Trace elements and the thyroid gland

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List of Abbreviations

TRH – thyrotropin releasing hormone

TSH – thyroid-stimulating hormone

T_4 – thyroxine

T_3 – triiodothyronine

MIT – monoiodotyrosine

DIT – diiodotyrosine

D1 – deiodinase type 1 (type I)

D2 – deiodinase type 2 (type II)

D3 – deiodinase type 3 (type III)

TG – thyroglobuline

TBG – thyroxine binding globuline

TTR – transthyretin

TPO-Antibodies – thyroid peroxidase Antibodies

TG-Antibodies – thyroglobulin Antibodies

TRAK – TSH-receptor-Antibodies

NIS – sodium/iodide symporter (Natrium/Iodide symporter)

ORD – outer ring deiodinations

IRD – inner ring deiodinations

MHC – major histocompatibility complex

HLA – human leukocyte antigen

AITD – autoimmune thyroid disease

IgM – Immunoglobulin M

IL-6 – Interleukin 6

TREG – regulatory T-cells

SPINA – Structure Parameter Inference Approach

cAMP – cyclic adenosine monophosphate

NTIS – non-thyroidal illness syndrome

SOD – superoxide dismutase

Gpx – glutathionperoxidases

1. INTRODUCTION

1.1. Hormonal regulation of the thyroid gland

The thyroid gland, especially its hormones triiodothyronine (T3) and thyroxine (T4) are crucial for the development of organs and their homeostasis (1). Their secretion is self-regulated by a negative feedback loop mechanism between the pituitary gland, the hypothalamus and the thyroid gland (2). This circuit is also known as the "hypothalamus-pituitary- thyroid (HPT) axis" (3). The thyrotropin- releasing- hormone (TRH), secreted from the hypothalamus, then reaches the anterior lobe of the pituitary gland and stimulates the secretion of TSH (2,3). Following this, TSH binds to its receptors (TSH-R) on the basolateral side of the follicular cells within the thyroid gland (4)**.** This receptor is a G-protein bound receptor (G_s, G_q) (5).

In response to TSH binding, the storage glycoprotein thyroglobulin (Tg), with the thyroid hormones within it, is reabsorbed in a process called endocytosis or micropinocytosis (6). Tg-containing vesicles rapidly associate with intracellular early endosomes. Some of these compounds could then react with lysosomes (6,7). Proteolytic activities in endolysosomes lead to cleavage of T3, T4 and other compounds from thyroglobulin (8). In people with a sufficiently high amount of stored iodine, T_4 is secreted in much higher quantity (80% up to 93%) than T_3 (20%- 7%) (5,8,9). The daily recommended intake of iodine for an adult is about 150µg to 250µg per day (10,11).

Mostly bound to proteins like thyroxine-binding globulin (TBG) and transthyretin (TTR), T_3 and T_4 reach the peripheral tissue (12). Simultaneously, especially T_3 shows inhibiting effects on the hypothalamus as well as the pituitary gland (13,14). At the target tissue, the hormones are transported through the cell membrane via passive diffusion as well as transporters such as the organic anion-transporting polypeptide 1C1, the mono-carboxylate 10 transporter (MCT10) and the MCT8 (4,15).

Within the target cells, so-called deiodinases (D1, D2 and D3) convert T_4 into the much more active form T_3 by 5´-deiodination D1 (16). Most of the circulating fT_3 is formed by the conversion of fT_4 (80%) (16). T_3 interacts, bound to its receptor, with the DNA enhancing certain processes of gene transcription (16). Thyroid hormones also have effects outside the nucleus. Among other things, Davis *et al.* were able to show in a model that T_3, as well as T_4, increases angiogenesis. It was also shown that the binding of the hormones to receptors activated the intracellular PI3 kinase/Akt signaling pathway, thereby mediating increased endothelial nitric oxide synthase (eNOS) (17,18). Furthermore, thyroid hormones also show

effects on muscles function (19). Overall effects are for example promotion of normal brain development, stimulation of lipolysis or synthesis of lipids and the increased expression of cardiac beta- receptors (8).

1.1.1. Synthesis of thyroid hormones

Interdependent and sequential steps are necessary for the synthesis of thyroid hormones:

After iodine reaches the thyroid gland, it is transported into the thyrocyte through the sodium/iodine symporter (NIS) at the basolateral side of the cell (2,5). Iodide is transported into the colloid via the counter transporter pendrin (20). Thyroid peroxidase (TPO) and H2O2 oxidize iodide to iodine thereby binding iodine in the process of organification to tyrosols within thyroglobulin (Tg) (21,22). In the following process of coupling, monoiodotyrosine (MIT) and diiodotyrosine (DIT) condensate with each other to finally form the thyroid hormones T_3 and T_4 (20,22,23). TPO as well as H2O2 also play one of the most essential roles here (20). For better understanding, this process is visualized in Figure 1.

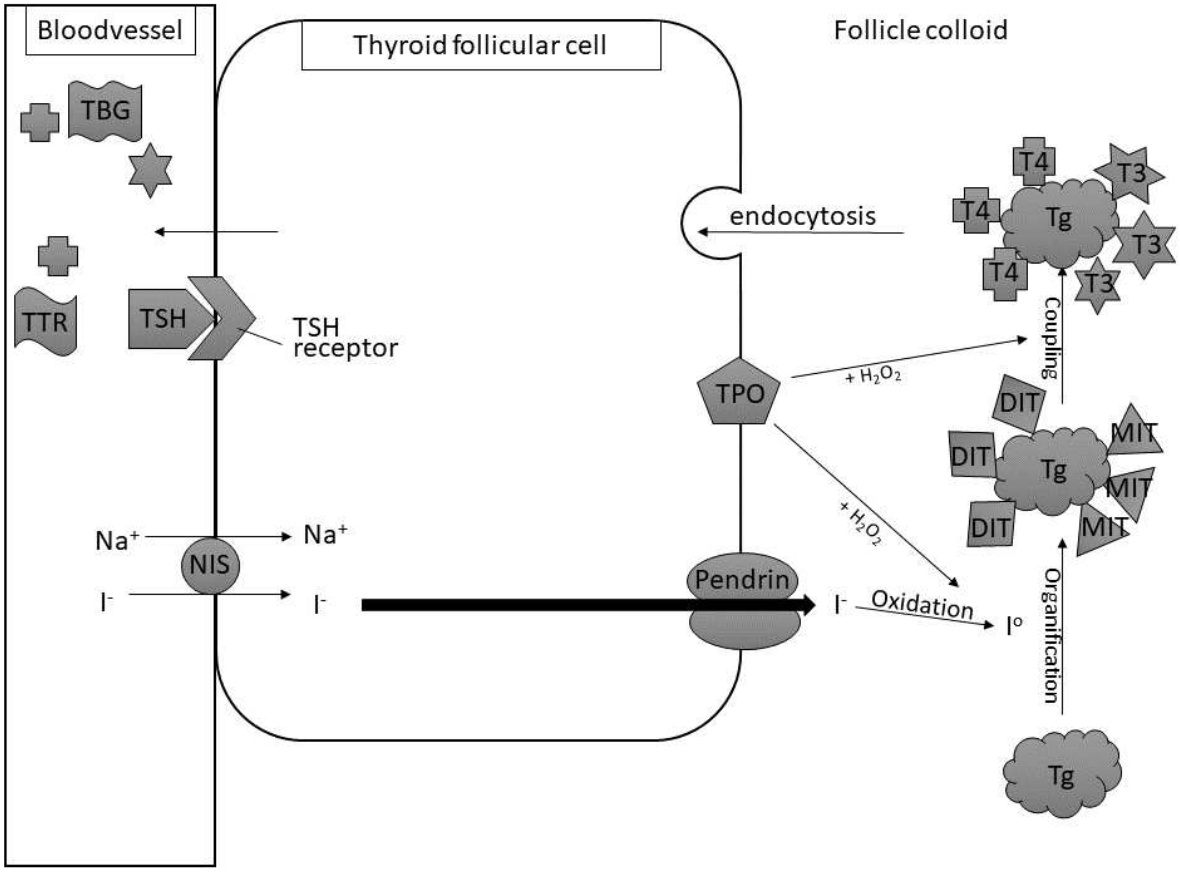

Figure 1. Formation of thyroid hormones. Abbreviations: TBG= thyroxine binding protein; TTR= transthyretin; TSH= thyroid stimulating hormone; Tg= thyroglobuline; T_3= triiodothyronine; T_4= thyroxine; MIT= monoiodothyrosine ; DIT= diiodothyrosine; TPO= thyroid peroxidase; Na= Natrium /Sodium; I= Iodide. Created by the author based on sources in parenthesis (2,5,10,12,20–24).

