Diploma thesis

The impact of thyroid therapy, both in hypo- and hyperthyroid patients on cardiovascular risk

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Graz, am 12.02.2014

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Expression of thanks

Dies ist ein weiterer wichtiger Schritt in meinem Leben. Rekapitulierend bin ich stolz auf meinen bisherigen Werdegang trotz seiner vielen Umwege und Stolpersteine. Außerdem möchte ich mich bei denjenigen bedanken, die mich in meinem Werdegang unterstützt und auf meinem Weg begleitet haben.

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Zusammenfassung

Die Behandlung von Schilddrüsenunter- bzw. –Überfunktion und deren Auswirkung auf das kardiovaskuläre Risiko der PatientInnen

Einleitung

Das Ziel der vorliegenden Arbeit ist es den Einfluss der Therapie von Schilddrüsenerkrankungen, sowohl bei Unter- als auch bei Überfunktion, auf die korrelierenden kardiovaskulären Risikofaktoren zu untersuchen. Wir nehmen an, dass eine Schilddrüsenfehlfunktion mit einem höheren kardiovaskulären Risiko einhergeht und folglich die Therapie prophylaktisch für koronare Herzerkrankung wirkt, wenn sich PatientInnen im euthyroiden Zustand befinden.

Patienten und Methoden

An unserer Studie nahmen insgesamt 96 PatientInnen, die basierend auf ihrer Schilddrüsenfunktion in hyper-, hypo- und euthyreot unterteilt wurden, teil. Bei den PatientInnen wurden am Beginn und nach 6 Monaten Therapie Schilddrüsen-, Fettstoffwechsel und anthropometrische Daten analysiert.

Ergebnisse

Es zeigten sich eindeutige Veränderungen der Schilddrüsenparameter entsprechend der zugrundeliegenden Schilddrüsenfehlfunktion. Es konnten bei PatientInnen erhöhte Fett- und Blutdruckwerte, systolisch und diastolisch, festgestellt werden. Im follow up zeigten sich bei den euthyreoten ProbandInnen signifikante Veränderungen betreffend BMI, Taillenumfamg, im Taillen zur Länge Verhältnis und beim diastolischen Blutdruck. Hypothyreote ProbandInnen wiesen zusätzlich noch signifikante Unterschiede beim systolischen Blutdruck auf. Bei den Fettwerten wiesen PatientInnen mit Schilddrüsenunterfunktion signifikante Unterschiede in HDL und LDL/HDL- Verhältnis im Vergleich zu den

Ausgangswerten auf. Bei den euthyreoten ProbandInnen konnten hingegen nur signifikante Veränderungen im LDL/HDL- Verhältnis festgestellt werden. In allen 3 Gruppen konnten signifikant niedrige ADMA-Spiegel nachgewiesen werden, wobei die Gruppe der Unterfunktion hochsignifikant niedrige Werte hatte. Hinsichtlich der Entzündungswerte konnten keine signifikanten Veränderungen beobachtet werden. Die Regressionsanalyse machte einen Zusammenhang zwischen Schilddrüsen- und Fettstoffwechsel im speziellen mit HDL und LDL deutlich.

Fazit

Zusammenfassend weisen die Ergebnisse auf eine mögliche präventive Wirkung der Therapie von Schilddrüsenerkrankungen bei normalgewichtigen PatientInnen hinsichtlich Arteriosklerose und in Folge koronare Herzerkrankungen sowohl bei Schilddrüsenunter- als auch Überfunktion hin. Es ist allerdings zu berücksichtigen, dass die vorliegende Arbeit eine Pilot Study ist, deren Ergebnisse erst in weiteren Studien bestätigt werden müssen.

Zukunftsperspektive

Weitere Untersuchungen werden nötig sein, um den Einfluss der unterschiedlichen Schweregrade von Schilddrüsenfehlfunktionen auf die Entwicklung von Arteriosklerose und folglich koronare Herzerkrankung darzulegen und im speziellen der therapeutische Ansatz bei adipösen PatientInnen.

Abstract

The impact of thyroid therapy, both in hypo- and hyperthyroid patients on cardiovascular risk

Introduction

The various thyroid diseases, including hyper-, eu- or hypothyroidism, represent a complex network depending on the functional behaviour of the thyroid, which is the basis for diagnosis and therapy. The aim of the present study is to investigate the implication of thyroid therapy and the related cardiovascular risk factors both in hyper- and hypothyroid patients. We hypothesise that thyroid dysfunctions are associated with cardiovascular risk factors and therefore thyroid therapy intervenes as prophylaxis for cardiovascular diseases after achieving normal state in patients.

Patients

In our case-based study we investigated a total number of 96 subjects. Patients were sub-grouped regarding their thyroid function into hyper- hypo and euthyroid. We analysed baseline characteristics including thyroid, lipid and anthropometric parameters at the beginning of the study and in the follow up after 6 months of treatment.

Results

Patients displayed significant thyroid abnormalities according to their underlying thyroid disorder. Further probands featured alterations of lipid, systolic and diastolic blood pressure levels. After 6 months of treatment hypothyroid patients revealed significantly lower ft 3 levels. Analyses exhibited significant differences of BMI, waist circumference, waist-to-length ratio and diastolic blood pressure in

euthyroid and significant changes in systolic blood pressure in hypothyroid patients. We found significant variations of HDL in hypothyroids and of LDL/HDL-ratio in hypothyroids just as in euthyroids. Investigation of ADMA unveiled significant low levels in hyper- and euthyroid patients and even highly significant low ones in hypothyroids. No significant changes were found regarding inflammatory parameters. Regression analyses revealed significant correlation between thyroid hormones and lipid parameters, especially HDL and LDL.

Conclusion

Recapitulating, our findings suggest a preventive impact of thyroid therapy in normal weight patients on atherosclerosis and subsequently on cardiovascular disease both in hypo- and hyperthyroidism. However, we have to notice that the present study is a pilot study and findings have to be proven in further clinical trials.

Interpretation/Future perspective

Further research is required to clarify the influence of various degrees of thyroid dysfunction in the development of atherosclerosis and cardiovascular morbidity, especially in terms of therapeutic approaches in obese patients.

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Glossary and acronyms

The following abbreviations are used in this diploma thesis:

Aa	Arteriae
AB	Antibodies
ADMA	Asymmetric dimethylarginine
BMI	Body-Mass-Index
BP	Blood pressure
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CHD	Coronary heart disease
cm	Centimetre
CRP	C-reactive protein
CT	Computed tomography
DIT	Diiodotyrosine
f	Female
Fig.	Figure
fT3	free triiodothyronine
fT4	free thyroxine
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
IG	Immunoglobulin
IL	Interleukin
kg	Kilogramme
l	Litre
LDL	Low-density lipoprotein
LT4	Levothyroxine
m	Male
m^2	Squaremetre
MDA	Malondialdehyde
MIT	Monoiodotyrosine
ml	millilitre
mmHG	millimetre of mercury
MRI	Magnetic resonance imaging
mRNA	Messenger RNA

Na^+-K^+-ATPase	Na/K-ATPase
oGTT	Oral glucose tolerance test
Ox-LDL	Oxidised-LDL
p	Significance level
PAS	Polyendocrine autoimmune syndrome
pg	picogram
pmol	picomole
PTHi	Intact parathyroid hormone
r	Correlation coefficient
SD	Standard deviation
SLE	Systemic lupus erythematosus
T3	Triiodothyronine
T4	Thyroxine
TBII	Thyrotropin Binding Inhibitory Immunoglobulins
TG	Thyroglobulin
TNF-alpha	Tumor necrosis factor alpha
TPO	Thyroid peroxidase
TPO-AB	Thyroid peroxidase antibodies
TRAK-AB	Thyrotropin receptor antibodies
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
TSI	Thyroid stimulating immunoglobulin
U	Unit
US	Ultrasound
Vv	Venae
µUnits	Microunits

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Table list

1 Introduction

1.1 Anatomy of the thyroid gland (1–3)

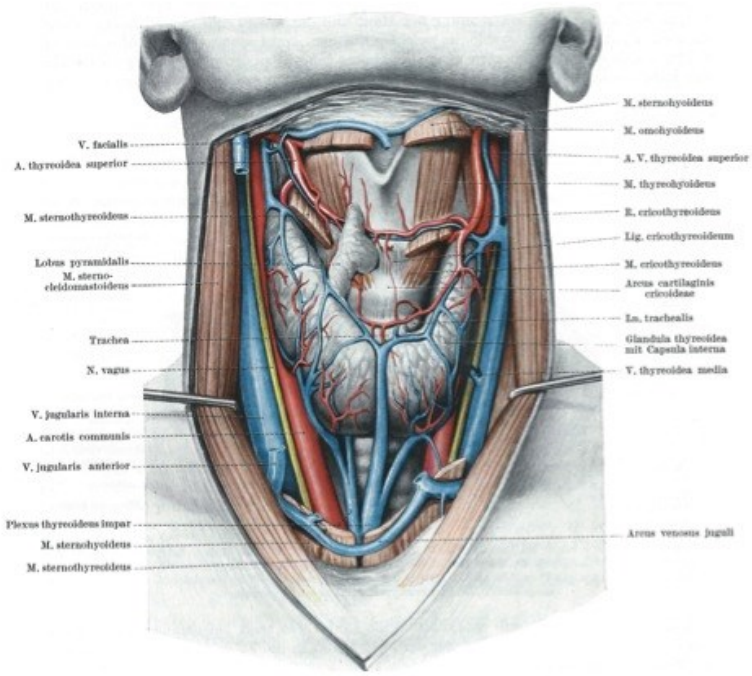


Figure 1. Anatomy of the thyroid gland. Adapted from Hafferl A. (1).

The thyroid gland is situated in the front of the lower neck about the 5th cervical to the 1st thoracic vertebrae directly in front of the trachea. It is made up of two lobes, which are connected by a narrow, median Isthmus. The left and the right lobe of the thyroid gland are conical and piriform. Further the two lobes diverge laterally and reach up to the oblique lines on the laminae of the thyroid cartilages. Figuratively spoken the thyroid gland appears to be like an “H”, which has two shorter lower arms than the two upper arms. Very often a small lobe, pyramidal lobe, ascends towards the hyoid bone incipient from the isthmus or one of the two lobes. The pyramidal lobe is attached to the hyoid bone by a string of connective tissue. In rare cases the pyramidal lobe can reach to the base of the tongue, which is then a remnant of the thyroglossal duct.

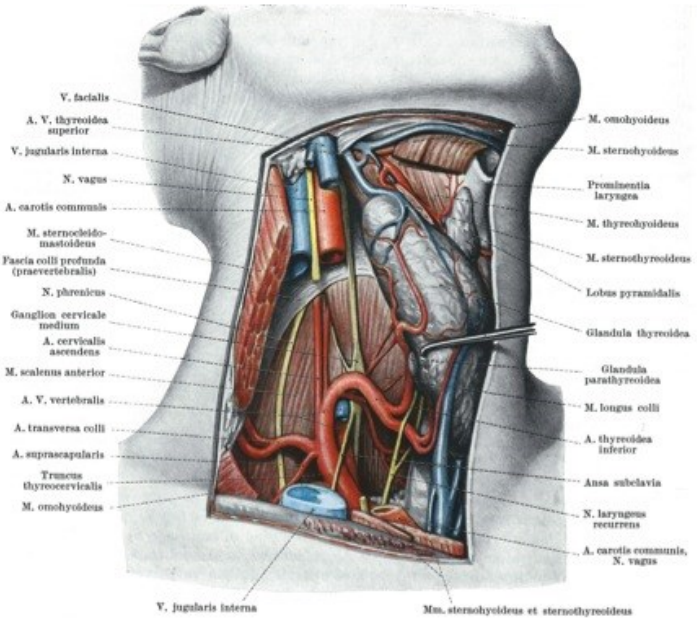
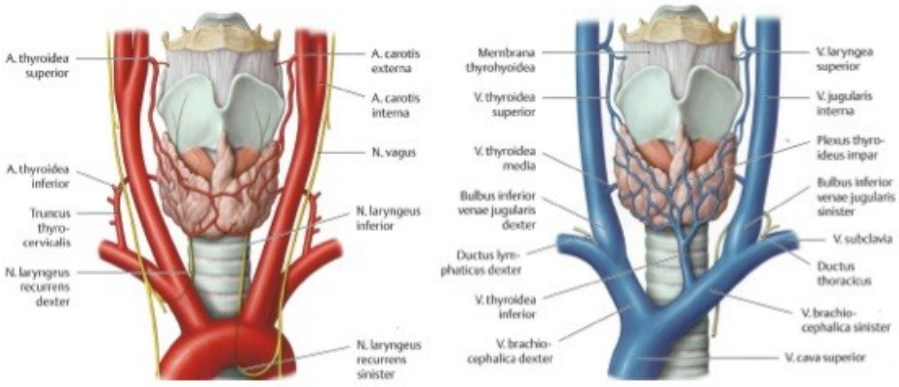


Figure 2. Anatomy of the thyroid gland. Modified from Hafferl A. (1).



Picture 3. Blood supply of the thyroid gland. Adapted from Schünke M et al. (3).

Two capsules cover the gland. The capsula interna and externa (fibrosa). The former is a thin layer, which accompanies the vessels into the lobes (septa) and simultaneously divides the lobes into lobules. The latter consists of several layers. The capsula fibrosa affixes the thyroid gland to the larynx and trachea. In contrast the thyroid gland is relocatable in its periphery, which enables the gland to follow the laryngeal movements. Between the capsula interna and externa run the main vessels of the thyroid gland. The blood supply is managed by Aa. thyroideae superiores et inferiors and at times by an arteria thyroidea ima. The venous drainage is generally via Vv. Thyroideae superiores, mediae et inferiors. The thyroid gland receives its innervation from fibres of the vagus nerve, sympathic trunk and at times the glossopharyngeal nerve.

The colour is brownish-red. The normal weight is approximately 20 - 25 grams. Unfortunately actual imaging devices can't plot the follicular structure. So the imaging displays a homogenous texture on cross-sectional imaging (US, CT, MRI). Because of its superficial location the thyroid gland is the perfect organ for ultrasound examination. Due to its highly vascularisation the thyroid gland presents intense contrast enhancement and increased signal on T_2 –weighted MRI. Radionuclide imaging can be performed with technetium pertechnetate (Tc^{99m}).

