Clinical aspects of endogenous hypothyroidism and subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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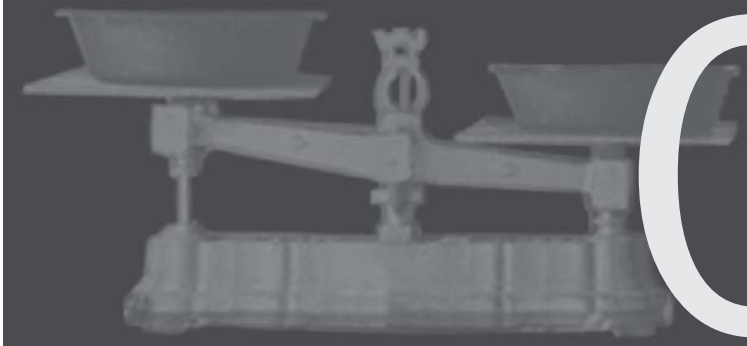

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General Introduction

Contents

I. Introduction

Differentiated thyroid carcinoma (DTC) is a rare disease with an incidence varying from 2-10/100.000 (1-4). The prevalence of DTC is, however, high because of the good prognosis. In general, 80% of the newly diagnosed tumors are differentiated tumors originating from the epithelial follicular cells. Median age at diagnosis is between 45 and 50 year with a female to male predominance of 2:1 (5).
DTC is associated with an excellent prognosis, with reported 10-year survival rates reaching 90% (6). This is because of a combination of the favorable biological behaviour of the tumor as well as the availability of effective therapy, consisting of total thyroidectomy followed by radioiodine ablation. After initial therapy, all patients with DTC are initially treated with high doses of thyroxin aiming at significantly suppressing thyrotropin (TSH) levels, resulting in a subclinical hyperthyroid state. The rationale of this approach is based on the potential harmful effects of TSH on tumor recurrence (7;8). However, long-term TSH suppression may be associated with potential harmful effects on various systems, including bone metabolism (9-11), glucose metabolism (12-14), the autonomic nervous system (15-18) and quality of life (19-23).
According to protocollized follow up, thyroxin replacement therapy can be transiently stopped in these patients to detect residual or recurrent disease by TSH stimulated thyroglobulin levels. As a result of this standardized procedure, patients become overtly hypothyroid within 4-6 weeks. This may reversely affect the systems influenced by subclinical hyperthyroidism, mentioned above.
DTC patients are an unique model to study the metabolic effects of thyroid hormone, both depletion and excess, on physiological systems, because these DTC patients are treated with total thyroidectomy and therefore don't produce any endogenous thyroid hormones. Thyroid hormone levels are well documented in these patients and can be exactly regulated by changing the thyroxin dosages. During clinical follow-up, patients are sometimes withdrawn from thyroxin, which creates a state of controlled hypothyroidism, whereas many patients will be treated with TSH suppressive dosages of thyroxin, thereby creating a state of subclinical hyperthyroidism. Moreover, there is no interfering effect from thyroid disease, like in patients substituted with thyroxin for autoimmune thyroid disease.
In this introductory chapter a general overview of DTC, thyroid hormones and the clinical consequences of exogenous subclinical hyperthyroidism and thyroxin withdrawal will be provided and the questions addressed in this thesis will be introduced.

II. Differentiated thyroid carcinoma

Pathogenesis
Genetic alterations are involved in the pathogenesis of thyroid carcinoma. The analysis of these genetic alterations is important not only for the diagnosis of DTC, but also for the understanding of the pathophysiology of thyroid disorders(24-26). Mutations in one of the three RAS-genes are frequently found in follicular adenomas and carcinomas. Benign hyperfunctioning nodules or adenomas are associated with mutations in the GSP and TSH receptor genes.
The recent identification of mutations in B-RAF, which are present in 40-60 % of papillary thyroid carcinomas (PTC), has improved the understanding of the molecular pathogenesis of PTC. B-RAF is a component of the RET RAS RAF cascade that activates MAP kinase. Almost all patients with PTC have rearrangements and mutations of B-RAF, RAS, RAF and TRK (neutrotrophic tyrosine kinase receptor). Translocations of RET, that are found in DTC, give rise to a chimeric protein consisting of an activated RET tyrosine kinase domain (24;27-

