Smoking and its influence on the quality of life in patients with autoimmune hypothyroidism : a retrospective case control study

Hagazy, Susan

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Susan Hagazy

SMOKING AND ITS INFLUENCE ON THE QUALITY OF LIFE IN PATIENTS WITH AUTOIMMUNE HYPOTHYROIDISM – A RETROSPECTIVE CASE CONTROL STUDY

Diploma thesis

Academic year:
2021/22

Mentor: Assoc. Prof. Sigrun Merger, MD

Coburg, July 2022

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Mostly, I would like to thank my mother, Sabine, who supported me in every way possible. Without her, I truly would never be able to pursue my goals and my dreams including becoming a physician.

I would like to thank my colleagues, Astrid and Paul, with whom I was able to create the database for our diploma theses.

Additionally, I would like to thank my mentor Priv.-Doz. Dr. med Sigrun Merger for the support and guidance during the diploma thesis.

Lastly, I would like to thank my friends and my brother for their support during the last 6 years.

LIST OF ABBREVIATIONS

Anti-Tg – Anti-Thyroglobulin

Anti-TPO – Anti-Thyroid Peroxidase

DIT - Diiodotyrosine

fT4 – Free Thyroxine

fT3- Free Triiodothyronine

ICMA – Immunochemiluminometric Assay

MCC – Medical Care Center

MIT – Monoiodotyrosine

NIS – Na/I-Symporters (Sodium-Iodide-Symporter)

QoL – Quality of Life

T3 – Triiodothyronine

T4 – Thyroxine

TBII – TSH Receptor-Blocking Antibodies

TBG – Thyroxine-Binding Globulin

Tg – Thyroglobulin

ThyPRO – Thyroid-Specific Patient-Reported Outcome

TSH – Thyroid-Stimulating Hormone

TSI – Thyroid-Stimulating Immunoglobulin

TV – Thyroid volume

1. INTRODUCTION

1.1. Thyroid gland

1.1.1. Anatomy and Development

The thyroid gland is one of the largest endocrine glands(1). It is located anteriorly of the trachea at the level of C5-T1 vertebrae between the cricoid cartilage and the suprasternal notch consisting of two lobes, the right and left lobe, which are connected by an isthmus (1–6). Furthermore, it is surrounded by a fibrous capsule which is thin and divides the gland with septa (3, 4, 7). Normally, the thyroid weighs between 12-20g and is soft in consistency (1, 2, 5, 7).

It is a highly vascularized gland. Its blood supply is secured by the superior and inferior thyroid arteries. The superior thyroid arteries supply mainly the anterosuperior aspect of the thyroid gland, whereas the inferior thyroid arteries supply the posteroinferior aspect of the thyroid gland. In some people (approx. 10%) the thyroid ima artery also supplies the thyroid gland. If the thyroid ima artery is present it will supply the isthmus of the thyroid gland (4–8). The venous supply of the thyroid gland is provided by the superior, middle, and inferior thyroid veins which will drain the superior poles, middle lobes, and inferior poles respectively. Whereas the inferior veins will drain into the brachiocephalic veins, the superior and middle veins will drain into the internal jugular vein (4, 5, 8).

The lymphatic vessels of the thyroid gland which usually are in proximity to the thyroid arteries communicate with the lymphatic vessels of the capsule. They will drain into pretracheal, paratracheal and prelaryngeal lymph nodes. While the pre- and paratracheal lymph nodes drain into the inferior deep cervical lymph nodes, the prelaryngeal lymph nodes drain into the superior deep cervical lymph nodes (4).

The innervation of the thyroid gland is derived from the superior, middle, and inferior cervical ganglia via the cardiac, superior, and inferior thyroid peri-arterial plexuses. These nerve fibers are responsible for the vasoconstriction of the blood vessels of the thyroid gland (4).

Posteriorly to each pole of the thyroid gland there are the 4 parathyroid glands which produce parathyroid hormone. Crossing the lateral borders of the thyroid gland there are the recurrent laryngeal nerves (4).

The development of the thyroid gland starts during the third week of gestation. It develops from the floor of the primitive pharynx. During its development the thyroid gland migrates along the thyroglossal duct to reach its final position in the neck. The thyroid gland normally starts with the synthesis of thyroid hormones which are thyroxine (T4) and triiodothyronine (T3) at the 11^{th} week of gestation (2).

The C-cells or parafollicular cells which are scattered throughout the thyroid gland derive from the neural crest and produce calcitonin which plays a minor role in the calcium homeostasis in contrast to parathyroid hormone and vitamin D. The trigger for the secretion of calcitonin is increased levels of calcium in the blood (2, 3).

The thyroid gland itself is made up of spherical thyroid follicles. The thyroid follicles consist of follicular cells or thyrocytes which enclose the colloid. The colloid is a fluid which contains large amounts of thyroglobulin (Tg) which is the precursor of thyroid hormones (2, 3).

1.1.2. Regulation of the thyroid axis

The thyroid axis as a classic example of an endocrine feedback loop includes the hypothalamus, the pituitary gland, the thyroid gland, and the peripheral target organs. The hypothalamus which produces, and releases thyrotropin-releasing hormone (TRH) stimulates the pituitary gland. Consequently, the pituitary gland will produce thyroid-stimulating hormone (TSH) which is secreted by the thyrotrope cells of the anterior pituitary gland (2, 9, 10).

TSH itself will stimulate the thyroid hormone synthesis and secretion by the thyroid gland. It will influence this process on several levels. It increases the release of thyroid hormones by augmenting the proteolysis of thyroglobulin. It will raise the activity of the iodide pumps as well as the iodination of tyrosine. Furthermore, it will augment the number of thyroid cells as well as their secretory activity and their size. The thyroid gland mainly produces & secretes thyroxine (about 93%) and in smaller amount triiodothyronine (about 7%) (1, 11). Even though the thyroid gland secretes mainly T4, almost all T4 will be converted to T3(1).

The production and secretion of thyroid hormones is regulated via a negative feedback loop. Thyroid hormones act mainly through the thyroid hormone receptor β2 to suppress the production of TRH and TSH which will inhibit further production of the thyroid hormones (2).

TSH itself which is the most useful marker of thyroid hormone action determines the "set-point" of the thyroid axis. As a result, high thyroid hormone levels will inhibit the TSH production as well as TRH stimulation of TSH. Vice versa, low levels of thyroid hormones will raise the production of TSH as well as TRH stimulation of TSH. The release of TSH like other pituitary hormones is in a pulsatile manner and follows a circadian rhythm (12). The highest levels of TSH can be measured at night. However, in contrast to other hormones the deviation is moderate, partially due to the long plasma half-life (50min). Because of the relatively long plasma half-life single measurements of TSH are adequate for determining its circulating level. For these measurements immunoradiometric assays are used which can differentiate between elevated, decreased and normal TSH values which can be used for the diagnosis of primary hyper- or hypothyroidism (2, 11).

1.1.3. Thyroid hormone synthesis & secretion

The first critical step in the thyroid hormone synthesis is the iodide uptake by the thyroid gland via the Sodium-Iodide-Symporters (NIS) in the thyrocytes from the blood circulation. Hereby, one iodine ion is transported together with two sodium ions into the cell (1). Thereby, the iodide is trapped within the cell (iodide trapping). Within the thyroid the iodide concentration is 30 times higher than in the blood. The trigger for a rise in uptake of iodine are low levels of circulating iodide which will also activate the synthesis of NIS. Iodine is ingested, absorbed from the gastrointestinal tract into the blood and then bound to serum proteins to prevent its excretion into urine (1–3). It is necessary to ingest iodine in sufficient levels (about 1mg/week) to produce normal amounts of thyroid hormone (1). After the uptake of iodide from the bloodstream, it will be pumped from the thyrocytes into the colloid by the iodide/chloride transporter or pendrin which pumps one iodide into the colloid space in exchange for one chloride. Within the colloid, iodide ions will be oxidized to an iodine molecule by the enzyme thyroperoxidase. These iodine molecules will bind to the thyrosyl residues of thyroglobulin (organification) which will lead to the formation of monoiodotyrosine (MIT) or diiodotyrosine (DIT) depending, if one or two iodine molecules are added to the tyrosyl residues respectively. T3 is formed when MIT and DIT are covalently conjugated whereas T4 is formed when two DITs are covalently conjugated. This formation still takes place within the thyroglobulin (3). Each thyroglobulin can store up to 30 molecules of T4 and a few molecules of T3 which can be later be released when they are needed (1). To free T3 and T4 which is necessary for these hormones to be active, thyroglobulin needs to be degraded. This is achieved by endocytosis by the thyrocytes and the degradation of the lysosomal proteases (1, 3). After the freeing of T3 and T4 from the thyroglobulin, they are secreted into the capillaries. The thyroid hormones are then transported to the target organ by being bound to either thyroxine-binding globulin, thyroxine-binding prealbumin or albumin. Nevertheless, the majority binds to thyroxine-binding globulin. Thyroid hormones are distributed slowly to their target organs because of the high affinity to their transporter proteins. Since the affinity of T4 to the transporter protein is higher than T3 it will take longer to be released (1, 3).

Not all iodinated tyrosine become thyroid hormones, the majority which is about three quarters remain in form of MIT or DIT in the thyroglobulin. When the formed thyroid hormones are released, MIT and DIT which are also in the thyroglobulin will be released as well. These, however, will be recycled within the gland by the enzyme deiodinase which will cleave the iodine from MIT or DIT (1).

1.1.4. Physiological functions

The thyroid gland and its hormones are known for influencing the body on many levels (13, 14). In general, thyroid hormones can either have an effect on the gene transcription within the nucleus (genomic effect) or have an effect by interaction with other enzymes (nongenomic effect) (1, 15). If they directly affect the gene transcription, they will interact with their receptors which are either near DNA strands or directly at the DNA strands. Once the thyroid hormones attach to their receptors, they will activate this process which will lead to new proteins being formed. When they cause actions independently from the gene description, then these effects are faster than those by gene transcription. Examples for these nongenomic actions are oxidative phosphorylation or regulation of iron channels (1).