1.2 Histology (4)

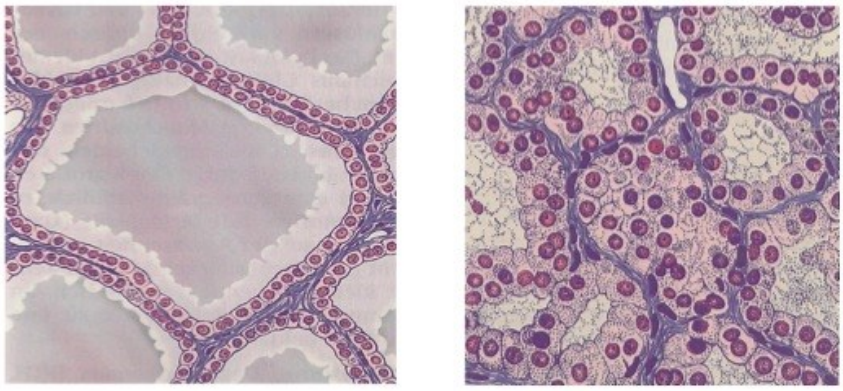


Figure 4. Histological structure of the thyroid gland. Adapted from Schünke M et al. (3).

Follicles are the main histological characteristic and simultaneously the functional units of the thyroid gland. Follicles are spheric and cystical cells, which are surrounded by a single-layered epithelium. The thyroid gland hormones are triiodthyronine (T3) and thyroxine (T4). The synthesis of thyroid hormones in the follicular cells starts with thyroglobulin (TG). Iodine is incorporated and linked to TG by the enzyme thyroid peroxidase (TPO). Then iodinated TG will be stored in the lumen of the thyroid follicles and gets released in response to thyroid stimulating hormone (TSH), which is produced by the anterior pituitary gland and stimulated by thyroid releasing hormone (TRH). Following TG reabsorption by thyrocytes and subsequent degradation, thyroid hormones T3 and T4 are secreted in the bloodstream. TRH is produced in the hypothalamus upon stimulation.

1.3 Physiology (5–8)

1.3.1 Synthesis and secretion of thyroid hormones

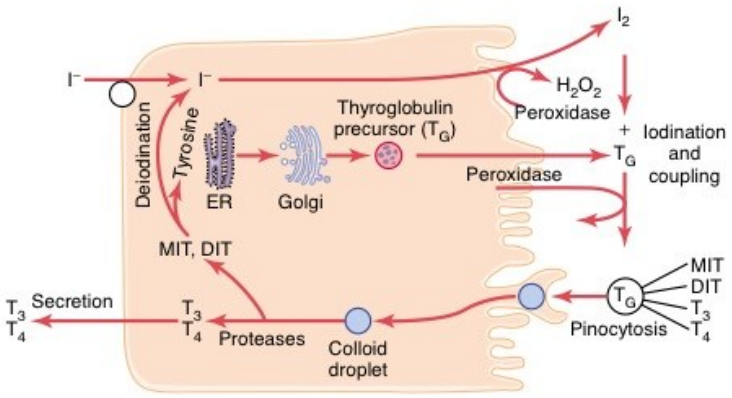


Figure 5. Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T3, triiodothyronine; T4, thyroxine; TG, thyroglobulin. Modified from Guyton AC. (5).

The thyroid gland secrets two metabolically active hormones thyroxine (T4) and triiodothyronine (T3). 93 % of T4 to 7% of T3. The function is qualitatively the same. But rapidity and effectiveness of performance is what makes the difference. T3 is approximately four times as potent as T4 although it persists in much smaller amounts and less time than T4. Normally the cells of the thyroid gland absorb around 20% of the ingested iodides from the circulating blood and provide them for synthesis of the thyroid hormones. The process, which is done by the basal membrane of the cells, is called iodide trapping. The working rate of these pumps depends on several factors, but the most important one is the concentration of thyroid-stimulating hormone (TSH). The thyroid cells are protein- secreting glandular cells, which synthesize and secrete thyroglobulin (TG) into the follicles. TG is composed of approximately 70 tyrosine amino acids, which mainly interact with iodine and form the thyroid hormones. The first essential step of formation is

to build the basis for combining iodide with tyrosine. That means oxidising iodide to either nascent iodine (I^0) or I_3- performed by the enzyme peroxidase. Then the iodinase promotes the binding of iodine with tyrosine (organification of thyroglobulin). First tyrosine gets iodised to monoiodotyrosine and then to diiodotyrosine. After that mono- and diiodotyrosine residues are coupled with one another. As a result we get the major hormone product thyroxine and the by-product triiodothyronine. After synthesis each thyroglobulin contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In the end thyroglobulin is stored in the follicles of the thyroid gland. This amount of thyroxine and triiodothyronine can cope with the supply of the body for up to 2 to 3 months in normal demand of thyroid hormones. As a matter of fact declining of synthesis of thyroid hormones and their corresponding physiologic effects do not appear within several months. The release of thyroxine and triiodothyronine from the thyroid gland is accomplished as follows. Thyroxine and triiodothyronine have to be separated from thyroglobulin to be released into the bloodstream. Thyroid cells digest thyroglobulin. This process starts with incorporating thyroglobulin by pinocytosis. Then these vesicles merge with lysosomes and form digestive vesicles. Multiple proteases digest thyroglobulin and release thyroxine and triiodothyronine, which diffuse into the surrounding capillaries. A big part of the iodinated tyrosine never gets released from the thyroid gland but will be recycled in formation of new thyroid hormones. In general the thyroid hormones activate nuclear transcription of large numbers of genes in their target cells e.g. enzymes, transport proteins and many others. But before interacting with the genes, thyroxine has to be converted into triiodothyronine by removing one iodide, because intracellular thyroid hormone receptors have higher affinity to triiodothyronine.

1.3.2 Effects of thyroid hormones on specific body mechanisms

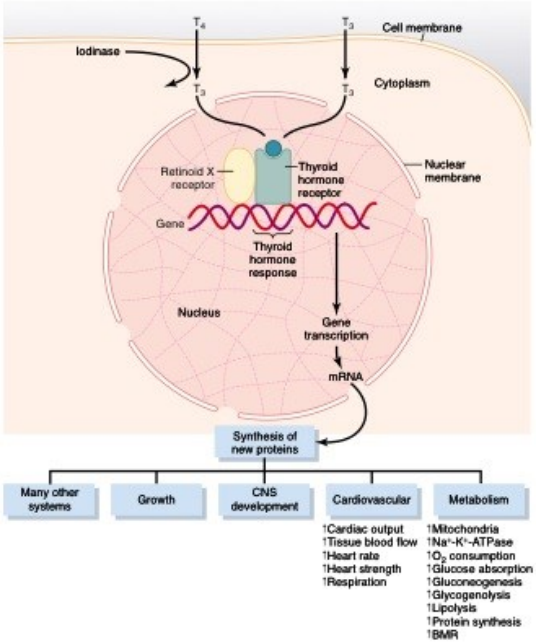


Figure 6. Thyroid hormone activation of target cells. Thyroxine (T4) and triiodothyronine (T3) readily diffuse through the cell membrane. Much of the T4 is deiodinated to form T3, which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid hormone response element of the gene. This causes either increases or decreases in transcription of genes that lead to formation of proteins, thus producing the thyroid hormone response of the cell. The actions of thyroid hormone on cells of several different systems are shown. mRNA, messenger ribonucleic acid. Adapted from Guyton AC. (5).

Generally speaking thyroid hormones increase cellular metabolic activity of nearly all tissues of the body. That means an increase in metabolic rate to 60 to 100 per cent above normal, protein synthesis, as well as protein catabolism, growth rate of young people. Further more an enhancement of activities in most of the other endocrine glands can be observed. Additionally we find acceleration in growth rate of young people and the rate of utilisation of foods for energy.

Considering the impact on the carbohydrate metabolism thyroid hormones induce rapid uptake of glucose, enhanced glycolysis and gluconeogenesis, augmented rate of absorption from the gastrointestinal tract and as a result even increased insulin secretion.

Concerning the fat metabolism thyroid hormones cause mobilisation of lipids from the fat tissue and therefore decrease of fat stores of the body, elevated free fatty

acid concentration in the plasma and expedited oxidation of free fatty acids by the cells.

Relating to the liver, highly concentrated thyroid hormones lower the amount of cholesterol, phospholipids and triglycerides in the plasma despite increasing the fatty acids. In contrast low thyroid levels mainly raise plasma concentration of cholesterol, phospholipids and triglycerides, which also leads to excessive storage of fat in the liver. On top of that persistent high levels of plasma cholesterol in hypothyroidism are associated with severe atherosclerosis and heart attack.

The enhanced production and use of enzymes for metabolism requires higher levels respectively uptake of vitamins, because vitamins are essential components not only of enzymes but also of coenzymes. Otherwise people can develop deficiencies.
As mentioned before extreme high thyroid hormones raise the basal metabolic rate 60 to 100 per cent above normal state. In contrast low levels reduce the rate to about 50 per cent normal.

Generally increased thyroid hormones diminish body weight and reverse. But sometimes people experience more appetite, which can cause contrasting effects on body weight.

To have a look at the cardiovascular system thyroid hormones induce the following effects.

First it shows increased blood flow and cardiac output. The fact of enhanced metabolism causes higher utilisation of oxygen, which means greater amounts of metabolic end- products. As a consequence the body augments the blood supply by vasodilatation and the cardiac output to more than 60 per cent than normal. And finally more work induces more heat, which has to be eliminated in the periphery thanks to vasodilation mentioned before. Further on thyroid hormones seem to have a special effect on the excitability of the heart rate leading to a remarkable rise in heart rate. This striking effect is of characteristic significance that it is clinically used for assessment of exaggerated or decreased thyroid

hormone levels in patients. Moreover slightly raised thyroid hormone levels increase the strength of the heart. This effect can also be observed in case of mild fever or during exercise. Apart from that enhanced thyroid hormones provoke loss of strength because of the exuberant protein catabolism. Sadly some patients die of cardiac decompensation on the basis of myocardial failure and the increased cardiac load caused by elevated cardiac output. And finally the average arterial pressure remains unspoiled but there are often enhanced systolic and lowered diastolic pressure levels in hyperthyroidism. The discordant systolic and diastolic values lie between 10 – 15 mmHg.

In terms of the respiratory system the body has to get rid of the accruing carbon dioxide by activating all necessary mechanisms of the respiratory system due to high metabolic rates.

In relation to the gastrointestinal system high levels of thyroid hormones provoke augmentation of secretion of digestive juices and motility of the gastrointestinal tract, which often leads to diarrhoea and constipation in contrast.

Referring to the central nervous system, thyroid hormones help in developing the brain by influencing the cerebration. Hyperthyroids often develop extreme nervousness and psychoneurotic tendencies like anxiety complexes or paranoia among others due to the excitatory effects of thyroid hormones on the central nervous system.

Furthermore thyroid hormones take effect on the musculoskeletal system. The effect on muscles is equivalent to the heart muscle. Slightly elevated thyroid hormones induce vigour but excessive levels weaken the muscle because of the high protein catabolism, whereas absence of thyroid hormones causes sluggishness and slow relaxation after contraction. Additionally patients often develop a fine muscle tremor, which is a characteristic sign in hyperthyroidism. This kind of tremor is different to Parkinson´s tremor and as well to shivering. The frequency is about 10 – 15 times per second. Enhanced reactivity of the neuronal synapses for muscle tonus is thought to be the genesis of the tremor. In clinical

practice the tremor serves to get a slight idea of the impact on the central nervous system by thyroid hormones.
Moreover hyperthyroidism leads to osteoporosis and elevated levels of calcium in blood and urine.

In respect of the effects on the renal system hyperthyroids show elevated glomerular filtration rate (GFR) whereas hypothyroids emerge disturbed renal perfusion and consequently a decrease of glomerular filtration rate.

Regarding the circadian rhythm hyperthyroid patients often report constant tiredness and sleep deficit. These symptoms arise from the effects of thyroid hormones on the muscle system and the nervous system explained further up. On the contrary hypothyroids display extreme somnolence despite having sleep between 12 and 14 hours.

Finally examining the effects on the endocrine system high levels of thyroid hormones concomitantly demand high levels of secretion of most of other endocrine glands e.g. glucose metabolism, insulin, glucocorticoid metabolism among others. Examining the effects on the gonads approximate normal level of thyroid hormones is essential for normal sexual function. A specific effect on the gonads can’t be displayed, because of the great variety and complexity of effects on them. The current scientific consensus delineates that the impact on the gonads proceeds from a combination of direct metabolic effects on the gonads as well as excitatory and inhibitory feedback mechanisms on the pituitary gland and subsequently on the gonads.

1.3.4 Regulation of thyroid hormone secretion

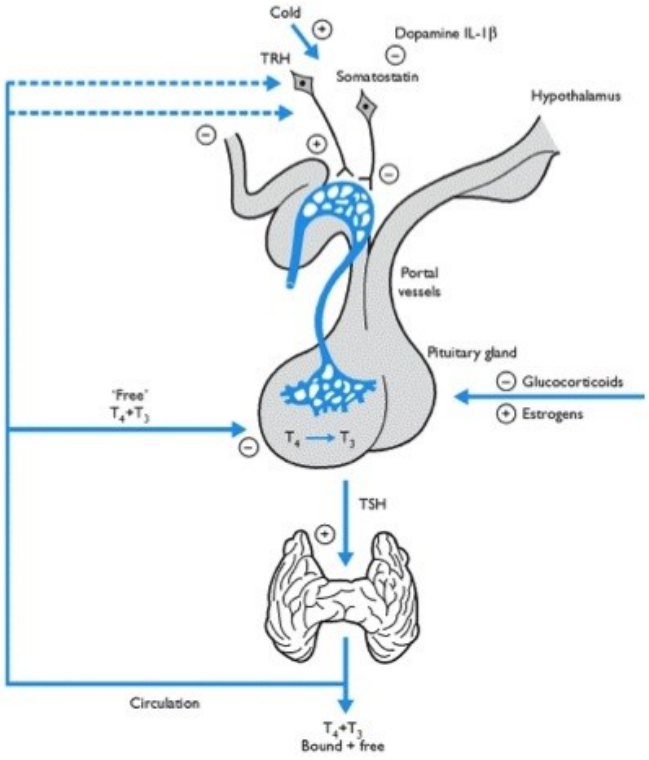


Figure 7. Regulation and feedback mechanism of the thyroid gland Modified from Nussey S. and Whitehead SA. (6).

Concerning the importance of normal metabolic activity the body has to measure out precisely the secretion of the thyroid hormones at all time. The body gets by with specific feedback mechanisms, which control the frequency of secretion of the thyroid gland accomplished by the hypothalamus and the anterior pituitary gland in the following way.