1.1.2. Diagnostics approach of the thyroid gland

A diagnostic approach for the evaluation of thyroid function can be done *in vivo* as well as *in vitro*. The former can be implemented by sonography, scintigraphy, real-time-elastography, suppressions tests and fine-needle-aspiration if necessary and depending on the indication (25,26). *In vitro* diagnostic consists of measuring the parameters present in serum such as TSH, free T_3 (fT3), and free T_4 (fT4) (2). For determination of etiology especially in suspected autoimmune thyroid disease, thyroid autoantibodies against thyroglobulin, thyroid peroxidase and/or TSH receptor (TgAK, anti-TPO-AK and TRAK) should be examined (27). TSH can be used as a screening tool. Hypothyroidism will be seen as an increase in TSH due to the missing inhibitory feedback mechanism of T_3 and T_4. In case of Hyperthyroidism, TSH will be decreased (2).

1.2. Hypo- and Hyperthyroidism

1.2.1. Definition and Etiology

In general, dysfunctions of the thyroid gland are typically hypothyroidism, due to a lack of thyroid hormones or hyperthyroidism due to excess secretion of thyroid hormones (28,29). Most commonly, hypothyroidism is of primary origin (28). Primary causes have their pathological mechanism at the level of the thyroid gland itself. In rare cases of secondary or tertiary dysfunction the pathology is based on the pituitary gland or hypothalamus, respectively (28). Etiological factors are for example iatrogenic hypothyroidism due to thyroidectomy, therapy with 131I (30) or after administration of amiodaron ("Wolff-Chaikoff effect" (28,31)) or lithium (28).

In the case of elevated thyroid parameters, a distinction should be made between two terms. On one hand, there is the so-called thyrotoxicosis which describes the clinical picture of elevated thyroid parameters without addressing the etiology of them. On the other hand, hyperthyroidism which is characterized by increased synthesis and secretion of thyroid hormones from the thyroid gland (29).

1.2.2. Development of Autoimmunity

Autoimmune (thyroid) diseases (AITD) have a complex mechanism of development. Prevalence ranges from 3 to 10% (32,33). Under physiological conditions, the immune system is able to differentiate between the cells of the body, and recognize them as "own", and exogenous cells or proteins as "foreign" with following destruction of those. This concept of self-antigen recognition and unresponsiveness is known as immunologic tolerance (32–34). More precisely, the distinctive coding and noncoding genetic diversity of so called human leukocyte antigen (HLA) alleles has a significant impact on this antigenic responses to self- and non- self- antigens (35).

Often, there is a combination of endogenous and exogenous trigger factors, leading to the activation of the autoimmune disease and the corresponding symptoms. On one hand, in case of AITD, specific HLA alleles are known. On the other hand, environmental or infectious causes may activate autoimmune diseases or trigger their onset (36). The exact interplay between genetic and environmental factors is still not fully known. Such interplay is also called epigenetics. Its influencing gene expression without changing the genetic code itself by

alteration of the modification patterns of histones, DNA methylation and RNA interference through microRNAs (37).

In general, self- antigens are presented by the major histocompatibility complex (MHC) molecules on the cellular membrane. MHC are encoded on the short arm of chromosome 6 (38). Such MHC is present either as MHC class 1 or MHC class 2. Class 1 (HLA-A,B,C) is presented by every nucleated cell of the body, including T- and B-lymphocytes (34). Cells of the immune system, for example dendritic cells, macrophages and B-cells presenting MHC Class 2 (HLA-DR, -DP, -DQ) molecules (33,34). For some autoimmune diseases, mutations, especially of HLA alleles are known and predicted to be, at least partially, responsible for the increased susceptibility in development of autoimmune diseases (33,35).

1.2.3. Epidemiology of Hypo- and Hyperthyroidism

Europe has the highest prevalence of iodine deficiency (39). This can lead to so-called iodine deficiency diseases. These include, among others, hypothyroidism, which occurs more frequently with moderate to high iodine deficiency (39). The autoimmune thyroid disease Hashimoto's thyroiditis is the most common cause of hypothyroidism in regions with sufficient iodine supply (28). Women are more affected than men (w:m = 10:1). The peak age ranges between 30 and 50 years of age (40).

Hyperthyroidism is most commonly caused by an autoimmune disease named Grave´s disease (Morbus Basedow) (29,41). The age-related incidence varies according to geography (41). Mostly, women are affected (5-10:1) with the highest prevalence between 30 and 60 years of age and the peak around 40 years (2,42).

1.2.4. Etiology and pathogenesis of AITD

Patients with an AITD often have a positive family history (50%). Hashimoto thyroiditis is often associated with certain HLA allele, namely HLA-DR3, -DR4 or -DR5, vitiligo, diabetes type 1 or rheumatoid arthritis diseases (43–45). Genetic loci, which are detected for the susceptibility are all parts of the T-cell receptor signaling as well as antigen presenting pathway. Those loci are TSHR/14q31.1., HLA/6p21, CTL4/2q33.2 and PTPN22/1q13.2 (46). In total, roughly 70% are caused by polymorphism of thyroid genes as well as immunoregulatory genes. Environmental factors may contribute for the rest (47). The exact pathogenesis and precipitating causes are not yet fully known.

Ultimately, in the case of hypothyroidism, the above factors and the resulting activated T cells lead to their infiltration into the thyroid gland and its destruction with the resulting hypothyroid state (47).

Grave´s Disease also shows a familial predisposition and an association as well as an increase of prevalence by the presence of HLA-DR3 (DRB1*03), DQA1*05 and DQB1*02 haplotype, at least in caucasians (38,45,48)**.** Previous infections should also be mentioned (48). Mostly present are stimulating antibodies towards the TSH-receptor (TRAb) producing thyroid hyperfunction causing thyroid gland enlargement and an increase in thyroid hormone production (38).

Antigens, which might be the target of thyroid autoimmunity are often thyroglobulin (TgAb), the TSH-receptor (TRAb) and thyroid peroxidase (TPOAb) (34). Patients with Hashimoto´s thyroiditis show a higher amount of TPOAb than TgAb (49). In case of Grave´s disease, the same antibodies are found in patients' sera. With a higher concentration of those antibodies, the specificity of the tests is increasing due to the fact, that such antibodies may also be seen in the general, healthy, population (49).

1.2.5. Clinical presentation and diagnostic approach of AITD

Characteristic symptoms of both dysfunctions are mostly predictable pathological influences and outcomes on the affected organs and tissues. In the case of missing thyroid hormones, the metabolism is reduced. Therefore, increase in body weight, constipation, cold intolerance and bradycardia can be part of the clinical presentation (28,50). In elderly, depression can be a sign of hypothyroidism. In general, there is a wide variety of symptoms (28). Patients with an untreated subclinical hypothyroidism have a higher risk of coronary heart disease, heart failure and atherosclerosis (51). For hyperthyroidism, reported symptoms are often weight loss, tachycardia, heat intolerance. In women, irregularities of the menstrual cycle may occur. Elderly often present with depression and weight loss (48).

