Diplomarbeit

Thyroidal Dysfunction, Lifestyle Behaviour and Obesity

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Beatrice Rehberger

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Gruber, Hans-Jürgen, Priv.-Doz. Mag. Dr.rer.nat

Graz, am 06.02.2014 Beatrice Rehberger

Eidesstattliche Erklärung

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Zusammenfassung

Einleitung: Die Schilddrüse stellt ein essentielles endokrines Organ im menschlichen Körper dar. Sie ist sowohl während der Entwicklung als auch im Erwachsenenalter von großer Bedeutung. Diese Bedeutung ist unter anderem auch daran erkennbar, dass Rezeptoren für Schilddrüsenhormone an beinahe jeder Körperzelle zu finden sind. Lebensstil – bezogene Erkrankungen wie arterielle Hypertonie, metabolisches Syndrom und viele mehr steigen in ihrer Inzidenz stark an und stellen die moderne westliche Gesellschaft vor große Herausforderungen. Zum Einen führen sie zu einer Vielzahl an Folgeerkrankungen, zum Anderen produzieren sie enorme Kosten für das Gesundheitssystem. Sie stehen im Verdacht im Zusammenhang mit Schilddrüsenfunktionsstörungen assoziiert zu sein. In der Literatur zeigen sich diesbezüglich widersprüchliche Ergebnisse. Daher ist es das Ziel dieser Studie, den möglichen Zusammenhang zwischen Schilddrüsenparametern und Lebensstil – bezogenen Erkrankungen als auch dem metabolischen Syndrom aufzuzeigen.

Methoden: Die Studienkohorte besteht aus 184 Probanden, davon 68% Frauen und 32% Männer. Diese unterteilen sich wiederum in eine gesunde Kontrollgruppe (34% Frauen, 16% Männer), Hyperthyroide (5% Frauen, 1% Männer), Hypothyroide (12% Frauen, 3% Männer) und euthyroide Schilddrüsenpatienten (17% Frauen, 12% Männer). Das Matching erfolgte nach Alter und Geschlecht. Die Auswertung der Laborwerte erfolgte an der Universitätsklinik für Innere Medizin, Abteilung für Endokrinologie, Graz. Die erhobenen Daten wurden mittels SPSS statistisch ausgewertet.

Ergebnisse: In unserer Studie fanden wir einige signifikante Unterschiede in den Messwerten Körpergewicht, Waist – to – hip Ratio und systolischer Blutdruck zwischen Euthyroiden und der Kontrollgruppe. Auch zwischen Euthyroiden und Hypothyroiden zeigten sich Unterschiede in den Bereichen Alter, Körpergröße, Hüftumfang und Waist – to – hip Ratio. Beim diastolischen Blutdruck fanden wir Unterschiede zwischen Euthyroiden und der Kontrollgruppe, Euthyroiden und Hyperthyroiden, Hypothyroiden und der Kontrollgruppe als auch zwischen Hypothyroiden und Hyperthyroiden. Auch bei den Schilddrüsenparametern, wie

fT4, TPO AK und TRAK fanden sich Unterschiede zwischen der gesunden Kontrollgruppe, Hyperthyroiden, Hypothyroiden und Euthyroiden. Bei den Parametern des Glukosemetabolismus fanden sich keine signifikanten Unterschiede zwischen den einzelnen Gruppen. In der durchgeführten Regressionsanalyse fanden wir starke Korrelationen zwischen den Schilddrüsenparametern und Parametern des Glukosemetabolismus in der gesunden Kontrollgruppe, den Hyperthyroiden und den Euthyroiden. Bezüglich der Schilddrüsenparameter und anthopometrischen Parametern fanden sich Zusammenhänge bei der gesunden Kontrollgruppe, den Hypothyroiden und den Euthyroiden.

Conclusio: Die Schilddrüsenfunktion scheint einen großen Einfluss auf das Körpergewicht, wie auch auf den Blutdruck und die Waist – to – hip Ratio zu haben. Deshalb ist es besonders wichtig, Schilddrüsenfunktionsstörungen bei Patienten möglichst frühzeitig zu erkennen und zu behandeln. Unsere Ergebnisse stimmen mit einer Vielzahl von aktuellen Studien überein. Deshalb ist es besonders wichtig, Patienten mit Schilddrüsenfunktionsstörungen möglichst früh und optimal zu behandeln, um deren Risiko für die Entwicklung eines metabolischen Syndroms zu minimieren.

Abstract

Introduction: The thyroid gland is an essential endocrine organ in the human body. Whilst growing up, thyroid hormones are required for a normal development of mental skills as well as for reaching full body function. Also for grown up people the correct amount of thyroid hormones is needed. Receptors for thyroid hormones are existing on nearly every cell in the body. Lifestyle – related diseases, like hypertension, metabolic syndrome and many more may be related to thyroid – hormone – levels. Metabolic syndrome is a growing problem in the western world, causing a lot of illnesses for the patients and a lot of costs for the health system. Literature shows puzzling results. So it is the aim of our study, to find correlations between thyroidal parameters and parameters of lifestyle – related diseases and metabolic syndrome.

Methods: Patients have been recruited when visiting the Department of Endocrinology of the Medical University Graz. The study cohort consists of 184. Patients have been sub grouped depending on their thyroid function into hyper-, hypo- and euthyroid. Euthyroid patients are patients with thyroid dysfunction, who already get treatment. For every patient, a proband was matched in age and sex. The study cohort consists of 68% females and 32% males. In detail, the study cohort consists of 34% healthy females, 5% hyperthyroid females, 12% hypothyroid females, 17% euthyroid females, 16% healthy males, 1% hyperthyroid males, 3% hypothyroid males and 12% euthyroid males. Laboratory analyses of the parameters from this prospective clinical trial have been analysed by the Endocrinology Laboratory, Department of Endocrinology and Metabolism, Medical University Graz. Clinical parameters have been analysed using SPSS.

Results: In our study we found significant differences in baseline characteristics in body weight, waist – to – hip ratio and systolic blood pressure between euthyroids and controls. We also found differences in age, body length, waist circumference and waist – to – hip ratio between euthyroids and hypothyroids. Regarding diastolic BP, we found differences between euthyroids and controls, euthyroids and hyperthyroids, hypothyroids and controls as well as between hypothyroids and hyperthyroids. We also found differences in basal TSH levels, fT4, TPO AB and TRAK regarding healthy controls, hyperthyroids, hypothyroids and euthyroids. In

parameters of the glucose metabolism, regarding glucose, insulin, c – peptide and HOMA – index, we found no significant differences between the four groups. We also performed regression analyses, where we found a strong correlation between parameters of the glucose metabolism and parameters of the thyroid function in healthy controls, hyperthyroids and euthyroids. Regarding thyroid parameters and antopometric parameters, we found significant correlation in healthy controls, hypothyroids as well as euthyroids.

Conclusion: Thyroid dysfunction seems to have a strong impact on body weight, waist – to – hip ratio and blood pressure. Therefore it is very important to recognise thyroid dysfunction in patients for a better treatment. Our findings are in line with many different studies. So this also supports the idea that thyroid dysfunction patients need to get adeaquat therapy in order to reduce a patient´s risk for metabolic disorders.

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Glossar und Abkürzungen

BMI – body mass index (kg/m²)
BMR – basic metabolic rate
BP – blood pressure (mmHg)
cAMP – cyclic Adenosinmonophosphate
CRP – C – reactive protein
DIT - diiodothyrosine
EGF – epidermal growth factor
fT3 – free triiodthyronin
fT4 – free tetraiodthyronin
hCG – human choriongonadotropine
HDL – high density lipoprotein
HOMA – homeostasis model assessment
IAAT – intra – abdominal adipose tissue
ICMA – immunochemiluminometric assay
IgA – immunoglobuline A
IgE – immunoglobuline E
IGF – insulin – like growth factor
IgG – immunoglobulin G
IgM – immunoglobuline M
IL – 6 – interleukine 6
LDL – low density lipoprotein
MIT – monoiodothyrosine
NAFLD – non – alcoholic fat liver disease
NOTHYS – Nitric Oxide Thyroid Study
PTHi – parathormone
ROS – radical oxygen species
rT3 – reverse T3
SCAT – sub – cutanous adipose tissue
SD – standard deviation
SPSS – Statistical Package for the Social Sciences
t3 – triiodthyronin
t4 – tetraiodthyronin
TBG – thyroid binding globulin
TGF – transforming growth factor
THBR – thyroid hormone binding ratio
TNF – tumour necrosis factor
TPO – thyroidal peroxidase
TPO – AB – antibodies against thyroidal peroxidase
TRAK – TSH – receptor antibodies
TR – thyroid hormone receptor
TRH – thyreotropin releasing hormone
TSH – thyroidal stimulating hormone
VHDL – very high density lipoproteins
VLDL – very low density lipoproteins
WHO – World Health Organisation

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1 Introduction

The thyroid gland is a very important organ in the human body, which is responsible for producing the two hormones triiodthyronin and tetraiodthyronin fT3 and fT4. The thyroid hormones T3 and T4 are involved in a wide variety of physiological functions including metabolism, growth and other hormone systems (1). Furthermore, thyroid hormones are also essentially involved in embryonic development at early stages (2). Especially while growing up, a normal range of these two hormones is essential for developing adequate mental ability. Also in adults, the right amount of thyroid hormones is essential for a normal function of the nervous system. Hyperthyroidism for instance causes hyperexcitability and irritability, whereas hypothyroidism leads to slowed speech, listlessness, impaired memory, somnolence and decreased mental capacity. It is one of the largest endocrine glands in the body. There are receptors for fT3 on nearly every cell in the body. The hormones of the thyroid gland effect many different processes in the body, such as growth, bone formation, nervous system, metabolism as well as cardiovascular and respiratory system. The various thyroid diseases represent a complex network, depending on the functional behaviour of the thyroid which is the basis for diagnosis and therapy (3). Classification guidelines define these diseases upon functional aspects into hyper-, eu-, or hypothyroidism reflecting excessive, normal or defective levels of thyroid hormones, as outlined in detail by Monaco (4).

1.1 Location and Anatomy

The thyroid gland is located in the neck below the thyroid cartilage (5). The thyroidal isthmus is found in front of the second to fourth tracheal ring. The thyroid consists of two lobes, the right and left lobe, which are connected by the thin thyroidal isthmus. In some cases, there is also an excessive pyramidal lobe on the top of the thyroidal isthmus, which can be seen as a remnant of the thyreoglossal ductus. The thyroid is covered by a fibrous sheath, which is formed by a very thin organ capsule and on the outside, by a fibrous capsule. The fibrous capsule consists of lamellae and is responsible for the connection between the thyroid gland and the trachea as well as the larynx. In-between the two layers, the big

thyroidal vessels, as well as the parathyroid glands can be found. These four parathyroid glands, which produce parathyroid hormone, are located posterior to each pole of the thyroid (6). The recurred laryngeal nerves transverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid vocal cord paralysis.

The thyroid is supplied by four arteries, two superior thyroidal arteries and two inferior thyroidal arteries (5). In 10 percent of all cases, a single thyroidal artery, which derives from the brachiocephal branch or directly of the aortic arch, reaches the thyroid gland in the area of the thyroidal isthmus. The four big arteries form anastomoses, which are also found in the area of the thyroidal isthmus. They are arched, which allows them to change their length in order to the normal rise and descent of the thyroidal gland while swallowing. Venous blood is drained by the superior and medial thyroidal veins to the internal jugular vein. The inferior thyroidal vein starts at the thyroidal isthmus and drains the blood to the brachiocephal veins, only in some cases also to the internal jugular vein. The nerves, supplying the thyroid have their origin in the nervus vagus and the truncus sympathicus, also sometimes the nervus glossopharyngeus.

The fibrose capsula is the envelope of the thyroid gland (7). It consists of a thin inner layer and a fibrose layer on the outside. The inner layer is sending septa to the inside of the thyroid, which separates it into lobules. Every lobule consists of many follicles. They have a diameter of 50-900µm and they are surrounded by a single-layer epithelia. Every follicle is filled with a very homogeny substance, called the colloid. The follicles are separated by tiny paths of connective tissue, the stroma. Every follicle is surrounded by a basal membrane and a close meshed capillary network.

The thyroid gland develops on the ground of the primitive pharynx during the third week of gestation (6). The developing gland migrates along the thyroglossal duct to reach its final location in the neck. This evolution accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of thyroglossal duct cysts along this development tract. Thyroid hormone synthesis normally begins at about eleven weeks´ gestation. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the juncture of the upper one – third to lower two – thirds of the gland.