Thyroid stimulating hormone (TSH) or thyrotropin is released by the anterior pituitary gland and induces secretion of thyroxine and triiodothyronine from the thyroid gland by increasing proteolysis of thyroglobulin, activity of iodide pump, iodination of tyrosine, size and secretory activity of the thyroid cells as well as increased numbers of thyroid cells. All in all TSH activates all secretory mechanisms of the thyroid glandular cells. But the most important one is to initiate the cleaving of thyroglobulin in thyroxine and triiodothyronine. The specific effect of TSH on its target cells in the thyroid gland is transmitted by “second messenger”

cyclic adenosine monophosphate (cAMP) system. To achieve that, TSH has to bind with specific TSH receptors on the basal membrane surfaces of the thyroid cell. The binding activates adenyl cyclase in the membrane, which again leads to more cAMP inside the cell. Subsequently cAMP operates as a second messenger to activate protein kinase, which starts off phosphorylation throughout the cell implying an immediate boost in secretion of thyroid hormones as well as prolonged growth of the thyroid glandular tissue itself.

TSH itself is regulated by thyrotropin-releasing hormone (TRH), which is produced in the hypothalamus and secreted by nerve endings in the median eminence of the hypothalamus. TRH is conveyed to the anterior pituitary gland by the hypothalamic-hypophyseal portal blood where TRH itself induces enhanced secretion of TSH after binding to TRH receptors in the pituitary cell membrane. This subsequently activates the phospholipase second messenger system inside the pituitary cells to produce large amounts of phospholipase C. Finally a cascade of second messengers including calcium ions and diacylglycerol eventually leads to TSH release. Many stimuli like cold and emotional reactions provoke increase respectively decrease of TRH and consequently TSH. High levels of thyroid hormones in plasma decrease right up to inhibit secretion of TSH even if the anterior pituitary gland has been separated from the hypothalamus. The purpose of this control is to ensure a constant concentration of free thyroid hormones in the circulating blood.

1.4 Diseases (9–14)

1.4.1 Overview of thyroid diseases

The various thyroid diseases represent a complex network depending on the functional behaviour of the thyroid, which is the basis for diagnosis and therapy (15). 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 (16). It is necessary to distinguish whether hormone levels reflect a primary biosynthetic problem of the thyroid gland, destruction of thyroid cells, e.g. by autoimmune diseases, iatrogenic causes or target tissue abnormalities. Euthyroid diseases include euthyroid goitre, most tumours, both benign and malign as well as various thyroiditis including acute and subacute thyroiditis, chronic autoimmune thyroiditis or Hashimoto´s disease in the euthyroid phase (17). Disease characterised by hyperthyroidism include diseases with thyroid gland hyperthyroidism, thyrotoxicosis and transient hyperthyroidism. The sub- group of thyroid gland hyperthyroidism includes hyperthyroid goitre, Basedow-Graves' disease, Plummer's´ disease and some rare forms like hyperthyroidism due to Hashimoto´s disease (Hashitoxicosis), inborn pituitary resistance to thyroid hormones and TSH-secreting tumours (18). Hypothyroidism includes thyroid gland hypofunction, both primary and secondary. Primary hypothyroidism includes chronic autoimmune thyroiditis in the hypothyroid phase (Hashimoto´s disease), end-stage Graves' disease and several late forms of diffuse and nodular goitre. Hypothyroidism may also be caused by iodine deficiency and very rare, by peripheral resistance to thyroid hormones (19). Wilders-Truschnig et al also suggest a strong involvement of active antigen-presenting cells in the iodine deficient goiter (20–23). 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 goiters (24). The function of the thyroid gland appears diverse in many thyroid disease onsets. Diffuse goitre, which becomes nodular with time may maintain normal hormonal production for many years but can also be associated with hypothyroidism depending on iodine supply (25–28). Hypothyroidism or hyperthyroidism are frequently caused by autoimmune thyroid

diseases as outlined above (29). Autoimmune hypo- or hyperthyroidism may depend on the presence of stimulating or blocking autoantibodies, which existence varies with time. It is now clear that Hashimoto´s thyroiditis can remit or progress to hyperthyroidism due to occurrence of TSH receptor auto-antibodies or destructive changes causing excessive hormone secretion (30). Frequently it may also develop to hypothyroidism in consequence of blocking antibodies or destruction of the thyroid gland. Recapitulatory it is obvious that history and modification of the disease have to be noticed concerning the therapeutic approaches because of the high variability of thyroid diseases. E.g. Graves' disease and postpartum thyroiditis are treated with anti-thyroid drugs at the onset of disease but subsequently thyroid hormone supplementation will be needed after patients becoming hypothyroid (31).

1.4.2 Graves' disease or Mb. Basedow

Graves' disease is an autoimmune disease. It is characterised by hyperthyroidism caused by circulating autoantibodies. These antibodies, Thyroid-stimulating immunoglobulins (TSI), bind to the thyrotropin receptor and induce growth of the gland itself as well as augmentation of synthesis of thyroid hormone. At times Graves' disease is part of more extensive autoimmune processes resulting in multiple organ dysfunction, which means that Graves' disease is associated with polyglandular syndromes e.g. diabetes mellitus type 1, systemic lupus erythematosus (SLE), autoimmune adrenal insufficiency among others (32).

The autoimmune process in Graves' disease is B and T lymphocyte mediated. The B and T cells are targeted at 4 established thyroid antigens: thyroglobulin, thyroid peroxidase, sodium-iodide symporter and the thyrotropin receptor. Nevertheless the thyrotropin receptor represents the primary autoantigen, causing hyperthyroidism, in Graves' disease. Therefore the circulating autoantibodies permanently stimulate the thyroid gland to enhance production of thyroid hormones, which consequently suppress pituitary thyrotropin secretion. The other antigens mentioned before appear less likely to be responsible in aetiology of hyperthyroidism in Graves' disease.

Further genetic predisposition to thyroid autoimmunity can be spotted in patients. Several susceptibility genes have been identified such as CD40, CTLA-4, thyroglobulin, TSH receptor, PTPN22 as well as HLA-DQA1 and HLA-DR3 (33,34). Some of these genes are idiosyncratic to either Graves' disease or Hashimoto's or to both of them. Additionally environmental factors or events in combination with genetic predisposition may have an impact on precipitating onset of Graves' disease. The incidence of the autoimmune hyperthyroidism (Graves' disease) is about 40 cases per 100 000 population per year. As with most autoimmune diseases, susceptibility is augmented in females. Hyperthyroidism caused by Graves' disease has a female to male ratio of 5:1. Graves' disease may arise in persons of any age, but typically in young women. The characteristic age range is 20 – 40 years of age. 2/3 of manifestations appear after the 35th year of life. The Wickham Study in the United Kingdom revealed that incidence is indicated to be 100 – 200 cases per 100 000 population per year (35). On top of that the incidence in women has been indicated to be 80 cases per 100 000 per year (36). Untreated Graves' disease can lead into severe Thyrotoxicosis called thyroid storm, which can be life-threatening. Long-lasting thyrotoxicosis causes severe weight loss with extreme catabolism of muscle and bone (37). Further Graves' disease is accompanied by ophthalmopathy, dermopathy and acropachy. Concerning the heart researches underline occurrence of cardiac hypertrophy in thyrotoxicosis of different aetiologies, dysrhythmia such as extrasystolic arrhythmia, atrial fibrillation and flutter as well as cardiomyopathy and congestive heart failure (38). Regarding ophthalmopathy in Graves' disease can lead to compromised vision and blindness due to corneal lesions or optic nerve compression in severe cases.

Clinical presentation of patients with Graves' disease is as follows. 70 – 90 % of patients present goitre with high vascularisation, which can be auscultated above the thyroid gland. Further they show psychomotoric agitation with a fine tremor of extended fingers, increased nervousness, restlessness, anxiety, irritability and insomnia. Considering cardiac symptoms patients appear with Sinus tachycardia, possible arrhythmias like extrasystoles and atrial fibrillation as well as increased blood pressure amplitude and systolic hypertension. Many patients lose weight

despite ravenous hunger because of high catabolism. Furthermore patients exhibit warm moist skin and soft thin hair accompanied with sweat and possible subfebrile temperatures due to intolerance to heat. Concerning the digestive system patients report increased bowel frequency with possible diarrhoea. Moreover myopathy can be found in patients with Graves' disease. 50 % display pathologic glucose tolerance. In respect of the endocrinal/reproductive system disturbances in menstrual cycles as well as infertility can be detected. Additionally to these general symptoms Graves' disease features special findings such as endocrine ophthalmopathy/orbitopathy in more than 90% of cases, the Graves' triad composed of goitre, exophthalmos and tachycardia in about 50% of cases, rarely pretibial myxoedema (<5% of cases) and acropachy. Finally patients can also appear with a specific form of hyperthyroidism called thyrotoxic crisis/coma. This syndrome can be evolved spontaneous in hyperthyroidism, often after iodine uptake in patients with autonomy of the thyroid gland, after stopping an antithyroid therapy, after thyroidectomy among others. According to Hermann there are 3 stages in thyrotoxic crisis/coma. Stage 1 is characterised by Tachycardia (>150/min) or tachyarrhythmia, fever up to 41°C, sweating, dehydration, psychomotor agitation, tremor, anxiety, vomiting, diarrhoea, muscle weakness and asthenia. Stage 2 shows additional disturbance of consciousness, somnolence, psychotic states and disorientation. And the last stage arises with coma accompanied by possible adrenocortical insufficiency and circulatory collapse. According to a Danish population-based register study Graves' disease patients showed higher mortality rates, in terms of mortality due to cardiovascular and lung disorders in comparison to general population (39).

Differential Diagnoses to Graves' disease are psychosis, other febrile illness e.g. infections, cocaine or amphetamine abuse, tachycardia of other origin, subacute thyroiditis, hyperhidrosis and vegetative dystonia. Hyperthyroidism is characterised by both increased sympathetic and decreased vagal modulation (40).

The workup of Graves' disease starts with examining patients' history for any iodinated drug, topical agents such as povidone- iodine or contrast media followed by the clinical picture of the patient. Afterwards laboratory studies are performed investigating basal TSH, free T3 and free T4 levels as well as TSH receptor

autoantibodies (TRAK-AB) and anti- TPO-AB. In detail the basal TSH-level, which is the usual screening test for Hyperthyroidism, is reduced. Free T3 and T4 levels are usually elevated in overt Hyperthyroidism whereas in subclinical hyperthyroidism the free T3 and T4 levels remain in normal range. In immunogenic hyperthyroidism such as Graves' disease TRAK-AB in > 95% and anti-TPO-AB in about 70% can be detected. Further imaging procedures are necessary. The ultrasound with colour-Doppler evaluation displays a defined or diffuse hypoechoic picture as well as hypervascularisation of the thyroid gland. Further a scintigraphy with Tc-99m-Pertechnetate (TcT) is performed to determine the TcT- uptake (TcTU) of the thyroid gland. In Graves' disease the TcTU is increased and shows a homogenous intensive radionuclide accumulation in immunogenic hyperthyroidism.

The treatment of Graves' disease involves on the one hand the relief of symptoms and on the other hand the restoration of euthyroid state. Restoration of euthyroidism can be achieved with antithyroid drugs, which block the synthesis of MIT and DIT but not the incretion of the already synthesized hormones T3 and T4, so called sulphur containing antithyroid drugs. These are e.g. Propylthiouracil, Thiamazol and Carbimazole. Other antithyroid drugs are perchlorates inhibiting the iodide uptake into the thyroid gland. All the side effects of hyperthyroidism are treated symptomatically if possible. E.g. adrenergic hyperfunction is treated with beta-adrenergic blockade. Additionally radioactive can be used for therapy of Graves' disease. As radioiodine therapy has a delay of weeks to operate, antithyroid drugs are applied before and afterwards. Indications for radioiodine therapy over antithyroid agents involve immunogenic hyperthyroidism (Graves' disease), thyroidal autonomy, recurrence of hyperthyroidism after thyroidectomy and contraindications for surgery among others. Thyroidectomy is no longer the recommended first-line therapy for Graves' disease. Euthyroidism should always be achieved first with antithyroid drugs. Subtotal resection of the thyroid gland (< 2ml residual thyroid gland) is the standard procedure in Graves' disease. Total thyroidectomy is executed in suspicion of malignancy. Surgery for hyperthyroidism has negligible mortality and acceptable morbidity in experienced hands. It is a definite option in selected cases. Immediate and permanent cure of hyperthyroidism is achieved, with no recurrences, after total thyroidectomy (41,42).

1.4.3 Hashimoto's Thyroiditis

Hashimoto's thyroiditis is part of the range of autoimmune thyroid diseases. Hashimoto's thyroiditis is accompanied by destruction of thyroid cells by various cell- and antibody-mediated immune processes. Iodine deficiency is the most common reason for Hypothyroidism worldwide whereas Hashimoto's thyroiditis is ranked first in iodine-sufficient regions. Moreover Hashimoto is the most frequent form of thyroiditis with a Prevalence of 5 – 10%. The incidence of Hashimoto is estimated to be 9 times higher in females. Predominantly Hashimoto afflicts women between 30 – 50 years. Additionally the average incidence of hypothyroidism increases with age in both sexes. Further Hashimoto shows increased incidence with other autoimmune disorders called polyendocrine autoimmune syndromes (PAS). E.g. PAS type 2 (carpenter syndrome): Addison's disease, diabetes mellitus type 1 and Hashimoto's or Graves' disease; or Schmidt syndrome: Addison's disease and autoimmune Hashimoto's thyroiditis.

Hashimoto's Thyroiditis is mainly caused by autoreactive T-cell-mediated cytotoxicity directed against thyroid cells mediating local inflammation and apoptosis. Local infiltrating inflammatory cells, such as T-cells, macrophages and dendritic cells mediate further expression of cytokines, which impair thyroid cell function and enhance T-cell-mediated cytotoxicity. The role of autoantibodies in inflammation and apoptosis has not really been cleared yet. People with classic Hashimoto's thyroiditis have antibodies interacting with thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG), and to a less extent, TSH receptor blocking Antibodies (TBII). The role of thyroid antibodies in thyroid cell destruction is unclear but anti-TPO fix complement and may cause secondary damage. TBII are responsible for hypothyroidism. Anyway 10 – 15% remain serum antibody negative, despite showing symptoms of Hashimoto's thyroiditis. Aetiology of Hashimoto's thyroiditis combines genetic and environmental factors. Genetic factors take the lead with 80 % in inducing immunity. In this process participate some HLA genes (HLA-DR3, -DR4, -DR5) and non-HLA genes (CTLA-4, CD40, PTPN22, TG, TSH). The remaining 20 % are ascribed to environmental factors (smoking, iodine intake, infectious conditions, physical and emotional stress

among others) and physiological conditions such as pregnancy, aging and female gender.