Thyroid hormones have a great impact on the metabolism of the body. Several of the following examples demonstrate their influence on the metabolic activity on various levels. Thyroid hormones can rise the metabolic activity on the cellular level by increasing the number and activity of the mitochondria as well as increase the activity of the active transport proteins within the cell membrane (1).

In addition, they are stimulating the metabolism of carbohydrates as well as fat which shows their important role in energy expenditure within the body. Within in the carbohydrate metabolism they boost glucose uptake which enables cells to use more glucose. They increase glycolysis as well as gluconeogenesis which supply the body additionally with more glucose by either splitting up glycogen into glucose or by creating new glucose respectively (1). Moreover, they raise the secretion of insulin as well as the absorption rate of glucose which will also secure glucose as energy. Insulin will promote the uptake of glucose and by increasing the absorption rate more glucose stays within the body to be used. All in all, thyroid hormone will promote the rise of metabolic enzymes which will be used in the carbohydrate metabolism (1, 15).

Similarly thyroid hormones will increase the fat metabolism by mobilizing the lipids. Consequently, there are more free fatty acids in the blood and more free fatty acids will be broken down in the cells (1, 15, 16).

Because the metabolism is increased many enzymes are needed which need vitamins to function. Vitamin a and K which are two fat soluble vitamins as well as all water-soluble vitamins can act as cofactor for these enzymes (17). Thus, many vitamins are needed in this state. In addition, the general basal metabolic rate is raised by 60-100% above the normal base line (1, 18). Therefore, when thyroid hormones are in effect, body weight will be lost in most

cases unless enough energy is supplied by food (2, 16). In addition, they also increase the heat production (18).

Thyroid hormones also have a tremendous influence on the cardiovascular system. They increase the heart rate, the cardiac output as well as the blood flow. The enhanced blood flow is due to the increased metabolism. Because of the increased metabolism more metabolic end products are available as well as more oxygen can be used which will lead to vasodilation and, as a result, increased blood flow. The heart rate raises because thyroid hormones seem to influence the excitability of the heart. Since the blood flow and the heart rate are increased the cardiac output is also increased. Furthermore, thyroid hormones increase heart strength in short-term. However, if thyroid hormones are excessively secreted over a longer period, it can lead to myocardial failure due to the protein catabolism (1, 18).

They also increase the respiration rate and depth because of the raised metabolism, oxygen usage and creation of carbon dioxide which needs to eventually be exhaled. Thyroid hormones also enhance the motility of the gastrointestinal tract as well as raise the secretion of digestive fluids (15, 18). They also increase the muscle strength by affecting the fast twitch muscle fibers if the hormone level is only marginally elevated (1, 19). If they are present overly elevated, then it will lead to protein catabolism which consequently will weaken the muscle since they are being catabolized (1).

Moreover, they also have an effect the central nervous system by increasing its activity which will cause raised alertness, wakefulness, and responsiveness to external stimuli. Nevertheless, its activity may be disconnected (1, 18).

Thyroid hormones affect the secretion of other endocrine glands. Because of their influence the secretion rate augments which will on the other hand raise the demand for the hormones by the body tissues (1, 18, 9).

Furthermore, thyroid hormones affect the sexual function especially if they are not present in sufficient amount. The consequence of less thyroid hormones than usual is decreased libido which can affect both sexes. Menorrhagia, polymenorrhea, or amenorrhea can be present in women. If the hormones are overly expressed then women may suffer from oligomenorrhea or amenorrhea and men may suffer from impotence (1).

1.1.5. Characteristics of thyroid hormones

Thyroxine and triiodothyronine differ in several characteristics which affects their effect. They differ in their amount in which they are secreted and present in the circulation, how strongly they are bound to the plasma proteins, how rapidly they are cleared and how strong their effect is. T4 is secreted about twenty times more than T3. Compared to T4, T3 is four

times more potent and has a shorter half-life. The half-life of T4 is 7-10 days compared to T3 with a half-life of 2 days. In addition, T3 is in smaller amounts in the blood (1, 2, 11).

1.1.6. Clinical examination

Since the thyroid gland influences the body on many levels, it is necessary to perform a whole body examination (2). When examining the thyroid gland, the neck should be inspected from the front and the side to see if there are any scars, goiter or other visible masses or distended veins. After the inspection, the thyroid gland should be palpated. The palpation should be done with both hands and can be performed either from behind or from the front. As the thyroid gland is located between the cricoid cartilage and the suprasternal notch at the level of C5-T1, the cricoid cartilage as a landmark should be first identified to locate the isthmus of the thyroid gland. Once the thyroid gland is identified the patient should be asked to swallow to assess the consistency of the gland and how the gland moves while the patient is swallowing. Besides the consistency the examiner should state the size of the gland, if there are any nodules, and if there is any tenderness or any fixation of the gland. Furthermore, the area of the thyroid gland can be auscultated, to check if a bruit is hearable which suggests hyperthyroidism esp. Graves' disease (20). To complete the examination of the neck the lymph nodes should be examined for lymphadenopathy. These include supraclavicular and cervical lymph nodes (2).

Except the examination of the thyroid gland itself, patients should also be examined for ophthalmopathy (e.g., exophthalmos in hyperthyroidism), dermopathy (palmar erythema in hyperthyroidism), and pathologies of the hand (clubbing or tremor in hyperthyroidism) (2, 20). Moreover, the patient should be examined for proximal myopathy which is best done by asking the patient to stand up. This is present in hypothyroidism. In addition, the patient should be examined for pretibial myxedema which can be found in Graves' disease. Finally, the reflexes should be tested. These are slowed down in hypothyroidism or brisk in hyperthyroidism (20).

1.1.7. Ultrasound

Ultrasound is the most common imaging technique evaluate the thyroid gland and its surrounding structures since it is safe, cost-effective and widely available (21). It is a good option to record any findings. Ultrasound can be used to measure the size, volume as well as nodules. If there are any nodules found in the ultrasound examination, their size, location, and consistency should be stated (20). Additionally, the vascularity of the gland should be examined by using Doppler. Increased vascularity can point to hyperthyroidism (22).

The picture of a normal thyroid gland shows a slightly more echo-dense structure compared to its surrounding structures and has an evenly ground glass appearance (21). The

volume of a normal thyroid gland excluding the isthmus is around 10-15ml for women and is around 12-18ml for men (23).

1.1.8. Laboratory evaluation

A diagnosis of hyper- or hypothyroidism can only be made if the patient has abnormal laboratory values together with clinical symptoms. The first test is the TSH immunochemiluminometric assay (ICMA) (24). This test measures if TSH is normal, elevated, or suppressed. For the test to be sensitive enough to detect abnormal values, the lower limit of the test should be at ≤ 0.1 mIU/L. If the TSH value is normal, this excludes primary thyroid dysfunction. Suppressed TSH will indicate hyperthyroidism and elevated TSH will indicate hypothyroidism. If the TSH ICMA confirms abnormal TSH values, the levels of thyroid hormones need to be measured which will confirm the diagnosis. Since the free or unbound thyroid hormones are the biologically active, these will be measured. This can be accomplished by either using radiolabeled T4 or an analogue to compete with the free thyroid hormone for binding to a solid-phase antibody or by ultracentrifugation or equilibrium dialysis to separate the unbound thyroid hormones. Normally, it is enough to test only fT4. However, there is the possibility that only fT3 is elevated. Therefore, a test for fT3 should be performed if TSH is suppressed and fT4 is normal (25, 26).

If an autoimmune thyroidal dysfunction is suspected autoantibody levels are measured. Usually, TPO antibodies are measured. There is a possibility that euthyroid patients have circulating autoantibodies against TPO. They have a higher risk to develop a thyroid dysfunction. TPO antibodies are usually elevated in autoimmune hypothyroidism and in 80% of Graves' disease. Additionally, Thyroid-Stimulating Immunoglobulins (TSIs) which are antibodies that attach to the TSH receptor and, consequently, activate the production of thyroid hormone can be found in patients with Graves' disease. Thyroglobulin levels, which are usually not isolated elevated, are usually raised in thyroiditis and indicates the destruction of thyroidal tissue with the freeing of Tg from the cells (2).

1.2.Hypothyroidism

Hypothyroidism is one of the most common endocrine disorders. This disorder results from low levels of thyroid hormone (11, 27, 28).

Its manifestation varies individually which can range from asymptomatic state to myxedema coma. Typical symptoms may include cold intolerance, dry skin, hair loss, decreased sweating, puffiness, weight gain, voice changes, sleep disturbances, menstrual cycle

abnormalities, constipation, muscle cramps and galactorrhea. However, these symptoms as mentioned before can be absent (11, 28, 29).

It can present as primary or secondary hypothyroidism. Primary hypothyroidism is present if the thyroid itself is not able to produce sufficient thyroid hormones. In contrast, secondary hypothyroidism is present if the pathology is not related to thyroid gland itself but to the pituitary gland or hypothalamus (11).

In iodine-deficient areas primary hypothyroidism is mostly due to the prevalent iodine deficiency. In iodine-sufficient regions, however, primary hypothyroidism is mostly due to autoimmune thyroid diseases such as Hashimoto thyroiditis (11, 30, 31). Nevertheless, there are other common causes which are often iatrogenic such as drugs (amiodarone, tyrosine kinase inhibitors (erlotinib, gefitinib, …) , biologics (anti-CTLA-4 or anti-PD-L1/PD-1 monoclonal antibodies),…) or therapies in the area of head and neck (radioactive iodine therapy, radiotherapy, thyroid surgery) (11).