1.2 Synthesis of thyroid hormones

The synthesis of the two thyroidal hormones T3 and T4 takes place in the thyroid follicular epithelial cell, as well as in the follicular lumen (2). Each step in this synthesis is stimulated by the thyroidal stimulating hormone TSH. It starts with the synthesis of thyroglobulin (Step 1). Thyroglobuline is synthesized from tyrosine and packed in secretory vesicels. In the secretory vesicels it reaches the follicular lumen. The iodine, which is essential for the production of thyroid hormones, is actively transported into the follicular cell via the iodine pump, which is a Na+ - I- cotransport. (Step 2). The next step (Step 3) is the oxidation of I- to I2. This reaction takes place in the follicular cell membrane and is catalyzed by a peroxidise enzyme. The peroxidase enzyme is inhibited by propylthiouracil, which is used in the treatment of hyperthyroidism. I2 is the reactive form and is now organified by the combination tyrosine on thyroglobulin as shown in step 4. In detail, tyrosine residues of thyroglobulin react with I2 to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) at the junction of the follicular cells and the follicular lumen. High levels of iodine inhibite the organification as well as the synthesis of thyroid hormones, which is called the Wolff – Chaikoff effect. In step 5, MIT and DIT are attached to thyroglobuline. During this process, two coupling reactions occur. When two molecules of DIT combine, T4 is formed. When one molecule of DIT combines with one molecule of MIT, T3 is formed. The thyroid gland produces more T4 then T3, although T3 is three to four times more potent than T4. This iodinated thyroglobulin is stored in the follicular lumen until the thyroid gland is stimulated to secrete thyroid hormones. In case of stimulation by TSH, iodinated thyroglobulin is taken back into the follicular cells by endocytosis (step 6). Lysosomal enzymes then digest thyroglobulin, releasing T4 and T3 into the circulation (step 7). The remaining MIT and DIT are deiodinated ba thyroid deidinase (step 8). The I2 that is released is reutilized to synthesize more thyroid hormones. In the circulation, most of the T3 and T4 is bound to thyroxine – binding globuline. When arrived in the peripheral tissues, T4 is converted to T3 by 5´-iodinase, or to rT3.

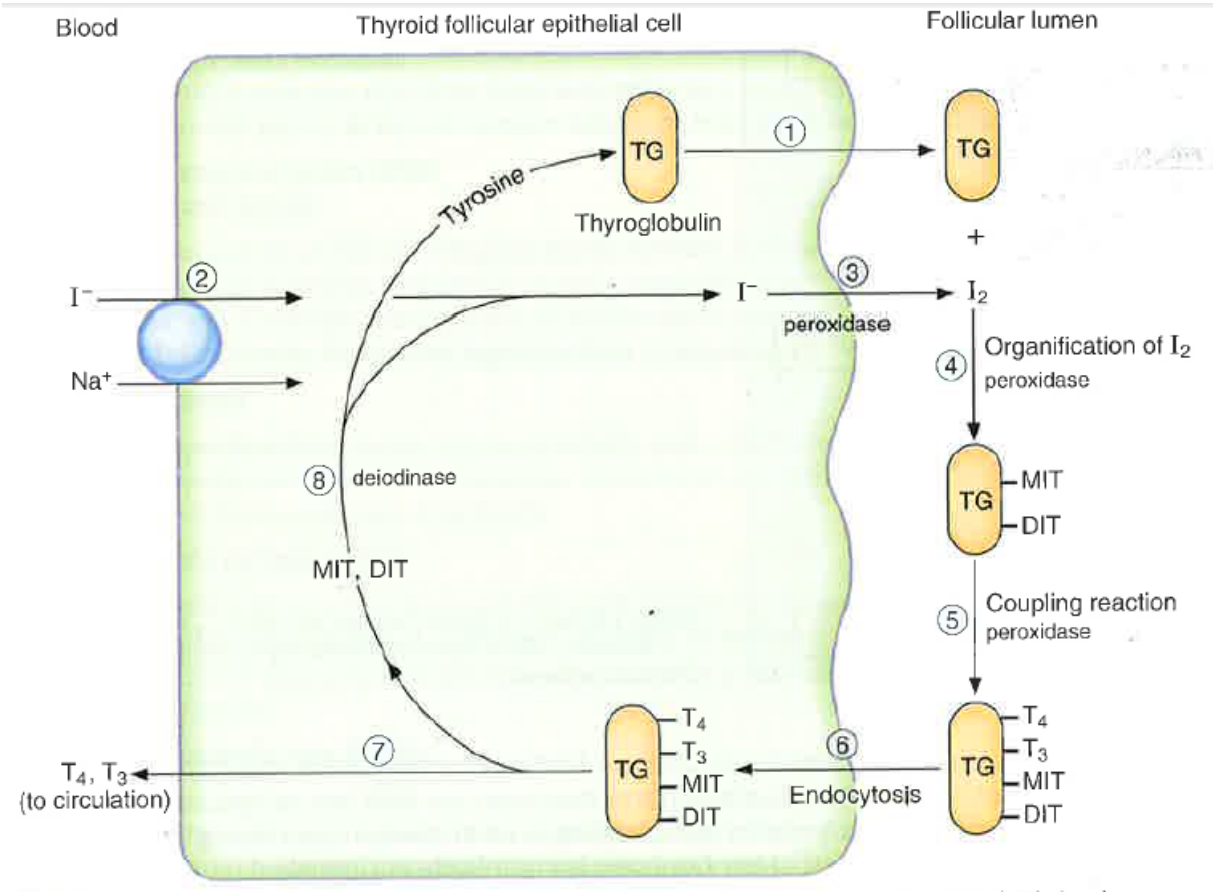

Figure 1

Figure 1 shows the steps of synthesis of thyroid hormones which are described in detail above (2).

1.3 Physiological function

The thyroid gland produces two hormones, which are very important for all metabolic processes in the body, triiodthyronin t3 and thyroxin t4 (8). Therefore, the production of thyroidal hormones is regulated by a negative feedback loop including the organs hypothalamus and pituitary gland.
The hypothalamus produces thyreotropin releasing hormone (TRH) to stimulate the pituitary gland. TRH is synthesised in hypothalamic neurones, in the amygdale and the brain stamp. In response to the increased TRH levels, the anterior pituitary produces a thyroidal stimulating hormone (TSH), which is a glandotropic hormone for the thyroid gland. TSH levels are regulating every process in the thyroid gland. In order to high TSH levels, the thyroid produces t3 and t4 and releases them into

the blood. High levels of thyroidal hormones suppress the production of TRH in the hypothalamus and there for also the production of TSH. In the opposite, low levels of t3 and t4 activate and increase the production of TRH by the hypothalamus and TRH then increases the TSH production of the anterior pituitary. There is more TSH in the blood again, which activates the thyroid gland again for the production of thyroid hormones. This process is called the negative feedback mechanism. Thyroid hormones have effects on growth, the central nervous system, the autonomic nervous system, the basal metabolic rate (BMR), the cardiovascular and respiratory systems and metabolism (2). Thyroid hormones act synergistically with the growth hormone and somatomedines to promote bone formation. They stimulate bone maturation with the result of ossification and fusion of the growth plates. Because the maturation of the central nervous system requires thyroid hormone in the perinatal period, screening for neonatal hypothyroidism is mandatory. Thyroid hormones act similar to the sympathetic nervous system in many ways. They up – regulate beta1 – adrenergic receptors in the heart, lead to increased oxygen consumption and an elevated basic metabolic rate in all tissues except the brain, gonads and spleen. The resulting higher heat production underlies the role of thyroid hormone in temperature regulation. Thyroid hormone increases the synthesis of Na+,K+-ATPase and consequently increases O2 consumption related to Na+ - K+ pump activity. Thyroid hormones lead to an increased cardiac output and an increased ventilation rate to make sure, so that all tissues are supplied with enough oxygen. The overall effect of thyroid hormone is catabolic. Thyroid hormones increase the glucose absorption from the gastrointestinal tract, the glucogenolysis, the gluconeogenesis, the glucose oxidation as well as the lipolysis. Protein synthesis and degradation are enhanced by thyroid hormones as well.

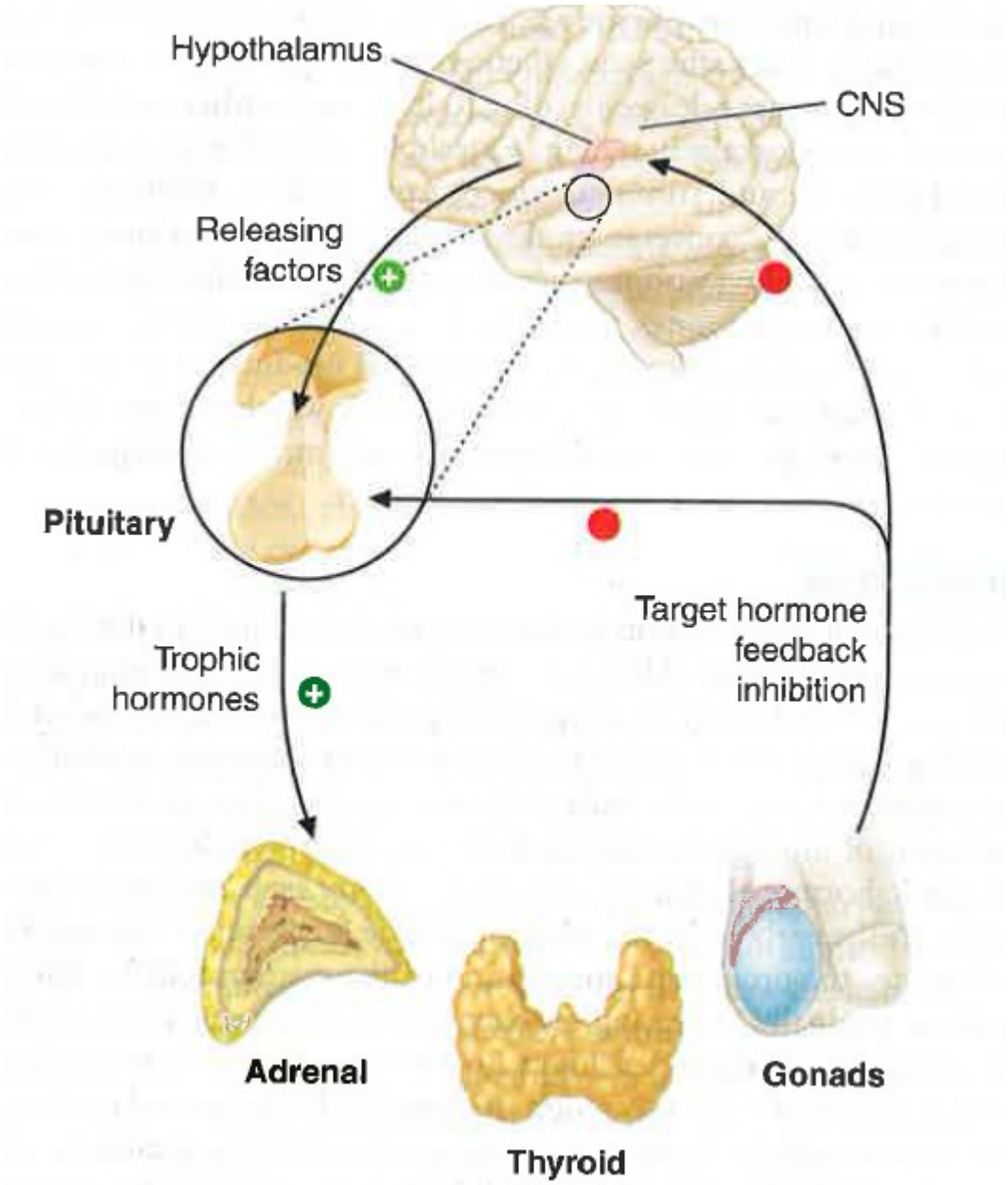

Figure 2

Figure 2 shows the organs affected by the pituitary and the negative feed – back mechanism (6).