A part of the diagnostic approach, despite the important clinical assessment and throughout physical examination, is doing bloodwork to determine the levels of TSH, fT_3 and fT_4 (48). Because symptoms show wide variability and do not need to be specific, the diagnosis of hypothyroidism is usually defined biochemically (28). In case of subclinical Hypothyroidism, TSH will be increased, whereas fT_4 is (still) within the normal range. As soon as the hypothyroidism becomes manifested, fT_4 will decrease and TSH further increases (28).

For suspected autoimmune thyroiditis, autoantibodies against thyroid peroxidase (TPO-Antibodies; positive in up to 90%) or against thyroglobulin (Tg-Antibodies; positive in 70% of cases) should be determined as well (52,53).

In Hyperthyroidism, the bloodwork will obtain decreased levels of TSH with either normal or increased levels of T_4 and T_3 (29). TSH-receptor stimulating antibodies (TSH-R[stim]-Ab= TRAb) can be measured as well (29). TRAb are more specific and abundant comparing to TPO-Ab and Tg-Ab (48). Where clinical presentation is not diagnostic for grave´s disease a radioactive iodid uptake, measurement of TRAb and/or the local blood flow should be assessed (54).

1.2.6. Treatment of hypo- and hyperthyroidism

Treatment of clinical hypothyroidism or subclinical hypothyroidism but with symptoms compromising patients quality of life and/or TSH values of more than 10 mIU/L is by lifelong replacement of the missing hormones (51,55). Levothyroxine is preferably administered as oral preparations (51,55). Persisting symptoms, reduced quality of life or insufficient peripheral action of thyroid hormones, may cause clinicians to treat their patients with additional T3 preparations (Liothyronine) (51). Although some studies showed partially improvement of patients health in the case of combined therapy, larger studies have to be done (51).

In Grave´s Disease, therapy also aims to restore the patient to an euthyroid state. Various methods are used for this purpose. No causal therapy is known. The choice of treatment depends, among other things, on the age of the patient and prior medical interventions. For this reason, there are the large groups of symptomatic treatment of possible tachycardia, drug thyrostatic treatment, surgical as well as radioactive iodine therapy (29,48,56)**.**

1.3. Trace elements

1.3.1. Selenium

Selenium (Se; atomic nr. 34, non-metal) is an essential trace element, discovered by Jöns Jakob Berzelius, a Swedish chemist, in 1817 (57). In mammals, it is part of the selenium-containing amino acid selenocysteine (Sec). Selenocysteine is the most abundant biological form of selenium (58). It is encoded by UGA, an unique stop codon on the mRNA. At least one of those selenocysteines are in cooperated into Selenoproteins. Selenoproteins play an important role in reduction- oxidation reactions, and have also metabolic and immunological properties (59,60). During gene transcription, RNA processing, translation and posttranslational activities, as well as through regulation of the stability of the relevant intermediates and final products, the expression of selenoproteins is regulated (61).

Selenium is naturally present in foods or can be ingested with supplements. In general, it is existent in organic (selenomethionine and selenocysteine) as well as inorganic (selenate and selenite) form (62). The human body is able to absorb roughly 90% of selenium in form of selenomethionine. Absorption preferably occurs in the large intestine, the cecum and the duodenum (62). In case of the inorganic forms, the amount decreases to 50% for selenite (63). Changes in the gut microbiota, restrictive diets and diseases like inflammatory bowel disease also affects the absorption of selenium (62). Food, which is high in selenium and serve as a good source of selenium are organ meats, seafoods, cereals, dairy products and Brazil nuts. The amount of selenium in plant- based food depends on the amount of selenium present in soil. Therefore, concentration of selenium depends strongly on the geographical location. Supplementation with selenium is mostly done by the ingestion of multivitamin or selenium tabs (64,65). The recommended daily intake by the FAO/WHO is 26 µg/day for women and 35 µg/day for men (57).

Severe deficiency of selenium is called “Keshan Disease” which shows dilated cardiomyopathy in women of child- bearing age and children (66). It may also be associated with total parenteral nutrition (66). Excessive amounts of selenium can be divided into acute or chronic toxicities. Selenosis is the form of chronic increased intake of selenium (64,67). Acute toxicity may present from alterations in the ST-interval on the ECG, unspecific gastrointestinal complaints like vomiting or nausea up to pulmonary edema and coma (67). Furthermore, high amount of selenium alteres, through action of the selenoprotein GPX1, regulators of glucose synthesis and glycolysis (62). Therefore, overexpression of this selenoprotein seem to induce insuline resistance (62).

1.3.2. Zinc

Zinc (Zn) was discovered in humans in the 1960s after a single case report of zinc deficiency (68,69). The human adult body contains roughly 2 to 3-4 grams of zinc (70,71). Concentration in plasma is only 12-16 μM. Hair has the highest amount of zinc per gram of dry tissue. The organ with the highest percentage of total body zinc are the muscles (71). Sources for zinc are especially meat, compared to vegetables as zinc is chelated by phytate and phosphate. The side of zinc absorption is the small intestine (72). Consumption of other cations like magnesium or calcium may interfere with the absorption of zinc from the gut (71). Altered gastrointestinal capacity of absorption or changes in diet habits also influence the absorption of zinc (72). Recommended daily intake is 15 mg/day for men and 12 mg/ day for women. Increased consumption may lead to deficiency of copper (73). The homeostasis of zinc is regulated through several steps of intake and reabsorption in the small intestine as well as other compartments of the body (72). Therefore decreased levels of zinc in the plasma are often seen in later stages and are not reflecting the actual zinc status within the body (72).

Actions of zinc are on the basis of cell proliferation, reduction of oxidative stress, metabolism and catalyzation of enzymes (69,74). Zinc also shows antioxidative properties (74). 30% of the intracellular zinc is within the nucleus and partially thought to be incorporated into gene regulating proteins (75). Additionally, zinc serves as a cofactor for more than 300 enzymes (76,77). Mechanisms of import and export, vesicle retention of zinc (zincosomes), and connection with metallothioneins all maintain its homeostasis in mammals (77). Deficiency of Zinc was documented by Prasad *et al*. in children. Clinical presentation consisted of anaemia, hepatosplenomegalie, skin changes, hypogonadism and retardation in growth as well as mentally (71). Etiology for development of zinc deficiency can be either inadequate intake and/ or consumption of competitive cations, malabsorption syndromes or genetically (Acrodermatitis enteropathica) (76). Furthermore, in states of zinc deficiency, cells of the immune system seem to be the first reacting (78). Increased amount of Zinc may cause so called fume fever due to a pathological pathway of zinc absorption. Such fevers are also documented with increased ingestion of other metals like cadmium and magnesium oxides. Patients often complain about arthalgias, myalgias, headache and malaise (79).

1.3.3. Selenium, zinc and the immune system

Selenium has several known beneficial effects on the immune system. Selenium is an important factor in glutathionperoxidases (Gpx). Here, the antioxidative properties in the extracellular space and the cytosol, especially in the gastrointestinal tract, are important to mention. Some Gpx remove Reactive oxygen species (ROS), for example hydrogen peroxide (H2O2), hydroxyl radical (OH) and lipid hydroperoxides (57,59,80). ROS have a potential damaging effect on cells by damaging for example the nucleic acids and subsequently may contribute to carcinogenesis (57). Supplementation of selenium has been shown to have cytoprotective effects in a variety of cell types, including neurons, astrocytes and endothelial cells (81). Deficient states of selenium caused a decrease of transcription of some selenoproteins in mice, for example Gpx1 in the liver and Gpx3 in the plasma, whereas some transcriptions were not influenced by a deficiency (82). This selection has been termed "hierarchy" of importance of functional selenoproteins. Animal studies showed an increase of intracellular free radicals followed by cell death in case of suppressed synthesis of selenoproteins (57,82,83).