1.3. Hashimoto thyroiditis

Hashimoto thyroiditis, also known as chronic autoimmune thyroiditis or chronic lymphocytic thyroiditis, is the most common cause of hypothyroidism in developed countries. This autoimmune disease will lead to progressive tissue fibrosis of the thyroid gland which is caused by antithyroid autoantibodies (27). The diagnosis is made by the combination of presence of autoantibodies, mainly Anti-TPO and Anti-Tg, clinical signs or symptoms during an examination, and the appearance of the thyroid gland during ultrasound (32). Unfortunately, the diagnosis is not easily established in the earlier stages of the disease (27). Most patients present with laboratory values of increased thyroid-stimulating hormone (TSH) and normal to low free thyroxine levels (27). Hashimoto thyroiditis affects up to ten times more women than men (1, 2, 33). Most patients develop this autoimmune disease between the age of 30-50 years (27, 34). Early symptoms are fatigue, dry skin, constipation, and weight gain. Symptoms during a later stage can include decreased sweating, cold intolerance, memory loss, peripheral neuropathy, muscle cramps, hair loss, etc. (27).

1.3.1. Etiology

The exact cause of Hashimoto is still not well understood and needs further research. However, most patients develop autoantibodies such as anti-thyroid peroxidase (anti-TPO), antithyroglobulin (anti-Tg) or TSH receptor-blocking antibodies (TBII). Anti-TPO is the mostly present. In many patients, anti-Tg and TBII can be found as well. However, a small percentage is serum antibody negative. These autoantibodies will target and attack the thyroid gland. In this process they will destroy the tissue of the thyroid gland which will not eventually

be able to produce adequate amounts of thyroid hormones and, therefore, it will lead to hypothyroidism. Like other autoimmune diseases Hashimoto thyroiditis is also associated with other autoimmune diseases. Furthermore, together with type-1 diabetes mellitus and autoimmune adrenal deficiency it can be part of the polyglandular autoimmune syndrome type 2 (27).

1.3.2. Pathophysiology

Like the etiology, the pathophysiology of Hashimoto thyroiditis is still unclear. It is thought that it is an autoimmune process which includes lymphocytic infiltration of the thyroid gland as well as fibrosis of the thyroid tissue. Regarding anti-TPO antibodies there is hardly evidence that it plays a role in the pathophysiology. In vitro it has been shown that it can kill thyrocytes by fixing complement and binding to thyrocytes. Additionally, there is a positive correlation between the presence of anti-TPO antibodies with the phase of active disease. Nevertheless, there seems to be no correlation between the severity of the disease and the autoantibody titer of anti-TPO in the serum (27, 35). In addition, anti-TPO does not seem to be a predictor for initial presentation and clinical outcome (36). Furthermore, it seems there is no association between anti-TPO level and thyroid function (37).

The thyroid gland usually appears either as a goiter or as an atrophic gland. There are several environmental factors which are linked to the development of autoimmune thyroiditis, such as smoking, high iodine intake, selenium deficiency, certain drugs and infectious disease like chronic hepatitis C (34).

1.3.3. Pathology

Thyroid gland in Hashimoto disease usually presents a symmetrical goiter which often has a noticeable pyramidal lobe. The tissue under the microscope shows diffuse processes of lymphoid infiltration, epithelial cell destruction and fibrosis. Hurthle or Askanazy cells which are slightly larger thyroid cells packed with mitochondria staining acidophilic are often present. Compared to these thyroid cells, the follicular spaces shrivel and the colloid may disappear or become scarce (34). The fibrosis depending on the stage of Hashimoto disease may vary in presentation between completely absent to severe (23, 34).

1.3.4. Ultrasonographic characteristics of the thyroid gland

There are three ultrasonographic characteristics which are commonly found in patients with Hashimoto thyroiditis: thyroid hypoechogenicity (23, 37–40), pseudonodules (37), and heterogenous parenchyma (23, 40). The hypoechogenicity of the thyroid gland may be due to

the infiltration of the thyroid gland by inflammatory cells. Both, pseudonodules and heterogenous parenchyma may be a linked to the fibroplastic proliferation (40).

Another commonly found feature is painless, diffusely enlarged thyroid gland (23).

Additionally, Doppler sonography may assist in diagnosing Hashimoto disease. Hereby, the frequency shift of blood flow will be measured. In Hashimoto thyroiditis, different vascular types may be seen, for example, hypovascularity, markedly increased vascularity, and focal thyroid inferno (23, 40). Especially, focal thyroid inferno may be specific for focal Hashimoto thyroiditis according to Fu *et al.* (40, 41). An atrophic gland denotes the end stage of Hashimoto thyroiditis (23).

However, ultrasound findings alone are not enough to establish a diagnosis. It is always necessary to compare the ultrasound findings with the laboratory data and clinical findings (21).

1.3.5. Clinical Manifestation

The clinical manifestation may change during the course of the autoimmune disease. In the beginning Hashimoto thyroiditis patients may exhibit hyperthyroid symptoms. This may be due to the initial destruction of the thyroid cells in which thyroid hormones are increasingly released into the bloodstream. When sufficient thyroid tissue is destroyed, then patients show symptoms of hypothyroidism. The begin of these symptoms is insidious. The symptoms may vary in their clinical manifestation and can affect almost any organ system. The skin itself tends to be dry and scaly especially on the extensor surfaces. Furthermore, the skin can show thinning of the epidermis and hyperkeratosis of the stratum corneum (2, 27).

Laboratory findings commonly show elevated thyroid-stimulating hormone (TSH), decreased levels of free thyroxine (fT4) and increased anti-TPO antibodies. Although these laboratory findings are typical, in earlier stages of Hashimoto thyroiditis the laboratory findings as well as symptoms of the patient can display as hyperthyroidism or as normal. These findings which may seem odd are because of the destruction of the thyroid gland may not be a constant process but rather be irregular (27).

1.4.The normal range of TSH and the change in paradigm

Recently, there might be a change in paradigm regarding the normal range of thyroid hormone levels (42). Current studies hinted that the previously normal TSH range as well as normal T3 and T4 concentration might not be the normal TSH range or normal T3 and T4 concentration for all individuals (13, 43, 44).

The TSH value is currently the main laboratory parameter which is, together with other examinations such as clinical examination or ultrasound, sufficient to assess the functional condition of the thyroid gland (26). However, different reference values for TSH are mentioned

which should define the normal range (45). There are studies where the TSH normal range was between 0.3-5.1 mIU/l, while there are suggestions that the normal value should be below 2.5 mU/l in 95% of the normal population (46, 47). In Germany, the normal TSH range is currently defined to be between 0,4 - 4,0 µU/ml (26, 45).

Furthermore, according to the study of Fontes, Coeli *et al.* there is a difference between age-groups where the TSH value rose with age which indicates that the TSH reference range raises with age and elderly patients might be misdiagnosed with hypothyroidism. Thus, these seemingly abnormal values of TSH might lead to unnecessary treatment (48, 49). However, there are contradicting opinions regarding high TSH values in elderly. Some studies imply there is no adverse effects faced and even might may suggest a prolonged lifespan of these individuals, while other studies associated high normal TSH values with increased mortality or did not find an association (50–52). In addition, previous studies concluded that there is a large individual variation between individuals (53, 54). In addition, the TSH value may also vary between different populations (55). Furthermore, some patients even though their thyroid hormone levels are within the reference range, they still experience impaired well-being (43, 44).

In addition, therapies try to influence the thyroid hormone secretion only indirectly via TSH. However, this type of therapy only works if the negative feedback mechanism is not disturbed and if the relationship between TSH and fT4 is not uncorrelated or even inverted. A disturbed relationship between TSH and fT4 might be the reason for not reestablishing quality of life under levothyroxine therapy even though the TSH values are within normal range (56).

1.5.ThyPRO-39 and Quality of life

The potential deviation from the normal range may imply that also the quality of life of patients with thyroid dysfunction, such as hypothyroidism, may be not always perceived the best if the patient is within the normal thyroid hormone level range. In the current literature the patients' wellbeing regarding hypothyroidism has only been assessed in 58 studies which used quantitative data. Of these studies, most of them focused on the hormone replacement treatment and which modifications have an effect on the quality of life (57).

They focused on the topic if monotherapy with levothyroxine or the combination therapy of levothyroxine and liothyronine were superior to the other. It was stated that, even though the monotherapy accomplished normal values of TSH in the patients, it often does not achieve euthyroidism in some patients because despite high fT4 values, fT3 remains lower than in the normal population implying a deficiency regarding the conversion from T4 to T3 (58). Regarding the quality of life, patients favored the combination therapy. It was stated that

hypothyroid patients benefited from the switch from monotherapy to the combination therapy by increased quality of life. However, some argue that the improvement in quality of life might be related to weight loss, whereas others don't find any correlation between these two variables (59, 60).

In addition, studies demonstrated that although the TSH value was in the normal range due to hormone replacement therapy the symptoms regarding impairment of psychological wellbeing persist (44, 61). Similarly, the study of Winther, Cramon *et al.* agrees that normal TSH does not imply a good quality of life (62). In contrast, other studies have demonstrated that higher TSH values are associated with a lower quality of life (63, 64). For example, in the study of Saravanan, Visser *et al.* showed that they found an association between quality of life an TSH and fT4. Higher TSH values were correlating with decreased quality of life and higher fT4 levels were correlating with better psychological well-being. However, they did not find a correlation between fT3 and psychological wellbeing (64).