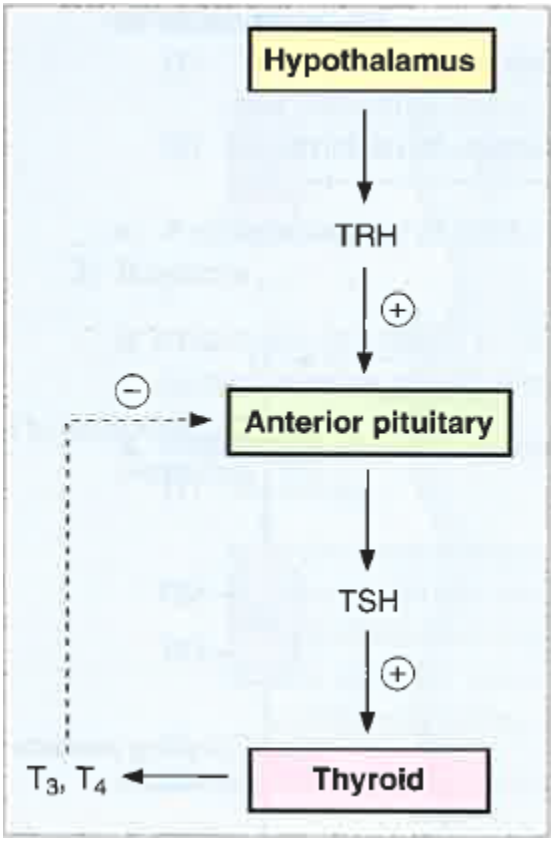

Figure 3

Figure 3 shows the regulation of the level of T3 and T4 (2).

1.4 Patho(physio)logy of thyroidal Dysfunction

There is a wide variety of causes for thyroidal diseases. Absence of iodine, as well as inflammation, various autoimmune processes as well as neoplasm can lead to thyroid dysfunction. Because of the wide distribution of reasons for thyroidal dysfunction, there is also a big field of different treatments.

Iodine deficit

The deficit of iodine in the food and drinking water was a big problem in areas, which have no access to the sea. Therefore people obtained a big lack of iodine supplementation, which mostly lead to mostly euthyroid goitre. People living in sea areas have enough supplementation of iodine due to eating sea food. Euthyroid goitre is endemic in Middle Europe. Euthyroid goitre is defined as an enlargement of the thyroid gland without any sign of an infectious or malignant process (9). The

WHO defines iodine deficiency as an iodine urine clearance of below 100 µg iodine/l. The answer of the thyroid gland to iodine deficiency is to increase the uptake of iodine, the reabsorption of iodine and the syntheses of t3. Otherwise it can also lead to failures in the process of adaption which can be the auto- and paracrine secretion of growth factors, like EGF (Epidermal Growth Factor), IGF (Insulin-like Growth Factor) and TGF (Transforming Growth Factor). Also hyperplasia and proliferation are forms of wrong adaption processes. Normally, endemic goitre leads to little disorders, like having discomfort while absorption of food for example. Wilders – Truschnig et al also suggest a strong involvement of active antigen – presenting cells in the iodine deficient goitre (10), (11), (12), (13). Moreover, Truschnig et al provide evidence that IgG is responsible for Thyroid cell growth in vitro and suggest that autoimmune growth mechanisms may be involved in the pathogenesis of both endemic and sporadic goitres (14). The thyroid function in many thyroid diseases frequently changes from that observed at the onset of disease. Diffuse goitres, which becomes nodular with time may maintain normal hormonal production for many years, but can also be associated with hypothyroidism depending on iodine supply (15), (16), (17), (18). Nowadays, salt is available with added iodine in middle Europe. This fact helped reducing the incidence of iodine deficit caused goitre.

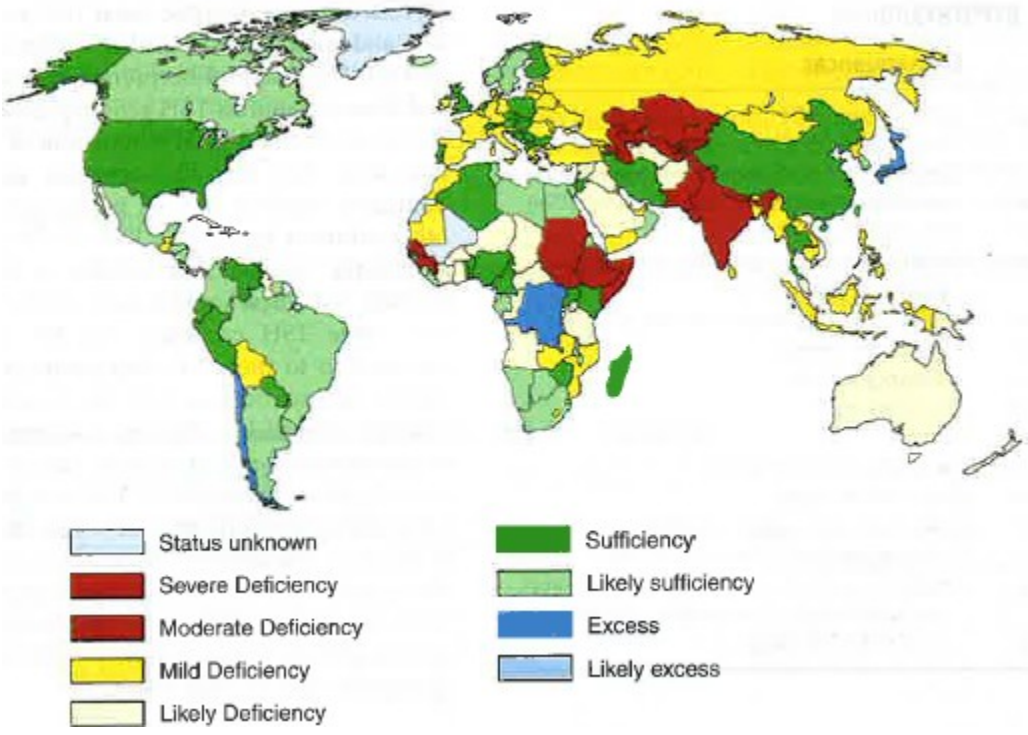

Figure 4

Figure 4 shows the world wide situation of the distribution of iodine in food (6).

Inflammation

Various inflammations can have an effect on the thyroidal function although most of the time, thyroid function does not change during inflammation (9). There are many different forms of thyroiditis caused by various reasons, such as infection, radiation or autoimmune processes for example. The only connection between all these forms is the histological proof of a thyroidal infection.

Neoplasm

There is a wide range of different types of thyroidal cancer (9). This thyroidal disease can be caused by radioactive isotopes, proven by the higher incidence of thyroidal cancer in high exposed areas, like Tschernobyl in Europe. Malignant tumours derived from the follicular epithelium are classified according to histological features (6). Anaplastic thyroidal cancer is aggressive, responds poorly to treatment and has a bad prognosis. As opposed to differentiated tumours, such as papillary thyroid cancer or follicular thyroid cancer, are often curable, and the prognosis is good for patients identified with early – stage disease. In some cases lymphomas and metastases can also be found in the thyroidal gland (9).

1.5 Diseases

Thyroidal diseases can be divided into diseases with thyroidal hyperfunction, hypofunction and euthyroid diseases.
Hyperthyroid diseases include hyperthyroid goitre, Grave's disease, Plummer's disease and some rare forms like hyperthyroidism due to Hashimoto's disease (Hashimoto toxicosis), congenital pituitary resistance to thyroid hormones and TSH – secreting tumours (19).

Grave's Disease

For unknown reason the body produces auto - antibodies, which are able to link to the TSH receptors in the thyroid gland (8). This leads to a constant production of thyroidal hormones. The negative feedback mechanism is switched off. Furthermore, antibodies against thyroidal peroxidise, TPO AB, can be seen. In these patients thyroid – stimulating immunoglobulin circulates in high concentrations. It is characterised by high circulating levels of thyroid hormones and, accordingly, low concentrations of TSH, which is caused by feedback inhibition on the anterior pituitary by thyroid hormones (2). It is characterized by high circulating levels of thyroid hormones and, accordingly, low concentrations of TSH, which is caused by feedback inhabitation of thyroid hormones on the anterior pituitary. The histological picture displays a mononuclear infiltration (9). The clinic of Grave's disease shows a various range of symptoms, although the classical triad is goitre, tachycardia and exophthalm. In more than 60% of all cases grave's disease is associated with endocrine orbitopathy, but only in 30% the thyroid gland is enlarged. In Germany, about 40% of all hyperthyroid diseases are caused by Grave's disease. In some cases also the non - pitting pretibial myxoedema occurs, which is pathognomonic for Grave's disease. The proof of TSH receptor antibodies (TRAK) in the patient's blood sample is characteristic for Grave's disease. Antibodies against the thyroidal peroxidise (TPO) can also be elevated. Normally patients recieve a thyreostatic monotherapy treatment. In cases of bad compliance, patients sometimes get a combination of thyreostatic medication and a substitution of thyroid hormones. After one year the dose of the medication is getting reduced and then completely stopped. About 50% of patients become hyperthyroid again and have to undergo a definitive treatment of Grave's disease, like radioiodine – therapy or a subtotal thyroidektomia.

Primary hyperthyroidism
- Graves' disease
- Toxic multinodular goiter
- Toxic adenoma
- Functioning thyroid carcinoma metastases
- Activating mutation of the TSH receptor
- Activating mutation of $G_{s\alpha}$ (McCune-Albright syndrome)
- Struma ovarii
- Drugs: iodine excess (Jod-Basedow phenomenon)

Thyrotoxicosis without hyperthyroidism
- Subacute thyroiditis
- Silent thyroiditis
- Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
- Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue

Secondary hyperthyroidism
- TSH-secreting pituitary adenoma
- Thyroid hormone resistance syndrome: occasional patients may have features of thyrotoxicosis
- Chorionic gonadotropin-secreting tumors[a]
- Gestational thyrotoxicosis[a]

Figure 5

Figure 5 shows the causes for hyperthyroidism (6).

Symptoms	Signs[a]
Hyperactivity, irritability, dysphoria	Tachycardia; atrial fibrillation in the elderly
Heat intolerance and sweating	Tremor
Palpitations	Goiter
Fatigue and weakness	Warm, moist skin
Weight loss with increased appetite	Muscle weakness, proximal myopathy
Diarrhea	Lid retraction or lag
Polyuria	Gynecomastia
Oligomenorrhea, loss of libido	

[a]Excludes the signs of ophthalmopathy and dermopathy specific for Graves' disease.

Figure 6

Figure 6 shows the main symptoms of hyperthyroidism (6).

Primary hypothyroidism includes chronic autoimmune thyroiditis in the hypothyroid phase (Hashimoto's disease), end-stage Grave's disease, and several late forms of diffuse and nodular goitre (19). Hypothyroidism may also be caused by iodine deficiency, as described above, and very rarely, by a peripheral resistance to thyroid hormones (20).

Hashimoto's disease

This is a type of chronic lymphocytic thyroiditis which can be shown in about 8% of all women over the age of 65 (9). It is an autoimmune disease where lymphocytes and autoantibodies destroy the thyroid tissue. In the result of a fine-needle puncture a lot of lymphocytes and plasmacells can be shown. There are two different types of Hashimoto's disease, on the one hand the classic form which is associated with goitre, and on the other hand the atrophic form. Some patients with Hashimoto's disease show other autoimmune diseases too. In most cases patients neither feel pain from the thyroidal infection nor have general symptoms at the beginning. In very rare cases, patients have a hyperfunction of the thyroid gland at the onset of Hashimoto's disease. In the course of the disease, patients start to show symptoms of the hypofunction of the thyroid gland, for example a gain in weight, constipation and sometimes paraesthesia. As a result of the negative feedback mechanism, hypothyroid patients show strongly elevated basal TSH – levels. It is now clear that Hashimoto´s thyroiditis can remit or progress to hyperthyroidism because of the presence of TSH receptor auto antibodies or because of destructive changes causing excess hormone secretion (21). The result of blood samples show elevated TPO antibodies and the ultrasound is performed to measure the volume of the thyroid gland (9). Also the echogenicity of the thyroid is examined during the ultrasound. Mostly the picture is of low echogenicity. In cases of hypofunction, patients receive a substitution of thyroid hormones but patients with initial hyperfunction of the thyroid gland are treated with Propranolol, a beta - blocker first. The initial therapy with Propranolol has to be checked after several weeks. Thyroid hormones up – regulate beta1 – adrenergic receptors in the heart, like the sympathetic nervous system does (2). Therefore, treatment with a beta – adrenergic blocking agent, such as Propranolol, is a useful adjunct therapy for hyperthyroidism.