42). Transcriptional and post-transcriptional mechanisms are thought to regulate MET overexpression as a secondary effects (43).
The genetic pathogenesis of follicular thyroid carcinoma (FTC) is less clear. However, it was found that FTC is related with rearrangements in PAX8 and PPAR-γ genes, which are traditionally associated with thyroid development (PAX 8) and cell differentiation and metabolism (PPAR-γ) (44). The chimeric protein acts as a dominant negative competitor for PPAR-γ. A downregulation of the PPAR-γ signaling route has been observed in experimental models of DTC (45).
The genetic alterations that are involved in the pathogenesis of DTC, result in proliferation by multiple pathways and the loss of thyroid specific proteins. Thyroid peroxidase (TPO) is believed to disappear in an early phase, followed by the disappearance of NIS.

Diagnosis

Fine needle aspiration (FNA) is the procedure of choice in patients presenting with thyroid nodules. The sensitivity of FNA is 90-95 %. The specificity of FNA is lower, 60-80%, when all patients with a non-benign FNA are referred for surgery (46). The distinction between benign and malignant follicular tumors is difficult to make by FNA, because the essential criterion for FTC is capsular invasion which can not be determined by cytology. Another problem is the differentiation between follicular adenoma and follicular variant of papillary thyroid carcinoma (FVPTC), because the essential criterion is the aspect of the nuclei. As a consequence, the frequency of FTC in hemi-thyroidectomies performed after suspicious outcome from FNA is only 20-30%.
The Tumor-Node-Metastases classification system is based on pathologic findings. This classification system divides patients into four stages, with progressively poorer survival with increasing stage. Recently, the 6th edition of the TNM system has become available (47). The most important difference with he 5th edition is the fact that the dimension of T1 has been extended to 1.5 cm and that tumors with limited extrathyroidal extension are designated T3 instead of T4, which has implications for the prognosis of DTC (48). Therefore, some experts propagate to continue the use of the 5th edition. In the studies in his thesis the 5th edition of the TNM staging system is used (49).

T0	No evidence of primary tumor
T1	Tumor 1 cm or less in greatest dimension
T2	Tumor > 1 cm, but nor more then 4 cm in greatest dimension, limited to the thyroid
T3	Tumor > 4 cm in greatest dimension limited to the thyroid
T4	Tumor of any size, beyond the thyroid capsule
Nx	Regional lymph nodes (cervical and upper mediastinum) cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
N1a	Metastasis in ipsilateral cervical lymph node(s)
N1b	Metastasis in bilateral, midline or contralateral cervical or mediastinal lymph node(s)
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Figure 1. TNM classification system 5th edition, AJJC, Adapted from (50)

Initial therapy

Initial therapy for DTC consists of near-total thyroidectomy followed by radioiodine ablation. There is still some controversy about the extent of thyroid surgery. However, there are strong arguments in favor of total or near-total thyroidectomy in all patients (51). Only very low-risk patients (T1 (< 1 cm) N0M0 (5th edition) DTC, unifocal) may be treated by hemi-thyroidectomy.