The onset of Hashimoto's thyroiditis remains frequently unnoticed. The majority of patients are diagnosed in the late stage, when the lymphocytic inflammatory destruction process has lead to a hypothyroidism. Nowadays, thanks to TSH screening, a reliable screening test for thyroid diseases enabled an early recognition of hypothyroid patients, who show unspecific initial symptoms like tiredness, weight gain and poor concentration. Patients with overt hypothyroidism present physical and mental decline in performance, poor motivation, tiredness, slowing down, altered facial appearance and prolonged Achilles tendon reflex time. Further they have increased sensitiveness to cold. Their skin appears to be dry, cool, pasty, pale-yellow and scaly. Hair turns dry and brittle. Patients often feel constipated. The voice sounds raw and hoarse. Due to hypercholesterinaemia people show early signs of arteriosclerosis. Regarding the heart hypothyroids can evolve a myedematous heart showing bradycardia, cardiac enlargement and low voltage ECG. Considering the effects on gonads hypothyroids display disturbed menstrual cycles, defects in spermatogenesis, infertility and increased abortion rates.

Nowadays extremely rare but the most dramatic form of hypothyroidism is myxoedema coma, which has high mortality despite intensive care. Apart from usual symptoms myxoedema coma is accompanied by often not measurable hypothermia, bradycardia, hypotonia, hypoventilation, seizures and coma. Generally there are other factors for manifestation like infections, operations or traumata.

As described above primary hypothyroidism in iodine sufficient areas is due to autoimmune hypothyroidism. The presence of pathognomonic symptoms and physical findings imply a serum TSH test to establish primary hypothyroidism. Additionally free T4 levels are detected to correctly interpret high TSH levels. The diagnosis is validated by evidence of anti-TPO-AB in 95 % of cases or anti-TG-AB in 70 % of cases. Then Ultrasonography is performed to evaluate the thyroid gland and exclude thyroid nodules. Further diagnostic measure is fine needle biopsy and

histological workup. Typically the thyroid gland shows, appropriate for a lymphocytic thyroiditis, diffuse lymphocytic and plasma cell infiltration and in end stages fibroses and atrophy.

The treatment of choice for Hashimoto's thyroiditis is thyroid hormone replacement. The drug of choice is Levothyroxine (LT4). To approach the individual dose LT4 has to be titrated by observing the well- being of the patient and the basal TSH level, which should be in normal range if circumstances respectively side effects permit to do so. Otherwise it is sufficient to approach TSH levels to a slightly elevated state. Usually the titration process lasts between 6 – 8 weeks.

1.4.4 Atherosclerosis

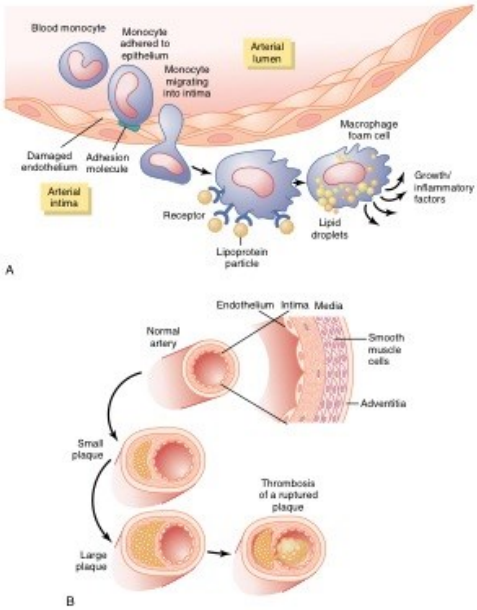


Figure 8. Development of atherosclerotic plaque. A: Attachment of a monocyte to an adhesion molecule on a damaged endothelial cell of an artery. The monocyte then migrates through the endothelium into the intimal layer of the arterial wall and is transformed into a macrophage. The macrophage then ingests and oxidizes lipoprotein molecules, becoming a macrophage foam cell. The foam cells release substances that cause inflammation and growth of the intimal layer. B: Additional accumulation of macrophages and growth of the intima cause the plaque to grow larger and accumulate lipids. Eventually, the plaque could occlude the vessel or rupture, causing the blood in the artery to coagulate and form a thrombus. Modified from Guyton AC. (5).

The word atherosclerosis is derived from Greek. Athere means focal accumulation of lipid and sclerosis thickening of arterial intima. Atherosclerosis is a systemic

inflammatory disease and affects large and medium-sized muscular arteries. The pathologic mechanisms are as follows: endothelial dysfunction, vascular inflammation and accumulation of lipids, cholesterol, calcium and cellular debris within the intima of the arterial wall.

Cardiovascular disease is the most common cause of death in Europa (4.35 million/year) and in the United States of America (2600/day). About 50% died from coronary heart disease and 33% from stroke provoked by atherosclerosis. In western industrial nations 300/100.000 inhabitants suffer myocardial infarction yearly and 30% result in death. Predominantly Atherosclerosis is an asymptomatic condition and therefore it is hard to determine the exact frequency. The process starts in childhood with fatty streaks and progresses by the years into lesions and culminates in organ specific clinical manifestations of the disease in the fifth and sixth decade of life. Usually men have a higher prevalence in coronary artery disease (CAD). Nevertheless women converge to men by 10 years after menopause. Furthermore diabetes and smoking eliminate the protection from heart disease associated with female sex.

The major risk factors for CAD can be classified in modifiable or non-modifiable:

1.) Lipid alterations
2.) Diabetes mellitus
3.) Obesity
4.) Age (m>45 y; f>55 y)
5.) Arterial hypertension
6.) Coronary heart disease (CHD)/ myocardial infarction in first degree relatives prior to the age of 55 in men or 65 in women
7.) Smoking

Beyond that other risk factors are e.g. physical inactivity, chronic kidney disease, inflammatory states in CHD patients, systemic lupus erythemathosus, rheumatoid arthritis, metabolic syndrome, chronic inflammation, lipid metabolism disorders (differing to major risk factors: e.g. increased lipoprotein(a) levels), glucose tolerance disorders and depression.

1) Considering lipid metabolism 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 (43). Furthermore a study by Roos et al. showed an association between subclinical hypothyroidism and hyperlipidaemia (44). Iqbal et al. also found a positive correlation between TSH and increased total cholesterol and LDL cholesterol in subclinical hypothyroid patients. (45)

2) Examining glucose metabolism a study by Maratou et al. clearly showed that not only in hypothyroid patients, but also in patients with subclinical hypothyroidism, insulin resistance was observed (46). Moreover, when determining insulin secretion and insulin sensitivity in hypothyroid patients some studies reveal no differences (47,48), others found decreased (49) as well as increased rates are described (46). 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 (50,51), or increased (52–56) and even decreased rates (57,58).

3) Obesity, beyond other dysfunctions contributes to an atherogenic lipid profile as well as to insulin resistance, independent of thyroidal dysfunction. Gruber et al. have shown lately that obesity reduces the bioavailability of nitric oxide, even in juveniles (59). Iacoballis et al. found an association between TSH, BMI and the adipocytokine leptin in uncomplicated obese women (60). Obermayer-Pietsch et al showed a direct influence of thyroid hormones on leptin regulation (61). In morbidly obese euthyroid patients, fT3 and TSH levels were found to be significantly increased compared to non-obese subject group (62). De Pergola et al. found a direct association between fT3, TSH and waist circumference in overweight and obese euthyroid women (63). Summarising there is substantial evidence for an interaction of thyroid disease and obesity; however results are in part conflicting.

Thyroid dysfunction may contribute to atherogenic lipid profile alterations, endothelial dysfunction, hormonal and hemodynamic changes and coagulation disturbances (64,65). It is hypothesised that, the family of thyroid hormone receptors (TR), which are ligand-binding transcription factors mediate these effects via T3 (66). Gene expression via TR/T3 includes at least 149 genes of the lipid and glucose metabolism, cell cycle, inflammation and stress response. Beyond TR, the transcription factor nuclear factor (NF) kappa B may also be involved (67,68). NF-kappa-B is a redox sensitive transcription factor, which is also involved in a wide variety of physiological pathways, including metabolism, inflammation and apoptosis. Antunes et al showed in a current study, that TSH strongly activates the NF-kappa-B pathway in adipocytes, which have been identified as TSH target cells (69,70).

Thyroid cells produce a number of pro-inflammatory molecules, which will tend to exacerbate the autoimmune process (71). Further inflammation and (pro-) inflammatory molecules accelerate atherosclerosis by impairing endothelial function (72,73) Moreover inflammatory markers, especially CRP, have been associated with thyroidal dysfunction and related cardiovascular risk in hypothyroid patients (74–76). Additionally Ozcan et al. currently found in patients with subclinical hypothyroidism increased CRP levels, which decreased during replacement therapy to a level comparable to controls (77). An inflammatory status and oxidative stress further contributes to atherogenic lipid-alterations, e.g. lipid peroxidation of low-density lipoproteins (LDL). Recently a study indicates oxidative stress, which contributed to lipid peroxidation, as MDA levels were significantly elevated, in patients with primary hypothyroidism (78).

Considering the association between atherosclerosis and rheumatoid disorders researches underline higher risk for respectively premature occurrence of atherosclerosis (79).

Although the pathophysiologic pathways are unclear, investigations reveal that patients with depressive symptoms exhibit increased risk of atherosclerotic progression as well as cardiovascular events (80,81).

1.4.5 Summary

Recapitulating, 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, dysfunction of the thyroid gland varies dependent on the stage of the disease, resulting in hypo-, hyper- and euthyroid function. Thyroid dysfunction has been implicated in numerous pathophysiological mechanisms, including cardiovascular disease (CD). However, the impact of thyroidal dysfunction on atherosclerosis, especially regarding the different causes and stages of atherosclerosis remain elusive to date. Thyroid dysfunction may be involved in CD, as it has been shown that thyroidal dysfunction is involved in various concomitant pathophysiological mechanisms like obesity, insulin resistance, inflammation and endothelial dysfunction. Cardiovascular diseases are beyond cancer the most life threatening diseases in the western world. As it has been shown not only the lipid metabolism but also inflammatory processes are strongly involved in cardiovascular disease. The impact of thyroidal diseases including autoimmune diseases of the thyroid gland is not investigated in detail to date. Especially possible beneficial effects of thyroid therapy on metabolic risk remain elusive. The current stage of knowledge on thyroid dysfunction and atherosclerosis is that neither hyper- nor hypothyroidism is advisable in respect of the cardiovascular system. Nevertheless a couple of questions remain:

How does thyroid dysfunction influence the different stages of atherosclerosis?
How do thyroid therapies with thyroid hormone supplementation or anti-thyroid drugs influence CD? Does thyroid therapy intervene in or probably prevent atherosclerosis? What is the impact of thyroid therapy on atherosclerosis related metabolic dysfunctions, especially regarding obesity, systemic low-grade inflammation, atherogenic lipid alterations and insulin resistance?

1.5. Hypothesis

We here hypothesise that thyroidal dysfunctions, especially hyper- and hypothyroidism, are implicated in cardiovascular disease. Further the various causes and stages of atherosclerosis may be influenced by thyroidal dysfunction. Hyper- and hypothyroidism may further be implicated in cardiovascular related disorders, thereby enhancing and triggering pathophysiological effects of atherosclerosis. Thyroid therapy may therefore not only normalise thyroid hormone levels, but also intervene in cardiovascular risk by reducing thyroid related metabolic effects.

1.6 Aim

The aim of the present study is to examine the impact of thyroid therapy, both in hypo- and hyperthyroid patients on cardiovascular risk. This is achieved by investigating thyroid disease patients before and after 6 months of therapy in the setting of the FWF Project NOTHYS (P22694-B18).

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, the nitric oxide pathway, inflammation, lipid profile, glucose metabolism, and hormones will be analysed in hyper- eu- and hypothyroid patients before and after 6 months of medication as well as in healthy controls. Additionally, body measurements including lipometry and oral glucose tolerance test will be performed.

2 Patients and Methods

2.1 Patients

Patients, who attended the Department of Endocrinology of the Medical University Graz due to possible thyroid dysfunction with a mean age between 19-75 years, were investigated, diagnosed and invited to participate in the study by an endocrinologist. Healthy probands were patients´ relatives and friends as well as not related ones, who were also examined by an endocrinologist including ultrasound of thyroid gland. They were age, gender and BMI matched. All subjects were anonymised with identification numbers. Patients were asked to attend the study before starting routine medication (baseline characteristics) and after 6 months of treatment (follow up). Every patient and proband was investigated by thyroid ultrasound, thyroid scintigraphy and fine needle punction if necessary. Subject examination implicated blood- and urine sampling as well as body measurements by lipometry. Additionally both lifestyle behaviour like smoking, physical activity and further medication, e.g. hormonal contraceptive was recorded by questionnaire.

Exclusion criteria for attendance were: malignant thyroid disease, medication affecting thyroid pathways, st. p. thyroidectomy, pregnancy and nursing.

A total number of 96 subjects, 48 patients and 48 healthy probands, joined the study shown in Table 1. Patients were sub-grouped regarding their thyroid function into hyper- hypo and euthyroid.

All probands signed an informed consent.

The ethics committee of the Medical University Graz, Austria approved the study. (20 - 361 ex 08/09)

2.2 Laboratory analyses and Lipometry

2.2.1 Analyses of thyroid parameters

The thyroid parameters free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH) as well as the auto-Immune antibodies TPO-AB and TRAK were analysed routinely at the Endocrinology Laboratory, Department of Endocrinology and Metabolism, Medical University Graz.

2.2.2 Analyses of metabolic disease related parameters

Analyses of metabolic disease related parameters included parameters of the lipid metabolism as well as inflammatory biomarkers and hormones. Parameters of the lipid metabolism including cholesterol, HDL- cholesterol, LDL- cholesterol triglycerides and oxidised LDL were analysed routinely at the KIMCL. Inflammatory as well as anti-inflammatory parameters including CRP, IL-6 and IL-10 were determined by ELISA (BenderMedSystems, Austria). The hormone status of PTH was done routinely at the KIMCL and the Endocrinology Laboratory, Department of Endocrinology and Metabolism, Medical University Graz.

2.2.3 Lipometry

The lipometer is a computerised optical system for precise evaluation of absolute thicknesses of subcutaneous adipose tissue in mm (79-83). This device was calibrated and evaluated by using computed tomography as reference. It has been examined by TUV Austria Services and was cleared for medical use. The data collection is a standardized set of 15 anatomically clearly defined body sites from neck to calf. The device interprets the information of individual body fat distribution. The topography of the subcutaneous adipose tissue is like an individual „fingerprint“ of every examined person. The profile of patients with metabolic syndrome shows a typical „apple-like“ body fat distribution. In addition to lipometry, height, weight, waist and hip circumference as well as blood pressure were quantified.