Primary

- Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
- Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicyclic acid, interferon-α and other cytokines, aminoglutethimide
- Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
- Iodine deficiency
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis
- Overexpression of type 3 deoiodinase in infantile hemangioma

Transient

- Silent thyroiditis, including postpartum thyroiditis
- Subacute thyroiditis
- Withdrawal of thyroxine treatment in individuals with an intact thyroid
- After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary

- Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
- Isolated TSH deficiency or inactivity
- Bexarotene treatment
- Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Figure 7

Figure 7 shows the causes for hypothyroidism (6).

Symptoms	Signs
Tiredness, weakness	Dry coarse skin; cool peripheral extremities
Dry skin	Puffy face, hands, and feet (myxedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia
Difficulty concentrating and poor memory	Peripheral edema
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Carpal tunnel syndrome
Dyspnea	Serous cavity effusions
Hoarse voice	
Menorrhagia (later oligomenorrhea or amenorrhea)	
Paresthesia	
Impaired hearing	

Figure 8

Figure 8 shows the main symptoms of hypothyroidism (6).

Euthyroid diseases include euthyroid goitre, most tumours, benign as well as malignant, various thyroiditis types including acute and subacute thyroiditis, chronic autoimmune thyroiditis or Hashimoto's disease in the euthyroid phase (22).

1.6 Diagnosis

In general, the basic steps in the diagnosis of thyroidal disorders include physical examination, laboratory evaluation of the thyroidal hormones, radioiodine uptake and thyroid scanning as well as thyroid ultrasound. Every step of diagnosing thyroidal diseases is shown in detail below.

Physical examination is the first step of the evaluation (6). It includes the search for signs of abnormal thyroid function and extrathyroidal features of ophthalmopathy and dermopathy. Each physical examination begins with the inspection of the seated patient from the front side and from the side, noting any surgical scars, obvious masses or distended veins. The thyroid can either be palpated with both hands from behind, or while facing the patient, using the thumbs to palpate each lobe. The combination of both methods is recommended, especially for detecting very small nodes. It is useful to let the patient flex his neck slightly in order to relax the muscles. In this position, the physician gets the best access to the thyroid gland. After locating the thyroid cartilage, the isthmus can be identified and followed laterally to locate each lobe. Normally the right lobe is slightly larger than the left lobe. By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner`s fingers. He should take note of the thyroid size, location and any tenderness or fixation. If nodules are detected, it is necessary to define their size, location and consistency. If the lower borders of the thyroid lobes are not clearly felt, a goitre can be retrosternal. Large retrosternal goitres can cause venous distention over the neck and difficulty in breathing, especially when the arms are raised. This effect is called the Pemberton`s sign. The examination of cervical and supraclavicular lymphoid nodes is also essential in every examination of the thyroid gland.

The measurement of thyroid hormones start with the determination of the level of TSH. Nowadays, immunochemiluminometric assays (ICMA) are used for the

determination of TSH. The high sensitivity of this method is essential to discriminate between the lower limit of the reference range and the suppressed values that occur with thyrotoxicosis. Because TSH levels change dynamically in response to alterations of T4 and T3, it is the logical approach is to first determine whether TSH is suppressed, normal or elevated. Normally, normal levels of TSH exclude a primary abnormality of the thyroidal function. An older method is the TRH suppression test. Because of the widespread availability of TSH ICMA, this method is obsolete today. The TRH suppression test detects the failure of TSH to rise after an intravenous bolus of 200 – 400 µg TRH. If an abnormal range of TSH is occurs, measurements of cycling thyroid hormones must follow to confirm either of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH) as the diagnosis. Radioimunoassays are widely available for the determination of serum total T4 and total T3. T4 and T3 are highly protein – bound, and numerous factors like illness, medication or genetic factors can influence protein binding. This is helping for the measurement of free (unbound) hormone levels. They give information about the biologically available hormone pool. Two direct methods are used for the measurement of unbound thyroid hormones. For the first one, the unbound thyroid hormone competes with radio-labelled T4 to bind to a solid – phase antibody. For the second one, unbound hormone fraction is physically separated by ultracentrifugation or equilibrium dialysis. An indirect method to estimate unbound thyroid hormone levels is to calculate the free T3 or free T4 index from the total T4 or T3 concentration and the thyroid hormone binding ratio (THBR). Total thyroid hormone levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone therapy tamoxifen), and decreased when TBG binding is reduced (androgens, nephritic syndrome). Genetic disorders and acute illness can also lead to abnormalities in thyroid hormone binding proteins, and various drugs (phenytoin, carbamazepine, salicylates and non steroidal anti-inflammatory drugs) can interfere with thyroid hormone binding. Because normally the patient is euthyroid in all these cases and unbound thyroid levels are normal, assays that measure the unbound hormone are preferable to those producing total thyroid hormone levels. In most cases, the unbound T4 level is sufficient to confirm thyrotoxicosis, but 2 – 5% of all patients only show an elevated T3 level, which is called T3 toxicosis. Unbound T3 levels should be measured if a patient shows suppressed TSH but normal unbound T4

levels. In some cases the use of TSH screening tests, especially without simultaneous T4 determination, can lead to mistakes, because any severe clinical illness can cause abnormal TSH levels. Rare causes for elevated TSH level can be a TSH – secreting pituitary tumour, thyroid hormone resistance and assay artefact. Suppressed levels of TSH, particularly < 0,1 mU/L, can also be seen in patients after the treatment of hyperthyroidism (because TSH can remain suppressed for several months) and in response to certain medications (in example, high doses of glucocorticoids or dopamine). Low levels of TSH can also occur during the first trimester of pregnancy, due to hCG secretion. Importantly, secondary hypothyroidism, caused by hypothalamic – pituitary disease, is associated with a variable (low to high – normal) TSH level, which is inappropriate for the low T4 level. In patients with suspected or proven pituitary disease, TSH should not be used to asses thyroid function.

1.7 Metabolic syndrome

Thyroid dysfunction may contribute to atherogenic lipid profile alterations, endothelial dysfunction, hormonal and hemodynamic changes and coagulation disturbances (23), (24). It is hypothesised that the family of thyroid hormone receptors (TR), which are ligand – binding transcription factors, mediate these effects via T3 (25). Gene expression via TR / T3 includes at least 149 genes of the lipid and glucose metabolism, cell cycle, inflammation and stress response. In contrast, Kim et al reported that serum fT4 levels and presence of metabolic syndrome were not associated after adjustment for age in euthyroid subjects (26). The metabolic syndrome is characterized by an accompanied systemic low grade inflammation, e.g. elevated C – reactive protein (CRP), interleukine 6 (IL – 6), tumour necrosis factor (TNF), and oxidative stress by radical oxygen species (ROS). Thyroid cells produce a number of pro – inflammatory molecules which will tend to exacerbate the autoimmune process (27). In hypothyroid patients, inflammatory markers, especially CRP have been associated with thyroidal dysfunction and related cardiovascular risk (28), (29), (30). Ozcan et al found in a current study increased CRP levels in patients with subclinical hypothyroidism, which decreased during replacement therapy to a level comparable to controls (31). An inflammatory status and oxidative stress further contributes to atherogenic

lipid alterations, e.g. lipid peroxidation of low density lipoproteins (LDL). Hypothyroidism is frequently associated with hypercholesterolemia and carries an increased risk for atherosclerosis. In contrast to hypothyroidism, hyperthyroidism has not been associated with increased LDL cholesterol, but is associated with increased oxidized LDL (32). A study by Roos et al showed an association between subclinical hypothyroidism and hyperlipidemia (33). Iqbal et al also found a positive correlation between TSH and increased total cholesterol and LDL cholesterol in subclinical hypothyroid patients (34). However, this correlation remained not significant when adjusted for BMI. The impact of BMI, especially obesity in thyroidal dysfunction has been investigated, but reveals no conclusive results to date. Obesity, beyond other dysfunctions contributes to an atherogenetic lipid profile as well as to insulin resistance, independent of thyroidal dysfunction. Iacoballis et al found an association between TSH, BMI and the adipocytokine leptin in uncomplicated obese women (35). Obermayer – Pietsch et al showed a direct influence of thyroid hormones on leptin regulation (36). In morbidly obese euthyroid patients, fT3 and TSH levels were found to be significantly increased compared to non – obese probands (37). De Pergola et al found a direct association between fT3, TSH and waist circumference in overweight and obese euthyroid women (38). Tagliaferri et al found, that in obese subclinical hypothyroid patients, only elevated TSH levels affected metabolism, without changes in body composition or lipid profile (39). Manji et al reported no association between BMI, TSH and fT4 in euthyroid patients and no differences in TSH and fT4 levels between lean and obese subjects (40). In a large population study with euthyroid patients, Knudsen et al found an association between TSH and BMI, further a negative correlation between BMI and fT4 levels but no correlation between BMI and fT3 (41). In another population based study, Nyrnes et al confirmed these findings, as they also showed an association between TSH and BMI (42). Interestingly, this association was only seen in non – smokers, but not in smokers. Regular exercise has been shown to have effects on the prevention for chronic diseases, like type 2 diabetes, atherosclerosis and colon and breast cancer (43), (44). Arikawa et al found out that exercise significantly decreases CRP levels in the exercise group compared to the non – exercise control group, and this effect was largely driven by changes in the CRP that occurred in the obese exercisers (45). They demonstrated that 16 weeks of aerobic exercise programme

significantly changes the levels of CRP in young women, especially in the obesed ones. Silvera et al found out that obese children and adolescents, with higher intra – abdominal adipose tissue (IAAT) are more prone to develop metabolic syndrome and non – alcoholic fat liver disease (NAFLD) than those with higher values of sub - cutanouse adipose tissue (SCAT), independent of possible confounding variables (46). Literature has shown that insulin resistance plays the important key role in the genesis of the NAFLD and also components of metabolic syndrome (47). This occurs mainly in subjects with present abdominal obesity. Silveira et al indicated in their results that IAAT was more important than SCAT in the genesis of the metabolic syndrome and NAFLD (48). This opinion is also supported by the findings of Després and Huang (47), (49). They suggest that not just the amount of total body fat, but moreover the distribution of excessive adipose tissue seems to determine the development of comorbidities. Therefore abdominal obesity is more dangerous to human health than subcutaneous adipose tissue. It is already proven that adulthood health is affected by risk factors which may determine cardiovascular diseases, such as dyslipidemia, type II diabetes and hypertension at early age (50), (51), (52). It is essential to detect these risk factors in order to prevent or treat obesity. Taken together, there is substantial evidence for an interaction of thyroid disease and obesity, however results are in part conflicting. Obesity is further accompanied by increased insulin resistance, which additionally contributes to the metabolic syndrome.

1.7.1 Glucose metabolism

In the glucose metabolism, insulin on the one hand and glucagon on the other hand, play a very important role in the regulation of a person`s blood glucose level (53). The endocrine pancreas is organized into three major cell types, the beta-, alpha-, and delta – cells. The other cells secrete pancreatic polypeptide. Gap junctions link beta cells to each other, alpha cells to each other, and beta cells to alpha cells for rapid communication. The portal blood supply of the islets allows blood from the beta cells, which are containing insulin, to bathe the alpha and delta cells, again for rapid cell – to – cell communication. Beyond fasting glucose and insulin, the HOMA – Index (homeostasis model assessment index) is used to investigate a patient´s risk for insulin resistance and prediabetic status. In detail, the HOMA – index is calculated as followed:

HOMA-Index = insulin (fasting, µU/ml) x glucose (fasting, mg/dl) / 405
or
HOMA-Index = insulin (fasting, µU/ml) x glucose (fasting, mg/dl) / 22,5.
The glucagon secretion is regulated by the bold glucose concentration. Decreased blood glucose leads to glucagon secretion. Glucagon itself has effects on the liver and adipose tissue via second messenger cAMP. Glucose increases the blood glucose concentration through increasing glucogenolysis and increasing gluconeogenesis. Glucagon increases blood fatty acid and ketoacid concentration. Glucagon increases urea production, because amino acids are used for gluconeogenesis, which is stimulated by glucagon, the resulting amino groups are incorporated into urea.

Factors that Increase Glucagon Secretion	Factors that Decrease Glucagon Secretion
↓ Blood glucose	↑ Blood glucose
↑ Amino acids (especially arginine)	Insulin
CCK (alerts alpha cells to a protein meal)	Somatostatin
Norepinephrine, epinephrine	Fatty acids, ketoacids
ACh	

ACh = acetylcholine; CCK = cholecystokinin.

Figure 9

Figure 9 shows the factors influencing the secretion of glucagon (53).

