SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Possible adverse effects of long term subclinical hyperthyroidism and short term overt hypothyroidism during the follow up of patients with differentiated thyroid cancer

By Annamaria Gazdag MD

Supervisor: Endre V. Nagy MD, PhD, DSc

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Supervisor: Endre V. Nagy MD, PhD, DSc

Doctoral School of Health Sciences, University of Debrecen

Head of the **Examination Committee**:	Margit Balázs, PhD, DSc
Members of the Examination Committee:	Gyula Bakó, MD, PhD, DSc
	Attila Mohácsi, MD, PhD

The Examination takes place at the Conference room of Department of Preventive Medicine, Faculty of Public Health, University of Debrecen, on May 24, 2018, at 11 a.m.

Head of the **Defense Committee**:	Margit Balázs, PhD, DSc
Reviewers:	Péter Igaz, MD, PhD, DSc
	Tibor Fülöp, MD, PhD
Members of the Defense Committee:	Gyula Bakó, MD, PhD, DSc
	Attila Mohácsi, MD, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. “A”, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on May 24, 2018, at 1 p.m

1. INTRODUCTION

Thyroid hormones exert several profound effects on the cardiovascular system. These effects can be studied in patients with differentiated thyroid cancer (DTC) who are treated with the combination of total thyroidectomy and radioidine ablative therapy. As part of the treatment, some of these patients are kept in the state of subclinical hyperthyroidism. As part of their follow up, lifelong thyroxin (T_4) therapy is interrupted by a short period of hypothyroidism yearly to measure thyroglobulin, the tumor marker of DTC.

Subclinical hyperthyroidism is associated with higher heart rate, frequent atrial premature beats, and increased prevalence of atrial fibrillation. Increased left ventricular mass (LVM) and diastolic dysfunction have also been reported in subclinical hyperthyroidism. Changes of the cardiovascular system are well characterized in hypothyroidism: bradycardia, prolongation and increased dispersion of the QT interval, increased blood pressure, particularly diastolic pressure, increased periferial vascular resistance with a reduced cardiac output, and left ventricular diastolic dysfunction. Overt hypothyroidism is related to coronary artery disease because of atherogen lipid profile, hypertension, hyperhomocysteinemia, elevated C-reactive protein levels, coagulation factor abnormalities, and endothelial dysfunction.

Endothelial dysfunction may initiate atherosclerosis; the detection of early atherosclerotic changes can contribute to the prevention of cardiovascular diseases. Measuring flow-mediated dilatation (FMD) is widely accepted for non-invasive evaluation of endothelial function. High-resolution ultrasound is used to measure changes in arterial diameter in response to reactive hyperaemia (endothelium-dependent flow-mediated vasodilatation). Nitrogen oxid (NO) plays a key role in vascular endothelial-mediated relaxation. The reduced endothel function, determined by FMD, is known to improve with thyroxin therapy in both subclinical and overt hypothyroidism.

One of the recently described tools for determining cardiovascular risk is arterial wall stiffness, which is an independent predictor of cardiac events via several mechanisms. Increased cardiac afterload, impaired coronary blood flow, direct atherogenic action and microvascular damage may be contributing factors. Arterial stiffness can be calculated from the aortic diameter and blood pressure measured simultaneously or can be determined by pulse wave analysis. Central arterial stiffness is reduced in untreated hyperthyroidism based on analysis of the central arterial pressure waveform. Increased total arterial stiffness has been reported in overt hyperthyroidism using echocardiography. Antithyroid drug therapy significantly reduced the stiffness of the common carotid artery in patients with Graves' disease. Overt and subclinical hypothyroid subjects have increased arterial stiffness; this is reversible by thyroxin replacement. Aortic stiffness has not been measured in subclinical hyperthyroidism.

2. AIMS

We aimed to examine endothelial and vascular wall function by

(1) FMD as the possible earliest marker of atherosclerosis

(2) aortic stiffness

(3) left ventricular systolic and diastolic functions

(4) haemostatic parameters

(5) metabolic parameters and

(6) markers of vascular injury

in patients with DTC who are on TSH suppressive doses of T_4, as well as after 4 weeks of T_4 withdrawal, in order to assess the cardiovascular impact of both long-term subclinical hyperthyroidism and iatrogenic short-term hypothyroidism.