2.2.4 Clinical safety parameters

To detect the physical condition the following parameters were examined routinely at the KIMCL. I.E. Hemogram, Electrolytes (Potassium, Phosphate, Sodium, Chloride, Calcium, Magnesium), Kidney (Creatinine, Urea, Uric acid), Liver (Bilirubin, Alkaline phosphatase, Gamma-glutamyltransferase, Aspartate-amino-transferase, Alanine-amino-transferase, choline esterase), Heart (Lactate dehydrogenase, Creatinekinase), 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, Haemoglobin, Albumin, Creatinine, Osmolarity)

2.3 Statistics

2.3.1 Statistical analysis

Results are presented as means ± standard deviations. Continuous variables were compared using student's t-test for independent samples or Mann-Whitney U test, depending on distribution of data. Paired variables were analysed using t-test for paired samples. Correlations between parameters were elaborated by linear regression analysis according to Pearson. P-values <0,05 were considered as statistically significant and P-values <0,01 as highly significant. Subsequent multiple testing by linear stepwise regression analysis was performed to determine the significance of test variables.

3 Results

3.1 Study cohort

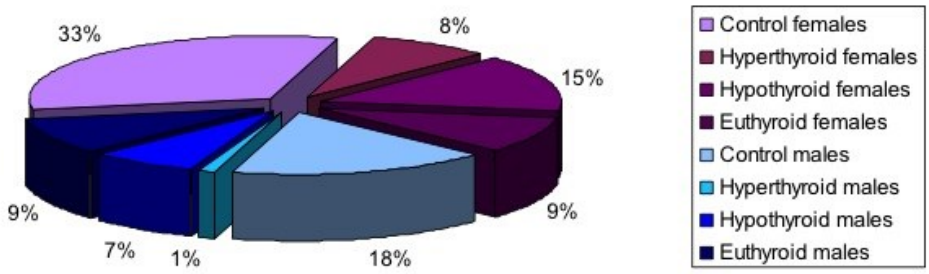


Figure 9. Relative distribution of study cohort

The relative distribution of the study cohort is displayed in Figure 9. Study cohort is based on 65% females and 35% males. In detail there are 31 healthy, 8 hyperthyroid, 14 hypothyroid and 9 euthyroid females compared with 17 healthy, 1 hyperthyroid, 7 hypothyroid and 9 euthyroid males.

3.2 Baseline characteristics

Table 1: Baseline characteristics of study cohort

Characteristics	Healthy	Hyperthyroid	Hypothyroid	Euthyroid
Sex [f/m]	31\7	8\1	14\7	9\9
Age [years]	37,6 ± 11,4	41,6 ± 8,0	34,2 ± 10,6	43,7 ± 14,6*[2]
Smoker [yes/no]	7\41	2\7	2\19	5\13
Physical Activity [h/w]	3,56 ± 2,86	1,44 ± 1,65*[1]	2,36 ± 2,53	2,83 ± 3,31
BMI [kg/m^2]	24,86 ± 5,09	26,18 ± 7,26	25,33 ± 5,58	25,03 ± 4,83
Bodyweight [kg]	72,30 ± 16,11	77,53 ± 20,55	72,81 ± 20,85	75,47 ± 17,36
Body length [cm]	170,9 ± 7,4	172,2 ± 3,6	168,4 ± 8,1	173,1 ± 9,4
Waist circumference [cm]	85,69 ± 11,74	94,11 ± 18,59	87,33 ± 16,86	89,19 ± 14,67
waist-to-hip ratio	0,86 ± 0,07	0,92 ± 0,10	0,87 ± 0,10	0,88 ± 0,08
waist-to-length ratio	0,50 ± 0,07	0,54 ± 0,11	0,51 ± 0,09	0,51 ± 0,07
systolic BP [mmHg]	118,1 ± 13,1	131,0 ± 17,2*[1]	126,9 ± 14,8*[1]	126,6 ± 16,9*[1]
diastolic BP [mmHg]	74,56 ± 9,71	75,00 ± 15,53	81,25 ± 7,78**[1]	75,78 ± 9,71

* p<0,05 (parametric, T-test); 1 compared to control; 2 compared to hypothyroid

Baseline characteristics are summarised in Table 1. The facts are presented as mean ± standard deviation (SD). Thyroid patients and healthy controls showed similar results in BMI, bodyweight, body length, waist circumference, waist-to-hip as well as waist-to-length ratio. Age was significantly higher (p<0,05) in euthyroid patients compared to hypothyroid ones. In terms of smoking we had 7 smokers out of 48 in healthy controls, 2 out of 9 in hyperthyroid, 2 out of 21 in hypothyroid and 5 out of 18 in euthyroid patients. We found a significant lower (p<0,05) amount of physical activity [h/w] in hyperthyroid group as against controls. Considering blood pressure (BP) we detected significantly elevated (p<0,05) systolic BP levels in thyroid patients than in healthy controls and further we discovered a highly significant (p<0,01) increased diastolic BP level in hypothyroids in comparison to controls.

Table 2: Thyroid parameters of study cohort

Characteristics	healthy	Hyperthyroid	Hypothyroid	Euthyroid
TSH basal [µUnits/l]	2,06 ± 085	0,01 ± 0,02$^{+++1,2}$	7,10 ± 7,14^{+++1}	1,80 ± 1,09$^{+++1,3}$
T3 [pmol/l]	5,04 ± 0,61	8,04 ± 3,62^{+1}	5,08 ± 0,61	5,02 ± 0,46
T4 [pmol/l]	13,80 ± 2,02	19,17 ± 12,07^{+1}	13,93 ± 2,55	14,84 ± 2,62
TPO-AB [U/ml]	8,96 ± 3,69	688,11 ± 834,34^{+++1}	307,71 ± 438,38^{++1}	246,67 ± 594,95^{++1}
TRAK-AB [U/ml]	0,69 ± 1,27	222,53 ± 248,92^{+++1}	3,45 ± 7,51^{++3}	6,92 ± 13,04^{++3}
PTHi [pg/ml]	36,32 ± 11,10	33,34 ± 14,40	34,26 ± 11,23	32,83 ± 12,15

+ 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 control; 2 compared to hypothyroid; 3 compared to hyperthyroid

Investigating the thyroid parameters, including TSH, fT3, fT4, TPO-AB and TRAK-AB revealed significant differences in levels of all groups (Table 2). We spotted highly significant (p<0,001) differences in levels of thyroid patients compared to controls. Beyond that we found highly significant lower (p<0,001) levels of TSH in hyperthyroids as well as in euthyroids compared with hypothyroid patients. Analysis of fT3 and fT4 showed significant differences (p<0,05) between hyperthyroid patients and healthy controls. Further we detected highly significant elevated parameters in TPO-AB in hyperthyroids compared to controls (p<0,001) as well as hypo- and euthyroid against controls (p<0,01). Investigations of TRAK-AB showed a highly significant difference between hyperthyroid patients and control group. Moreover TRAK-AB levels in hypothyroid and euthyroid patients were highly significant lower (p<0,01) in comparison to hyperthyroids. Patients and controls showed similar results in PTHi.

Table 3: parameters of lipid metabolism and cardiovascular risk factors in healthy controls and thyroid dysfunction patients

Characteristics	healthy	Hyperthyroid	Hypothyroid	Euthyroid
Cholesterol	187,10 ± 32,54	207,33 ± 47,23	202,14 ± 33,28	189,11 ± 34,35
HDL	68,88 ± 18,71	65,33 ± 33,26	69,62 ± 17,87	65,39 ± 20,76
LDL	106,71 ± 26,48	114,57 ± 35,85	114,48 ± 38,59	110,94 ± 26,45
LDL/HDL ratio	2,88 ± 0,85	4,02 ± 2,37	3,21 ± 1,48	3,12 ± 0,93
Triglyceride	84,40 ± 47,22	147,22 ± 152,21	90,67 ± 32,21	92,72 ± 37,96
Ox-LDL	34,44 ± 13,28	34,82 ± 13,04	36,18 ± 12,12	34,11 ± 14,50
ADMA	0,91 ± 0,34	1,07 ± 0,41	0,78 ± 0,25	0,73 ± 0,20$^{+1,3}$
CRP	1,84 ± 2,08	3,80 ± 4,07	3,03 ± 3,98	1,94 ± 2,09
IL-6	2,19 ± 4,70	5,30 ± 9,31	7,94 ± 22,07	2,71 ± 4,89
IL-10	4,44 ± 6,92	4,16 ± 1,60	4,99 ± 6,78	7,03 ± 8,50

+ $p<0,05$ (non parametric, Mann-Whitney-U-test);
1 compared to control; 3 compared to hyperthyroid

Investigation of parameters of lipid metabolism and cardiovascular risk factors including Cholesterol, HDL, LDL, LDL/HDL- ratio, triglycerides, ox– LDL, CRP, IL-6 and IL-10 in healthy controls and thyroid dysfunction patients revealed no significant difference except ADMA. Euthyroid patients showed significant lower ADMA-scores compared to healthy controls and hyperthyroids (Table 3).

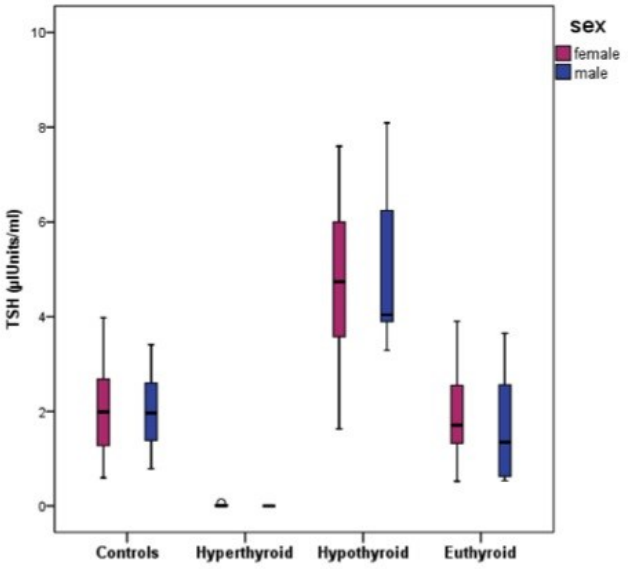


Figure 10. Box and Whisker Plot of TSH

Analysis of participants regarding gender revealed no significant disparity (Fig. 10).

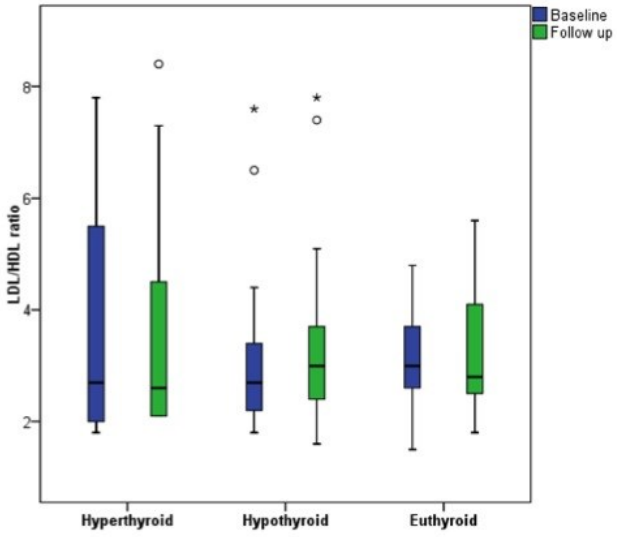


Figure 11. Box and Whisker Plot of baseline and follow up

Analyses of LDL/HDL ratio before and after 6 months of treatment summarised in Figure 11