Selenium is also an important influencing factor of the innate and acquired immune system at both, the humoral and the cellular level (80). Current studies on selenium and its benefits for the immune system are controversial. Many studies have investigated (additional) vitamin E deficiency in addition to selenium deficiency. In vitro, as well as some animal studies have shown that selenium deficiency may lead to reduced proliferation of T- and B-lymphocytes and thus to altered production of antibodies. However, these aspects are also dependent on age, sex, species and antigen exposure. Eskew *et al*. considered the cause of the reduced proliferation of lymphocytes in the general deficiency of the animals, than in the specific deficiency of selenium (84). Human studies showed increased and faster cellular immune response to poliovirus vaccination (85).

Zinc´s extensive participation in the immune system includes the capacity to regulate the generation and signaling of a wide range of inflammatory cytokines in a number of cell types, for example IL-6 in Macrophages or type 2 of T-helper cells (78). Cytokines, secreted during inflammatory processes, show effects on both zinc transporters (ZnT and Zip) by down- as well es upregulation of those (78). Bao *et al*. demonstrated for example a decrease of C-reactive protein after supplementation of zinc (45 mg/day) for six month to 40 healthy elderly people (73).

1.3.4. Selenium, zinc and the thyroid gland.

The thyroid gland is the organ, with the highest amount of selenium per gram of tissue (0,2-2µg/g). Here, Selenium serves as antioxidant in form of synthesized selenoproteins, by removing ROS which is physiologically formed by the synthesis of thyroid hormones (64,86). Furthermore, it is an important participant in the metabolism of thyroid hormones (80). A deficiency of selenium seems to spare the thyroid gland in the sense of unchanged hormone profiles at least in healthy individuals and maintained expression of thyroid selenoproteins (87). In patients with increased TPO-Antibodies and hypothyroidism is has been shown, that the level of oxidative stress is slightly increased (88).

Zinc also serves as an antioxidant by removing ROS in human vascular endothelial as well as monocytic cells (73). Supplementation of zinc is known to reduce the production of ROS in cell culture and animal models (73). The action of thyroid hormones modify the metabolism of zinc as well as zinc influencing their metabolism (89). In the thyroid gland, zinc is part of the superoxide dismutase (SOD) (90). SOD serves important catalytic and therefore antioxidative action in the conversion of superoxide molecules (91). Zinc also plays an important role in the conversion of thyroxine to triiodothyronine (90). Studies regarding zinc being beneficial for the treatment of thyroid diseases are controversial. As a cofactor, zinc has an integrative role on the activity of deiodinases (9). Complete understanding of interaction has not been yet established (9). Furthermore, zinc is thought to be an essential part of the triiodothyronine receptor, contributing to the nuclear action of this hormone (75).

1.4. Deiodinases

Within the human body, there are three different types of so-called deiodinases (D1, D2 and D3) (92). Their action is to either activate or inactivate thyroid hormones (93). On their active side, the amino acid selenocysteine has an important influence on their catalytic activity (94). D1 and D2 seem to be responsible for the activation of T_3 by deiodination of T_4. In humans, especially type 2 5´-deiodinases (D2) are important for the conversion of T_4 into T_3 by the reductive elimination of iodide and are thought to be the primary source for extrathyroidal T_3 generation (95). Type 3 5-deiodinases (D3) are important in the inactivation of T_4 by the formation of rT_3.

Monodeiodination at the 5 or 3 positions of the tyrosyl ring are comparable inner-ring deiodinations (IRD), and those at the 3´or 5´positions (phenolic ring) are analogous outer- ring

deiodinations (ORD) (92). Deiodinases, in general, are selenocysteine-dependent membrane enzymes. Organ specific distribution of the deiodinases are listed in Table 1.

Table 1 Distribution of deiodinases throughout the body

	D1	D2	D3
Organ	Liver, kidney, thyroid, pituitary gland and heart	Skin, placenta, thymus, pituitary gland, brown adipose tissue, pineal gland.	Placenta, brain, several tissues except pituitary, thyroid, kidney, adult healthy liver
Essential amino acid residues	Histidine, selenocysteine, cysteine, phenylalanine	Selenocysteine	Selenocysteine
Enzyme induction	T_3, retinoids, TSH and cAMP in thyroid only; testosterone in the liver	cAMP; ANP and CNP via cGMP in glial cells,	T_3, FGF, EGF

Abbreviation: cAMP= cyclic adenosine monophosphate; CNP= C-type natriuretic peptide; cGMP= cyclic guanosine monophosphate; FGF= fibroblast growth factor; EGF= epidermal growth factor; D1= deiodinase type 1; D2= deiodinase type 2; D3= deiodinase type 3; (59,95,96).

By having a major role in the conversion and activation of thyroid hormones, different polymorphisms of the responsible genes may influence their action. Genes for deiodinases are located at Chromosome 1 (D1) and Chromosome 14 (D2). In case of D1 polymorphism D1-C785T may decrease the peripheral conversion of T4 into T3 by down- regulation of D1 protein activity. Such findings were mostly seen in elderly patients, pointing towards the possibility, that the conversion of T4 to T3 changes from D2 toward D1 with an increase in age (97). Additionally, the importance of D2 regarding energy expenditure was seen in animal studies. Cold-induced thermogenesis in brown adipose tissue has been demonstrated to be dependent

on cyclic adenosine monophosphate (cAMP)-mediated acceleration of D2-catalyzed T3 synthesis. (95).

Conversion of T_4 into T_3 by D2 at the level of the pituitary gland is an indicator for the importance of D2 within the HPT axis. Here, D2 allows the pituitary gland to respond to variations in circulating T_4 levels. TSH secretion itself is regulated by serum T_3 as well as intracellular pituitary T_3 produced by D2 (51). Polymorphism of D2, especially the DIO2Thr92Ala has shown to affect the stability and activity of the enzyme, which then alters the metabolism of thyroid hormones and may reduce the conversion of T_4 into T_3 (98).

Furthermore, deficient levels of selenium can interfere with the expression of D2 at the level of translation. According to DePalo *et al*., it also induces a reduction in the activity of D1 in the liver of rats (99,100). Other studies suggest that the reduction of those 5´Deiodinases are organ- specific with their maintained activity within the thyroid gland itself (101). As already mentioned above, zinc also has demonstrated to serve as a cofactor in the activity of deiodinases (9).

1.5. Determination of the activity of the thyroid gland and the peripheral tissue

A simple method to evaluate thyroid homeostasis and the capability of the conversion of T_4 into T_3 may be done by the measurement of TSH, fT_3, fT_4 and by calculating the ratio of fT_3 and fT_4 (T3/T4 ratio) (102).

As described by Dietrich *et al.* (103), and mentioned before, TSH, T_3 as well as T_4 may be helpful in the sense of a screening tool but their predictive values are still poor. Biological variations and preceding reduction in the quality of life despite adequate monotherapy with levothyroxine and reduced activity of deiodinases due to polymorphism are partially still under question (51,97,104). In Patients with a primary disorder of the thyroid gland as well as being in an euthyroid state, presenting a point of equilibrium within the HPT axis. This so called setpoint is, where TSH and fT_4 are in equilibrium (51). Such setpoint may be modulated by any change of any step within the aforementioned feedback loop including a therapy with Levothyroxine (L-Thyroxine, L-T4), mutations of the thyroid hormone transporter MCT8, or polymorphisms of the deiodinases (102). Since 1956 different cybernetic models were developed. Calculation of the secretory capacity of the thyroid gland (SPINA-GT) as well as the sum activity of the peripheral deiodinases (SPINA-GD) was translated for medical purposes. Furthermore, Jostel´s TSH Index (TSHI or sTSHI) for the assessment of the

thyrotropic pituitary function was implemented (104). SPINA is the abbreviation for “structure parameter inference approach”. By the calculation of SPINA-GT one can differentiate between an euthyroid state or a pathology on the level of the thyroid gland itself (104). SPINA-GD refers to the total step-up activity of the peripheral deiodinases, mainly 5´-deiodinase (104).