We aimed to address the following questions:

1. Is the endothelial function measured by FMD in the brachial artery altered in subclinical hyperthyroidism and/or overt hypothyroidism?
2. Is the possible alteration of the endothelial function mediated by NO?
3. Is the aortic stiffness altered in subclinical hyperthyroidism and/or overt hypothyroidism?
4. Is the left ventricular systolic and diastolic function altered?
5. How does the lipid- and metabolic parameterese change in subclinical hyperthyroidism and/or overt hypothyroidism? 6.
6. How do the recently identified atherosclerosis risk factors (homocystein, C-reactive protein, fibrinogén, von Willebrand faktor) interact with the tested functions of the vascular wall?

3. PATIENTS AND METHODS

3.1. Patients

Twenty four women (mean age 42.4±8.07 years) who had had total or near-total thyroidectomy for DTC were included in the study. Patients with known ischemic heart disease, stroke, cardiac failure, hypertension, diabetes mellitus, renal or liver failure, other systemic or malignant diseases (other than thyroid cancer) were excluded from the study. In 21/24 cases, ^{131}I ablation was also performed. Three of the 24 patients declined the recommended ^{131}I treatment. All patients were classified as “high or intermediate risk” of DTC recurrence on the basis of the American Thyroid Assotiation (ATA) and European Thyroid Assotiation (ETA) guidelines, hence all had been on TSH-suppressive therapy continuously for 30±21 (mean±SD) weeks and were taking no other medications (TSH 0.24±0.11 mU/L). Their yearly follow up included TSH stimulated serum thyroglobulin (Tg) level (achieved by 4 weeks thyroxin withdrawal), anti-Tg antibodies (aTg), neck ultrasonography and, if indicated, whole-body radioiodine scan. The first Tg

measurment was at least 6 month after ^{131}I treatment in parallel with aTg. Four of 24 patients were Tg positive (Tg > 2 ug/L); in these patients, whole-body scan (WBS) was performed. WBS was positive in 3 of them due to small thyroid remnant and ^{131}I ablation was repeated. One Tg postive, WBS negativ patient was followed and consequent Tg measurments were negative. Another 3 patients were Tg negativ, aTg positive.

Twenty two healthy volunteers, matched for age, served as euthyroid controls (TSH: 1,64±1,05 mU/l). The same criteria were used in control subject selection, except that they had had no history of thyroid disease. They were not taking any medication known to influence thyroid and/or cardiac function. All study subjects gave written informed consent.

3.2 Methods

Patients were studied on the day before T_4 withdrawal (subclinical hyperthyroidism) and four weeks later, before readministration of T_4 (hypothyroidism). Controls were evaluated only once. Blood samples were collected between 08.00-09.00 a.m. after an overnight fast for determination of TSH, free thyroxin (fT_4), free triiodothyronin (fT_3), thyroglobulin, cholesterol, triglyceride, low-densitiy lipoprotein cholesterol (LDL-C), high-densitiy lipoprotein cholesterol (HDL-C), total homocystine (Hcys), C-reactiv protein (CRP), fibrinogen and von Willebrand factor activity (vWF). Blood pressure was measured and body mass index (BMI) calculated. FMD and NMD were measured only in DTC patients in a self-controlled study. Results of echocardiography measurments were compared with healthy controlls. FMD and echocardiographic measurements were carried out by two independent investigators who were unaware of the patients' clinical data.

3.2.1. Biochemical measurements

TSH, fT_4, fT_3, Tg, aTg, cholesterol, triglyceride, LDL-C, HDL-C, Hcys, CRP, fibrinogen and vWF were measured by commercially available assays according to the manufacturers' recommendations.