3.3 Regression analyses of thyroid parameters

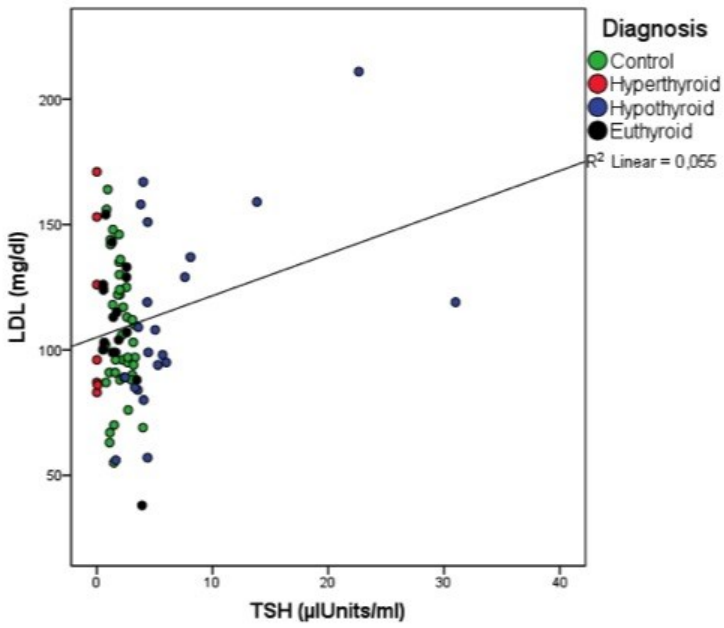


Figure 12a. Regression analysis of TSH and LDL in study cohort

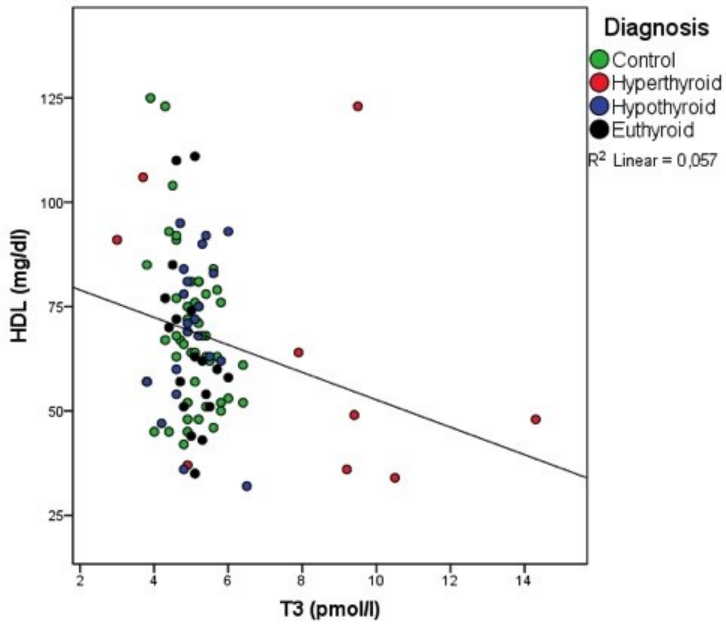


Figure 12b. Regression analysis of T3 and HDL in study cohort

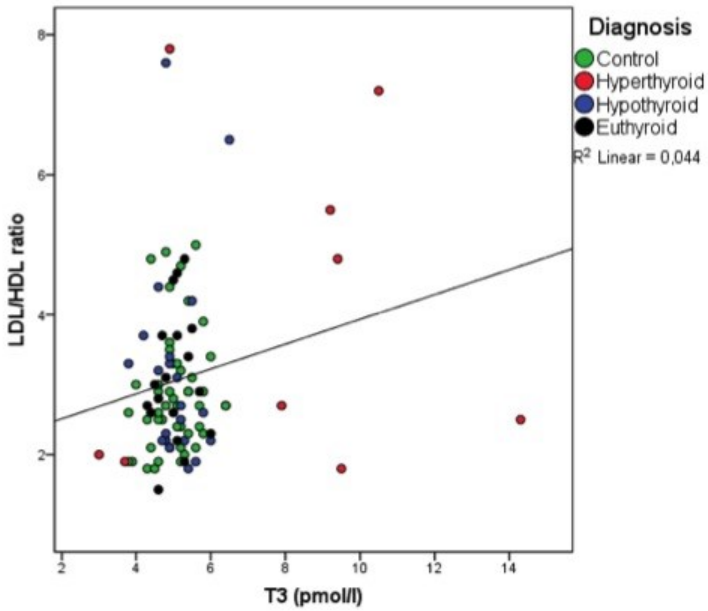


Figure 12c. Regression analysis of T3 and LDL/HDL ratio in study cohort

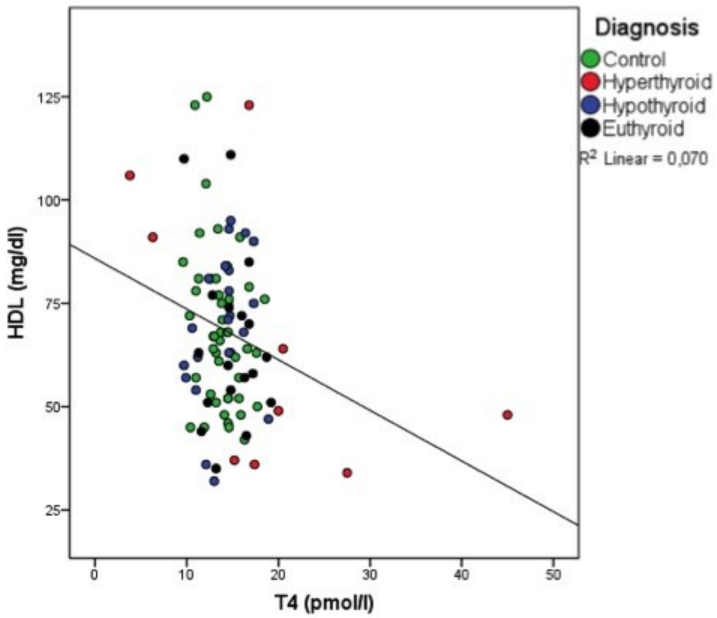


Figure 12d. Regression analysis of T4 and HDL in study cohort

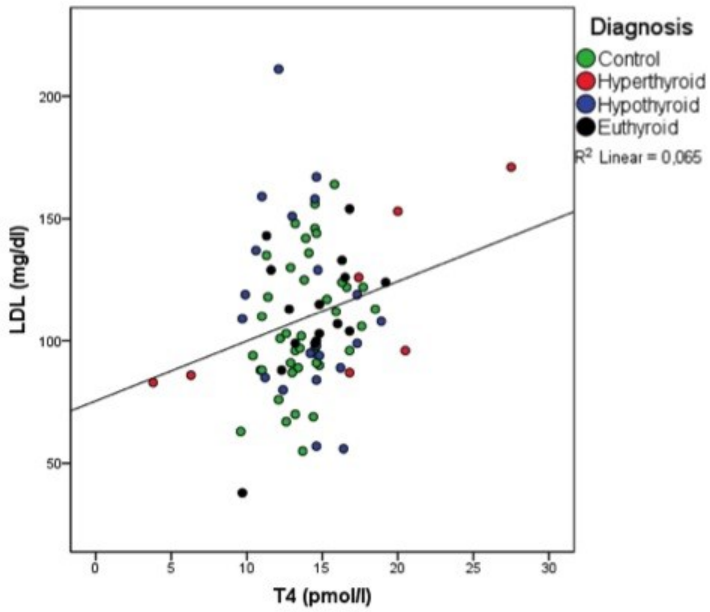


Figure 12e. Regression analysis of T4 and LDL in study cohort

To determine possible correlations of thyroid parameters, we performed linear regression analyses between thyroid parameters and physical activity, body measurement parameters, BP and lipid parameters (Figure 12a – e). We found significant correlations between TSH and LDL (p = 0,003; r = 0,235), T3 and HDL (p = 0,019; r = - 0,239), T3 and LDL/HDL- ratio (p = 0,039; r = 0.211), T4 and HDL (p = 0,009; r = - 0,264) also between T4 and LDL (p = 0,019; r = 0,255).

3.4 Effects of thyroid therapy

Table 4: characteristics of patients before and after 6 months of treatment

Characteristics	Hyperthyroid		Hypothyroid		Euthyroid	
	Baseline	follow up	Baseline	follow up	Baseline	follow up
Physical Activity [hours/week]	1,44 ± 1,65	2,39 ± 2,29	2,36 ± 2,53	2,55 ± 2,24	2,83 ± 3,31	2,28 ± 2,23
BMI [kg/m^2]	26,18 ± 7,26	26,40 ± 6,28	25,33 ± 5,58	26,34 ± 7,15	25,03 ± 4,83	25,33 ± 4,69*
Bodyweight [kg]	77,53 ± 20,55	79,73 ± 18,65	72,81 ± 20,85	73,04 ± 20,05	75,47 ± 17,36	76,23 ± 17,19
Body length [cm]	172,22 ± 3,63	172,44 ± 3,54	168,43 ± 8,16	168,75 ± 7,94	173,11 ± 9,44	172,89 ± 9,08
Waist circumference [cm]	94,11 ± 18,59	96,67 ± 15,26	87,33 ± 16,86	88,69 ± 15,37	89,19 ± 14,67	92,28 ± 12,38*
waist-to-hip ratio	0,92 ± 0,10	0,92 ± 0,06	0,87 ± 0,10	0,88 ± 0,09	0,88 ± 0,08	0,91 ± 0,09
waist-to-length ratio	0,54 ± 0,11	0,56 ± 0,09	0,51 ± 0,09	2,64 ± 9,70	0,51 ± 0,07	0,52 ± 0,07*
systolic BP [mmHg]	131,00 ± 17,23	127,22 ± 23,46	126,95 ± 14,82	120,56 ± 12,94*	126,67 ± 16,96	119,59 ± 12,39
diastolic BP [mmHg]	75,00 ± 15,53	76,33 ± 12,85	81,25 ± 7,78	79,06 ± 7,59	75,78 ± 9,71	71,24 ± 10,25*
Cholesterol	207,33 ± 47,23	206,33 ± 60,48	202,14 ± 33,28	169,52 ± 35,51	189,11 ± 34,35	187,29 ± 38,39
HDL	65,33 ± 33,26	60,67 ± 22,93	69,62 ± 17,87	64,71 ± 21,22*	65,39 ± 20,76	60,47 ± 21,51
LDL	114,57 ± 35,85	130,86 ± 50,83	114,48 ± 38,59	122,44 ± 33,72	110,94 ± 26,45	117,50 ± 25,84
LDL/HDL- ratio	4,02 ± 2,37	3,10 ± 2,40	3,21 ± 1,48	3,44 ± 1,63*	3,12 ± 0,93	3,35 ± 1,11*
Triglyceride	147,22 ± 152,21	124,67 ± 133,77	90,67 ± 32,21	85,62 ± 28,56	92,72 ± 37,96	85,59 ± 43,57
Ox-LDL	34,82 ± 13,04	39,64 ± 25,18	36,18 ± 12,12	32,77 ± 10,90	34,11 ± 14,50	34,46 ± 9,40
ADMA	1,07 ± 0,41	0,68 ± 0,13*	0,78 ± 0,25	0,58 ± 0,17**	0,73 ± 0,20	0,60 ± 0,08*

CRP	3,80 ± 4,07	14,86 ± 37,24	3,03 ± 3,98	2,36 ± 3,07	1,94 ± 2,09	1,65 ± 1,70
IL-6	5,30 ± 9,31	3,71 ± 5,19	7,94 ± 22,07	5,93 ± 23,36	2,71 ± 4,89	1,56 ± 2,84
IL-10	4,16 ± 1,60	4,59 ± 3,09	4,99 ± 6,78	5,41 ± 8,34	7,03 ± 8,50	4,17 ± 4,11
TSH basal [µUnits/l]	0,01 ± 0,02	3,28 ± 5,42	7,10 ± 7,14	6,24 ± 14,78	1,80 ± 1,09	1,88 ± 1,39
T3 [pmol/l]	8,04 ± 3,62	9,19 ± 9,83	5,08 ± 0,61	4,71 ± 0,67*	5,02 ± 0,46	5,48 ± 1,37
T4 [pmol/l]	19,17 ± 12,07	20,31 ± 19,93	13,93 ± 2,55	14,86 ± 2,12	14,84 ± 2,62	16,08 ± 2,76
TPO-AB [U/ml]	688,11 ± 834,34	661,38 ± 1177,92	307,71 ± 438,38	193,94 ± 339,06	246,67 ± 594,95	148,81 ± 276,02
TRAK-AB [U/ml]	222,53 ± 248,92	83,14 ± 150,86	3,45 ± 7,51	1,66 ± 2,35	6,92 ± 13,04	9,75 ± 20,80
PTHi [pg/ml]	33,34 ± 14,40	44,03 ± 11,66*	34,26 ± 11,23	32,59 ± 8,01	32,83 ± 12,15	36,43 ± 13,61

* p<0,05 (parametric, T-test); ** p<0,01 (parametric, T-test); compared to appropriate baseline group

Characteristics of patients before and after 6 months of treatment are summarised in table 4. After 6 months of treatment probands showed no difference in physical activity, bodyweight, waist-to-hip ratio and of course in body length. But we detected a significant difference ($p<0,05$) of BMI, waist circumference, waist-to-length ratio and diastolic blood pressure in euthyroid patients compared to their appropriate baseline group. Furthermore we found significant ($p<0,05$) changes of systolic blood pressure levels in hypothyroids compared to their initial value. Considering the lipid metabolism we revealed significant variation ($p<0,05$) of HDL-value in hypothyroid probands in comparison to their baseline group. Analysis of LDL/HDL-ratio showed significant differences ($p<0,05$) in hypo- and euthyroid patients in relation to their appropriate baseline group. Investigation of ADMA-score indicated significant lower ($p<0,05$) levels in hyper- and euthyroid patients and even highly significant lower ($p<0,01$) ones in hypothyroids regarding their baseline group. Analysis of inflammatory parameters displayed no significant variation. Referring to thyroid parameters we spotted significant lower ($p<0,05$) levels of T3 in hypothyroid and significant higher ($p<0,05$) levels of PTHi in hyperthyroid patients compared with their appropriate baseline group. Investigation of remaining thyroid parameters including TSH, T4, TPO-AB, TRAK-AB unveiled no significant changes.

4 Discussion

In the present study, we investigated the impact of thyroid therapy in hypo-, hyper- and euthyroid patients and appropriate healthy controls on cardiovascular risk. In Respect of thyroid parameters we spotted highly significant distinguishing levels of TSH both in comparison to controls and within subgroups of thyroid patients. Further analyses showed significant high levels of fT3 as well as fT4 levels in hyperthyroids in relation to controls. On top of that we investigated TPO- and TRAK-AB. The results demonstrated highly significant changes in TPO-AB level in thyroid disorders as against in control group. TRAK-AB were higher in thyroid patients but highly significant raised in hyperthyroids compared to controls, whereas highly significant low levels were detected in hypo- and euthyroid patients in relation to hyperthyroids. These findings are congruent to current knowledge and understanding of thyroid diseases, as described in detail. Analyses of BP exhibited significant elevated systolic BP levels in patients with thyroid disorder compared to control group. Moreover we unveiled highly significant altered diastolic BP levels in hypothyroids against controls. Our findings exactly go along with current knowledge and researches of thyroid disorders (82–85). Mittag j. et al. discovered an association between thyroid hormone and the central nervous system in regulating cardiovascular functions (86). Furthermore Inal S. et al detected a risk of developing non-dipper blood pressure in normotensive patients with either overt or subclinical hypothyroidism induced by elevated TSH levels (87). Additionally Spitzweg C and Reincke M. outlined that raised systolic BP is typical for hyperthyroidism and high diastolic BP can be found regularly in hypothyroid patients (88). In contrast to literature investigation of patients lipid profile featured no significant alterations in lipid parameters including cholesterol, HDL, LDL, triglycerides and ox-LDL (82,89,90). Interestingly ADMA was significantly lower in euthyroids in comparison to control group (91).

After 6 months of treatment we re-examined thyroid patients in our study cohort. In view of anthropometric parameters analyses we detected significant lower systolic BP levels in hypothyroids as well as lower diastolic BP levels in euthyroids compared to appropriate baseline group. According to researches thyroid therapy has a favourable effect on blood pressure, both systolic and diastolic. Dernellis J. and Panaretou M. elaborated the effect of hormone replacement therapy on aortic stiffness and hypertension (92). Faber J. et al. hypothesize potentially beneficial changes in hemodynamic parameters in subclinical hypothyroidism (93). Further on Lakshmi V. et al. detected a positive impact on autonomic status in hypothyroid patients (94). Euthyroids slightly but significantly displayed an increase in BMI and waist circumference contrary to 6 months before. Svare A. et al. suggest a possible weight gain due to elevated TSH levels after evaluating data from the HUNT study in Norway (95). In respect of lipid parameters examinations revealed a slightly but not significant improvement in total cholesterol and triglycerides. Even if investigations unveiled lower HDL and higher LDL values und subsequently changes in LDL/HDL- ratio, patients remained in normal range. These outcomes contradict Pearce EN (96) and Dullaart RP (97). Furthermore we detected significant lower levels of HDL and highly significant lower levels of ADMA in hypothyroids. Additionally euthyroids presented significant lower ADMA levels. Our findings correspond in part to outcomes of the following studies. Arikan E. et al. outlined alterations of ADMA levels both in hypo- and hyperthyroid patients (98). By contrast Hermenegildo C. et al. only revealed altered ADMA levels in hyperthyroids (99). Moreover Ozcan O. et al. discovered reduction of ADMA levels after thyroxine treatment in subclinical hypothyroid patients (77). Further investigations illustrated a significant increase in LDL/HDL- ratio in hypo- and euthyroid patients. Considering the inflammatory parameters we could not find any significant changes to baseline characteristics partly contradicting literature, despite inflammation being a factor in thyroid diseases as well as atherosclerosis and cardiovascular disease. Taddei S. et al. claim endothelial dysfunction in Hashimoto's thyroiditis induced by low-grade inflammation (100). Additionally Nanda N. et al. assert low-grade inflammation being the link between higher oxidative stress and the underlying cardiovascular risk in hypothyroid patients (101). Whereas the study of Hueston WJ. et al. suggests no association between cardiac inflammation respectively CRP and subclinical hypothyroidism (102).