Several studies have already shown a correlation of SPINA-GT with creatinine clearance as well as with the volume of the thyroid gland. SPINA-GD correlated to age and B-type natriuretic peptide (BNP). Furthermore, a correlation was seen between TSH and SPINA-GD (104). The aforementioned disorders of the deiodinases may be captured by the calculation of SPINA-(s)GD as this parameter evaluates the conversion of T_4 into T_3. In patients, with polymorphism of deiodinases, additional replacement of T_3 may be therefore useful (104). SPINA-GT has shown to be significantly increased in diseases like Grave´s Disease or toxic adenoma and decreased in Hashimoto´s thyroiditis (104).

2. OBJECTIVES

2.1. Aims of the study

The aim of our study was to investigate if both trace elements correlate with TSH, T_4, T_3 and/or the level of TPO-Antibodies in the blood. We also explored the effects of selenium and zinc on the calculated secretory capacity of the thyroid gland and the step-up activity of the peripheral deiodinases. Jostel´s TSH Index and the thyrotroph thyroid hormone sensitivity index (TTSI) were also considered.

2.2. Hypothesis

1. Patients with increased levels of TPO-Antibodies have lower levels of SPINA-GD
2. Selenium correlates with thyroid function parameters
3. Selenium correlates with calculated parameters related to the function of the HPT-axis
4. Zinc correlates with thyroid function parameters
5. In the presence of reduced amount of zinc, it correlates with calculated parameters related to the function of the HPT axis.

3. MATERIALS AND METHODS

3.1. Study Design

For this retrospective study, already collected data, between 2015 and November 2017, of patients from the endocrinology department of the REGIOMED Hospital in Coburg, Germany were enrolled in this study. In total 90 cases fulfilled the inclusion criteria.

Inclusion criteria were measured serum selenium and zinc levels, any disturbances on thyroid level, measured TPO-Antibodies and older than 18 years of age. Patients with cancer, an acute infection and pregnancy were excluded.

Any participant with a TPO-Ab value of more than 16 IU/ml was enrolled into one group. Cases, with less than 16 IU/ml of TPO-Antibodies were collected into another group.

3.2. Data Collection

This retrospective cross-sectional study used already collected and anonymized data of the department of endocrinology of the REGIOMED hospital in Coburg. According to the official homepage of the local water supplier, the amount of selenium in the ground water was below the recommended value of 0.010 mg/L. During an email contact with the local water supplier, these values would be confirmed again. Testing is performed by using the DIN EN ISO 11885 (E22): 2009-09 [G]. Regarding zinc, no values were found on the official homepage.

3.3. Laboratory analysis and reference values

Blood samples were taken after a fasting period of at least 12 hours. Blood pressure, heart rate and similar parameters were collected by a trained assistant. Body mass index was measured manually by taking the standardized calculation. Measurements of TSH, fT_3 and fT_4 were done by the laboratory of the REGIOMED hospital Coburg with the ECLIA Method (ROCHE Cobas e 601) (Coburg, Germany). Antibodies were sent to an external laboratory (MVZ Labor Dr Volkmann&Kollegen GbR, Karlsruhe, Germany). The used method for measurement of the TPO-Antibodies (TPO-Ab) and the thyroglobulin Antibodies (TgAb) was the TRACE- Technic (ThermoFisher; Krypter compact PLUS (Brahms)).

Selenium and zinc were measured by the same laboratory. Determination of selenium and zinc was done by using the AAS-Method (Perkin Elmer AAnalyst 600). The reference values, given by the laboratory were 660- 1100 µg/L for zinc and 50- 120 µg/L for selenium.

3.4. Ethical Approval

This retrospective study earned its approval by the IRB of the Medical School Regiomed Coburg on March 18, 2022.

3.5. Statistical Analysis

For building plot-graphs, Microsoft Excel for Windows was used. Statistical analysis was done by using IBM SPSS Statistics (Version 28.0.1.1 (15)). For the calculation of the secretory capacity of the thyroid gland, the sum activity of peripheral deiodinases and other calculated parameters of (estimated) homeostasis, the program SPINA Thyr (Version 4.2.0.861; provided by sourceforge.net) was used. The reference values for all parameters given by SPINA Thyr were set by the program as seen in Table 2. Normality was determined by the Shapiro-Wilk-test. To determine differences between both groups, the t-test was used for normal distributed data and the Mann-Whitney U test, where normality was not met. Chi- square or fisher´s exact was used where appropriate. Correlation analysis was performed by the two-tailed Spearman´s rho. Correlation was done between selenium, zinc and thyroid function tests as well as between selenium, zinc and the calculated values of SPINA Thyr Same correlations were done by excluding patients who were treated with additional T3 supplementation with focusing on the correlation between selenium, zinc and SPINA-GD. Statistical significance was set with a P value of <0.05.

Table 2 Reference values of the SPINA Thyr variables.

	Reference values
GT	1.41- 8.67 pmol/s
GD	20.0-40.0 nmol/s
sGD	-
TTSI	100-150
TSHI	1.3-4.1
sTSHI	-

4. RESULTS

In this study, a total of 90 cases of whom 42 cases had TPO-Antibodies below 16 IU/ml (Group 1) and 48 above this value (Group 2), were enrolled. Average age of group 1 was significantly lower (p= 0.012, 95% CI [-0.962 - -0.119]) with 42.43 ± 12.47 years of age compared to 49.42 ± 13.25 in group 2 as illustrated in Table 3. Both groups showed no significant differences neither in body mass index, systolic and diastolic blood pressure nor in heartrate (p= 0.974, p= 0.731, p= 0.602, p= 0.310, respectively).

Table 3. General characteristics of both groups

Variables	**TPO-Antibodies[a] <16 IU/ml (n=42)**	**TPO-Antibodies[a] >16 IU/ml (n=48)**	***P***
Age (years)	42.43 ± 12.47	49.42 ± 13.25	**0.012**[*]
Male gender	3 (7.1%)	4 (8.3%)	0.906[†]
Body mass index (kg/m^2)	27.35 ± 5.19	28.01 ± 5.19	0.974[‡]
Systolic Blood Pressure (mmHg)	136.45 ± 16.52	136.48 ± 21.82	0.731[‡]
Diastolic Blood Pressure (mmHg)	83.69 ±14.12	82.31 ± 11.41	0.602[‡]
Heartrate (bpm)	81.52 ± 13.48	77.73 ± 12.64	0.310[‡]

Data is presented as Mean ± standard deviation, Median and interquartile range (IQR) or as frequency n (%)

[*] t-test

[†] Chi- square test

[‡] Mann-Whitney U test

[a] thyroid peroxidase

The intake of different medication is shown in Table 4. Only for the intake of L-thyroxine there is a significant difference between increased TPO-Antibodies and lower ones (P=0.033).

Table 4. Intake of medication in both groups

Medication	TPO-Antibodies[a] <16 IU/ml (n=42)	TPO-Antibodies[a] >16 IU/ml (n=48)	*P*
L-Thyroxine (T4)	23 (54.8%)	36 (75%)	**0.033**[*]
Liothyronine (T3)- in combination with T4	5 (11.9%)	3 (6.3%)	0.212[*]
Beta blocker	4 (9.5%)	12 (25%)	0.095[†]
Selenium supplement	6 (14.3%)	5 (11.9%)	0.778[†]
Zinc supplement	5 (11.9%)	3 (6.3%)	0.465[†]

Data is presented as frequency n (%)
[*]Chi-square
[†] 2-sided Fisher´s exact test
[a] thyroid peroxidase

As illustrated in Table 5, both groups differ from each other only in regard of their TPO-Antibodies (P <0.001). Selenium as well as zinc were higher in the group with increased TPO-Antibodies compared to the group with lower TPO-Antibodies. The differences were not significant (p= 0.241 and p= 0.484). TSH, T3 and T4 were not significantly different between both groups as well (P= 0.358, P= 0.179, P= 0.607, respectively). Values are written as Mean with their corresponding standard deviation (Mean ± SD) or as median with interquartile range (Median IQR).