NO synthesis was determined by measuring the metabolites of nitric oxide, NO_2 and NO_3. For determination of NO_2+NO_3, proteins were precipitated from plasma (0.5 ml) by 100 µl of 35 % sulfosalycylic acid and samples were centrifuged in an Eppendorf centrifuge (10 min, 10 000 g). 0.4 ml of protein free plasma was inserted into a syringe containing Cu-platted cadmium granules. The NO_3 was reduced to NO_2 in the syringe, and 0.3 ml of sample was mixed with 0.3 ml of Griess reagent (1 part of 0.1 % of naphthylethylendiamide and 1 part of 1 % sulfanilamide), and was incubated at 60 °C in water bath for 20 min. The absorbance of samples was determined in a spectrophotometer (Hewlett Packard 8453) at 546 nm. Calibration curve was prepared using analytical grade of $NaNO_2$, and was used for determination of NO_2+NO_3 in plasma samples.

3.2.2 Flow-mediated (FMD) and nitrate-mediated (NMD) dilatation

Vascular studies of the brachial artery were performed non-invasively. High-resolution ultrasound was used to measure changes in arterial diameter in response to reactive hyperaemia (endothelium-dependent,

flow-mediated vasodilatation) as well as to glyceryltrinitrate (NTG, an endothelium-independent vasodilator) with a 7.0 MHz linear array transducer on a Philips HDI-5000 system (Philips Medical Systems, USA). FMD and endothelium-independent vasodilatation were assessed by measuring the percent change in the brachial artery diameter during reactive hyperaemia and after NTG.

3.2.3 Aortic strain and stiffness

Transthoracic echocardiography was performed by using Philips HDI-5000 system (Philips Medical Systems, Bothell, USA) 2.5 Mhz-probe at the left lateral decubitus position in a standard manner. M mode tracings of the ascending aorta were obtained in the parasternal long axis views. From the M mode recordings, aortic systolic and diastolic diameters (Aos and Aod, respectively) were measured. Aos was determined at the time of the full opening of the aortic valve and Aod was determined at the peak of QRS. Simultaneously, cuff brachial artery systolic (SBP) and diastolic (DBP) blood pressures were measured and recorded. The aortic elasticity parameters, the aortic strain and aortic stiffness indexis were calculated using the following formulas:

Aortic Strain (%) = 100 × (Aos - Aod) / Aod.

Aortic Stiffness Index [beta] = ln (SBP/DBP) / Aortic Strain

3.2.4. Left ventricular dimensions

M-mode measurements of LV internal dimensions in diastole (LVDD) and systole (LVDS), and end-diastolic posterior wall (PW) and interventricular septum (IVS) thicknesses and left atrium anteroposterior diameter were obtained using the standard technique. LV fractional shortening, a measure of the percent change in LV dimensions with systole, was calculated.

LVM was corrected for body surface area to obtain LVM index (LVMI). Two dimensional left ventricular ejection fraction (LVEF) was also aquired by the summation method.

3.2.4. Diastolic function

The peak early transmitral filling velocity during early diastole (E), peak transmitral atrial filling velocity during late diastole (A), and E/A ratio were used as left ventricular diastolic function parameters. Quantitative diastolic data were derived from TDI data. The sample volume (4 mm3) was placed in the LV basal portion of anterior, inferior, septal and lateral walls (using the 2- and 4-chamber images) The following parameters (mean values calculated from three consecutive beats) were derived: early diastolic velocity (e’), late diastolic velocity (a’), e’/a’ and E/e’ ratio. Parameters of the patient groups were compared to controls.

3.2.6. Statistical analysis

All statistical analyses were performed by using the SAS for Windows (8.2 cary/nc SAS® Institute Inc. USA) statistical package. Continuous data were expressed as mean±standard deviation. Relationships between the continuous variables were evaluated by Pearson's or Spearman's correlation analysis. Comparisons between control, subclinical hyperthyroid and hypothyroid groups for continuous variables were made by one way ANOVA and post-hoc Tukey's test. To improve the normality of the data distribution, triglyceride values were log-transformed for analysis. Simple linear regression analysis was performed to asses the relationship between changes of aortic stiffness, FMD and other parameters. To investigate the independent effect of the different factors on changes of stiffness and FMD, a multiple stepwise linear regression model was used. The multivariate model consisted of the changes of stiffness index and FMD as dependent variable, and independent variables that had had significant correlation with changes of stiffness index and FMD in the simple linear regression analysis. $p<0.05$ was considered statistically significant.