Researchers were also looking for a link between quality of life and autoantibody titers. Anti-TPO titer especially was connected to quality of life. Watt, Hededüs *et al.* in their case-control study showed an association between several scale components of the ThyPRO and Anti-TPO including "Goiter Symptoms", "Depressivity", "Anxiety", "Emotional Susceptibility" and "Impaired Social Life" (42). Some studies including Ott, Promberger *et al.* suggest an negative association between quality of life levels with Anti-TPO levels (65–67). Thus, autoimmunity might affect quality of life independent of thyroidal impairment (42). Other studies even suggest that Anti-TPO might be linked to anxiety, mood disorders and postpartum depression (68, 69). In contrast, Saravanan, Visser *et al.* did not find any association between Anti-TPO and psychological well-being (64).

Since the quality of life as a measurement is very subjective there are questionnaire which try to successfully attempt to reflect this subjective feeling into an objective score (70, 71). Among them is the ThyPRO-39 questionnaire. This questionnaire was specifically designed to assess the quality of life of patients with thyroid dysfunctions. It was created by Watt, Hegedüs *et al.* by first identifying important areas of the quality of life which are important for patient with thyroid dysfunction as well as testing how valid and reliable this instrument is (72, 73). The ThyPRO-39 is a good instrument which has good responsiveness, can identify relevant treatment effects and has a good validity and reliability even its translated versions (71, 73–77). In 2015, it was already translated into 13 different languages (78).

The original version of the ThyPRO questionnaire contains 85 items while the short version of it contains only 39 items. However, the shortened ThyPRO questionnaire which was

developed in 2015 compared to its original version still has good measuring properties and has maintained its good responsiveness and clinical validity (79). The items can be categorized into these 13 scales which include “Goiter Symptoms”(question 1a-1h), “Hyperthyroid Symptoms” (question 1l-1t), “Hypothyroid Symptoms” (question 1q-1ee), “Eye Symptoms” (question 1w-1bb), “Tiredness” (question 2a-3b), “Cognitive Problems” (question 4a-4f), “Anxiety” (question 5b-5e), “Depressivity” (question 6a-6g), “Emotional Susceptibility” (question 7c-7h), “Impaired Social Life” (question 8a-8c), “Impaired Daily Life” (question 9a-9e), “Cosmetic Complaints” (question 11a-11e), and “Overall QoL-impact” (question 12) (76).

The QoL score of the short version of the ThyPRO-39 ranges from “0-100” with “100” being the highest possible score and “0” the lowest possible score (76). The higher the score the lower is the quality of life (71, 79). In 2021, the validity and reliability of the German version of the short ThyPRO was verified and is recommended for clinical and research purposes (76).

1.6.Smokers and hypothyroidism

Regarding, Hashimoto thyroiditis or hypothyroidism and smoking there are several opinions. On one hand, the study of Fukata, Kuma *et al.* demonstrated a raised risk of hypothyroidism in Hashimoto thyroiditis (80). On the other hand, the study of Vestergaard showed no association between smoking and the risk to develop Hashimoto thyroiditis (81).

In contrast, many other studies imply that there is a negative association between smoking and hypothyroidism (82–84). For example, Asvold, Bjøro *et al.* indicate that smoking and hypothyroidism are negatively associated where current smokers had a lower prevalence of overt hypothyroidism compared to non-smokers (82). Similar results were present in the study of Knudsen, Bülow *et al.* which showed a negative association between smoking and subclinical hypothyroidism (83).

Furthermore, the study of Jorde and Sundsfjord indicated that smokers have lower serum TSH levels and higher fT3 and fT4 levels than non-smokers (85). The lower TSH value in smokers compared to non-smokers were also detected by Berlin, Astor *et al.* (86).

In addition, smokers seem to have lower Anti-TPO and/or Anti-Tg presence (86, 87). Similar results showed the study of Wiersinga. It was shown that the risk of developing thyroid peroxidase and thyroglobulin autoantibodies and thus subclinical and overt hypothyroidism is apparently reduced by current smoking (88). However, there are also studies who could not demonstrate the association between lower autoantibodies and smoking (84). Thus, the relationship between smoking and autoantibodies is still controversial.

Moreover, even though smoking is harmful in many ways, smoking cessation is associated with an increased risk of developing overt hypothyroidism. This increased transient risk is during the first two years after quitting smoking (89, 90).

2. OBJECTIVES

The main aim of this study was to compare the quality of life between smokers and non-smokers with autoimmune hypothyroidism to assess if there is an association between smoking and quality of life. Moreover, the quality of life was compared with TSH, fT3, fT4, the auto-antibody-titers (Anti-TPO, Anti-Tg).

Hypotheses:

1. The quality of life is better in smokers than non-smokers.
2. The autoantibody titer is lower in smokers than in non-smokers.
3. The group of smokers has higher fT3 &fT4 levels and lower TSH levels than the group of non-smokers.
4. Quality of life correlates negatively with fT4.
5. The parameters (TV, TSH, fT3, fT4, Anti-TPO, Anti-Tg) differ between the quartiles of the score of quality of life.
6. The quality-of-life score is different between the quartiles of Anti-TPO.
7. The Anti-TPO correlates with scales of the ThyPRO-39.

3. MATERIALS AND METHODS

3.1. Study design

This retrospective case-control study was carried out in the endocrinology department in the Regiomed hospital in Coburg. The data was collected in the period of July 2016 to October 2021 by the department of endocrinology. The data was entered into an excel database in the period of July 2021 to March 2022.

3.2. Study Population

From the 503 patients who consented to be part of a study by filling out an anamnestic questionnaire together with a ThyPRO-39 questionnaire, 61 patients were selected who fulfilled the inclusion and did not fulfill the exclusion criteria. Inclusion criteria were autoimmune hypothyroidism and patients in the REGIOMED hospital in Coburg. Exclusion criteria were malignant diseases, hyperthyroidism, and hypothyroidism of non-autoimmune origin. Of the 61 patients, 52 (85.24%) patients were non-smokers, and 9 (14.75%) patients were smokers.

3.3. Clinical and laboratory measurements

The data was collected via questionnaire ThyPRO-39, an anamnestic questionnaire, blood tests and sonography by the stuff of the endocrinology department in the Regiomed hospital in Coburg. The anamnestic questionnaire was used to divide the patients into the groups according to their data regarding their smoking status.

For the assessment of the quality of life, the ThyPRO questionnaire was applied. Hereby, the quality of life was measured by a 4-point Likert scale which has been defined for the answers “no at all” as “0”, “a little” as “1”, “some” as “2”, “quite a bit” as “3” and “very much” as “4”. The short version of ThyPRO contains 39 items and the QoL score ranges from “0-100” with “100” being the highest possible score and “0” the lowest possible score (76). The higher the score the lower is the quality of life (71, 79).

The scales of the ThyPRO-39 include “Goiter Symptoms”, “Hyperthyroid Symptoms”, “Hypothyroid Symptoms”, “Eye Symptoms”, “Tiredness”, “Cognitive Problems”, “Anxiety”, “Depressivity”, “Emotional Susceptibility”, “Impaired Social Life”, “Impaired Daily Life”, “Cosmetic Complaints”, and “Overall QoL-impact” (76).

Furthermore, the data from the laboratory results (TSH, fT3, fT4, Anti-TPO, Anti-Tg) and the size of the thyroid from previous ultrasound scans, which were collected by the endocrinology department in the Regiomed hospital in Coburg, were used. The concentration of TSH, fT3, and fT4 was determined by an immunoassay device (Abbott Alinity i, Abbott GmbH, Wiesbaden, Germany) while the concentration of the autoantibodies was assessed by

another immunoassay device (BRAHMS KRYPTOR compact PLUS, BRAHMS GmbH, Hennigsdorf, Germany).

3.4. Statistical Analysis

For this study, JASP version 0.16.3 (JASP Team, Amsterdam, The Netherlands) and Microsoft® Excel® for Microsoft 365 MSO version 2205 (Microsoft Corporation, Redmond, WA, USA) was used. An analysis of normality of data distribution will be applied by using the Shapiro-Wilk test. To test the hypothesis if smoking influences the quality of life, TSH, fT3, fT4, Anti-APO, and Anti-Tg in patients with autoimmune hypothyroidism an independent sample t-Test is applied. The equality of variances is tested by the Levene's test. Moreover, to see if there is a difference between the groups in respect to thyroid size, thyroid antibodies, and thyroid parameters (TSH; fT3; fT4) an independent sample T-Test is used. In addition, the Pearson's test is used, to see there is a correlation between thyroid volume (TV), thyroid antibodies (Anti-TPO; Anti-Tg), and thyroid parameters (TSH; fT3; fT4) regarding quality of life (QoL). For all tests, the confidence interval is 95% ($p=0.05$), to see if the results are statistically significant.

4. RESULTS

As shown in the **Table 1**, the median of TSH is 1.22 mU/l which is within the normal range (0.3-4.0 mU/l) of the applied immunoassay. Similarly, the median of fT3 which is 2.78 ng/l and the median of fT4 which is 10.3 ng/l are within normal range. The normal range of fT3 is 1.6-3.9 ng/l, whereas the normal range of fT4 is 7.0-14.8 ng/l. The median of Anti-TPO is 340 U/ml, whereas the median of Anti-Tg is 42 U/ml. The lower limit of Anti-TPO is 60 U/ml, whereas for Anti-Tg it is 33 U/ml. The QoL score ranges from 0-100 which 100 as the worst possible score and 0 as the best possible score. The median of QoL score of the patients is 36. The median of the total volume (TV) of the thyroid gland is 8.75ml which shows slightly smaller volumes than the normal average volume of 10-15ml for women and of 12-18ml for men.

Regarding the gender distribution in this study, 56 (91.8%) patients are female and only 5 (8.19%) are male.

