formation and therefore being a risk factor for developing a stroke, is less commonly discussed. The aim of this study is to observe if there could be a possible connection between thyroid functional parameters and the occurrence of a stroke, by investigating numerous laboratory parameters. We hypothesize that patients that experienced a stroke differ from their thyroid functional and coagulation parameters to patients that did not experience a stroke.

Materials and methods: This study was conducted in the form of retrospective case-control study. There are 134 patients in the stroke group, whereas the non-stroke group consists of 139 patients. All of them are older than 18 years and were admitted and diagnosed at the hospital of Coburg at the time between 2020 and 2023. Only patients with obtained thyroid functional and coagulation parameters were included into this study. The blood test that was the first one obtained in the hospital, was used for further analysis.

Results: When comparing the stroke and non-stroke groups, FT_3, TSH, PTT, Quick values, and the FT_3/FT_4 ratio were significantly different. FT_3 correlated with FT_4 in both groups, and with TSH, PTT, and Quick in the non-stroke group. FT_4 only showed a correlation with FT_3 and TSH in both groups, and TSH correlated with FT_3 in the non-stroke group and TSH in both groups. Among patients taking anticoagulants, FT_3, TSH, PTT, and Quick values were significantly different, while only Quick differed in those not taking anticoagulants. Patients taking thyroid medication showed no significant differences between the stroke and non-stroke groups, but those not on thyroid medication had significantly different TSH and PTT values.

Conclusion: It was confirmed that patients that experienced a stroke show higher FT_3 and lower TSH values compared to patients that did not suffer from stroke. Patients with a stroke show a different relation of FT_3/FT_4 in comparison to the non-stroke group. It was verified that patients that suffered from a stroke display lower PTT and higher Quick values than patients that did not experience a stroke. The sole correlation between thyroid function and coagulation parameters was observed with FT_3, which is related to PTT and Quick in the non-stroke group. Anticoagulants seem to influence FT_3 and TSH values in the blood, whereas thyroid medication affects PTT values.

9. CROATIAN SUMMARY

Naslov: Retrospektivna analiza utjecaja funkcionalnih parametara štitnjače na tromboembolijske događaje

Ciljevi: Poznato je da tiroidni hormoni imaju brojne učinke na tjelesne sustave i funkcije, ali njihov utjecaj na zgrušavanje krvi i stvaranje tromba, te time kao faktor rizika za razvoj moždanog udara, rjeđe se raspravlja. Cilj ovog istraživanja je promatrati može li postojati moguća povezanost između funkcionalnih parametara štitnjače i pojave moždanog udara, istražujući brojne laboratorijske parametre. Pretpostavljamo da se pacijenti koji su doživjeli moždani udar razlikuju od svojih tiroidnih funkcionalnih i koagulacijskih parametara u odnosu na pacijente koji nisu doživjeli moždani udar.

Materijali i metode: Ovo istraživanje provedeno je u obliku retrospektivne studije slučaj-kontrola. U grupi s moždanim udarom nalazi se 134 pacijenata, dok u grupi bez moždanog udara ima 139 pacijenata. Svi su stariji od 18 godina i bili su primljeni i dijagnosticirani u bolnici u Coburgu u razdoblju između 2020. i 2023. godine. U istraživanje su uključeni samo pacijenti s dobivenim funkcionalnim i koagulacijskim parametrima štitnjače. Krvni test koji je prvi dobiven u bolnici korišten je za daljnju analizu.

Rezultati: Pri usporedbi grupa s moždanim udarom i bez moždanog udara, vrijednosti FT_3, TSH, PTT, Quick te omjer FT_3/FT_4 značajno su se razlikovale. FT_3 je korelirao s FT_4 u obje grupe, te s TSH, PTT i Quick u grupi bez moždanog udara. FT_4 je pokazao korelaciju samo s FT_3 i TSH u obje grupe, dok je TSH korelirao s FT_3 u grupi bez moždanog udara i TSH u obje grupe. Među pacijentima koji uzimaju antikoagulanse, vrijednosti FT_3, TSH, PTT i Quick bile su značajno različite, dok se samo Quick razlikovao kod onih koji nisu uzimali antikoagulanse. Pacijenti koji su uzimali lijekove za štitnjaču nisu pokazali značajne razlike između grupa s moždanim udarom i bez moždanog udara, ali oni koji nisu uzimali lijekove za štitnjaču imali su značajno različite vrijednosti TSH i PTT.

Zaključci: Potvrđeno je da pacijenti koji su doživjeli moždani udar imaju više vrijednosti FT_3 i niže vrijednosti TSH u usporedbi s pacijentima koji nisu imali moždani udar. Pacijenti s moždanim udarom pokazuju drugačiji omjer FT_3/FT_4 u usporedbi sa skupinom bez moždanog udara. Verificirano je da pacijenti koji su pretrpjeli moždani udar imaju niže vrijednosti PTT i više vrijednosti Quick u usporedbi s pacijentima koji nisu doživjeli moždani udar. Jedina korelacija između funkcije štitnjače i parametara koagulacije uočena je s FT_3, koji je povezan s PTT i Quick u skupini bez moždanog udara. Čini se da antikoagulansi utječu na vrijednosti FT_3 i TSH u krvi, dok lijekovi za štitnjaču utječu na vrijednosti PTT.