Finally examination of thyroid parameters including TSH, fT3, fT4, TPO-AB and TRAK-AB demonstrated no significant changes except fT3 levels in hypothyroid patients. Generally the thyroid parameters were all approximating their optimum levels thanks to thyroid therapy.

The fascinating results of lipid parameters drove us to perform regression analyses of thyroid parameters with lipid and anthropometric parameters. Regression analyses revealed on the one hand positive correlations between TSH and LDL, fT3 and LDL/HDL- ratio as well as fT4 and LDL and on the other hand negative correlation between fT3 and HDL as well as fT4 and HDL. Our findings go exactly along with literature.

Recapitulating, our findings demonstrate here that thyroid therapy in normal weight patients has a preventive impact on atherosclerosis and subsequently on cardiovascular disease both in hypo- and hyperthyroidism. The pathophysiologic mechanisms of atherosclerosis combined with thyroid disorders remain still unclear to date. However, the association between thyroid disorders and cardiovascular disease have already been attested because of the implication of thyroid dysfunction in hypertension, metabolic disorders such as dyslipidaemia, metabolic syndrome, obesity, diabetes mellitus and glucose tolerance disorders. Therefore thyroid therapy achieves restoration of normal thyroid conditions in patients, resolving of comorbidities in thyroid disorders and subsequently prophylaxis of atherosclerosis and cardiovascular disease. Finally further research is required to clarify the influence of various degrees of thyroid dysfunction in the development of atherosclerosis and cardiovascular morbidity, especially in terms of therapeutic approaches in obese patients.

Bibliography

1. Hafferl A. Lehrbuch der topographischen Anatomie. Zweite Auflage. Berlin, Göttingen, Heidelberg: Springer; 1957. 937 p.
2. Streicher J, Anderhuber F, Pera F, Waldeyer A. Waldeyer - Anatomie des Menschen Lehrbuch und Atlas in einem Band. [Internet]. Berlin: De Gruyter; 2012 [cited 2013 Nov 9]. Available from: http://public.eblib.com/EBLPublic/PublicView.do?ptiID=893640
3. Schünke M, Schulte E, Schumacher U. Prometheus LernAtlas der Anatomie. Stuttgart: Thieme; 2012.
4. Lüllmann-Rauch R. Taschenlehrbuch Histologie 10 Tabellen. Stuttgart; New York, NY: Thieme; 2009.
5. Guyton AC. Textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders; 2006. 1116 p.
6. Nussey S, Whitehead SA. Endocrinology: an integrated approach. Oxford, UK: Bios; 2001.
7. Klinke R, Baumann R. Physiologie: 68 Tabellen. Stuttgart; New York, NY: Thieme; 2010.
8. Silbernagl S, Lang, Florian. Taschenatlas Pathophysiologie. Stuttgart; New York, NY: Thieme; 2009.
9. Herold G. Herold's internal medicine Vol. 1. Köln: Herold; 2010.
10. Herold G. Herold's internal medicine Vol. 2. Köln: Herold; 2010.
11. MSD Sharp & Dohme GmbH (Haar) B, Mark H. Das MSD-Manual der Diagnostik und Therapie. München: Elsevier, Urban & Fischer; 2007.
12. Pschyrembel W. Pschyrembel Klinisches Wörterbuch: 2014. Berlin [u.a.]: De Gruyter; 2013.
13. Böcker W, Heitz PU. Pathologie: hrsg. von W. Böcker ... [et al.]; Koordination: Ph.U. Heitz. München: Urban & Fischer in Elsevier; 2012.
14. Oxford textbook of medicine. 5th ed. Oxford ; New York: Oxford University Press; 2010.
15. Werner SC. Classification of thyroid disease. Report of the Committee on Nomenclature. The American Thyroid Association. I. J Clin Endocrinol Metab.

1969 Jun;29(6):860–2.
16. Monaco F. Classification of thyroid diseases: suggestions for a revision. J Clin Endocrinol Metab. 2003 Apr;88(4):1428–32.
17. Elte JW, Bussemaker JK, Haak A. The natural history of euthyroid multinodular goitre. Postgrad Med J. 1990 Mar;66(773):186–90.
18. Beck-Peccoz P, Chatterjee VK. The variable clinical phenotype in thyroid hormone resistance syndrome. Thyroid Off J Am Thyroid Assoc. 1994;4(2):225–32.
19. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev. 1993 Jun;14(3):348–99.
20. Drexhage HA, Mooij P, Wilders-Truschnig MM. Thyroid growth stimulating immunoglobulins in sporadic and endemic colloid goitre. Thyroidol Aprim. 1990 Dec;2(3):99–105.
21. Brezinschek HP, Wilders-Truschnig M, Leb G, Eber O, Dohr G, Lanzer G, et al. Thyroid growth promoting serum-IgG in endemic goiter. Acta Med Austriaca. 1990;17 Suppl 1:26–7.
22. Dimal P, Wilders-Truschnig M, Leb G, Beham A, Eber O, Hebenstreit J, et al. Thyroid infiltrating dendritic cells, epitheloid cells and giant cells in iodine deficiency. Acta Med Austriaca. 1990;17 Suppl 1:43.
23. Dimal P, Wilders-Truschnig M, Mooij P, Leb G, Eber O, Langsteger W, et al. Expression of various MHC class II molecules and of intracellular adhesion molecule-1 (ICAM-1) on focal clusters of dendritic cells in iodine deficiency goitres. Clin Exp Immunol. 1993 Jun;92(3):397–403.
24. Wilders-Truschnig MM, Drexhage HA, Leb G, Eber O, Brezinschek HP, Dohr G, et al. Chromatographically purified immunoglobulin G of endemic and sporadic goiter patients stimulates FRTL5 cell growth in a mitotic arrest assay. J Clin Endocrinol Metab. 1990 Feb;70(2):444–52.
25. Studer H, Peter HJ, Gerber H. Natural heterogeneity of thyroid cells: the basis for understanding thyroid function and nodular goiter growth. Endocr Rev. 1989 May;10(2):125–35.
26. Wilders-Truschnig MM, Kabel PJ, Drexhage HA, Beham A, Leb G, Eber O, et al. Intrathyroidal dendritic cells, epitheloid cells, and giant cells in iodine deficient goiter. Am J Pathol. 1989 Jul;135(1):219–25.
27. Wilders-Truschnig MM, Leb G, Warnkross H, Langsteger W, Eber O, Dimal

P, et al. Involvement of the immune system in iodine deficient goiter. Thyroidol Aprim. 1992 Apr;4(1):53–5.

28. Wilders-Truschnig MM, Warnkross H, Leb G, Langsteger W, Eber O, Tiran A, et al. The effect of treatment with levothyroxine or iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients. Clin Endocrinol (Oxf). 1993 Sep;39(3):281–6.

29. Volpé R. The role of autoimmunity in hypoendocrine and hyperendocrine function: with special emphasis on autoimmune thyroid disease. Ann Intern Med. 1977 Jul;87(1):86–99.

30. Volpé R. The natural history of autoimmune thyroid disease. Thyroidol Aprim. 1988 Apr;(1):13–20.

31. Thyroid diseases: clinical fundamentals and therapy. Boca Raton: CRC Press; 1993. 664 p.

32. Cruz AAV, Akaishi PMS, Vargas MA, de Paula SA. Association between thyroid autoimmune dysfunction and non-thyroid autoimmune diseases. Ophthal Plast Reconstr Surg. 2007 Apr;23(2):104–8.

33. Jacobson EM, Tomer Y. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. J Autoimmun. 2007 May;28(2-3):85–98.

34. Iwama S, Ikezaki A, Kikuoka N, Kim H-S, Matsuoka H, Yanagawa T, et al. Association of HLA-DR, -DQ genotype and CTLA-4 gene polymorphism with Graves' disease in Japanese children. Horm Res. 2005;63(2):55–60.

35. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf). 1977 Dec;7(6):481–93.

36. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995 Jul;43(1):55–68.

37. Riis ALD, Jørgensen JOL, Gjedde S, Nørrelund H, Jurik AG, Nair KS, et al. Whole body and forearm substrate metabolism in hyperthyroidism: evidence of increased basal muscle protein breakdown. Am J Physiol Endocrinol Metab. 2005 Jun;288(6):E1067–1073.

38. Uchida T, Takeno K, Goto M, Kanno R, Kubo S, Takahashi S, et al. Superior thyroid artery mean peak systolic velocity for the diagnosis of

thyrotoxicosis in Japanese patients. Endocr J. 2010;57(5):439–43.
39. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Graves' disease and toxic nodular goiter are both associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study. Thyroid Off J Am Thyroid Assoc. 2013 Apr;23(4):408–13.
40. Chen J-L, Chiu H-W, Tseng Y-J, Chu W-C. Hyperthyroidism is characterized by both increased sympathetic and decreased vagal modulation of heart rate: evidence from spectral analysis of heart rate variability. Clin Endocrinol (Oxf). 2006 Jun;64(6):611–6.
41. Pradeep PV, Agarwal A, Baxi M, Agarwal G, Gupta SK, Mishra SK. Safety and efficacy of surgical management of hyperthyroidism: 15-year experience from a tertiary care center in a developing country. World J Surg. 2007 Feb;31(2):306–312; discussion 313.
42. Genovese BM, Noureldine SI, Gleeson EM, Tufano RP, Kandil E. What is the best definitive treatment for Graves' disease? A systematic review of the existing literature. Ann Surg Oncol. 2013 Feb;20(2):660–7.
43. Oge A, Sozmen E, Karaoglu AO. Effect of thyroid function on LDL oxidation in hypothyroidism and hyperthyroidism. Endocr Res. 2004 Aug;30(3):481–9.
44. Roos A, Bakker SJL, Links TP, Gans ROB, Wolffenbuttel BHR. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007 Feb;92(2):491–6.
45. Iqbal A, Jorde R, Figenschau Y. Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromsø Study. J Intern Med. 2006 Jul;260(1):53–61.
46. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol Eur Fed Endocr Soc. 2009 May;160(5):785–90.
47. Al Sayed A, Al Ali N, Bo Abbas Y, Alfadhli E. Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. Endocr J. 2006 Oct;53(5):653–7.
48. Brenta G, Berg G, Arias P, Zago V, Schnitman M, Muzzio ML, et al. Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L-T(4) treatment. Thyroid Off J Am Thyroid Assoc.

2007 May;17(5):453–60.

49. Dessein PH, Joffe BI, Stanwix AE. Subclinical hypothyroidism is associated with insulin resistance in rheumatoid arthritis. Thyroid Off J Am Thyroid Assoc. 2004 Jun;14(6):443–6.

50. Asano T, Okumura M. Insulin delivery rate in response to glucose and arginine infusion in hyperthyroidism. Diabetologia. 1982 Aug;23(2):108–13.

51. Taylor R, McCulloch AJ, Zeuzem S, Gray P, Clark F, Alberti KG. Insulin secretion, adipocyte insulin binding and insulin sensitivity in thyrotoxicosis. Acta Endocrinol (Copenh). 1985 May;109(1):96–103.

52. Ahrén B, Lundquist I, Hedner P, Valdemarsson S, Scherstén B. Glucose tolerance and insulin and C-peptide responses after various insulin secretory stimuli in hyper- and hypothyroid subjects before and after treatment. Diabetes Res Edinb Scotl. 1985 Mar;2(2):95–103.

53. Dimitriadis G, Baker B, Marsh H, Mandarino L, Rizza R, Bergman R, et al. Effect of thyroid hormone excess on action, secretion, and metabolism of insulin in humans. Am J Physiol. 1985 May;248(5 Pt 1):E593–601.

54. Jap TS, Ho LT, Won JG. Insulin secretion and sensitivity in hyperthyroidism. Horm Metab Res Horm- Stoffwechselforschung Horm Métabolisme. 1989 May;21(5):261–6.

55. Shen DC, Davidson MB. Hyperthyroid Graves' disease causes insulin antagonism. J Clin Endocrinol Metab. 1985 May;60(5):1038–41.

56. O'Meara NM, Blackman JD, Sturis J, Polonsky KS. Alterations in the kinetics of C-peptide and insulin secretion in hyperthyroidism. J Clin Endocrinol Metab. 1993 Jan;76(1):79–84.

57. Ikeda T, Fujiyama K, Hoshino T, Takeuchi T, Mashiba H, Tominaga M. Oral and intravenous glucose-induced insulin secretion in hyperthyroid patients. Metabolism. 1990 Jun;39(6):633–7.

58. Roti E, Braverman LE, Robuschi G, Salvi M, Gardini E, d' Amato L, et al. Basal and glucose- and arginine-stimulated serum concentrations of insulin, C-peptide, and glucagon in hyperthyroid patients. Metabolism. 1986 Apr;35(4):337–42.

59. Gruber H-J, Mayer C, Mangge H, Fauler G, Grandits N, Wilders-Truschnig M. Obesity reduces the bioavailability of nitric oxide in juveniles. Int J Obes 2005. 2008 May;32(5):826–31.

60. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. Clin Endocrinol (Oxf). 2005 Apr;62(4):487–91.

61. Obermayer-Pietsch BM, Frühauf GE, Lipp RW, Sendlhofer G, Pieber TR. Dissociation of leptin and body weight in hyperthyroid patients after radioiodine treatment. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2001 Jan;25(1):115–20.

62. Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, et al. Thyroid function in humans with morbid obesity. Thyroid Off J Am Thyroid Assoc. 2006 Jan;16(1):73–8.

63. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf). 2007 Aug;67(2):265–9.

64. Duntas LH. Thyroid disease and lipids. Thyroid Off J Am Thyroid Assoc. 2002 Apr;12(4):287–93.

65. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab. 2002 May;87(5):1996–2000.

66. Crunkhorn S, Patti M-E. Links between thyroid hormone action, oxidative metabolism, and diabetes risk? Thyroid Off J Am Thyroid Assoc. 2008 Feb;18(2):227–37.

67. Namba H, Saenko V, Yamashita S. Nuclear factor-kB in thyroid carcinogenesis and progression: a novel therapeutic target for advanced thyroid cancer. Arq Bras Endocrinol Metabol. 2007 Jul;51(5):843–51.

68. Videla LA, Fernández V, Tapia G, Varela P. Thyroid hormone calorigenesis and mitochondrial redox signaling: upregulation of gene expression. Front Biosci J Virtual Libr. 2007;12:1220–8.

69. Antunes TT, Gagnon A, Langille ML, Sorisky A. Thyroid-stimulating hormone induces interleukin-6 release from human adipocytes through activation of the nuclear factor-kappaB pathway. Endocrinology. 2008 Jun;149(6):3062–6.