Table 1. Baseline laboratory and ultrasound findings of the investigated population

	TV[a]	**TSH[b]**	**fT3[c]**	**fT4[d]**	**Anti-TPO[e]**	**Anti-Tg[f]**	**QoL[g]**
Valid	26	41	41	41	27	26	40
Median	8.750	1.220	2.780	10.300	340.000	42.000	39.000
Std. Deviation	4.020	1.418	0.308	1.429	4146.071	223.621	19.025
Shapiro-Wilk	0.965	0.886	0.976	0.969	0.569	0.574	0.939
P-value of Shapiro-Wilk	0.511	< .001	0.511	0.331	< .001	< .001	0.032
Range	16.500	6.070	1.190	5.800	19170.000	960.000	67.000
Minimum	3.100	0.010	2.190	7.600	30.000	10.000	11.000
Maximum	19.600	6.080	3.380	13.400	19200.000	970.000	78.000
25th percentile	6.825	0.680	2.510	9.600	78.000	16.250	23.500
50th percentile	8.750	1.220	2.780	10.300	340.000	42.000	39.000
75th percentile	11.775	2.360	2.930	11.400	2250.000	116.500	55.250

Legend

[a] Total Volume of Thyroid Gland
[b] Thyroid-Stimulating Hormone
[c] Triiodothyronine
[d] Thyroxine
[e] Anti-Thyroid Peroxidase
[f] Anti-Thyroglobulin
[g] Quality of Life

Table 2. Differences regarding laboratory parameters and Quality of life between smokers and non-smokers

				95% CI for Rank-Biserial Correlation	
	W	**df p**	**Rank-Biserial Correlation**	**Lower**	**Upper**
TSH[a]	130.000	0.015	0.757	0.368	0.920
fT3[b]	60.500	0.568	-0.182	-0.657	0.396
fT4[c]	48.000	0.262	-0.351	-0.749	0.232
Anti-TPO[d]	26.000	0.463	-0.278	-0.758	0.397
Anti-Tg[e]	45.000	0.421	0.304	-0.374	0.771
QoL[f]	67.500	0.425	-0.229	-0.653	0.305

Note. For the Mann-Whitney test, effect size is given by the rank biserial correlation.
Legend
*Mann-Whitney U test
a Thyroid-Stimulating Hormone
b Triiodothyronine
c Thyroxine
d Anti-Thyroid Peroxidase
e Anti-Thyroglobulin
f Quality of Life

There is no normal distribution in the group of non-smokers concerning TSH, Anti-TPO, and Anti-Tg. There is no statistically significant difference between smokers and non-smokers regarding quality of life (*P*=0.425), Anti-TPO (*P*=0.463), Anti-Tg (*P*=0.421), fT3 (*P*=0.568), and fT4 (*P*=0.262). In contrast, there is a statistically significant difference between smokers and non-smokers in TSH value (*P*=0.015). The mean for TSH of the smokers is 0.385, while the non-smokers have a mean of 1.798. The TSH value is smaller in the smoker group than in the non-smoker group [95%CI 0.368; 0.920] (**Table 2**, **Figure 1**).

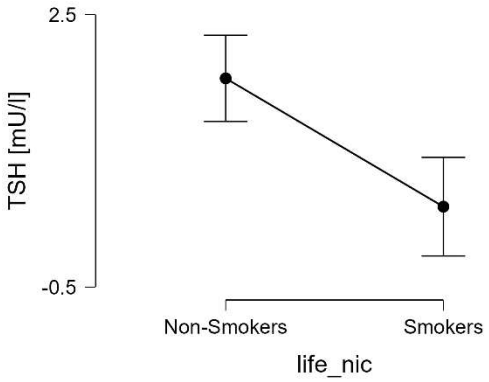

Figure 1. TSH value between smokers and non-smokers

A Pearson's correlation shows a statistically significant correlation with r=0.572, *P*<0.010 between fT4 and QoL score. There is a positive, linear association between QoL score and fT4 (*P*=0.003) [95%CI 0.228, 0.789].

There is no difference between the quartiles of the score quality of life in relation to thyroid volume (**Figure 2**).

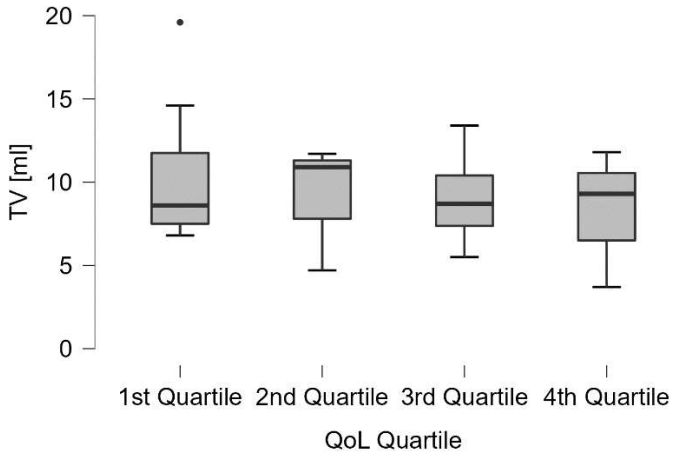

Figure 2. Boxplot between thyroid volume and quartiles of the quality-of-life score

There is no difference between the quartiles of the score of quality of life and the level of TSH (**Figure 3**).

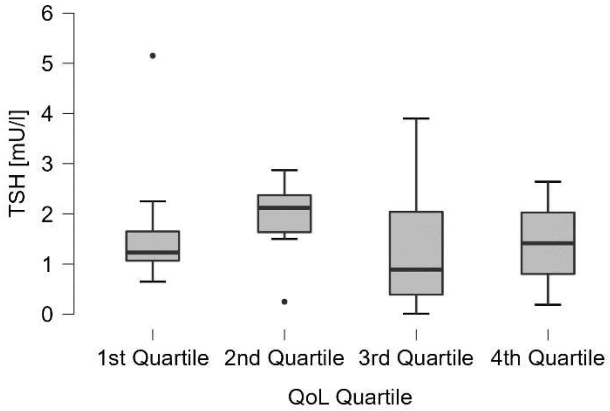

Figure 3. Boxplot between TSH and quartiles of quality-of-life score

The first and second quartile of QoL regarding fT3 have a greater variance and include higher values of fT3. In the fourth quartile of QoL is the lowest median of fT3 (**Figure 4**).

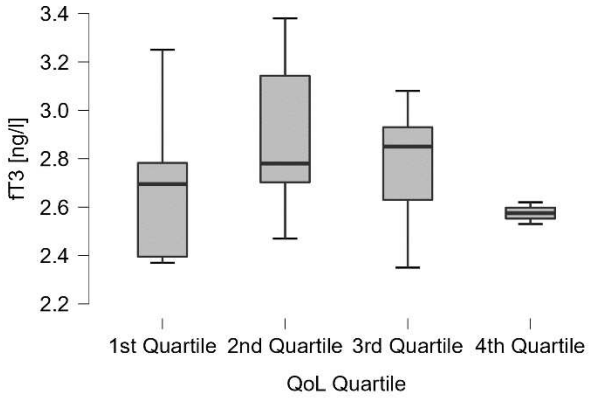

Figure 4. Boxplot between fT3 and quartiles of quality-of-life score

There is a difference between the quartiles of QoL regarding fT4. The higher the fT4 score the higher is the quality-of-life score and the worse is the quality of life (**Figure 5**).

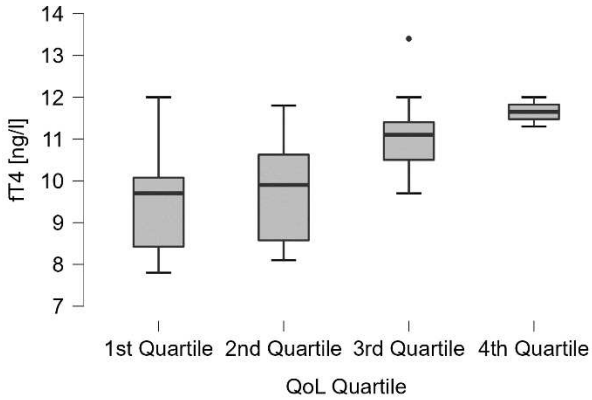

Figure 5. Boxplot between fT4 and quartiles of quality-of-life score

There is no difference between the quartiles of the QoL and the autoantibody concentration (Anti-TPO, Anti-Tg) within the serum as seen in **Figure 6** and **7**.

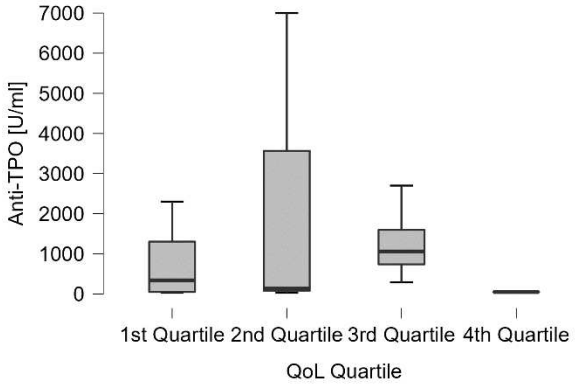

Figure 6. Boxplot between Anti-TPO and quartiles of quality-of-life score

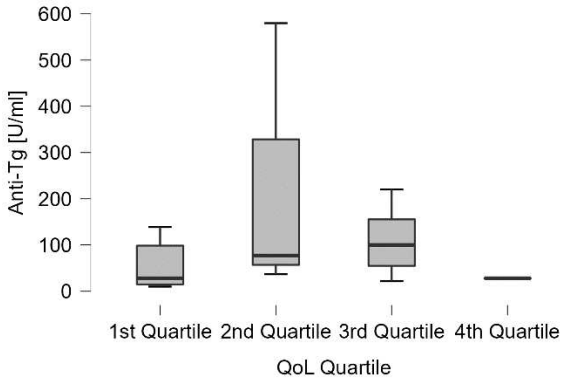

Figure 7. Boxplot between Anti-Tg and quartiles of quality-of-life score

There is no difference between the quartiles of Anti-TPO and the quality-of-life score, except that the medians of QoL in the first and second quartile are lower than in the third and fourth quartile as seen in **Figure 8**.