Table 5. Amount of TSH, T3, T4, TPO-Antibodies, Selenium and Zinc in both groups

Blood tests	TPO-Antibodies[d] < 16 IU /ml (n= 42)	TPO-Antibodies[d] > 16 IU /ml (n= 48)	*P*[*]
TSH[a] (µIU/L)	1.12 IQR 0.93	1.65 IQR 2.13	0.358
T3[b,] (pg/ml)	3.03 IQR 0.66	2.81 IQR 0.66	0.179
T4[c] (ng/dl)	1.26 IQR 0.47	1.36 IQR 0.46	0.607
TPO-Antibodies[d] (IU/ml)	0.95 IQR 2.0	102.65 IQR 377.3	**<0.001**
Selenium (µg/L)	86.70 IQR 29.48	91.58 ± 18.16	0.241
Zinc (µg/L)	721.51 ± 115.66	738.69 ± 119.07	0.491[†]

Data is presented as Mean ± standard deviation or as Median with interquartile Range(IQR)
[*] Mann-Whitney U-test
[†] Independent samples t-test
[a] Thyroid-stimulating hormone
[b] triiodothyronine
[c] thyroxine
[d] thyroid peroxidase antibodies

SPINA-GD as well as SPINA-GT were both lower in the group with increased TPO-Antibodies. The results were not significant. There were no statistical differences between both groups in regard of the values of GT, GD, sGD, TSHI, sTSHI and TTSI of SPINA seen (p= 0.671, p= 0.176, p= 0.172, p= 0.221, p= 0.206, p= 0.133, respectively). Results are visualized in Table 6 as median and their corresponding interquartile range (Median IQR).

Table 6. Differences regarding SPINA values between both groups

Calculated parameters	**TPO-Antibodies[g] < 16 IU/ml (n=42)**	**TPO-Antibodies[g] > 16 IU/ml (n=48)**	***P****
SPINA-GT[a] (pmol/s)	4.26 IQR 4.19	4.08 IQR 4.36	0.671
SPINA-GD[b] (nmol/s)	25.46 IQR 7.84	22.82 IQR 7.74	0.167
sGD[c]	-0.91 IQR 1.57	-1.42 IQR 1.55	0.172
TSHI[d]	2.40 IQR 1.02	2.70 IQR 1.20	0.221
sTSHI[e]	-0.49 IQR 1.58	0.03 IQR 1.77	0.206
TTSI[f]	88.50 IQR 120	120.50 IQR 183	0.133

Data is presented as Median and its interquartile range (IQR)

* Mann-Whitney U test

[a] Structure Parameter Inference Approach- secretory capacity of the thyroid gland

[b] Structure Parameter Inference Approach- step-up activity of peripheral deiodinases

[c] standardized structure parameter inference approach-step-up activity of peripheral deiodinases

[d] Jostel´s TSH Index

[e] standardized Jostel´s TSH Index

[f] thyrotroph thyroid hormone sensitivity index

[g] thyroid peroxidase

By excluding the patients which received additional therapy with T3, SPINA-GD was not significantly lower in the group of increased TPO-Antibodies compared to the group with lower TPO-Antibodies (23.63 IQR 7.98 vs. 25.77 IQR 6.54; p= 0.125, respectively) as illustrated in Figure 2.

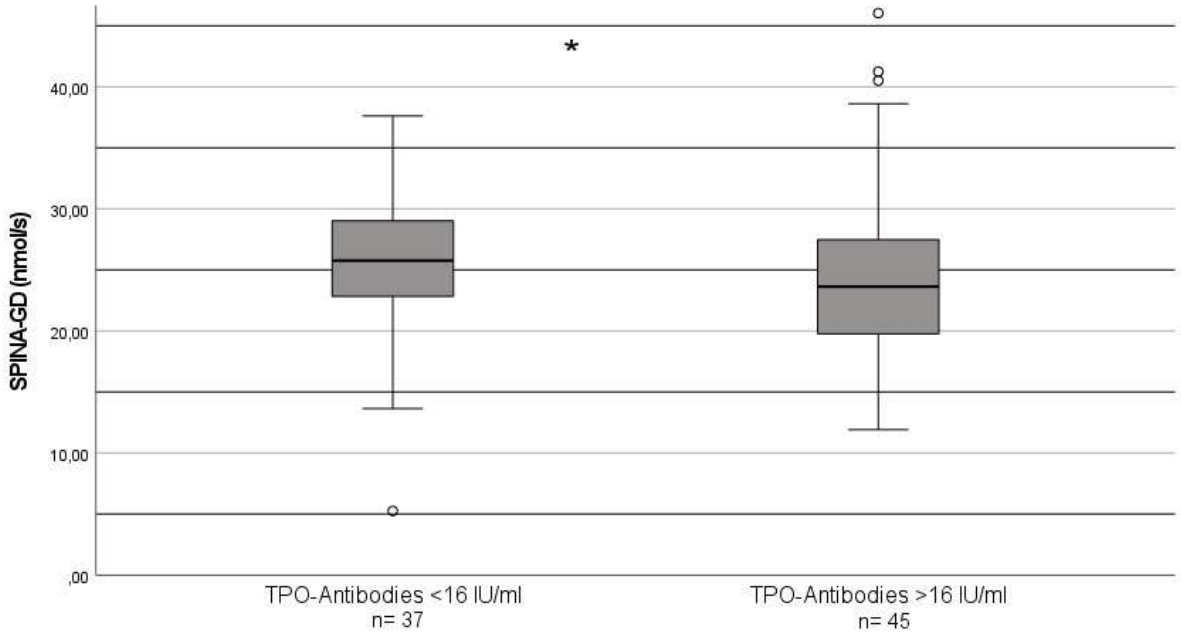

Figure 2. SPINA-GD between both groups without the additional intake of T3
Data are presented as Median IQR
* Mann-Whitney U test, $P = 0.125$

25 participants (27.78%) in total were below the reference value of zinc. Within the group of reduced levels of TPO-Antibodies (n= 42), 33.3% (n= 14) were below the value of 660 µg/L versus 22.92% (n= 11) in the group with increased TPO-Antibodies (n= 48). No significant difference was seen between both groups (P = 0.350 (Chi-square test)). No participant was above the value of 1100 µg/L.

In the group of reduced zinc, there was a significant correlation between zinc and the heart rate as well as between zinc and TTSI and sTSHI (rho= 0.643, p= 0.033; rho= 0.763, p= 0.006; rho= 0.606, p= 0.048, respectively).

For selenium, no participant was below the reference value of 50 µg/L. Four of each group were above the upper limit of 120 µg/L (9.52 % vs 8.33%, Pearson chi-square = 0.333). Due to the low number of patients per group, no statistical analysis was done.

Selenium showed a significant negative correlation in the group of high TPO-Antibodies with TSH, TSHI and TTSI (rho= -0.354, P= 0.021; rho= -0.305, P= 0.050*; rho= -0.455, P= 0.002*, respectively). In the group of increased TPO-Antibodies, selenium only inversely correlated significantly with T3 (rho= -0.319, P= 0.027). Results are illustrated in Table 7.