4. RESULTS

4.1 Changes in humoral parameters

In subclinical hyperthyroidism, the mean TSH level was 0.24 ± 0.11 mU /L while the fT_3 and fT_4 levels were within the normal ranges (4.79 ± 0.46 and 18.39 ± 2.33 pmol/L, respectively). After discontinuation of T_4 for 4 weeks, all 24 subjects achieved a hypothyroid state, as evidenced by TSH levels (89.8 ± 29.36 mU/L) and low serum fT_4 and fT_3.

Blood pressure and BMI were not significantly different in hypothyroidism compared to subclinical hyperthyroidism and euthyroid state.

Cholesterol (7.43±1.23 vs 4.75±1.14 mmol/L), triglyceride (7.43±1.23 vs 4.75±1.14 mmol/L), and LDL-C (4.55±1.1 vs. 2.7±0.89 mmol/L) increased in hypothyroidism significantly compared to subclinical hyperthyroidism. Hcys was significantly higher in the hypothyroid state than in subclinical hyperthyroidism (12.95±4.49 vs. 9.62±2.29 umol/L) and was the lowest in euthyroid controls (8.67±0.87 umol/L). Mean HDL-C levels were unchanged. Average CRP levels exceeded 1.0 mg/L in both hypothyroidism and subclinical hyperthyroidism (low cardiovascular risk: < 1.0 mg/L). However, CRP values were significantly higher in subclinical hyperthyroidism than in hypothyroidism (5.55±5.15 vs. 4.39±5.16 mg/L). The fibrinogen (4.01±0.84 vs. 3.23±0.50 g/L) and vWF values (130.63±29.97 vs. 90.09±25.92 %) were higher in subclinical hyperthyroidism, although the mean value of vWF remained within the reference range.

4.2 Vascular parameters

In hypothyroidism, FMD was lower than in subclinical hyperthyroidism (6.79±4.44 vs. 14.37±8.33 %), whereas the vasodilatation in response to NTG was not different. The NO values were higher in subclinical hyperthyroidism than in hypothyroidism (32.34±7.0 umol/L vs. 24.56±6.71 umol/L).

4.3 Aortic strain and stiffness

Aortic stiffness increased significantly in both the hypothyroid (6.04±2.55) and subclinical hyperthyroid (9.27±4.81) groups compared to controls (3.92±1.84). However, in hypothyroidism, values falling between the subclinical hyperthyroid and control groups were observed. The difference in aortic stiffness was also significant between subclinical hyperthyroidism and overt hypothroidism.

4.4 LV dimensions

As far as LV dimensions and ejection fraction are concerned, no significant changes were observed in M-mode measurrments (LVEDD, LVESD, IVS, PW and fractional shortening) and in the two dimensional study (LVM, LVMI and LVEF) either during T_4 withdrawal, or when compared with healthy controls.

4.5 Diastolic function

Diastolic function parameters, E-, A-, e'- waves were significantly lower in both subclinical hyperthyroidism (60.30±10.53 cm/s vs. 72.12±7.23 cm/s; 43.75±9.37 cm/s vs. 45.23±4.67 cm/s; 5.52±0.89 cm/s vs. 5.96±1.23 cm/s) and overt hypothyroidism (62.98±9.76 cm/s vs. 72.12±7.23 cm/s; 42.71±7.78 cm/s vs. 45.23±4.67 cm/s; 5.78±1.02 cm/s vs. 5.96±1.23 cm/s) compared to healthy controls. a'-wave was significantly higher in the two hormonal abnormalities compared to controls (5.48±0.9 cm/s vs. 4.45±1.34 cm/s; 5.08±1.11 cm/s vs. 4.45±1.34 cm/s). The E/A (1.47±3.67 cm/s vs. 1.59±3.67 cm/s; 1.37±4.16 cm/s vs. 1.59±3.67 cm/s) and e'/a' (1.13±0.98 cm/s vs. 1.34±1.02 cm/s; 1.0±0.14 cm/s vs. 1.34±1.02 cm/s) were significantly lower in subclinical hyperthyroidism. E/e' was higher in subclinical hyperthyroidism and hypothyroidism, than control (10.99±1,7 vs 9.85±2.28; 10.47±1.0 vs 9.85±2.28). Heart rate was lower in hypothyroidism and higher in subclinical hyperthyroidism (70.6±6,78 beats/min. vs. 78.35±7,23 beats/min).