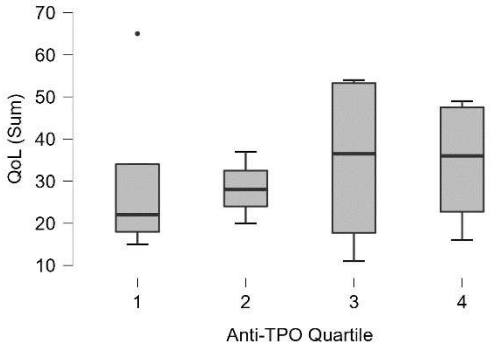

Figure 8. Boxplot between quality-of-life score and quartiles of Anti-TPO

A Pearson's correlation shows a statistically significant correlation with r=0.641, *P*<0.010 between Anti-TPO and "Impaired Social Life". There is a positive, linear association between "Impaired Social Life" and "Anti-TPO" (*P*=0.007) [95%CI 0.213, 0.863].

5. DISCUSSION

Previous studies hinted that the normal thyroid hormone level range might not be the normal hormone level range for all individuals (13, 44). This suggests that abnormal values might lead to unnecessary treatment and that some patients have his or her perfect thyroid hormone level in a range which might not necessarily be considered within the normal range (43). This may indicate that also the quality of life of patients with thyroid dysfunction, such as in autoimmune hypothyroidism, may be not always perceived the best if the patient is within the normal thyroid hormone level range. Additional studies imply, that there is an association between autoantibody levels in hypothyroidism and the quality of life (66, 67). Since it was shown that the risk of developing thyroid peroxidase and thyroglobulin autoantibodies and thus subclinical and overt hypothyroidism is apparently reduced by current smoking (88), the aim of the study is to see if there is an association between quality of life and smoking as well as see if there are other parameters which might influence quality of life.

In this study the quality of life was not better in the smoker group compared to the non-smoker group. The data suggests that the autoantibody titers of Anti-TPO and Anti-Tg were not lower in the group of smokers than in the non-smoker group. Furthermore, the data also implies that fT3 and fT4 levels were not higher in the smokers group compared to the non-smokers group. However, it supports the theory that the TSH value in the group of smokers was statistically significantly lower than in the group of non-smokers. Furthermore, the analysis identified that the quality of life did correlate with fT4 as well as that fT4 differed between the quartiles of the score of the quality of life. However, it did not identify any differences of the parameters (TV, TSH, fT3, Anti-TPO, Anti-Tg) between the quartiles of the score of the quality of life.

This study could not back up the hypothesis that quality of life might be different between the smokers and non-smokers, even though the TSH value was statistically significantly lower in the smoker group compared to the non-smoker group. This might be because most patients were euthyroid according to their blood test results. Another reason might be that other studies showed that patients with normal TSH values could have persistent symptoms which did not reside after the thyroid hormone replacement treatment (44, 61, 91). Thus, there are probably other factors which influence the quality of life more than TSH values within the normal range. Furthermore, the median of the score of quality of life was 39 on a scale from 0-100 with the lowest score at 11 and the highest score at 78. This low median supports the fact that most patients are at the time of data collection euthyroid which reflects a relative, good quality of life as expected in patients from a medical care center.

Similarly, this study was not able to show that there is a significant difference between the groups regarding autoantibodies. However, the influence of smoking and autoantibodies is controversial. Some studies show a lower antibody concentration in relation to smoking (86, 88). Nevertheless, the study from Cho, Choi *et al.* could also not support that claim (84). Yet, the sample size might also be a factor why this hypothesis was not confirmed.

In contrast to previous studies, this study could also not demonstrate the effect of higher fT3 and fT4 values in group of smokers compared to in the group of non-smokers (85, 92). Since the sample size in general was so small, it could skew the statistic and consequently this effect was not visible. Additionally, the experimental group was significantly smaller than the control group which could also influence the statistic. This great difference between the experimental and the control might be because of the demographics in Germany, since only 18.6% of females and 26.4% of males in Germany smoke. This percentage is even lower in Bavaria which might explain the great difference between the two group (93).

Like other studies, the TSH level was lower in smokers compared to non-smokers (85–87, 92). Thus, current smoking seems to lower the TSH level. However, no conclusions can be regarding the quality of life. Nevertheless, since other factors can influence the TSH values as well, it is possible there are confounding factors involved such as age, medications, genetic factors or environmental factors (92).

The quality-of-life score correlated with fT4. However, it correlated contrarily to the expected direction. The correlation was the positive and linear which means the higher fT4 the higher the quality-of-life score, thus, the lower the perceived quality of life. However, all the patients fT4 values were within normal range (7.0-14.8 ng/l) with the highest value of 13.4 ng/l. Nevertheless, it seems that the correlation might be accidental. In the linear regression analysis was an error of independence according to the Durbin-Watson Test (0.901), although there were no outliers and both variables were normally distributed. However, studies show that higher fT4 values within the normal range increase the risk of atrial fibrillation, which would support the negative association between quality of life and higher fT4 values within normal range (94–96).

Since this sample size is quite small, the parameters (TV, TSH, fT3, fT4, Anti-TPO, Anti-Tg) were compared within the quartiles of the quality-of-life score. Hereby, there were no differences between the quartiles regarding the parameters (TV, TSH, fT3, Anti-TPO, Anti-Tg). The total volume of the thyroid (TV) of the patient within the study was even smaller than the normal range. Thus, there might be no effect, since the patients might not have any dysphagia or feeling any obstruction within their throat where an enlarged thyroid gland causes these

problems (97). Furthermore, there is no clear difference between the quartiles of the quality-of-life score and TSH. However, it is unexpected that the median value of TSH in the second quartile was higher compared to all the other quartiles. In addition, there was no differences between the quartiles of the QoL and the autoantibody concentration (Anti-TPO, Anti-Tg) contrary to previous studies (65–67). There is no difference between the quartiles of Anti-TPO and the quality-of-life score. However, it is noticeable that the medians of QoL in the first and second quartile of the Anti-TPO titer are lower than in the third and fourth quartile.

In contrast to previous results of this study, Anti-TPO positively correlated with the scale "Impaired Social Life" of the ThyPRO-39 questionnaire. Similar results were shown Watt, Hegedüs, *et al.* (42). However, this study cannot demonstrate a correlation between "Goiter Symptoms", "Depressivity", "Anxiety", "Emotional Susceptibility" and Anti-TPO. Maybe the sample size was too small to show a correlation between these items and Anti-TPO.

Unfortunately, this study has several limitations. First of all, the sample size was very small especially in the experimental group of smokers compared to the control group of non-smokers which might not be representative of the general population in the area of Upper Franconia. The reason for the small sample size can be that the questionnaire was only recently distributed because the reliability and validity of the short ThyPRO-39 in German was only verified in 2021. Thus, the patients were only assessed with this questionnaire after its reliability and validity was established (76). In addition, the sample size between the groups was not equal. However, this might reflect the smoking rate in Germany, esp. in Bavaria. According to this statistic, only 16.6% of women and 24.6% of men in Bavaria smoke (93). Since all the smokers in this study were female, it might be expected that the percentage of smokers within the study is so low (14.75%). Thus, there were more subjects within the control group than in the experimental group. The predominance of women in this study is not surprising since women are more prone to Hashimoto disease than men (1, 2). Moreover, this is a retrospective case-control study which by study design does not allow to draw any causal conclusions. Lastly, due to missing values the statistical analysis might be skewed and, thus, it might not confirm the lowering effect of smoking on the antibody titer which was shown in other studies.

The value of this study is that it does not show any correlation between quality of life and TSH which might indicate that the people with normal values of TSH might still have not a good quality of life and the symptoms might persist.

For future investigations, the sample size needs to be increased. Furthermore, all the examinations including blood tests should be performed on the same day to improve the data assuring a better comparison between the blood values, quality of life and thyroid gland size.

In addition, a cohort study as a study design should be applied to be able to draw causal conclusions. Moreover, there might be other factors which influences the quality of life in autoimmune hypothyroid patients including age, comorbidities such as other autoimmune diseases, or TSH range regarding individual levels.

6. CONCLUSIONS

1. There was no statistically significant difference in the quality of life between smokers and non-smokers.
2. There was no statistically significant difference between the autoantibody titer between smokers and non-smokers.
3. There was no statistically significant difference between fT3 & fT4 levels between smokers and non-smokers. However, there is a significant difference between smokers and non-smokers regarding TSH. The TSH level are lower in the group of smokers than in non-smokers.
4. Quality-of-life score correlates positively with fT4.
5. The parameters (TV, TSH, fT3, Anti-TPO, Anti-Tg) differ not between the quartiles of the score of the quality of life. However, fT4 differs between the quartiles of the score of the quality of life.
6. The quality-of-life score is not different between the quartiles of Anti-TPO.
7. There is a positive linear correlation between the “Impaired Social Life” and Anti-TPO. However, Anti-TPO does not correlate with the other scales of the ThyPRO.

7. REFERENCES

1. Hall JE, Guyton AC. Thyroid Metabolic Hormones. In: Guyton and Hall textbook of medical physiology. p. 951–63.

2. Jameson JL, Mandel SJ, Weetman AP. Thyroid gland Physiology and Testing. In: Harrison's principles of internal medicine. p. 2692–8.