Table 7. Spearman´s correlation between selenium and TSH,T4,T3, SPINA-GD,GT,TSHI and TTSI

Parameter		**TPO- Antibodies[d] <16 IU/ml (n=42)**	**TPO- Antibodies[d] >16 IU/ml (n=48)**
TSH[a]	Spearman´s rho	- 0.354	0.272
	*P**	**0.021**	0.061
T4[b]	Spearman´s rho	0.087	-0.148
	*P**	0.582	0.315
T3[c]	Spearman´s rho	0.165	-0.319
	*P**	0.297	**0.027**
TPO-Antibodies[d]	Spearman´s rho	0.167	0.153
	*P**	0.291	0.299
SPINA-GT[e]	Spearman´s rho	0.260	-0.271
	*P**	0.097	0.062
SPINA-GD[f]	Spearman´s rho	-0.021	-0.106
	*P**	0.895	0.474
TSHI[g]	Spearman´s rho	-0.305	0.244
	*P**	**0.050**	0.095
TTSI[h]	Spearman´s rho	-0.455	0.267
	*P**	**0.002**	0.067

*significant p-values are marked
[a] Thyroid stimulating hormone
[b] thyroxine
[c] triiodothyronine
[d] thyroid peroxidase
[e] Structure Parameter Inference Approach- secretory capacity of the thyroid gland
[f] Structure Parameter Inference Approach- sum activity of peripheral deiodinases
[g] Jostel´s TSH Index
[h] thyrotroph thyroid hormone sensitivity index

Zinc failed to correlate significantly in any of the groups as illustrated in Table 8. Within the group of increased TPO-Antibodies, zinc correlated with a higher coefficient with T3 although both values were not significant (rho= 0.254 vs -0.040, both P >0.05). Zinc correlated negatively with TPO-Antibodies in the case of increased Antibodies although this result is not significant (p= 0.264).

Table 8. Spearman´s correlation between zinc and TSH, T4, T3, SPINA GD, GT, TSHI and TTSI

Parameter		**TPO-Antibodies[d] <16 IU/ml (n=42)**	**TPO-Antibodies[d] >16 IU/ml (n=48)**
TSH[a]	Spearman´s rho	0.039	0.025
	P *	0.809	0.865
T4[b]	Spearman´s rho	-0.046	0.080
	P *	0.772	0.588
T3[c]	Spearman´s rho	-0.040	0.254
	P *	0.801	0.082
TPO-Antibodies[d]	Spearman´s rho	0.095	-0.164
	P *	0.552	0.264
SPINA-GT[e]	Spearman´s rho	-0.043	0.000
	P *	0.787	1.000
SPINA-GD[f]	Spearman´s rho	-0.025	0.161
	P *	0.875	0.273
TSHI[g]	Spearman´s rho	0.063	0.049
	P *	0.693	0.742
TTSI[h]	Spearman´s rho	-0.032	0.099
	P *	0.842	0.502

*significant p-values are marked
[a] Thyroid stimulating hormone
[b] thyroxine
[c] triiodothyronine
[d] thyroid peroxidase
[e] Structure Parameter Inference Approach- secretory capacity of the thyroid gland
[f] Structure Parameter Inference Approach- sum activity of peripheral deiodinases
[g] Jostel´s TSH Index
[h] thyrotroph thyroid hormone sensitivity index

Excluding the cases which were additionally treated with T3, neither selenium nor zinc correlated significantly with SPINA-GD (both P>0.05)as shown in Table 9.

Table 9. Spearman´s correlation between selenium, zinc and SPINA-GD, with exclusion of participants additional intake of T3

Parameter		**TPO-Antibodies[a] <16 IU/ml (n=37)**	**TPO-Antibodies[a] >16 IU/ml (n=45)**
SPINA-GD[b] X selenium	Spearman´s rho	-0.034	-0.102
	P *	0.840	0.504
SPINA-GD[b] X zinc	Spearman´s rho	0.005	0.211
	P *	0.978	0.163

* significant p-values are marked
[a] thyroid peroxidase
[b] Structure Parameter Inference Approach- sum activity of peripheral deiodinases

Significant positive correlation between zinc and the heartrate as well as a positive correlation between selenium and age were seen as secondary outcome and represented in Table 10.

Table 10. Secondary outcomes of spearman´s correlation

Parameter		**TPO-Antibodies[a] <16 IU/ml (n=42)**	**TPO-Antibodies[a] >16 IU/ml (n=48)**
age X selenium	Spearman´s rho	0.080	0.338
	P *	0.616	**0.019**
Heart rate X zinc	Spearman´s rho	0.362	0.034
	P *	**0.019**	0.820

* significant p-values are marked
[a] thyroid peroxidase

5. DISCUSSION

Although the identification and treatment of autoimmune thyroid disease has been practiced for a long time, it continues to be a global health problem. To address this problem, many studies have been conducted on identification, treatment, and outcome. With this study we wanted to evaluate the influence of selenium and zinc on functional parameters of the thyroid gland as well as on the calculable SPINA-GT, SPINA-GD, TSHI and TTSI.

In this conducted study, none of the patients had a clinically diagnosed selenium deficiency. A Zinclevel below the reference values was present in 25 patients (27.78%). SPINA-GD showed in this study, to be non-significant lower in the group of elevated TPO-Antibodies, compared to the group with low TPO-Antibodies. This result was unaffected by the exclusion of participants with additional intake of T3. In our study we were not able to demonstrate a significant difference between both groups in regard of selenium and zinc. Furthermore, we could not prove any correlation between selenium, zinc and the TPO-Antibodies. A correlation between selenium, zinc and SPINA-GD could not be established. We observed a correlation, in the group of low TPO-Antibodies, between selenium and TSH as well as with TSHI and TTSI. Selenium showed also an inverse correlation with triiodothyronine in the group of elevated TPO-Antibodies.

The hormonal secretion of the thyroid gland is largely unaffected by the level of selenium. Selenium itself is part of the active side of deiodinases which enzymatically produce triiodothyronine (87,94). Furthermore, TSH-receptors are also present on the anterior pituitary gland, expressed on subclasses of folliculo- stellate cells (105) .

The effect of selenium on the thyroid gland, especially in the case of autoimmune thyroid diseases was topic of several studies. In a study, patients treated with levothyroxine and additional selenium showed a decrease in the amount of TPO-Antibodies as well as an increase in their well-being (106) In a follow up study, performed on 47 patients with autoimmune thyroiditis, by Gartner and Gasnier, a significant decrease in the amount of TPO-Antibodies over the course of six months in the case of additional daily supplementation of 200 µg of selenium was demonstrated (107). Duntas *et al.* also demonstrated a decrease of TPO-Antibodies over a longer course of supplementation of 200µg of selenium but without a statistical significance between both groups in regard of TPO-Antibodies, TSH, free T3 and T4 (108). Healthy men, fed with selenium in different concentrations over a period of 120 days by Hawkes *et al.,* showed an increase in their levels of TSH. This was the case in the group fed with high concentration of selenium (109). Another study, done by the same group, found no effect on thyroid hormones by the supplementation of high- selenium supplements of

300µg/day (110). TSH itself has several hormones, gonadotropins, which are binding to the same receptor as they show similarities in their binding properties. Such hormones are LH, FSH, estrogen and hCG (102). As most of the patients with thyroid dysfunctions are female, possible hormonal influences should therefore be encountered in following studies (28,102).

It has been found, that patients with non- thyroidal illness syndrome (NTIS) show reduced levels of TSHI. In seriously ill or starving patients, especially in the setting of intensive care units, NTIS is often found. Its´ characteristics are low levels of fT3, high rT3, normal or decreased levels of TSH and ,over a longer period of time, decreased fT4 as well (111). The introduction of this mathematical model is based on the fact, that patients may still report symptoms or reduction of their quality of life despite adequate therapy with T4 and TSH levels within the reference range. The intraindividual set point of equilibrium and the narrow therapeutic range around it may be a cause for the differences in treatment response (104). At the level of the anterior pituitary gland, TSH secretion depends on the level of T3 as well as T3 generated by type II deiodinases (D2) directly in the gland (95).

As polymorphism in regard of deiodinases may cause altered reaction and activation of T3 (51,95,97,98), this topic should also be further investigated to evaluate possible changes of SPINA-GD in accordance and if additional intake of selenium and/ or zinc may improve the rate of conversion despite the genetic polymorphism. As zinc has activity as a cofactor for the deiodinases on one hand and seems to be involved in the genetic action of triiodothyronine on the other hand unpredictable confounding factors may not be assessed here and should be incorporated in further studies (9,76,77).