4.6 Correlation between changes in aortic stiffness and laboratory parameters

By simple regression analysis, changes of FMD while on T_4 suppressive therapy correlated in a positive manner with changes of NO (r=0.67, p=0.0006), as well as with vWF (r=0.54, p=0.005) and fibrinogen (r=0.45, p=0.01) levels. There was no significant correlation between LDL-C and FMD. Changes in fT_3, fT_4, and TSH on T4suppressive therapy did not significantly correlate with changes of FMD (FMD vs. fT_3 r=-0.14, P=0.56, FMD vs fT_4 r=-0.18, P=0.48, FMD vs TSH r=-0.17, p=0.52) or with changes in vWF (vWF vs. fT_3 r=-0.21, P=0.55, vWF vs. fT_4 r=-0.24, p=0.21, vWF vs. TSH r=-0.03, P=0.78), or NO (NO vs. fT_3 r=-0.11, P=0.67, NO vs fT_4 r=-0.13, p=0.45, NO vs TSH r=-0.21, p=0.21).

Stepwise multiple regression analysis of changes in various clinical variables in the patients on T_4 suppressiv therapy included changes of NO, vWF, fibrinogen, fT_4 and LDL-C. Only NO and fibrinogen emerged as independent factors associated in a positive manner with FMD change.

By simple regression analysis, changes of aortic stiffness index during transition from subclinical hyperthyroidism to hypothyroidism correlated with changes of vWF (r=0.61, p=0.013), fT_4 (r=0.65, p=0.01) and fibrinogen (r=0.51, p=0.01) in a positive manner, while with LDL-C in a negative manner (r= - 0.49, p=0.01).

Stepwise multiple regression analysis is included aortic stiffness index, vWF, fibrinogen, fT_4 and LDL-C; only vWF and fT_4 emerged as independent factors associated in a positive manner with aortic stiffness.

5. DISCUSSION

The aim of this study was to compare the cardiovascular effects of long-term subclinical hyperthyroidism and short-term overt hypothyroidism. These hormonal states are part of the therapy and follow-up of DTC patients: subclinical hyperthyroidism is aimed to keep TSH, a known groth factor in DTC, in the low or unmeasurable range, while T_4 treatment is withdrawn for 4 weeks once a year to achieve TSH stimulation of thyroglobulin synthesis, the tumor marker in DTC.

In the present study we examined endothelial function together with NO, aortic stiffness, left ventricular systolic and diastolic functions, metabolic parameters and hemostatic factors in patients with DTC who were on TSH-suppressive doses of T_4, as well as after 4 weeks of T_4 withdrawal. In our study we focused on a selected series of patients without known atherosclerotic diseases and risk factors. The parameters were compared in a self-controled study, while echocardiography results were compared with healthy controls.

In subclinical hyperthyroidism, the FMD and NO was markedly higher and lipid profile was better than in hypothyroidism. The constellation of the parameters measured predisposes to acclereated atherosclerosis in hypothyroidism; however, this hypothyreoid phase is very short, and readminsitration of T_4 improves endothelials function. NO is the mediator of FMD, and the elevation of NO level was found to be an independent determinant of improvement of FMD by multiplex regression analysis. There was no association between changes of FMD and LDL-C; it seems that T_4 therapy can improve the FMD independently from the lipid profile. Endothelial dysfunction is thought to be an important factor in the development of atherosclerosis, hypertension, and heart failure. The endothelium is a specific target of thyroid hormones in human. Several potential mechanisms have been proposed to explain abnormal endothelial function. Endothelial cells contain nuclear T_3 receptors, endothelium dependent vasodilatation is modulated by T_3. It has been also shown that thyroid hormones cause rapid relaxation of vascular smooth muscle cells isolated from rat. Patients with subclinical hypothyroidism were shown to develop endothelium dysfunction resulting from a reduction in NO availability, an alteration partially independent of lipid changes, and reversed by T_4 supplementation. Elevated ADMA levels in hypothyroidism and in

hyperthyroidism may affect the maintenance of vascular function and integrity through inhibiting NO synthase that is responsible of NO production.