3. Mescher AL. Endocrine glands. In: Junqueira's basic histology Text and atlas. p. 413–37.

4. Moore KL. Viscera Of Neck. In: Clinically oriented anatomy. p. 1018–40.

5. Khan YS, Farhana A. StatPearls: Histology, Thyroid Gland. Treasure Island (FL); 2022.

6. Allen E, Fingeret A. StatPearls: Anatomy, Head and Neck, Thyroid. Treasure Island (FL); 2022.

7. Maenhaut C, Christophe D, Vassart G, Dumont J, Roger P, Opitz R. Endotext: Ontogeny, Anatomy, Metabolism and Physiology of the Thyroid. South Dartmouth (MA); 2000.

8. Graefe H, Biermann E, Mandapathil M, Weber M, Merkel M, Meyer JE. Schilddrüsenmedizin für HNO-Ärzte. HNO 2018;66:937–50.

9. Pirahanchi Y, Tariq MA, Jialal I. StatPearls: Physiology, Thyroid. Treasure Island (FL); 2022.

10. Mariotti S, Beck-Peccoz P. Endotext: Physiology of the Hypothalamic-Pituitary-Thyroid Axis. South Dartmouth (MA); 2000.

11. Patil N, Rehman A, Jialal I. StatPearls: Hypothyroidism. Treasure Island (FL); 2022.

12. Samuels MH, Henry P, Luther M, Ridgway EC. Pulsatile TSH secretion during 48-hour continuous TRH infusions. Thyroid 1993;3:201–6.

13. Biondi B. The normal TSH reference range: what has changed in the last decade? J Clin Endocrinol Metab 2013;98:3584–7.

14. Bowers J, Terrien J, Clerget-Froidevaux MS, Gothié JD, Rozing MP, Westendorp RGJ et al. Thyroid hormone signaling and homeostasis during aging. Endocr Rev 2013;34:556–89.

15. Bauer DC, McPhee SJ. Thyroid Disease: An introduction to clinical medicine. In: Pathophysiology of disease. p. 571–91.

16. Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev 2014;94:355–82.

17. Freeland-Graves JH, Bavik C. COENZYMES. In: Encyclopedia of Food Sciences and Nutrition. Elsevier; 2003. p. 1475–81.

18. Armstrong M, Asuka E, Fingeret A. StatPearls: Physiology, Thyroid Function. Treasure Island (FL); 2022.

19. Shahid MA, Ashraf MA, Sharma S. StatPearls: Physiology, Thyroid Hormone. Treasure Island (FL); 2022.

20. Wilkinson IB, Raine T, Wiles K, Goodhart A, Hall C, O'Neill H. The thyroid: examination. In: Oxford handbook of clinical medicine. p. 84–5 Available from: URL: https://ebookcentral.proquest.com/lib/kxp/detail.action?docID=4941588.

21. Blum M. Ultrasonography of the Thyroid [Endotext]. South Dartmouth (MA); 2000.

22. Vita R, Di Bari F, Perelli S, Capodicasa G, Benvenga S. Thyroid vascularization is an important ultrasonographic parameter in untreated Graves' disease patients. J Clin Transl Endocrinol 2019;15:65–9.

23. Chaudhary V, Bano S. Thyroid ultrasound. Indian J Endocrinol Metab 2013; 17:219–27.

24. Caruso B, Bovo C, Guidi GC. Causes of Preanalytical Interferences on Laboratory Immunoassays - A Critical Review. EJIFCC 2020;31:70–84.

25. Harrison's principles of internal medicine.

26. Abrams J, Abrams N. Diagnostik und konservative Therapie von Schilddrüsenerkrankungen. HNO Nachrichten 2016;46:22–6.

27. Mincer DL, Jialal I. StatPearls: Hashimoto Thyroiditis. Treasure Island (FL); 2022.

28. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. The Lancet 2017;390:1550–62.

29. Zieren HU. Autoimmunerkrankungen der Schilddrüse. CME 2021;18:9–17.

30. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012;18:988–1028.

31. Arthur JR, Beckett GJ. Thyroid function. Br Med Bull 1999;55:658–68.

32. Caturegli P, Remigis A de, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 2014;13:391–7.

33. Wu H, Zhang B. Ultrasonographic appearance of focal Hashimoto's thyroiditis: A single institution experience. Endocr J 2015;62:655–63.

34. Akamizu T, Amino N. Endotext: Hashimoto’s Thyroiditis. South Dartmouth (MA); 2000.

35. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, RoliÅ„ski J, Yang X-F. Immune Disorders in Hashimoto's Thyroiditis: What Do We Know So Far? J Immunol Res 2015;2015:979167.

36. Chou K-M, Huang B-Y, Chen C-H, Lin J-D, Chiu SY-H, Lee C-C. Correlation and presentation of thyroid functional status with thyroid autoantibodies in long-term follow-up of autoimmune thyroiditis: A study of 116 cases. J Formos Med Assoc 2015;114:1039–46.

37. Peretianu D. Antithyreoperoxidase Antibodies (ATPO) in Hashimoto Thyroiditis: Variation of Levels and Correlation with Echographic Patterns. Acta Endo (Buc) 2005;1:61–78.

38. Marcocci C, Vitti P, Cetani F, Catalano F, Concetti R, Pinchera A. Thyroid ultrasonography helps to identify patients with diffuse lymphocytic thyroiditis who are prone to develop hypothyroidism. J Clin Endocrinol Metab 1991;72:209–13.

39. Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid 2000;10:251–9.

40. Wu G, Zou D, Cai H, Liu Y. Ultrasonography in the diagnosis of Hashimoto's thyroiditis. Front Biosci (Landmark Ed) 2016;21:1006–12.

41. Fu X, Guo L, Zhang H, Ran W, Fu P, Li Z et al. "Focal thyroid inferno" on color Doppler ultrasonography: a specific feature of focal Hashimoto's thyroiditis. Eur J Radiol 2012;81:3319–25.

42. Watt T, Hegedüs L, Bjorner JB, Groenvold M, Bonnema SJ, Rasmussen AK et al. Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism? Eur Thyroid J 2012;1:186–92.

43. Führer D, Brix K, Biebermann H. Understanding the Healthy Thyroid State in 2015. Eur Thyroid J 2015;4:1–8.

44. Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Nat Rev Endocrinol 2014;10:164–74.

45. Soh SB, Aw TC. Laboratory Testing in Thyroid Conditions - Pitfalls and Clinical Utility. Ann Lab Med 2019;39:3–14.

46. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34.

47. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab 2005;90:5483–8.

48. Fontes R, Coeli CR, Aguiar F, Vaisman M. Reference interval of thyroid stimulating hormone and free thyroxine in a reference population over 60 years old and in very old subjects (over 80 years): comparison to young subjects. Thyroid Res 2013;6:13.

49. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:4575–82.

50. Gussekloo J, van Exel E, Craen AJM de, Meinders AE, Frölich M, Westendorp RGJ. Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004;292:2591–9.

51. Inoue K, Tsujimoto T, Saito J, Sugiyama T. Association Between Serum Thyrotropin Levels and Mortality Among Euthyroid Adults in the United States. Thyroid 2016;26:1457–65.

52. Waring AC, Arnold AM, Newman AB, Bùžková P, Hirsch C, Cappola AR. Longitudinal Changes in Thyroid Function in the Oldest Old and Survival: The Cardiovascular Health Study All-Stars Study. J Clin Endocrinol Metab 2012;97:3944–50.

53. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068–72.

54. Nagayama I, Yamamoto K, Saito K, Kuzuya T, Saito T. Subject-based reference values in thyroid function tests. Endocr J 1993;40:557–62.

55. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 2011;21:5–11.

56. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Recent Advances in Thyroid Hormone Regulation: Toward a New Paradigm for Optimal Diagnosis and Treatment. Front Endocrinol (Lausanne) 2017;8:364.

57. Borson-Chazot F, Terra J-L, Goichot B, Caron P. What Is the Quality of Life in Patients Treated with Levothyroxine for Hypothyroidism and How Are We Measuring It? A Critical, Narrative Review. J Clin Med 2021; 10.

58. Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011; 6:e22552.

59. Michaelsson LF, La Cour JL, Medici BB, Watt T, Faber J, Nygaard B. Levothyroxine/Liothyronine Combination Therapy and Quality of Life: Is It All about Weight Loss? Eur Thyroid J 2018;7:243–50.

60. Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JGP et al. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 2005;90:2666–74.

61. Saravanan P, Chau W-F, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 2002;57:577–85.

62. Winther KH, Cramon P, Watt T, Bjorner JB, Ekholm O, Feldt-Rasmussen U et al. Disease-Specific as Well as Generic Quality of Life Is Widely Impacted in Autoimmune Hypothyroidism and Improves during the First Six Months of Levothyroxine Therapy. PLoS One 2016;11:e0156925.

63. Morón-Díaz M, Saavedra P, Alberiche-Ruano MP, Rodríguez-Pérez CA, López-Plasencia Y, Marrero-Arencibia D et al. Correlation between TSH levels and quality of life among subjects with well-controlled primary hypothyroidism. Endocrine 2021;72:190–7.

64. Saravanan P, Visser TJ, Dayan CM. Psychological well-being correlates with free thyroxine but not free 3,5,3'-triiodothyronine levels in patients on thyroid hormone replacement. J Clin Endocrinol Metab 2006;91:3389–93.

65. Ott J, Promberger R, Kober F, Neuhold N, Tea M, Huber JC et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid 2011;21:161–7.

66. Müssig K, Künle A, Säuberlich A-L, Weinert C, Ethofer T, Saur R et al. Thyroid peroxidase antibody positivity is associated with symptomatic distress in patients with Hashimoto's thyroiditis. Brain Behav Immun 2012;26:559–63.

67. Yalcin MM, Altinova AE, Cavnar B, Bolayir B, Akturk M, Arslan E et al. Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto's thyroiditis? Endocr J 2017;64:425–9.