Proinsulin is synthesized as a single – chain peptide. When insulin is needed, proteases remove the connecting peptide, which is called C – peptide. The concentration of C – peptide is used to monitor beta cell function in diabetic patients who are receiving exogenous insulin, because the C – peptide is packaged and secreted along with insulin. Insulin secretion is mainly regulated by the blood glucose concentration. High levels of blood glucose lead to increasing insulin secretion. An initial burst of insulin is followed by sustained secretion. Insulin down – regulates its own receptors in target tissues. This is the reason, why the number of insulin receptors rises in starvation and decreases in obesity. Insulin acts on the liver, adipose tissue and muscle. It decreases blood glucose concentration, blood fatty acid and ketoacid concentration, blood K+ concentration,

as well as blood amino acid concentration. Thus, insulin is anabolic. The mechanisms for decreasing blood glucose concentration are various. First, it increases uptake of glucose into target cells by directing the insertion of glucose transporters into cell membranes. As glucose enters the cells, the blood glucose concentration decreases. Second, it helps forming glucogen from glucose in muscle and liver, and simultaneously inhibits glycogenolysis. Third, it decreases gluconeogenesis because it increases the production of fructose 2,6 – bisphosphate and thereby increasing phosphofructokinase activity. In effect, substrate is directed away from glucose formation.

Factors that Increase Insulin Secretion	Factors that Decrease Insulin Secretion
↑ Blood glucose	↓ Blood glucose
↑ Amino acids (arginine, lysine, leucine)	Somatostatin
↑ Fatty acids	Norepinephrine, epinephrine
Glucagon	
GIP	
Ach	

ACh = acetylcholine; GIP = glucose-dependent insulinotropic peptide.

Figure 10

Figure 10 shows the factors influencing the secretion of insulin (53).

Adipose tissue has an endocrine function for the production multiple adipokines causing inflammatory process and insulin resistance (47), (54), (55). Visceral adipose tissue has increased atherosclerotic capacity because particularly adipose tissue located in the abdominal region is related to higher lipolysis and higher release of adipokines (47). Abdominal fat also produces a high amount of adipokines, such as tumor necrosis factor – alpha and interleukine – 6 (56). They have a strong relation to insulin resistance. Tumour necrosis factor – alpha has an effect on insulin metabolism cascade, activating proinflammatory pathways that impair insulin signalling at the level of the insulin receptor substrate proteins, causing insulin resistance. Tumour necrosis factor – alpha inhibits the expression of adiponectin, which leads to an elevation in serum free fat acid by stimulation of

hepatic lipogenesis and lipolysis, contributing for insulin resistance and may lead to the development of non – alcoholic fat liver disease (47), (54), (57). Investigations on thyroidal dysfunction related alterations in the glucose metabolism reveal completely puzzling results. Interestingly, in the study by De Pergola, the observed association of thyroid parameters with obesity was not associated with insulin resistance, metabolic parameters or blood pressure (38). In contrast, a current study by Maratou et al clearly showed that not only in hypothyroid patients, but also in patients with subclinical hypothyroidism, insulin resistance was observed (58). Moreover, when determining insulin secretion and insulin sensitivity in hypothyroid patients some studies reveal no differences (59), (60), others found decreased (61) and also increased rates are described (58). Beyond hypothyroidism, hyperthyroidism has also been implicated in affecting insulin secretion and glucose metabolism. However, results are also controversial as some studies found no differences (62), (63), or increased (64), (65), (66), (67), (68) and even decrease rates (69), (70). Different findings in the above mentioned studies may at least in part be due to different study settings regarding age, BMI as well as gender (71).

1.7.2 BMI and age

The body – mass – index, also called BMI, is an important index for evaluation and comparison of a patient´s body composition. In spite of presenting several limitations, BMI is the most widely used and accepted index for classifying overweight and obesity (72). Wallner – Liebmann et al suggest to use measurements of the subcutanouse fat tissue for comparison of fat distribution between subjects (73). They compared BMI and subcutaneous fat pattern in young athletes and non – athletes. When adjusted to BMI, athletes showed less sub cutanouse fat then athletes. Besides the BMI, also parameters like waist – to – hip – ratio, waist – to – length – ratio and waist circumference give clues about metabolic disorders. All these parameters have been analyzed in the study and are shown in detail below. We also used the lipometry, as also shown by Wallner – Liebmann et al, to compare the exact distribution of subcutaneous fat. Moon et al found out that in euthyroid men, low levels of fT3 and fT4 were significantly associated with increased pericardial fat volume and BMI (74).

1.7.3 Blood Pressure

Hypertension in adults is a widely spread problem in the western civilisation. Therefore, several studies have shown that hypertension in adults has its onset in childhood, which is resulting in increasing concern with monitoring the blood pressure in children (75), (76). Both, in children and adolescent, the prevalence of high blood pressure has been increasing (77), (78), (79), (80). Increased blood pressure in children increases the prevalence of hypertension and also hypertension – related diseases like cardiovascular diseases in later adulthood (78), (81). Due to these findings, an early detection and intervention in children with elevated blood pressure is an important action for controlling and preventing hypertension in adulthood. Zhang et al formed groups of adolescent with normal weight, overweight and obesity by using the BMI (82). They observed for both, girls and boys, an increasing trend in systolic and diastolic blood pressure, and the prevalence of high blood pressure from the normal weight group to the overweight and obese groups. Compared to general obesity, central obesity seems to be more strongly associated with cardiovascular risk factors (83), (84), (85). Various studies have shown that increasing free fat acid in the circulation leads to increasing formation of low density lipoproteins (LDL) and very low density lipoproteins (VLDL) as well as the reduction of high density lipoproteins (HDL) and very high density lipoproteins (VHDL), which results in atherosclerosis and elevation of blood pressure (86), (87). In two large populations of elderly probands, van der Deure et al revealed no correlation between thyroid parameters and blood pressure or the presence of hypertension (88). Their data suggests that thyroid function is no important determinant of hypertension. In contrary, serum TSH – levels were positively associated with the prevalence of hypertension in several population – based cohort studies, but the associations were minimal, with a rise of about 6 mmHg in systolic blood pressure within the reference range of serum TSH (89), (90). Gumieniak et al showed that lower fT4 and higher basal TSH are associated with hypertension in euthyroid subjects and additionally, fT4 has a stronger relationship with hypertension than TSH (91).

1.7.4 Smoking and metabolic syndrome

Several studies have shown an association between smoking behaviour and weight (92), (93), (94). People who are overweight and trying to reduce weight are

more likely to start smoking (95), (96). Chiolero et al found out that overweight adults who already have a history of dieting are more likely to start smoking (97). The majority of smokers started smoking during their adolescence (98). In adolescence, mainly body weight concerns and dieting behaviours are the strongest reasons for starting to smoke, especially for girls (95), (96). Regarding younger smokers, some studies revealed no association between smoking and weight, whereas regarding older smokers, heavy smoking may also be associated with higher weight (99), (100), (101). This idea is also supported by some studies who found out that light smokers mainly weight less, while heavy smokers tend to weight more (100), (101), (97). Some studies support the idea that the weight protective effect of smoking may only be restricted to long – term smokers and light smokers (99). Mackay et al revealed no significant dose – relationship between the number of cigarettes smoked daily and the risk of being obese along current smokers (102). The aim of their study was to explore the effects of active smoking and smoking cessation on overweight and obesity. They also wanted to know the effects of smoking duration, smoking dose and the time from quitting smoking. They revealed that the risk of being obese is higher in people who had required three or more quit attempts even after adjusting for time from cessation, than in people who succeeded to quit smoking after only one or two attempts. Just in some older adults there was association between reduced risk of being overweight and smoking, but there was no evidence that smoking protects from being overweight for younger people. In vivo animal experiments suggest that the application of nicotine can reduce weight, even without reducing calorific intake (92), (97), (103). This may be through less efficient absorption and storage of calories and an increased metabolic rate and thermogenesis resulting in an increased effort for energy. Also metabolic, sensory and behavioural pathways have been considered being possible reasons by which active smoking is able to reduce weight (104), (105), (106), (107). In opposite, smoking can also influence weight distribution which leads to central fat accumulation (97), (108). This is a strong risk factor for the development of metabolic syndrome, diabetes and cardiovascular disease.

1.8 Summery

In summary, thyroid diseases display a wide variety of different disorders, including inflammatory and hormonal diseases of the thyroid gland, autoimmune diseases and malign and benign tumours. Moreover, thyroidal dysfunction varies dependent on the stage of the disease, resulting in hypo-, hyper- and euthyroid function. Thyroid hormones are essential for a normal living, and are especially required during growing up and for developing normal mental skills. Testing and screening for thyroidal dysfunction normally starts with the determination of TSH levels and is followed as outlined in the algorithms above, due to the result of TSH level testing. Varies studies about metabolic syndrome, glucose metabolism and thyroid parameters showed connections, whereas other studies revealed no significant correlation.

1.9 Hypothesis

We here hypothesise that there is a connection between thyroidal dysfunction and patients´ metabolic risk, especially on obesity – related dysfunction.

1.10 Aims

Thyroidal dysfunctions display a wide variety of diseases, like inflammatory and autoimmune diseases. Moreover, thyroidal dysfunctions are also discussed to be involved in obesity and related metabolic risk. The aim of the present study is to investigate the connection between thyroidal disorders and metabolic syndrome, as well as glucose metabolism. This is achieved by investigating patients with thyroidal dysfunctions and healthy controls in the clinical pilot study NOTHYS as part of the FWF (Fonds zur Förderung der wissenschaftlichen Forschung) Project. The clinical trial pilot study NOTHYS is designed to investigate various metabolites and biomarkers in pre and post treated patients with thyroid dysfunctions and healthy controls. In detail, parameters of thyroid function, inflammation, lipid profile, glucose metabolism and hormones will have been analyzed in hyper-, eu- and hypothyroid patients as well as in healthy controls. Additionally, body measurements including lipometry and oral glucose tolerance test was performed. Due to the high prevalence of metabolic disorders in the modern industrialized

civilization, a better understanding is essential for improving treatment for patients showing symptoms of metabolic disorders.

2 Methods

2.1 Study design

Patients have been recruited when visiting the Department of Endocrinology of the Medical University Graz. Patients with possible thyroid dysfunction have been diagnosed by an endocrinologist and have been invited to participate the study. Healthy age and gender matched volunteers have also been examined by an endocrinologist. All probants participating the study have been anonymized by coding with identification numbers. The study was approved by the Ethics Committee of the Medical University Graz

2.2 Study cohort

The study cohort consists of 184 people. Patients have been sub grouped depending on their thyroid function into hyper- hypo- and euthyroid. The group of euthyroid patients is defined as all the patients with thyroid dysfunction, who did already get thyroid medication and reached again normal blood levels of thyroid parameters in blood sampling. The mean age was between 24 and 52 years. Patients and probands have been matched in sex, age and BMI. In detail, the study cohort includes 92 healthy controls, 11 hyperthyroid patients, 28 hypothyroid patients and 53 euthyroid patients. For routinely diagnostic procedures, every patient and proband was evaluated by thyroid ultrasound and also, if necessary, by fine needle punction. They all have been seen by a specialist for endocrinology and blood and urine sampling was taken. We also did body measurements, including length and weight measurements, and the measurement of the subcutaneous fat distribution by using the lipometer. Further, lifestyle behaviour like smoking, alcohol consumption and physical activity as well as possible further medications like for example hormonal contraceptives have been questioned.

2.3 Exclusion criteria

The exclusion criteria of this study are: malignant thyroid disease, pregnancy, nursing mothers, chronic illness, medication affecting thyroid parameters, concurrent infections as well as diabetes.

2.4 Laboratory analyses

All thyroid parameters, including TSH basal, ft3, ft4, as well as autoimmune antibodies TPO AB, TRAK and PTHi, have been analysed routinely by the Endocrinology Laboratory, Department of Endocrinology and Metabolism, Medical University Graz. Also the parameters of glucose metabolism, glucose, insulin, and c-peptide, have been analyzed routinely. All of these parameters have been analyzed out of fasting blood samples.

2.5 Lipometry

The lipometer is a computerised optical system for precise measurement of absolute subcutaneous adipose tissue in mm (109), (110), (111), (112), (113). There are 15 well defined anatomical parts all over the body, which allows the comparison of the subcutaneous adipose tissue distribution. The distribution of the subcutaneous adipose tissue is like a fingerprint, which allows the creation of fat distribution profiles such as „apple like“ or “pear like” body fat distribution, which are associated with metabolic risk. The lipometer was evaluated and programmed by using computer tomography pictures as reference. Beyond lipometry, height, weight, waist- and hip- circumference as well as blood preassure were additionally determined.