In tumor stages of T2 and higher a total thyroidectomy is indicated (52-54). Near-total thyroidectomy results in lower recurrence rates than more limited thyroidectomy because many papillary tumors are multifocal and bilateral (55;56). In addition, total thyroidectomy facilitates total ablation with iodine-131 and reveals a higher specificity of thyroglobulin (Tg) as a tumor marker (52-55). Complications of total thyroidectomy are laryngeal nerves palsy in 2 % of DTC patients and hypoparathyroidism. The latter occurs in 1/3 of patients after total thyroidectomy, but persists longer then 3 months in only 2 % (50).
Controversy also exists about the routine use of iodide-131 ablation of thyroid remnants. However, many clinics give postoperative iodide-131 ablation for three reasons. First, iodide-131 destroys any remaining normal thyroid tissue thereby increasing the specificity of detectable serum Tg levels and positive whole-body scintigraphy indicating persistent or recurrent disease (5;54;57). Second, iodide-131 may destroy occult microscopic carcinomas, thereby decreasing the risk of recurrence thyroid carcinoma (8;54;58;59). Third, the use of large amounts of iodide-131 for therapy permits post ablative scanning to detect recurrent disease (60;61). A meta-analysis showed that the use of iodide-131 to prevent recurrence or death is uncertain (62). A beneficial effect is probably only present in patients with high risk or irradical surgery (8;53;63;64). Many authors are more careful advising I-131 ablation since various papers reported a relation between I-131 therapy and non-thyroid carcinoma (65-67).
In patients with a very low risk of recurrence/mortality (T1 (<1 cm) N0M0 unifocal) I-131 is not indicated. I-131 ablation is still the treatment of choice in patients with a high risk of recurrence/mortality 1) T3 or T4, 2) any T N1, and 3) Any T M1, and incomplete tumor resection (68;69). Controversy exists about patients with a low risk (T1 (>1 cm)N0M0, T2N0M0 or T1(<1 cm)N0M0 multifocal) of recurrence/mortality (50).
After initial therapy, all patients with DTC are treated with high doses of thyroxin aiming at significantly suppressing thyrotropin (TSH<01 mU/L) levels. The rationale of this approach is based on the potential harmful effects of TSH on tumor recurrence (7;8). One study demonstrated a preventive effect of TSH suppression on tumor recurrence or progression only in high risk DTC patients (70). However, long-term TSH suppression may be associated with potential harmful effects on various systems including bone metabolism, glucose metabolism, the autonomic nervous system and quality of life. The recent European Consensus on thyroid cancer (71), recommended that not all patients with DTC should be indiscriminately treated with TSH suppressive therapy because this represents in effect a state of subclinical hyperthyroidism, as defined by suppressed serum TSH levels (below 0.4 mU/l), in the presence of normal serum levels of (free) thyroxin. A recent analysis of our institution showed that TSH levels are positively associated to thyroid carcinoma related death and relapse (72). This effect became apparent at TSH levels above 2 mU/L and is in line with other studies (73).

Follow-up

The purpose of follow-up protocols in DTC is the early detection of tumor recurrence or metastatic disease in order to optimize additional treatment. Most patients during follow up have been cured definitely, and, as a consequence, have a low pre-test probability for recurrent disease. Therefore, the sensitivity of the diagnostic test must be adequate to detect the few patients with evident thyroid carcinoma, whereas specificity must also be high to avoid unnecessary treatments in patients without recurrent disease. In addition, the burden of diagnostic tests for the patient should be kept at a minimum.

a. Thyroglobulin

Thyroglobulin (Tg) is produced by normal or neoplastic thyroid follicular cells and Tg production is stimulated by TSH. In patients treated with a total thyroidectomy and I-131 ablation, Tg should be undetectable. The clinical interpretation of Tg is hampered by the

following analytical problems:
1. lack of universal standardization of the Tg assays, which results in considerable inter-assay variability (74),
2. a high intra-assay variability, which results in a poor comparability of results obtained within one patient during follow-up,
3. “hook” effects may be present, which affect IMA methods in particular and can lead to inappropriately low- or normal range Tg values in sera with very high serum Tg concentrations,
4. the presence of Tg auto-antibodies that can lead to lower or higher Tg levels.

Despite these analytical problems, Tg measurements are still the basis in the follow-up in DTC. Several studies have been performed on the diagnostic value of Tg measurements. The interpretation of these studies is difficult, because 1. heterogeneous patient groups with respect to initial therapy are included, 2. the time points of Tg measurements after diagnosis are not clearly indicated, and 3. fixed Tg cut-off levels are used, without receiver operator curve (ROC) analyses. The application of ROC data is essential, as a chosen cut-off level is a subjective choice based on the balance between a desired percentage of missed recurrences versus unnecessary therapies. Therefore, in the recent European consensus paper, it was recommended to define institutional Tg cut-off levels (71). In addition, most studies provide data on the diagnostic value of Tg for tumor presence, but do not give data on the *prognostic* significance for recurrence or death. The few studies that were published on the prognostic significance of Tg measurements used fixed cut-off levels, contained selected subgroups of patients, and included either Tg measurements at one time point or at undefined time points (75-79).
We, therefore, performed a study on the diagnostic and prognostic value of Tg in a homogeneous group of DTC patients with respect to initial therapy, using Tg measurements at 5 defined time-points after diagnosis, in combination with ROC analyses (chapter 2).