The age was significantly different in our study between both groups with a higher mean of age in the group with high TPO-Antibodies. This may be screwed by having a relatively small sample size although thyroid dysfunction is relatively frequent among the elderly with autoimmune thyroid failure being the most common cause of hypothyroidism. Autoantibodies become more prevalent with age (112,113).

Taking into account, that selenium is also present in the soil and therefore influencing the amount of ingested selenium through soil-based vegetables, grains *et cetera*, further studies may conduct and include possible geographical sources and probes of this area to measure the "base" of selenium intake (64,65). Furthermore, diet habits should be accessed in detail to collect data about the amount and the type of food, the participants are consuming. The same is the case for zinc as absorption and the homeostasis of zinc is altered by gastrointestinal diseases, menstrual flow and severity of hair loss, just to mention a few of them (72). Furthermore, zinc

status within plasma is not reliable due to changes of zinc in inflammatory states, stress or even postprandial (72).

Zinc revealed no significant correlation except in the subgroup of low zinc status. Here, it correlated with sTSHI as well as with TTSI. To our current knowledge, no studies have been performed in this regard so far. A study by Turan *et al.* showed, that seleneium as well as zinc was significantly lower in a group of 98 patients with euthyroid multinodular goiter compared to healthy patients. Neither selenium nor zinc correlated with thyroid hormones (74).

Our study had several limitations. Firstly, this study was a retrospective study. Here, is to mention, that the length of active disease and changes within the treatment were not accessible. Additionally, sample size of our study was relatively low. Possible interindividual differences and variations may not be seen. Furthermore, dietary changes, intake of supplements besides those listed and/ or gastrointestinal changes, which can be encountered as confounding factors were not further assessed in this study (62). Levels of hormones (LH, FSH) as well as the exact timing of the menstrual cycle were not recorded in this study (72,102). Both trace elements are somehow affected by the digestive tract (62,72). Some species of *Lactobacillus* also seem to influence the formation of deiodinases, therefore selenium as well as the propper function of thyroid hormones (62). Aspects, which were not encountered in this study.

Above mentioned studies partially express the complexity of this field of endocrinology and the broad range of possible influencing factor on every step of the hypothalamic- pituitary-thyroid axis. As a result, further studies have to be conducted to provide further insight into the complex interplay of hormonal axis, its exogenous as well as endogenous regulating and modulating factors and the opportunity of additional treatment of patients with adequate supplementation with selenium and/or zinc.

6. CONCLUSION

There was no significant difference in regard of selenium and zinc between both groups.

SPINA-GD has shown to be lower in the group of high TPO-Antibodies but this result is not significant. By excluding those participants which were treated with additional T3, SPINA-GD was not significantly lower in the group with increased TPO-Antibodies.

There was no significant correlation in none of both groups between selenium and SPINA-GD. Exclusion of those, who were treated with additional T3 substitution, did not change correlation in aforementioned parameter and selenium.

In the group of increased TPO-Antibodies, selenium demonstrated a significant negative correlation with triiodothyronine. Selenium significantly correlated inversely with TSH, TSHI and TTSI in the group of TPO-Antibodies below 16 IU/ml.

Comparing both groups, the correlation coefficient between zinc and triiodothyronine was higher in the group of increased TPO-Antibodies, although none of the results were significant.

As 25 participants had blood levels of zinc below the reference value a spearman´s correlation was done here as well. Here, significant positive correlations were seen between zinc and sTSHI as well as with TTSI.

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8. SUMMARY

Objectives:

Selenium as well as zinc seem to have an important role in thyroid metabolism as well as in the synthesis of hormones. Autoimmune thyroid diseases are one of the most common thyroidal dysfunctions in iodide sufficient areas. As both trace elements showed beneficial effects in previous studies, we wanted to further investigate this topic. The aim of our study was to elaborate a possible correlation of selenium and zinc with thyroid function tests, TPO-Antibodies as well as the calculated parameter of the secretory capacity of the thyroid gland (SPINA-GT), sum activity of peripheral deiodinases (SPINA-GD), the thyrotroph thyroid hormone sensitivity index (TTSI) and Jostel´s TSH Index (TSHI).

Methods:

In total, we included 90 patients from the outpatient department of endocrinology of the REGIOMED hospital in Coburg, Germany. The time span of the retrospective study was already collected data from 2015 until November 2017. Blood tests were drawn after a fasting period of at least 12 hours. Body mass index was calculated from height and body weight obtained. Blood pressure and heart rate was measured according to standard.

Results:

SPINA-GD showed to be not significant lower in the group with high levels of TPO-Antibodies. There was no significant difference neither in regard of the selenium level nor in regard of the level of SPINA-GD between both groups. Selenium showed significant correlation with TSH, TSHI and TTSI in the group of low TPO-Antibodies and with T3 in the group of high TPO-Antibodies. By excluding cases which were additionally treated with T3, neither zinc nor selenium correlated significantly with SPINA-GD. As secondary outcome, selenium correlated significantly with the age and zinc with the heart rate of the participants.

Conclusion:

People with increased TPO-Antibodies showed lower levels of SPINA-GD, higher levels of TPO-Antibodies and slightly higher levels of selenium. Influences of selenium on thyroid function tests were only in regard of triiodothyronine seen. Further, prospective studies have to be conducted to get more insight into this broad and complex topic of thyroid gland diseases and possible influences of selenium and zinc.

9. CROATIAN SUMMARY

Naslov:

Elementi u tragovima I štitnjača

Sažetak:

Čini se da selen i cink imaju važnu ulogu u metabolizmu štitnjače, kao iu sintezi hormona. Autoimune bolesti štitnjače jedna su od najčešćih disfunkcija štitnjače u dovoljnim područjima jodida. Budući da su oba elementa u tragovima pokazala korisne učinke u prethodnim studijama, željeli smo dodatno istražiti ovu temu. Cilj našeg istraživanja bio je razraditi moguću korelaciju selena i cinka s testovima funkcije štitnjače, TPO-Antitijela kao i izračunati parametar sekretornog kapaciteta štitne žlijezde (SPINA-GT), sumsku aktivnost perifernih deiodinaza (SPINA-GD), indeks osjetljivosti hormona tirotrofa štitnjače (TTSI) i Jostelov TSH indeks (TSHI).

Metode:

Ukupno je uključeno 90 pacijenata s ambulantnog odjela endokrinologije bolnice REGIOMED u Coburgu u Njemačkoj. Vremenski raspon retrospektivne studije već su prikupljeni podaci od 2015. do studenoga 2017. Krvni testovi su napravljeni nakon razdoblja posta od najmanje 12 sati. Indeks tjelesne mase izračunat je iz visine i dobivene tjelesne težine. Krvni tlak i otkucaji srca mjereni su prema standardu.

Resultati:

SPINA-GD pokazala se ne značajnijom nižom u skupini s visokom razinom TPO-antitijela. Nije bilo značajne razlike ni u pogledu razine selena ni u pogledu razine SPINA-GD između obje skupine. Selen je pokazao značajnu korelaciju s TSH- om, TSHI-jem i TTSI-jem u skupini niskih TPO-antitijela i s T3 u skupini visokih TPO-antitijela. . Isključujući slučajeve koji su dodatno tretirani T3, ni cink ni selen nisu značajno korelirali sa SPINA-GD-om. Kao sekundarni ishod, selen je značajno korelira s dobi i cinkom s otkucajima srca sudionika.

Zaključak:

Osobe s povećanim TPO-Antitijelima pokazale su nižu razinu SPINA-GD, višu razinu TPO-antitijela i nešto višu razinu selena. Utjecaji selena na testove funkcije štitnjače bili su samo u odnosu na trijodtironin. Nadalje, potrebno je provesti prospektivne studije kako bi se dobio bolji uvid u ovu široku i složenu temu bolesti štitnjače i mogućih utjecaja selena i cinka.

10. CURRICULUM VITAE

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