2.6 Clinical safety parameters

To determine the general state of health the following parameters will be determined routinely at the KIMCL (klinisches Institut für medizinische und chemische Labordiagnostik) including Hemogram, Electrocytes (Potassium, Phosphate, Sodium, Chloride, Calcium, Magnesium), Kidney (Creatinine, Urea, Uric acid), Liver (Bilirubin, Alkaline phosphatise, Gamma-glutamyltransferase, Aspartate-amino-transferase, Alanine-amino-transferase, Cholin esterase), Heart (Lactate dehydrogenase, Creatine kinase), Pancreas (P-amylase, Lipase); Serum proteins (Total protein, Albumin, Immunoglobulin (Ig)-G, Ig-A, Ig-M, Ig-E), Iron-Metabolism (Iron, Transferrin, Ferritin), Uretic parameters (Leukocytes, pH, Protein, Glucose, Ketone, Erythrocyte, Bilirubin, Hemoglobin, Albumin, Creatinine, Osmolarity).

2.7 Interpretation

The pilot study NOTHYS was a prospective study to investigate the pathophysiology of thyroidal dysfunction. Hypothesis have been generated and evaluated by explorative data analyses. Clinical parameters have been analysed in patients with thyroid disease, with hyper-, hypo- and euthyroid dysfunction, as well as in healthy, age- and gender matched controls. The number of cases was based on comparable studies. Data were recorded in an SPSS data base according to the guidelines of the “Österreichisches Datenschutzgesetz 2000”. In detail, test variables have been compared between healthy volunteers and patients with hyper-, hypo- and euthyroid dysfunction to identify thyroid disease specific parameters. This is achieved by statistical analyses using chi2-Test, Student`s t-Test and Mann-Whitney-U-Test, depending on the distribution of data. Additionally, correlation analysis and multiple modelling were performed to investigate the underlying pathophysiological mechanisms. Depending on the distribution of data, correlation analyses by linear regression according to Pearson or Spearman have been performed, as well as partial correlation analysis.

3 Results

3.1 Relative distribution of patients in the study cohort

The relative distribution of patients in the study cohort is shown in Figure 1. The study cohort consists of 68% females and 32% males. These two groups are divided into four subtypes. These subtypes are healthy controls, hyperthyroid probands, hypothyroid probands and euthyroid probands. The study cohort consists of 34% healthy females, 5% hyperthyroid females, 12% hypothyroid females, 17% euthyroid females, 16% healthy males, 1% hyperthyroid males, 3% hypothyroid males and 12% euthyroid males.

Table 1
Baseline characteristics of the study cohort

	Controls	Hyperthyroid	Hypothyroid	Euthyroid
Sex (f/m)	63/29	10 /1	22 / 6	31/22
Age (years)	36,6 ± 11,4	40,8 ± 8,5	34,5 ± 9,8	40,5 ± 12,2^{*2}
Smoker (n/y)	74/18	8/3	25/3	37/16
Physical Activity [hours/week]	4,10 ± 4,89	1,27 ± 1,72	3,75 ± 5,74	3,25 ± 7,73
Body length (cm)	170,7 ± 8,0	170,4 ± 5,5	168,3 ± 7,6	172,6 ± 7,4^{*2}
Body weight (kg)	70,56 ± 13,4	71,12 ± 14,91	69,26 ± 15,72	75,70 ± 15,03^{*1}
BMI (kg/m²)	24,24 ± 4,21	24,40 ± 4,56	24,24 ± 4,31	25,27 ± 4,15
Waist circumference (cm)	84,17 ± 10,71	87,27 ± 11,07	83,96 ± 12,99	90,07 ± 11,53^{*2}
Waist-to-hip ratio	0,844 ± 0,07	0,88 ± 0,08	0,85 ± 0,08	0,89 ± 0,08^{*1,2}
Waist – to - length ratio	0,97 ± 4,62	0,51 ± 0,06	0,49 ± 0,07	0,51 ± 0,06
Systolic BP (mmHg)	118 ± 12	121 ± 12	124 ± 13	127 ± 19^{++1}
Diastolic BP (mmHg)	74,48 ± 9,37	72,18 ± 7,18	79,77 ± 7,65^{*1,3}	79,13 ± 10,47^{*1,3}

* p<0,05 (parametric T-test); $^{++}$ p<0,01 (non parametric Mann-Whitney U test); 1 compared to controls; 2 compared to hypothyroid; 3 compared to hyperthyroid

3.2 Baseline characteristics of study cohort

Table 1 describes the mean distribution of body meassurements in the study cohort. Age distribution is quite similar along the four groupes: controls 36,6 ± 11,4, hyperthyroid 40,8 ± 8,5, hypothyroid 34,5 ± 9,8 and euthyroid 40,5 ± 12,2. A

significant difference was only found between euthyroids and hypothyroids. In the controls, there have been 18 of 74 smokers, in hyperthyroid 3 of 8, in hypothyroid 3 of 25 and in euthyroid 16 of 37. Patients and controls have been matched in age, gender and BMI: Due to this matching, no significant distribution was found in BMI. BMI was in controls 24,24 ± 4,21, in hyperthyroid 24,40 ± 4,56, in hypothyroid 24,24 ± 4,31 and in euthyroid 25,27 ± 4,15. Physical activity was meassured in hours per week. In controls it was 4,10 ± 4,89, in hyperthyroid 1,27 ± 1,72, in hypothyroid 3,75 ± 5,74 and 3,25 ± 7,73 in euthyroid. Body lenght distribution was 170,7 ± 8,0 in controls, 170,4 ± 5,5 in hyperthyroid, 168,3 ± 7,6 in hypothyroid and 172,6 ± 7,4 in euthyroid. There was found a significant difference in the body lenght between euthyroid and hypothyroid. In controls, body weight was 70,56 ± 13,4, in hyperthyroid 71,12 ± 14,91, in hypothyroid 69,26 ± 15,72 and 75,70 ± 15,03 in euthyroid. It was a significant difference in bodyweight between euthyroid and controls. Waist circumference was 84,17 ± 10,71 in controls, 87,27 ± 11,07 in hyperthyroid, 83,96 ± 12,99 in hypothyroid and 90,07 ± 11,53 in euthyroid. We found a significant difference between euthyroid and hypothyroid in waist circumference. Difference was also found in waist-to-hip ratio. In controls, waist-to-hip ratio was 0,84 ± 0,07, in hyperthyroid 0,88 ± 0,08, in hypothyroid 0,85 ± 0,08 and 0,89 ± 0,08 in euthyroid. Significant difference occured between euthyroid and controls on the one hand, and between euthyroid and hypothyroid on the other hand. Waist-to-lenght ratio was in controls 0,97 ± 4,92, in hyperthyroid 0,51 ± 0,06, in hypothyroid 0,49 ± 0,07 and in euthyroid 0,51 ± 0,06. Systolic blood preassure was 118 ± 12 in controls, 121 ± 12 in hyperthyroid, 124 ± 13 in hypothyroid and 127 ± 19 in euthyroid. Highly significant difference was found in systolic blood preassure between euthyroid and controls. Diastolic blood preassure was 74,48 ± 9,37 in controls, 72,18 ± 7,18 in hyperthyroid, 79,77 ± 7,65 in hypothyroid and 79,13 ± 10,47 in euthyroid. Significant difference occured between hypothyroid and controls as well as between hypothyroid and hyperthyroid. We also found a significant difference between euthyroid and controls on the one side, as well as between euthyroid and hyperthyroid.

Table 2
Thyroid parameters of the study cohort

	Controls	Hyperthyroid	Hypothyroid	Euthyroid
TSH basal (µUnits/ml)	2,08 ± 0,78	0,02 ± 0,02$^{+++1,2}$	7,83 ± 7,08$^{+++1,3}$	1,68 ± 1,05$^{+++1,2,3}$
ft3 (pmol/l)	5,07 ± 0,61	8,08 ± 4,75	4,79 ± 0,60	4,95 ± 0,55
ft4 (pmol/l)	13,94 ± 1,92	19,76 ± 13,60^{+1}	13,76 ± 2,39	15,03 ± 2,13
TPO AB (U/ml)	8,42 ± 3,58	494 ± 782^{+++1}	317 ± 420^{+++1}	179 ± 447$^{+++1,+3}$
TRAK (U/l)	0,52 ± 1,08	189± 234$^{+++1,2}$	2,71 ± 6,73	3,82 ± 9,26$^{++1,+++3}$
PTHi (pg/ml)	34,37 ± 9,38	33,65 ± 14,34	33,52 ± 8,15	37,91 ± 14,40

$^{+}$ p<0,05 (non parametric Mann-Whitney U test); $^{++}$ p<0,01(non parametric Mann-Whitney U test);
$^{+++}$ p<0,001(non parametric Mann-Whitney U test); 1 compared to controls; 2 compared to hypothyroid; 3 compared to hyperthyroid

3.3 Thyroid parameters of the study cohort

The mean distribution of thyroid parameters in the study cohort is shown in Table 2. Basal TSH Level in µUnits/ml was 2,08 ± 0,78 in healthy controls, 0,02 ± 0,02 in hyperthyroid, 7,83 ± 7,08 in hypothyroid and 1,68 ± 1,05 in euthyroid. A significant difference was found between hyperthyroid and controls, as well as between hyperthyroid and hypothyroid. We also found significant differences between hypothyroid and controls, also in euthyroid and controls, euthyroid and hypothyroid and euthyroid and hyperthyroid. In the study cohort, the ft3 level was measured in pmol/l. It was 5,07 ± 0,61 in controls, 8,08 ± 4,75 in hyperthyroid, 4,79 ± 0,60 in hypothyroid and 4,95 ± 0,55 in euthyroid. Ft4 level, also in pmol/l was 13,94 ± 1,92 in controls, 19,76 ± 13,60 in hyperthyroid, 13,76 ± 2,39 in hypothyroid and 15,03 ± 2,13 in euthyroid. There was a significant difference in ft4 level only between hyperthyroid and controls. In controls, TPO AB ,in U/ml, were 8,42 ± 3,58, in hyperthyroid 494 ± 782, in hypothyroid 317 ± 420 and in euthyroid 179 ± 477. Wide difference of TPO AB occurred between hyperthyroid and controls, hypothyroid and controls as well as euthyroid and controls. There was also found a significant difference in TPO AB between euthyroid and hyperthyroid. TRAK level in U/l was 0,52 ± 1,08 in healthy controls, 189 ± 234 in hyperthyroid, 2,71 ± 6,73 in hypothyroid and 3,82 ± 9,26 in euthyroid. We found wide differences between hyperthyroid and controls, hyperthyroid and hypothyroid, as well as euthyroid and hyperthyroid. There was also a significant difference between euthyroid and controls. PTHi in pg/ml was 34,37 ± 9,38 in controls, 33,65 ± 14,34

in hyperthyroid, 33,52 ± 8,15 in hypothyroid and 37,91 ± 14,40 in euthyroid. Along this parameter, no significant differences occurred in the groups of the study cohort.

Table 3
Parameters of the glucose metabolism in healthy controls and thyroid dysfunction patients

	Controls	Hyperthyroid	Hypothyroid	Euthyroid
Glucose (mg/dl)	89,53 ± 20,77	86,82 ± 9,85	86,44 ± 9,66	87,40 ± 12,61
Insulin (µU/ml)	5,36 ± 6,91	6,79 ± 3,48	6,28 ± 3,45	7,43 ± 9,11
C - Peptid (ng/ml)	1,65 ± 1,15	1,54 ± 0,60	1,61 ± 0,75	1,45 ± 1,05
HOMA Index	1,18 ± 1,46	1,48 ± 0,80	1,35 ± 0,96	1,65 ± 2,1

3.4 Parameters of glucose metabolism in healthy controls and thyroid dysfunction patients

Table 3 presents the spreading of parameters of glucose metabolism along the study cohort. Glucose, in mg/dl was 89,53 ± 20,77 in controls, 86,82 ± 9,85 in hyperthyroid, 86,44 ± 9,66 in hypothyroid and 87,40 ± 12,61 in euthyroid. These glucose parameters are fasting glucose parameters. Insulin level, in µU/ml was 5,36 ± 6,91 in controls, 6,79 ± 3,48 in hyperthyroid, 6,28 ± 3,45 in hypothyroid and 7,43 ± 9,11 in euthyroid. C-Peptide, measured in ng/ml was 1,65 ± 1,15 in controls, 1,54 ± 0,60 in hyperthyroid, 1,61 ± 0,75 in hypothyroid and 1,45 ± 1,05 in euthyroid. HOMA Index was 1,18 ± 1,46 in healthy controls, 1,48 ± 0,80 in hyperthyroid, 1,35 ± 0,96 in hypothyroid and 1,65 ± 2,10 in euthyroid. There was found no significant difference in any of these parameters of the glucose metabolism between the four groups.