70. Sorisky A, Antunes TT, Gagnon A. The Adipocyte as a novel TSH target.

Mini Rev Med Chem. 2008 Jan;8(1):91–6.
71. Weetman AP. Cellular immune responses in autoimmune thyroid disease. Clin Endocrinol (Oxf). 2004 Oct;61(4):405–13.
72. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol. 2008 Sep;103(5):398–406.
73. Cabral MD, Teixeira P de FS, Leite SP, Vaisman M. [Markers of endothelial function in hypothyroidism]. Arq Bras Endocrinol Metabol. 2009 Apr;53(3):303–9.
74. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, et al. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis. 2003 Feb;166(2):379–86.
75. Luboshitzky R, Herer P. Cardiovascular risk factors in middle-aged women with subclinical hypothyroidism. Neuro Endocrinol Lett. 2004 Aug;25(4):262–6.
76. Pérez A, Cubero JM, Sucunza N, Ortega E, Arcelús R, Rodriguez-Espinosa J, et al. Emerging cardiovascular risk factors in subclinical hypothyroidism: lack of change after restoration of euthyroidism. Metabolism. 2004 Nov;53(11):1512–5.
77. Ozcan O, Cakir E, Yaman H, Akgul EO, Erturk K, Beyhan Z, et al. The effects of thyroxine replacement on the levels of serum asymmetric dimethylarginine (ADMA) and other biochemical cardiovascular risk markers in patients with subclinical hypothyroidism. Clin Endocrinol (Oxf). 2005 Aug;63(2):203–6.
78. Baskol G, Atmaca H, Tanriverdi F, Baskol M, Kocer D, Bayram F. Oxidative stress and enzymatic antioxidant status in patients with hypothyroidism before and after treatment. Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc. 2007 Sep;115(8):522–6.
79. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum. 2005 Oct;52(10):3045–53.
80. Wellenius GA, Mukamal KJ, Kulshreshtha A, Asonganyi S, Mittleman MA. Depressive symptoms and the risk of atherosclerotic progression among patients with coronary artery bypass grafts. Circulation. 2008 May 6;117(18):2313–9.
81. Pizzi C, Santarella L, Costa MG, Manfrini O, Flacco ME, Capasso L, et al. Pathophysiological mechanisms linking depression and atherosclerosis: an

overview. J Biol Regul Homeost Agents. 2012 Dec;26(4):775–82.

82. Velkoska Nakova V, Krstevska B, Bosevski M, Dimitrovski C, Serafimoski V. Dyslipidaemia and hypertension in patients with subclinical hypothyroidism. Pril Makedon Akad Na Nauk Umet Oddelenie Za Biološki Med Nauki Contrib Maced Acad Sci Arts Sect Biol Med Sci. 2009 Dec;30(2):93–102.

83. Chen H, Xi Q, Zhang H, Song B, Liu X, Mao X, et al. Investigation of thyroid function and blood pressure in school-aged subjects without overt thyroid disease. Endocrine. 2012 Feb;41(1):122–9.

84. Mazza A, Beltramello G, Armigliato M, Montemurro D, Zorzan S, Zuin M, et al. Arterial hypertension and thyroid disorders: what is important to know in clinical practice? Ann Endocrinol. 2011 Sep;72(4):296–303.

85. Stabouli S, Papakatsika S, Kotsis V. Hypothyroidism and hypertension. Expert Rev Cardiovasc Ther. 2010 Nov;8(11):1559–65.

86. Mittag J, Lyons DJ, Sällström J, Vujovic M, Dudazy-Gralla S, Warner A, et al. Thyroid hormone is required for hypothalamic neurons regulating cardiovascular functions. J Clin Invest. 2013 Jan 2;123(1):509–16.

87. Inal S, Karakoç MA, Kan E, Ebinç FA, Törüner FB, Aslan M. The effect of overt and subclinical hypothyroidism on the development of non-dipper blood pressure. Endokrynol Pol. 2012;63(2):97–103.

88. Spitzweg C, Reincke M. [Thyroid diseases and hypertension]. Internist. 2010 May;51(5):603–4, 606–8, 610.

89. Pesić M, Antić S, Kocić R, Radojković D, Radenković S. [Cardiovascular risk factors in patients with subclinical hypothyroidism]. Vojn Pregl Mil-Med Pharm Rev. 2007 Nov;64(11):749–52.

90. Toruner F, Altinova AE, Karakoc A, Yetkin I, Ayvaz G, Cakir N, et al. Risk factors for cardiovascular disease in patients with subclinical hypothyroidism. Adv Ther. 2008 May;25(5):430–7.

91. Böger RH. Asymmetric dimethylarginine (ADMA): a novel risk marker in cardiovascular medicine and beyond. Ann Med. 2006;38(2):126–36.

92. Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J. 2002 Apr;143(4):718–24.

93. Faber J, Petersen L, Wiinberg N, Schifter S, Mehlsen J. Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. Thyroid Off J

Am Thyroid Assoc. 2002 Apr;12(4):319–24.
94. Lakshmi V, Vaney N, Madhu SV. Effect of thyroxine therapy on autonomic status in hypothyroid patients. Indian J Physiol Pharmacol. 2009 Sep;53(3):219–26.
95. Svare A, Nilsen TIL, Bjøro T, Asvold BO, Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf). 2011 Jun;74(6):769–75.
96. Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. Curr Cardiol Rep. 2004 Nov;6(6):451–6.
97. Dullaart RP, van Doormaal JJ, Hoogenberg K, Sluiter WJ. Triiodothyronine rapidly lowers plasma lipoprotein (a) in hypothyroid subjects. Neth J Med. 1995 Apr;46(4):179–84.
98. Arikan E, Karadag CH, Guldiken S. Asymmetric dimethylarginine levels in thyroid diseases. J Endocrinol Invest. 2007 Mar;30(3):186–91.
99. Hermenegildo C, Medina P, Peiró M, Segarra G, Vila JM, Ortega J, et al. Plasma concentration of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, is elevated in hyperthyroid patients. J Clin Endocrinol Metab. 2002 Dec;87(12):5636–40.
100. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, et al. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. J Clin Endocrinol Metab. 2006 Dec;91(12):5076–82.
101. Nanda N, Bobby Z, Hamide A. Inflammation and oxidative stress in hypothyroids: additive effects on cardiovascular risk. Indian J Physiol Pharmacol. 2011 Dec;55(4):351–6.
102. Hueston WJ, King DE, Geesey ME. Serum biomarkers for cardiovascular inflammation in subclinical hypothyroidism. Clin Endocrinol (Oxf). 2005 Nov;63(5):582–7.

Appendix

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Thyroid dysfunctions influence patients' anthropometric parameters, lipid metabolism and oxidative stress – a clinical trial pilot follow-up study

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Object

Thyroid dysfunctions are supposed to be implicated in metabolic risk. We assessed the effects of hyper-, hypo- and eu-thyroidism on patients´ lipid metabolism and oxidative stress from a six month follow-up clinical pilot study.

Methods

- A study cohort of 96 Caucasian probands was grouped into hyperthyroid (n=9), hypothyroid (n=21) and euthyroid (n= 18) patients and healthy controls (n=48) (Figure 1).

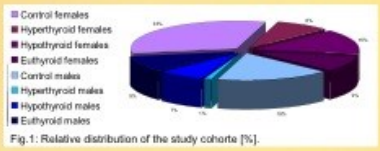

Fig.1: Relative distribution of the study cohorte [%].

- Blood collection was performed by venous puncture after an overnight fast. Blood was immediately centrifuged and serum samples were aliquoted and stored at -80 °C until analysis.
- After the first blood collection, patients received their individual medication and underwent a six month follow-up.
- The following parameters were analysed in patients before and after six months of medication and in healthy controls:

thyroid status

Thyroid Stimulating Hormeone (TSH basal), free Triiodothyronine (fT3), free Thyroxine (fT4), Thyroid Peroxidase Antibody (TPO-AB), Thyroid Receptor Antibody (TRAK), intact Parathormone (PTHi)

inflammation

C-reactive protein (CRP), interleukin 6 (IL-6), interleukin 10 (IL-10)

lipid metabolism and stress parameters

cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TG), oxidized LDL (ox-LDL), asymmetric dimethylarginine (ADMA)

- Additionally, we measured the body weight, length, waist and hip circumference, BMI as well as blood pressure (BP).

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Results

Analyses of routine thyroid parameters confirmed patient's status. Anthropometric baseline characteristics were comparable between groups. BP was significantly higher in all baseline patient groups compared to controls. Baseline versus follow-up analyses revealed that euthyroid follow-ups had a significant increased BMI, waist circumference and waist-to-length ratio. Further, euthyroid and hypothyroid follow-ups had a significantly lower BP.

Table 1: Baseline and follow-up characteristics of study cohorte before and after six months of treatment

Characteristics	Hyperthyroid (n=9)		Hypothyroid (n=21)		Euthyroid (n=18)		Healthy Controls (n=48)
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up	Baseline
Sex [f/m]	8:1		14:7		9:9		31:17
Age [years]	41 ± 8		34 ± 10		43 ± 14 *#		37 ± 11
Smoker [yes/no]	2:7		2:19		5:13		7:41
Physical Activity [h/week]	1.4 ± 1.6	2.3 ± 2.2	2.3 ± 2.5	2.5± 2.2	2.8 ± 3.3	2.2 ± 2.2	3.5 ± 2.8
BMI [kg/m²]	26 ± 7	26 ± 6	25 ± 5	26 ± 7	25 ± 4	25± 4*	24 ± 5
Bodyweight [kg]	77 ± 20	79 ± 18	72 ± 20	73 ± 20	75± 17	76 ± 17	72 ± 16
Bodylength [cm]	172 ± 3	172± 3	168 ± 8	168 ± 7	173 ± 9	172 ± 9	170 ± 7
Waist circumference [cm]	94 ± 18	96 ± 15	87± 16	88 ± 15	89 ± 14	92 ± 12*	85 ± 11
Waist-to-hip ratio	0.92 ± 0.10	0.92 ± 0.06	0.87 ± 0.10	0.88 ± 0.09	0.88 ± 0.08	0.91 ± 0.09	0.86 ± 0.07
Waist-to-lenght ratio	0.54 ± 0.11	0.56 ± 0.09	0.51 ± 0.09	2.64 ± 9.70	0.51 ± 0.07	0.52 ± 0.07*	0.50 ± 0.07
Systolic BP [mmHg]	131 ± 17	127 ± 23	126 ± 14	128 ± 12*	126 ± 16	119 ± 12	118 ± 13
Diastolic BP [mmHg]	75 ± 15	76 ± 12	81 ± 7	79 ± 7	75 ± 9	71 ± 10*	74 ± 9
Cholesterol [mg/dl]	207.3 ± 47.2	206.3 ± 60.4	202.1 ± 33.2	169.5 ± 35.5	189.1 ± 34.3	187.2 ± 38.3	187.1 ± 32.5
HDL [mg/dl]	65.3 ± 33.2	60.6 ± 22.9	69.6 ± 17.8	64.7 ± 21.2*	65.3 ± 20.7	60.4 ± 21.5	68.8 ± 16.7
LDL [mg / dl]	114.5 ± 3	130.8 ± 60.8	114.4 ± 38.5	122.4 ± 33.7	110.9 ± 26.4	117.5 ± 25.8	106.7 ± 26.4
HDL-LDL ratio	4.02 ± 2.37	3.10 ± 2.40	3.21 ± 1.48	3.44 ± 1.63*	3.12 ± 0.93	3.35 ± 1.11*	2.88 ± 0.85
Triglyceride [mg/dl]	147.2 ± 152.2	124.6 ± 133.7	90.6 ± 32.2	85.6 ± 28.5	92.7 ± 37.9	85.5 ± 43.5	84.4± 47.2
Ox-LDL [U/l]	34.8 ± 13.0	39.6 ± 25.1	36.1 ± 12.1	32.7 ± 10.9	34.1 ± 14.5	34.4 ± 9.4	34.4 ± 13.2
ADMA [µmol/l]	1.07 ± 0.41	0.68 ± 0.13*	0.76 ± 0.25	0.58 ± 0.17**	0.73 ± 0.20	0.60 ± 0.08*	0.91 ± 0.34
CRP [mg/l]	3.8 ± 4.0	14.8 ± 37.2	3.0 ± 3.9	2.3 ± 3.0	1.9 ± 2.0	1.6 ± 1.7	1.8 ± 2.0
IL-6 [pg/ml]	5 ± 9	3 ± 5	7 ± 22	5 ± 23	2 ± 4	1± 2	2 ± 4
IL-10 [pg/ml]	4 ± 1	4 ± 3	4 ± 6	5 ± 8	7 ± 8	4 ± 4	4 ± 6
TSH basal [µU/l]	0.0 ± 0.0	3.2 ± 5.4	7.1 ± 7.1	6.2 ± 14.7	1.8 ± 1.0	1.8 ± 1.3	2.0± 0.8
fT3 [pmol/l]	8.0 ± 3.6	9.1 ± 9.8	5.0 ± 0.6	4.7 ± 0.6*	5.0 ± 0.4	5.4± 1.3	5.0± 0.6
fT4 [pmol/l]	19.1 ± 12.0	20.3 ± 19.9	13.9 ± 2.5	14.8 ± 2.1	14.8± 2.6	16.0 ± 2.7	13.8 ± 2.0
TPO-AB [U/ml]	686.1 ± 834.3	661.3±1177.9	307.7 ± 436.3	193.9 ± 339.0	246.6 ± 594.9	148.8 ± 276.0	8.9 ± 3.6
TRAK [U/ml]	222.5 ± 248.9	83.1 ± 190.8	3.4 ± 7.5	1.6± 2.3	6.9 ± 13.0	9.7 ± 20.8	0.6 ± 1.2
PTHi [pg/ml]	33.3 ± 14.4	44.0 ± 11.6*	34.2 ± 11.2	32.5± 8.0	32.8 ± 12.1	36.4 ± 13.6	36.3 ± 11.1

Data are presented as means ± standard deviations. Continuous variables were compared using Students t-test for independent samples. *p<0.05, ** p<0.01; # compared to healthy controls; § compared to hypothyroid.

Observations on lipid metabolism revealed that hypothyroid and euthyroid follow-ups showed declined HDL levels and significant higher HLD-LDL ratios compared to their pre-treated state. Cholesterin, LDL, TG, oxLDL levels and inflammatory markers were comparable in baseline and follow-ups. Furhtermore, we found significantly declined asymmetric dimethylarginine (ADMA) levels in all three follow-up groups.

Conclusion

The present follow-up study revealed that thyroid dysfunctions influence patients' anthropometric parameters, HDL-LDL ratio and ADMA levels indicating a higher risk for developing the metabolic syndrome.