68. Carta MG, Loviselli A, Hardoy MC, Massa S, Cadeddu M, Sardu C et al. The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. BMC Psychiatry 2004;4:25.

69. Harris B, Othman S, Davies JA, Weppner GJ, Richards CJ, Newcombe RG et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. BMJ 1992;305:152–6.

70. Quinque EM, Villringer A, Kratzsch J, Karger S. Patient-reported outcomes in adequately treated hypothyroidism - insights from the German versions of ThyDQoL, ThySRQ and ThyTSQ. Health Qual Life Outcomes 2013;11:68.

71. Watt T, Cramon P, Hegedüs L, Bjorner JB, Bonnema SJ, Rasmussen ÅK et al. The thyroid-related quality of life measure ThyPRO has good responsiveness and ability to detect relevant treatment effects. J Clin Endocrinol Metab 2014;99:3708–17.

72. Watt T, Hegedüs L, Rasmussen AK, Groenvold M, Bonnema SJ, Bjorner JB et al. Which domains of thyroid-related quality of life are most relevant? Patients and clinicians provide complementary perspectives. Thyroid 2007;17:647–54.

73. Watt T, Hegedüs L, Groenvold M, Bjorner JB, Rasmussen AK, Bonnema SJ et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol 2010;162:161–7.

74. Rehman MU, Ali SS, Khan N, Ahmad I, Ullah I. Using Thypro 39 Scale For Predicting The Quality Of Life In Hypothyroid Patients At Lady Reading Hospital. J Ayub Med Coll Abbottabad 2020;32:395–9.

75. Hegedüs L, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, Perros P. Primary hypothyroidism and quality of life. Nat Rev Endocrinol 2022;18:230–42.

76. Tabriz N, Gloy K, Schantzen A, Fried D, Weyhe D, Uslar V. Validity and reliability of the German version of the shortened thyroid-specific quality of life questionnaire (ThyPRO-39de). Endocr Connect 2021;10:1065–72.

77. Watt T, Barbesino G, Bjorner JB, Bonnema SJ, Bukvic B, Drummond R et al. Cross-cultural validity of the thyroid-specific quality-of-life patient-reported outcome measure, ThyPRO. Qual Life Res 2015; 24:769–80.

78. Sawicka-Gutaj N, Watt T, Sowiński J, Gutaj P, Waligórska-Stachura J, Ruchała M. ThyPROpl--The Polish version of the thyroid-specific quality of life questionnaire ThyPRO. Endokrynol Pol 2015; 66:367–80.

79. Watt T, Bjorner JB, Groenvold M, Cramon P, Winther KH, Hegedüs L et al. Development of a Short Version of the Thyroid-Related Patient-Reported Outcome ThyPRO. Thyroid 2015;25:1069–79.

80. Fukata S, Kuma K, Sugawara M. Relationship between cigarette smoking and hypothyroidism in patients with Hashimoto's thyroiditis. J Endocrinol Invest 1996;19:607–12.

81. Vestergaard P. Smoking and thyroid disorders--a meta-analysis. Eur J Endocrinol 2002;146:153–61.

82. Asvold BO, Bjøro T, Nilsen TIL, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. Arch Intern Med 2007;167:1428–32.

83. Knudsen N, Bülow I, Laurberg P, Perrild H, Ovesen L, Jørgensen T. High occurrence of thyroid multinodularity and low occurrence of subclinical hypothyroidism among tobacco smokers in a large population study. J Endocrinol 2002;175:571–6.

84. Cho NH, Choi HS, Kim KW, Kim H-L, Lee S-Y, Choi SH et al. Interaction between cigarette smoking and iodine intake and their impact on thyroid function. Clin Endocrinol (Oxf) 2010;73:264–70.

85. Jorde R, Sundsfjord J. Serum TSH levels in smokers and non-smokers. The 5th Tromsø study. Exp Clin Endocrinol Diabetes 2006;114:343–7.

86. Belin RM, Astor BC, Powe NR, Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2004;89:6077–86.

87. Sawicka-Gutaj N, Gutaj P, Sowiński J, Wender-Ożegowska E, Czarnywojtek A, Brązert J et al. Influence of cigarette smoking on thyroid gland--an update. Endokrynol Pol 2014;65:54–62.

88. Wiersinga WM. Smoking and thyroid. Clin Endocrinol (Oxf) 2013;79:145–51.

89. Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Banke Rasmussen L et al. Smoking cessation is followed by a sharp but transient rise in the incidence of overt autoimmune hypothyroidism - a population-based, case-control study. Clin Endocrinol (Oxf) 2012;77:764–72.

90. Laurberg P, Andersen S, Pedersen IB, Knudsen N, Carlé A. Prevention of autoimmune hypothyroidism by modifying iodine intake and the use of tobacco and alcohol is manoeuvring between Scylla and Charybdis. Hormones (Athens) 2013;12:30–8.

91. Thatipamala P, Noel JE, Orloff L. Quality of Life After Thyroidectomy for Hashimoto Disease in Patients With Persistent Symptoms. Ear Nose Throat J 2020:145561320967332.

92. Babić Leko M, Gunjača I, Pleić N, Zemunik T. Environmental Factors Affecting Thyroid-Stimulating Hormone and Thyroid Hormone Levels. Int J Mol Sci 2021; 22.

93. Mccarthy N. Smoking rates in Germany. Statista 2019 Nov 19 [cited 2022 Jun 24]. Available from: URL: https://www.statista.com/chart/20011/share-of-the-population-who-smoked-in-german-federal-states/.

94. Chaker L, Heeringa J, Dehghan A, Medici M, Visser WE, Baumgartner C et al. Normal Thyroid Function and the Risk of Atrial Fibrillation: the Rotterdam Study. J Clin Endocrinol Metab 2015;100:3718–24.

95. Baumgartner C, Da Costa BR, Collet T-H, Feller M, Floriani C, Bauer DC et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation 2017;136:2100–16.

96. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FDR, Wilson S et al. Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med 2007;167:928–34.

97. Greenblatt DY, Sippel R, Leverson G, Frydman J, Schaefer S, Chen H. Thyroid resection improves perception of swallowing function in patients with thyroid disease. World J Surg 2009;33:255–60.

8. SUMMARY

Objectives: To evaluate the quality of life of patients with autoimmune hypothyroidism and compare if there are any differences between smokers and non-smokers

Materials and methods: A retrospective case-control study was done in the department of endocrinology of the Regiomed hospital in Coburg. In the Medical Care Center (MCC) of the 61 patients selected, 52 were non-smokers, and 9 were smokers. Patients' data was assessed by the ThyPRO-39 questionnaire, an anamnestic questionnaire, blood tests, and ultrasound examination of the thyroid gland.

Results: There was no statistically significant difference in the quality of life between smokers and non-smokers (*P*=0.425). There was no statistically significant difference between the autoantibody titer of Anti-TPO (*P*=0.463) and Anti-Tg (*P*=0.421) between smokers and non-smokers. There was no statistically significant difference between fT3 (*P*=0.568) & fT4 levels(*P*=0.262) between smokers and non-smokers. TSH was statistically significantly lower in the smoker group compared to the non-smoker group (*P*=0.015). The quality-of-life score correlates positively with fT4 (r=0.572, *P*=0.003). In the boxplot the parameters (TV, TSH, fT3, Anti-TPO, Anti-Tg) did not differ between the quartiles of the score of the quality of life. However, fT4 differs between the quartiles of the score of the quality of life. The quality-of-life score did not differ between the quartiles of Anti-TPO. Anti-TPO positively correlates with "Impaired Social Life (r=0.641, *P*=0.007).

Conclusion: Except TSH, there was no statistically significant difference between the smokers and non-smoker regarding the quality of life. The quality-of-life score correlates positively with fT4. Anti-TPO positively correlates with "Impaired Social Life"

9. CROATIAN SUMMARY

Pušenje i njegov utjecaj na kvalitetu života u bolesnika s autoimunom hipotireozom – retrospektivna studija kontrole slučaja

Cilj: Procijeniti kvalitetu života bolesnika s autoimunom hipotireozom i usporediti postoje li razlike između pušača i nepušača.

Materijali i metode: Retrospektivna studija slučaj-kontrola napravljena je na odjelu za endokrinologiju bolnice Regiomed u Coburgu. U Centru za medicinsku skrb (MCC) od 61 odabranog pacijenta, 52 su bila nepušača, a 9 pušača. Podaci o pacijentima procijenjeni su upitnikom ThyPRO-39, anamnestičkim upitnikom, krvnim pretragama i ultrazvučnim pregledom štitnjače.

Rezultati: Nije bilo statistički značajne razlike u kvaliteti života između pušača i nepušača (*P*=0,425). Nije bilo statistički značajne razlike između titra autoantitijela Anti-TPO (*P*=0,463) i Anti-Tg (*P*=0,421) između pušača i nepušača. Nije bilo statistički značajne razlike između razina fT3 (*P*=0,568) i fT4 (*P*=0,262) između pušača i nepušača. TSH je bio statistički značajno niži u skupini pušača u odnosu na skupinu nepušača (*P*=0,015). Ocjena kvalitete života pozitivno korelira s fT4 (r=0,572; *P*=0,003). U boxplot-u parametri (TV, TSH, fT3, Anti-TPO, Anti-Tg) nisu se razlikovali između kvartila ocjene kvalitete života. Međutim, fT4 se razlikuje između kvartila ocjene kvalitete života. Ocjena kvalitete života nije se razlikovala između kvartila Anti-TPO. Anti-TPO pozitivno korelira s „Oštećenim društvenim životom (r=0,641; *P*=0,007).

Zaključak: Osim TSH, nije bilo statistički značajne razlike između pušača i nepušača u kvaliteti života. Ocjena kvalitete života pozitivno korelira s fT4. Anti-TPO pozitivno korelira s "oštećenim društvenim životom"