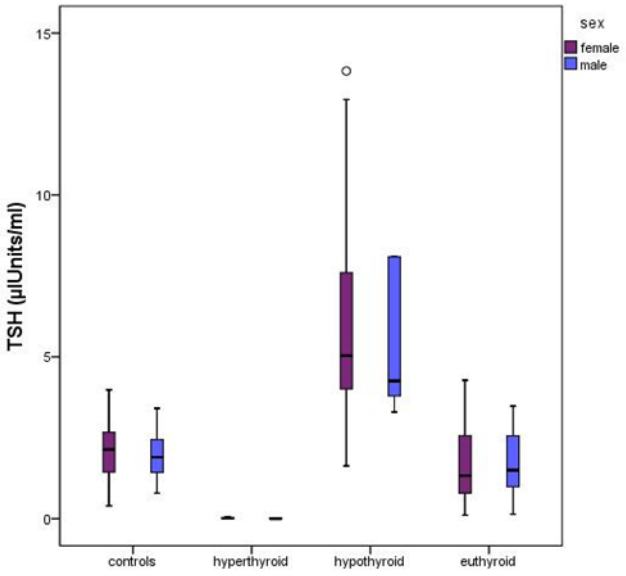

Figure 11
Figure 11 shows Box and Whisker Blot of TSH in various groups and between male and female.

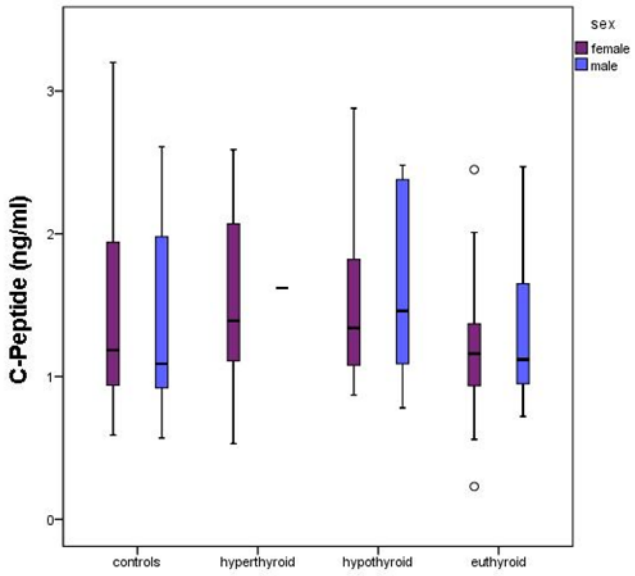

Figure 12
Figure 12 shows Box and Whisker Plot of c – peptide.

	Controls		Hyperthyroid		Hypothyroid		Euthyroid	
single linear regression analyses of TSH	Regression	Significance	Regression	Significance	Regression	Significance	Regression	Significance
Physical Activity [hours/week]	0,033	0,756	0,354	0,286	0,167	0,405	0,074	0,6
Body lenght [cm]	0,04	0,706	0,005	0,383	0,019	0,323	0,132	0,347
Body weight [kg]	0,08	0,451	0,163	0,631	0,153	0,428	0,183	0,19
BMI [kg/m²]	0,04	0,704	0,163	0,619	0,183	0,362	0,168	0,23
Waist circumference [cm]	0,086	0,416	0,109	0,749	0,09	0,655	0,122	0,384
Waist-to-hip ratio	0,136	0,199	0,205	0,546	0,073	0,717	0,025	0,861
Waist - to - length ratio	0,048	0,654	0,097	0,777	0,114	0,573	0,109	0,437
Systolic BP [mmHg]	0,072	0,5	0,255	0,443	0,135	0,351	0,197	0,158
Diastolic BP [mmHg]	0,031	0,339	0,038	0,773	0,038	0,64	0,146	0,235
Glucose [mg/dl]	0,232	0,028	0,002	0,394	0,032	0,874	0,01	0,343
Insulin [µU/ml]	0,17	0,108	0,062	0,856	0,098	0,627	0,284	0,039
C - Peptid [ng/ml]	0,31	0,003	0,147	0,666	0,102	0,612	0,217	0,118
HOMA Index	0,131	0,214	0,014	0,367	0,093	0,644	0,285	0,038
single linear regression analyses of T3	Regression	Significance	Regression	Significance	Regression	Significance	Regression	Significance
Physical Activity [hours/week]	0,134	0,065	0,063	0,853	0,105	0,602	0,023	0,87
Body lenght [cm]	0,243	0,02	0,106	0,755	0,144	0,473	0,435	0
Body weight [kg]	0,133	0,209	0,013	0,369	0,263	0,185	0,373	0,005
BMI [kg/m²]	0,018	0,869	0,057	0,868	0,424	0,028	0,196	0,16
Waist circumference [cm]	0,062	0,438	0,039	0,773	0,275	0,165	0,243	0,079
Waist-to-hip ratio	0,102	0,338	0,22	0,516	0,073	0,719	0,201	0,15
Waist - to - length ratio	0,066	0,536	0,12	0,725	0,38	0,05	0,068	0,631
Systolic BP [mmHg]	0,225	0,034	0,252	0,455	0,057	0,786	0,18	0,196
Diastolic BP [mmHg]	0,203	0,043	0,061	0,86	0,04	0,85	0,037	0,791
Glucose [mg/dl]	0,119	0,262	0,11	0,748	0,116	0,565	0,162	0,251
Insulin [µU/ml]	0,132	0,211	0,445	0,171	0,084	0,675	0,071	0,615
C - Peptid [ng/ml]	0,035	0,741	0,757	0,007	0,105	0,604	0,023	0,837
HOMA Index	0,153	0,133	0,419	0,199	0,075	0,709	0,057	0,687
single linear regression analyses of T4	Regression	Signifikanz	Regression	Signifikanz	Regression	Signifikanz	Regression	Signifikanz
Physical Activity [hours/week]	0,074	0,486	0,18	0,537	0,009	0,365	0,116	0,409
Body lenght [cm]	0,233	0,026	0,025	0,342	0,218	0,274	0,01	0,343
Body weight [kg]	0,163	0,123	0,033	0,324	0,313	0,112	0,09	0,521
BMI [kg/m²]	0,037	0,725	0,046	0,833	0,275	0,166	0,105	0,456
Waist circumference [cm]	0,118	0,267	0,054	0,876	0,116	0,565	0,077	0,583
Waist-to-hip ratio	0,203	0,046	0,053	0,877	0,064	0,75	0,239	0,085
Waist - to - length ratio	0,009	0,331	0,06	0,861	0,031	0,879	0,056	0,683
Systolic BP [mmHg]	0,263	0,013	0,296	0,377	0,269	0,161	0,084	0,551
Diastolic BP [mmHg]	0,103	0,31	0,082	0,811	0,015	0,344	0,064	0,65
Glucose [mg/dl]	0,201	0,057	0,223	0,51	0,296	0,134	0,254	0,063
Insulin [µU/ml]	0,074	0,484	0,435	0,121	0,078	0,639	0,036	0,796
C - Peptid [ng/ml]	0,044	0,676	0,757	0,007	0,035	0,862	0,118	0,393
HOMA Index	0,111	0,235	0,439	0,118	0,134	0,507	0,043	0,726

Table 4

Table 4 shows regression analysis.

3.5 Regression analysis

Regression analysis revealed correlation between TSH and glucose (r =0,232, p=0,028) as well as between TSH and c – peptide (r=0,31, p=0,003), both in controls. We also found correlation in controls between T3 and body length (r=0,243, p=0,02), T3 and systolic blood pressure (r=0,225, p=0,034) and between T3 and diastolic blood pressure (r=0,209, p=0,049). In controls, regression analysis of T4 showed significant correlation with body length (r=0,233, p=0,026), waist – to – hip ratio (r=0,209, p=0,046) and with glucose (r=0,201, p=0,057). In hyperthyroid, the regression analysis revealed correlation between T3 and c – peptide (r=0,757, p=0,007) and between T4 and c – peptide (r=0,757, p=0,007). We also found significant correlation between T3 and BMI (r=0,424, p=0,028) and T3 and waist – to – length ratio (r=0,38, p=0,05) in hypothyroid. Regression analysis showed correlation between TSH and insulin (r=00,284, p=0,039) and between TSH and HOMA – index (r=0,285, p=0,038) in euthyroid. In this group, we also found significant correlation between T3 and body length (r=0,495, p=0) and T3 and body weight (r=0,379, p=0,005).
Regression analysis of TBO, TRAK and pTHi revealed no significant correlation (data not shown).

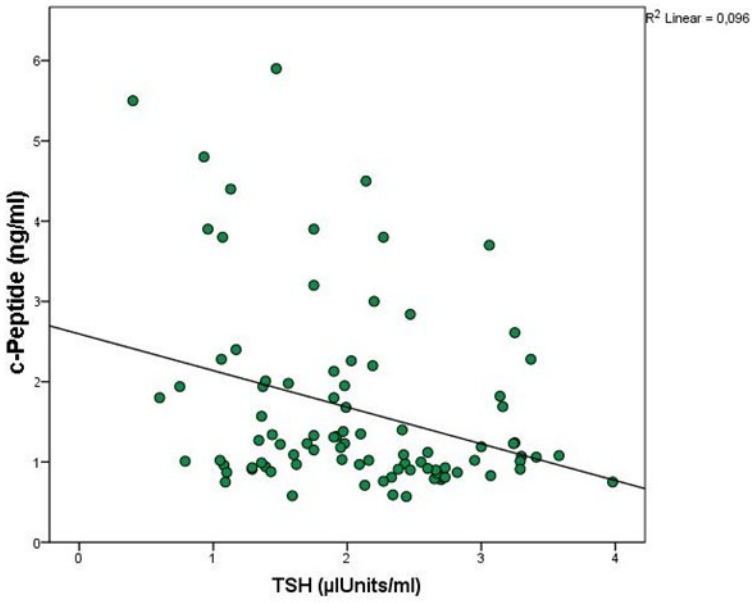

Figure 13

Figure 13 shows regression analysis of TSH and c – peptide in healthy controls.

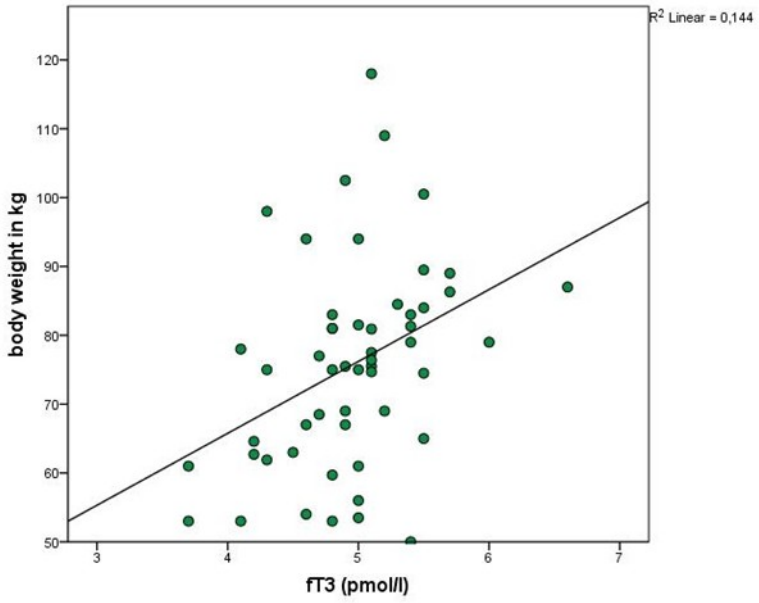

Figure 14

Figure 14 shows regression analysis of fT3 and body weight in euthyroid.