b. Thyroxin withdrawal versus rhTSH
Serum Tg measurements, I-131 ablation and diagnostic I-131 whole body scans are based on the responsiveness of DTC to TSH (80). TSH stimulated Tg measurements have superior diagnostic value in DTC compared to Tg measurements on thyroxin replacement therapy (81). High serum levels can be achieved by thyroxin withdrawal or injection with recombinant human TSH (rhTSH), which has less impact on quality of life (82). rhTSH is an adequate method to detect recurrence or metastases (78;83-85). A rhTSH stimulated Tg level greater than 2 mg/ml predicts persistent disease (78;83;86), whereas a rhTSH stimulated Tg level lower than 0.5 mg/dl has a 98 % likelihood of detecting patients free of tumor (78). Whole body scans performed after rthTSH-injections have a similar sensitivity and negative predictive value compared to thyroxin withdrawal (83-85). However, more negative whole body scans were found after rhTSH-injections compared to thyroxin withdrawal (83-85). The sensitivity and negative predictive value of Tg values after rhTSH-injections are 96.3 % and 99.5 % respectively by combining these measurements with a neck ultrasound (87).
Several studies have reported that radioiodine ablation of thyroid remnants after rhTSH-injections is as effective as ablation after thyroxin withdrawal (88;89). Radioiodine ablation after rhTSH-injections in patients with recurrence or distant metastases results in a beneficial effect in 75 % of patients (90;91). However, rhTSH has not been approved for this indication.

c. I-131 scintigraphy, Ultrasound, and FDG-PET
The result of iodine-131 whole body scanning depends on the presence and the ability of thyroid-cancer tissue to accumulate iodine-131 in the presence of high serum TSH concentrations. Diagnostic RaI whole body scintigrapies have a much lower sensitivity than ultrasound and Tg measurements. Therefore, the routine use of RaI scintigraphy in

the diagnostic follow-up of DTC patients is no longer recommended (87;92). Ultrasound combined with FNA had the highest sensitivity (even higher than Tg) for local recurrence and lymph node metastases in recent papers (87;93;94). Thus, ultrasound has an important place in he follow up of DTC. 18-F Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be useful in patients with elevated serum Tg levels, in whom no RaI uptake is observed after diagnostic or post-therapeutic scintigraphy. The sensitivity of FDG-PET is increased with elevating serum Tg levels and after TSH stimulation (95). Robbins *et al* showed that FDG-PET positivity is associated with worse survival (96).

III. Thyroid hormones

The production of thyroid hormones by the thyroid is regulated by the hypothalamus-pituitary-thyroid axis. Thyrotropin releasing hormone (TRH), which is produced by the hypothalamus, stimulates the secretion of thyrotropin (TSH) by the anterior pituitary. TSH promotes the thyroid to synthesize the prohormone tetraiodothronine (T4) in the thyroid. Iodide is actively taken up by the thyroid gland by the sodium-iodide-symporter (NIS) at the basolateral plasma membrane. The expression and activity of NIS are controlled by TSH. Thyrogobulin, which is synthesized by the follicular cells, is then iodinated with one or two iodides to form monoiodotyrosine (MIT) or diiodotyrosine (DIT). This process is catalyzed by the enzyme thyroid peroxidase (TPO). Two DIT molecules are then coupled to form T4 and one DIT and one MIT molecule are coupled to form T3. The thyroid secretes approximately 90 % T4, 10 % triiodothyronine (T3) and less then 1 % reverse T3. The T3 molecule is the active form of thyroid hormone. The majority of the active form of thyroid hormone T3 is derived from conversion of T4 to T3 in peripheral tissues, such as the liver (see deiodinases). T4 and T3, in turn, have a negative effect on the TRH secretion by the hypothalamus and TSH secretion by the pituitary. Iodide is important for the synthesis of thyroid hormones.

Deiodinases

Peripheral thyroid metabolism is mainly regulated by the iodothyronine deiodinases D1, D2 and D3 (97;98). D1 convertes the prohormone T4 in T3, plays a role in the breakdown of rT3 (97;99) and is expressed in liver, kidney, thyroid and pituitary and at lower levels in other tissues as skeletal muscle, spleen and lung. D2 is essential for the production of T3 through outer ring deiodination of T4. It is present in brain, skeletal muscle, thyroid, pituitary, brown adipose tissue (BAT) and aortic smooth muscle cells (97;100-104). D3 inactivates T3 and prevents T4 activation by innerring deiodination (98) and is present in brain, skin, placenta and fetal tissues (97).