Aortic stiffness and diastolic heart function were worse in both hypothyroidism and subclinical hyperthyroidism compared to controls, and subclinical hyperthyrodism was more disadvantageous in this respect. T_4 was an independent factor associated in a positive manner with aortic stiffness. Only few data are available on aortic stiffness in hyperthyroidism. Sympathetic activation increases arterial wall stiffness. Manifestations of hyperthyroidism resemble the effect of cathecholamine excess: the sensitivity of resistance vessels to the vasoconstrictive action of norepinephrine is enhanced . β1-adrenergic blockade was associated with normalization of total arterial stiffness. Vascular inflammation causes degradation of collagen and elastin, evokes changes in the proteoglycan composition and hydration status, and results in medial calcification leading to increased arterial stiffness. Low-grade inflammation caused endothelial dysfunction and impaired NO availability in patients with subclinical hypothyroidism. Thyroid hormone reduces systemic vascular resistance and causes activation the renin-angiotensin-aldosteron system. T_3 directly stimulates the synthesis of renin substrate in the liver. Consequevent sodium reabsorption, increased blood volume and preload contribute to the characteristic increase in cardiac output. Chronic hemodynamic overload causes increased myocardial contractility, cardiac hypertrophy, increased left-ventricular mass; contractile protein synthesis is increased. The faster heart rate in hyperthyroidism result an earlier return of the forward pressure wave in systole, resulting in a greater overlapping in the forward and reflected pressure waves. It has been suggested in earlier studies that diastolic dysfunction in subclinical hyperthyroidism resulted from increased LVM. However, no significant increases in LVM was found either by us or by other groups. Dörr et al. showed that decreased serum TSH levels were not associated with an elevated risk of left ventricular hypertrophy, but overt hyperthyrodism is an independent risk factor for left ventricular hypertrophy. Thyroid hormones influence calcium regulation in myocytes, such as increase Ca++-ATPase activity and decrease phospholamban expression, and increase Ca-influx. Increase in intracellular calcium may be cause of mediated diastolic stiffness in hyperthyroid rats heart.

We detected only slight impairement in aortic stiffness and diastolic function in acute short-term hypothyroidism. Aortic stiffness is likely related to myxoedema of the arterial wall. However, our data do not support this notion and are consonant with the findings of other studies, hat argued against the role of LDL-C in increased aortic stiffness. Impaired diastolic function in hypopthyroidism due to slow myocardial relaxation results from altered intracellular calcium handling, decreased activity of the sarcoplasmatic reticulum calcium ATPase and /or increased expression of phospholamban. Myofibrill swelling, mucopolysaccharides accummlation can be detected in hypothyroid heart.

Another important consequence of the present investigation was that thyroxin induced subclinical hyperthyroidism evoked a distinct pattern of alteration in the coagulation system: fibrinogen and vWF, the hemostatic factors associated with cardiovascular risk, were significantly higher in patients on T_4 suppressive therapy. However, it should be noted that the higher vWF remained within the normal range and fibrinogen exceeded it only slightly. This observation, however, does not necessarily imply a lack of a biological component. Our findings also suggest that improvement in FMD is associated with the increase in serum

vWF and fibrinogen levels. In subclinical hyperthyroidism a prothrombotic profile has been described: in thyroidectomized thyroid cancer patients, while taking L-T_4, higher factor VIII, plasminogen activator inhibitor (PAI-1), fibrinogen and lower protein C levels were found. These changes may be associated with hypercoagulability. In the majority of the studies, hypothyroidism represented a hypocoagulable state. Decreased platelet adhesiveness, abnormal bleeding time, decreased level of factors VIII, IX, X, and low vWF activity have been described in these patients. Decreases in the coagulation factors in hypothyroidism could be explained by the generalized reduction of protein synthesis. In a recent study, a direct stimulatory effect of T_3 on fibrinogen synthesis has been observed. However, most recent studies have suggested a hypercoagulable state in hypothyroidism with low fibrinolytic activity. Our data partly support the results of previous studies concerning a prothrombotic biochemical milieu evoked by subclinical hyperthyroidism.