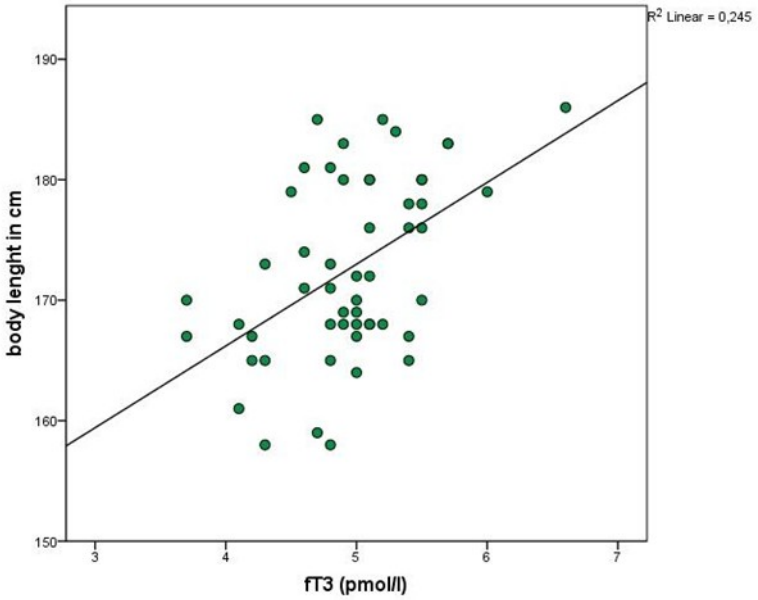

Figure 15

Figure 15 shows regression analysis of fT3 and body length in euthyroid.

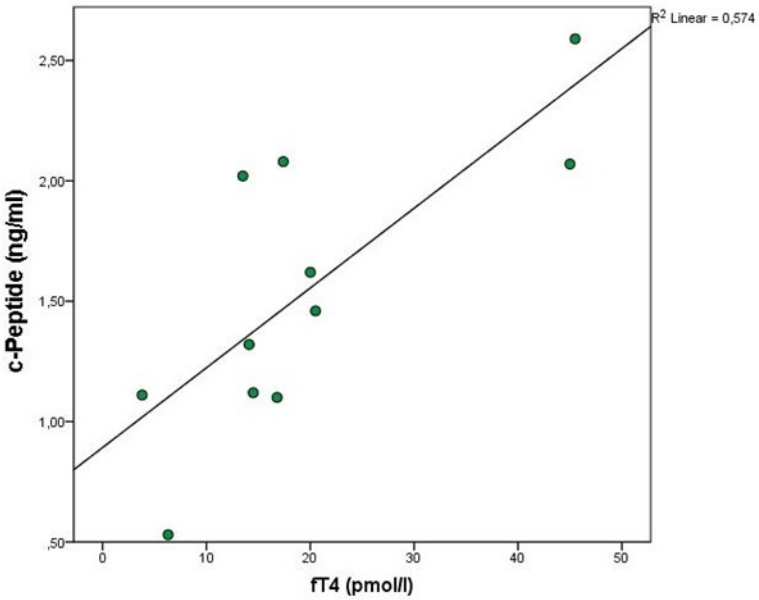

Figure 16

Figure 16 shows regression analysis of fT4 and c – peptide in hyperthyroid.

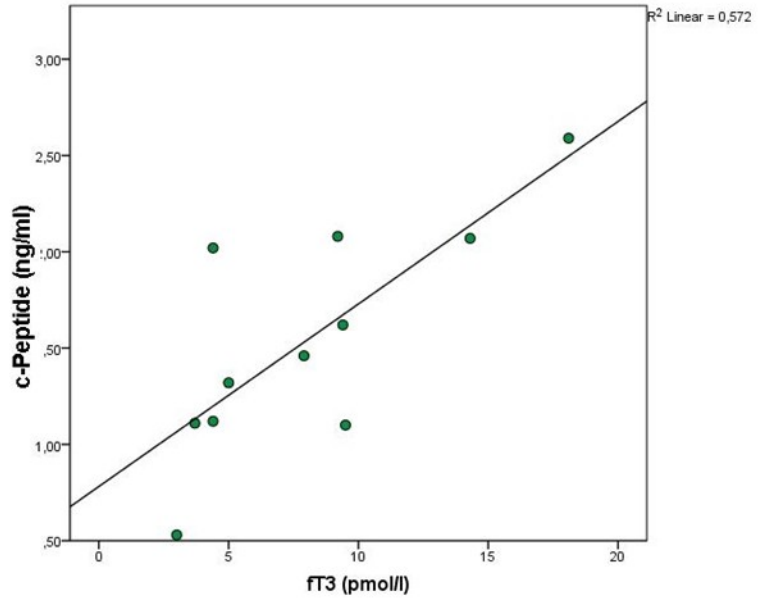

Figure 17

Figure 17 shows regression analysis of fT3 and c – peptide in hyperthyroid.

4 Discussion

Interestingly, regarding antopometric parameters, we found significant difference between euthyroid and hypothyroid in body length and waist circumference and a difference in body weight between euthyroid and healthy controls. Regarding waist – to – hip ratio, we found differences between euthyroid and controls, as well as between euthyroid and hypothyroid. The systolic blood pressure showed a difference between euthyroid and healthy controls. Also in diastolic blood pressure, we found differences between euthyroid and controls, euthyroid and hyperthyroid, but also between hypothyroid and controls and hypothyroid and hyperthyroid.

Regarding thyroid parameters, we found highly significant differences between hyperthyroid and controls as well as hyperthyroid and hypothyroid in basal TSH – levels. We were also able to show differences between hypothyroid and healthy controls, regarding basal TSH – levels. Euthyroid patients showed differences in TSH – levels to all three other groups. We show here a difference between hyperthyroids and healthy controls regarding fT4 – levels. In TBO antibodies, we found significant differences between hyperthyroid and healthy controls, hypothyroid and controls, euthyroid and controls as well as between euthyroid and hyperthyroid. Regarding TRAK, we found differences between hyperthyroid and healthy controls on the one hand and between hyperthyroid and hypothyroid on the other hand. We also found significant difference between euthyroid and healthy controls and euthyroid and hyperthyroid, regarding TRAK.

Regression analyses revealed significant correlation between thyroid parameters and the glucose metabolism. We found correlation between TSH and glucose and TSH and c – peptide, both in controls. In this group, we also found significant correlation of T3 with body length, systolic and diastolic blood pressure. We are able to show correlation of T4 with body length, waist – to – hip ratio and glucose in healthy controls. In hyperthyroid, we found correlation between c – peptide and T3 as well as between c – peptide and T4. Our data shows correlation between T3 and antopometric parameters like BMI and waist – to – hip ratio in hypothyroid subjects. Regression analyses revealed significant correlation between thyroid parameters and parameters of the glucose metabolism also in euthyroid subjects.

Here we can show correlation between TSH and insulin and also between TSH and HOMA – index. In this group, correlation occurred between thyroid parameters and antopometric parameters as well. We can show correlation between T3 and body length and T3 and body weight.
Regarding thyroid parameters, our findings are in line with the current doctrine. As already described in the introduction, in hyperthyroid patients, mainly having Grave´s disease, the body is producing autoantibodies, which are able to link in the TSH – receptors on the thyroid gland (8), (2). This is leading to a constant production of thyroid hormones. Also antibodies against thyroidal peroxidase can be found. Regarding our findings, we are completely in part with this doctrine. In hypothyroid subjects, we showed elevated levels of basal TSH and also strongly elevated levels of TBO – AB. These findings are also in line with the current doctrine, as already outlined above (9), (21). In euthyroid subjects, we found slightly depressed basal TSH – levels and elevated TPO – AB and TRAK. This can be explained because these are patients who have been hypothyroid or hyperthyroid patients now getting treatment to reach normal levels of T3 and T4. This treatment does not lead to an elimination of TBO – AB or TRAK (9).
In baseline characteristics, we found differences in age between euthyroid and hypothyroid. This is due to our study cohort. Furthermore, differences in body length and waist circumference were found regarding euthyroid and hypothyroid. We also found a difference in body weight between euthyroid subjects and healthy controls. This finding is in part with the study of Iacoballis et al (35) and Michalaki et al (37). Regarding waist circumference, we found that euthyroid subjects of our study cohort tend to have higher waist circumference than healthy controls. This is in line with the findings of De Pergola et al (38). It is also supported by Tagliaferri et al who found no changes in body composition or lipid profile in obese subclinical hypothyroid patients (39). Our findings according waist – to – hip ratio are supported by many different authors as outlined above in chapter metabolic syndrome (35), (37), (39). In opposite, Manji et al reported no association between BMI, TSH and fT4 in euthyroid patients and no differences in TSH and fT4 levels between lean and obese subjects (40). Regarding blood pressure, systolic as well as diastolic blood pressure was significantly higher in euthyroid than in the healthy control group. Also along hypothyroids the diastolic blood pressure turned out to be higher than in healthy controls and in hyperthyroid. Euthyroid tend to have

higher diastolic blood pressure than hyperthyroids too. These findings are in line with various studies examining the correlation between thyroid parameters and blood pressure (91), (89), (90). A positive correlation between thyroid parameters and elevated blood pressure was shown, though the elevation was just about 6 mmHg in systolic blood pressure in the reference rage of TSH. In contrary, van der Deure et al showed no impact of thyroidal parameters on the elevation of blood pressure and the prevalence of hypertension (88). De Pergola et al mentioned that the observed association of thyroid parameters with obesity was not associated with insulin resistance, parameters of the metabolic syndrome or blood pressure (38).

We are able to show correlation between thyroid parameters and the glucose metabolism in healthy controls, hyperthyroids and euthyroids. This correlation did not occur in hypothyroid subjects. Knudson et al found an association between TSH and BMI but no correlation between BMI and fT3 (41). These findings are also supported by Nyrnes et al (42). Our findings regarding T3 and c – peptide as well as T4 and c – peptide in hyperthyroids are in line with the findings of Ahren et al (64), Dimitriadis et al (65), Jap et al (66), O´Meara et al (67) and Shen et al (68). In opposite, Ikeda et al (69) and Roti et al (70) found negative correlation whereas Asano et al (62) and Taylor et al (63) found no connection between thyroid parameters and the glucose metabolism. According to Moon et al, low levels of fT3 and fT4, still being in the normal range, are significantly associated with increased pericardial fat volume and BMI in healthy male subjects (74).

5 Conclusion

Summing up, we found significant differences in antopometric parameters along the four groups of our study cohort. These findings go in line with many studies as already outlined above. Thyroid dysfunction seems to have a strong impact on body weight, waist – to – hip ratio and blood pressure. Therefore it is very important to recognise thyroid dysfunction in patients for a better treatment. Also in regression analysis, we revealed significant correlations between parameters of the thyroid function and parameters of the glucose metabolism as well as antopometric parameters. So this also supports the idea that thyroid dysfunction patients need to get adeaquat therapy in order to reduce a patient´s risk for metabolic disorders.

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7 Lebenslauf

Beatrice Rehberger

Angaben zur Person

Geboren am. 19.05.1990
Familienstand: ledig
Wohnort: Leonhardstraße 38, 8010 Graz
Telefon: 0664/1118643
E-Mail: beatricerehberger@gmail.com
Österreichische Staatsbürgerschaft

Schulbildung

1996-2000: Volksschule Frankenmarkt
2000-2008: Bundesgymnasium Vöcklabruck
Ab 2008: Studium der Humanmedizin und Zahnmedizin an der medizinischen Universität Graz

Sprachen

Englisch (8 Jahre Unterricht im Gymnasium)
Französisch (6 Jahre Unterricht im Gymnasium)
Chinesisch (1 Jahr an der Meduni Graz)

Famulaturen

3 Wochen Chirurgie am LKH Vöcklabruck
3 Wochen Gynäkologie und Geburtshilfe am LKH Vöcklabruck
2 Wochen Neurologie am LKH Vöcklabruck
3 Wochen Pädiatrie in Victoria, Mahé, Seychellen
3 Wochen Pädiatrie am LKH Vöcklabruck
2 Wochen Unfallchirurgie am LKH Vöcklabruck

6. Studienjahr
7 Wochen Innere Medizin am Klinikum Passau (Gastrologie, Kardiologie)
6 Wochen Anästhesie und Intensivmedizin am Klinikum Passau (OP, Intensivstation)
3 Wochen Gynäkologie und Geburtshilfe am Klinikum Passau
Alle anderen Bereiche des praktischen Jahres habe ich in Graz absolviert.

Interessen

Sport: Laufen, Reiten, Yoga
Lesen, Reisen