The deiodinases adjust the thyroid hormone levels of individual tissues in response to various conditions. The peripheral conversion of T4 to T3 is increased during *hypothyroidism* (97;105;106). Extrathyroidal T3 production changes from PTU sensitive to PTU insensitive during hypothyroidism in rats, representing an increase in the conversion of T4 to T3 by D2 and a decreased conversion by D1 (107). D1 gene transcription is decreased in liver and kidney during hypothyroidism (108), which is related to the presence of two T3 response elements in the human D1 gene (97;108-110). Thyroid status regulates D2 activity both at the pre- and posttranslational level. D2 activity is increased in different tissues predominantly during hypothyroidism by a decrease in substrate (T4)-induced degradation of D2 protein (97;111-113). Hypothyroidism elevates D2 mRNA in rat brain and BAT (97;100;114;115). D2 mRNA expression and activity were found in skeletal muscle samples from healthy subjects (103;116). This is fascinating, because D2 could therefore play a role in peripheral and intracellular T3 production (103). Maia *et al*. reported that D2 is a major source of T3 during euthyroidism and could therefore play an important role during hypothyroidism

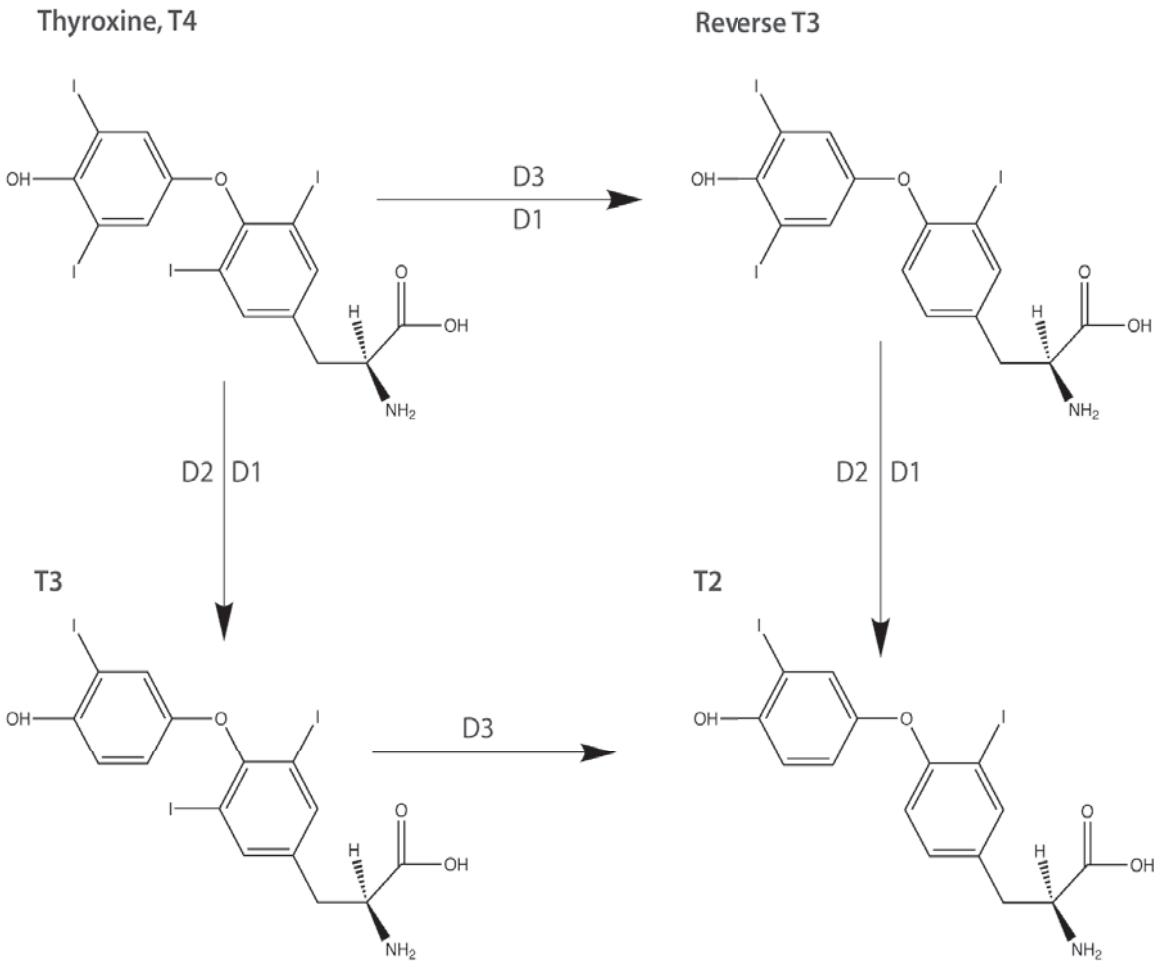

Figure 1. Structure of the iodothyronines and their activation and inactivation by iodothyronine deiodinase.

(117). As patients treated for DTC have no thyroid tissue left, we hypothesized that during hypothyroidism D2 in skeletal muscle could be essential in promoting the conversion of T4 to T3 (chapter 3).

Several polymorphisms in D2 have been described (118-120), with most studies investigating the consequences of the D2-Thr92Ala polymorphism. This D2-Thr92Ala polymorphism has been associated with BMI and insulin resistance in obese subjects and type 2 diabetes mellitus (118;119), although this was not confirmed in another study (121). The maximal velocity of D2 in vitro in thyroid and skeletal muscle of homozygous carriers of the Ala92 allele was decreased by 3–10-fold (118).

IV. Bone metabolism

Thyroid hormone impacts on bone metabolism, ranging from decreased skeletal development in childhood hypothyroidism to an increased risk for osteoporosis in hyperthyroidism (11;122;123). Thyroid hormone indirectly promotes osteoclast formation and activation by inducing the expression of cytokines, prostaglandins and the receptor activator of nuclear factor NF-κB ligand (RANKL) (124-126). RANKL, the key molecule in osteoclast differentiation, binds to its receptor, RANK, which is expressed on dendritic cells, T cells, osteoclast precursors and mature osteoclasts (127;128). RANKL promotes the survival of RANK positive T cells (127), stimulates osteoclast differentiation (129-133), increases