In hypothyroidism, atherogen lipid profile and higher homocystein levels as the well known cardiovascularis risk factors were found. In both subclinical hypertyroidism and overt hypothyroidism, we deteceted low-grade inflammation as shown by the CRP levels; this may further predispose the patients to atherosclerosis.

These changes were accompanied by a remarkable improvement of endothelial function, and elevation of nitric oxide concentration. From the viewpoint of atherosclerosis and fatal or non-fatal cardiovascular events, the L-T_4 induced iatrogenic subclinical hyperthyroidism is associated with a slight but long lasting thyrotoxic state, better endothelial function (as characterized by FMD and NO) while slightly impaired vascular injury markers (higher vWF and fibrinogen) and inflammatory status (CRP) in subclinical hyperthyroidism. We conclude that these apparently opposing mechanisms may compensate for each other at the level of the vessel wall.

In conclusion, our results show that long-term TSH-suppressive T_4 therapy has both advantageous and disadvantageous effects at the level of the vessel wall. These opposite effects may compensate each other limiting the harmful effect of T_4 on vessel wall. Thyroxin withdrawal, even as short as 4 weeks, has several adverse effects on the heart and the vessel wall. We speculate that four weeks are not enough to develop the entire spectrum of effects of hypothyroidism on peripheral tissues. As subclinical hyperthyroidism is sustained for decades in these patients, the undesirable changes caused by this condition may be more important in DTC patients. The degree of TSH suppression in patients with DTC should be kept at the possible minimum, considering the potential benefits and risks of treatment, especially in patients with cardiovascular comorbidities, in agreement with the current international recommendations.

6. SUMMARY

DTC is the most frequent endocrine tumor, the prognosis of which is very good with adequate therapy (operation, radiiodine ablation and T_4 suppressive therapy). The purpose of T_4 treatment is not only thyroid hormon substitution after total thyroidectomy, but to block the TSH-dependent tumor progression. TSH stimulated serum Tg level via T_4 withdrawal is the most important part of yearly follow up of patients with DTC.

The aim of this study was to investigate endothelial function together with NO, aortic stiffness, left ventricular systolic and diastolic functions, metabolic parameters and hemostatic factors in patients with DTC while on TSH suppressive doses of T_4, as well as after 4 weeks of T_4 withdrawal, in order to assess the cardiovascular impact of both long-term subclinical hyperthyroidism and short-term hypothyroidism.

In subclinical hyperthyroidism both FMD and NO were markedly higher and lipid profile was better than in hypothyroidism. Aortic stiffness and diastolic function were unfavorable both in hypothyroidism and subclinical hyperthyroidism vs. controls, and subclinical hyperthyroidism was found to exert a more marked adverse effect on these factors. Fibrinogen and vWF, the hemostasis factors associated with cardiovascular risk, were significantly higher in subclinical hyperthyroidism. In hypothyroidism, an atherogen lipid profile and higher homocystein level were found. We deteceted low-grade inflammation by CRP level in both subclinical hypertyroidism and hypothyroidism, which may predispose to atherosclerosis.

In conclusion, our results confirm that both long-term TSH suppressive T_4 therapy and consequent subclinical hyperthyroidism and hypothyroidism resulting from thyroxin withdrawal have several adverse effects on the heart and vessel wall. The degree of TSH suppression in patients with DTC should be kept at the possible minimum, based on individually determined potential benefits and risks of treatment, especially in patients with cardiovascular comorbidities.

7. APPENDIX

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List of publications related to the dissertation

1. Gazdag, A., Nagy, E., Erdei, A., Bodor, M., Berta, E., Szabó, Z., Jenei, Z.: Aortic stiffness and left ventricular function in patients with differentiated thyroid cancer.
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List of other publications

3. Erdei, A., Steiber, Z., Gazdag, A., Bodor, M., Berta, E., Szász, R., Szántó, A., Ujhelyi, B., Barna, S., Berényi, E., Nagy, E.: Az endokrin orbitopathia differenciáldiagnosztikája.
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