the activity of mature osteoclasts (130;134;135) and stimulates survival of osteoclasts by preventing apoptosis (135). Contact with stromal cells and M-CSF also promotes osteoclast differentiation (136;137). Thyroid hormone inhibits chondrocyte proliferation and promotes hypertrophic differentiation, mineralization, matrix synthesis but also apoptosis of chondrocytes in the growth plate.

Overt hyperthyroidism results in an increased risk for osteoporosis (123), the pathophysiology of which is multifactoral (124), including shortening of the bone remodelling cycle (138) and acceleration of bone turnover (139). The effects of *subclinical hyperthyroidism* on bone metabolism are not clear. Several studies have addressed this issue, but there is no consensus largely because of differences in study design, including patient groups, methodology used, follow-up time and choice of outcome parameters. To study the effects of subclinical hyperthyroidism on bone mineral density, we performed a systematic review including all clinical studies on TSH suppressive thyroxin therapy in thyroid cancer patients (chapter 4).

An interesting development has been the discovery of the *TSH* receptor (TSHR) in bone (140-142). TSHR knockout and haploinsufficient mice with normal thyroid hormone levels have decreased bone mass suggesting that TSH might directly influence bone remodeling (141;143;144). This is intriguing, because effects on bone metabolism that were previously ascribed to high thyroid hormone levels could also be attributed to suppressed TSH levels (143-145). Abe *et al*. suggested that TSH inhibits osteoclast formation and survival by attenuating JNK/c-jun and NFκB signaling in response to RANK-L and inhibits osteoblast differentiation and type 1 collagen expression as well by downregulating Wnt and VEGF signaling (141). The same group found also that TSH directly inhibits Tumour Necrosis Factor-α (TNF-α) production and that TNF-α is the critical cytokine mediating the downstream antiresorptive effects of TSH on the skeleton (146). Other studies suggest that serum TSH activates the type 2 deiodinase in osteoblasts, thereby linking TSH and increased local thyroid hormone availability (142). Furthermore, in animal studies, low doses of TSH increased bone volume and improved microarchitecture in ovariectomized rats (147), without increasing serum thyroid hormone levels.

It was recently reported that the TSHR-Asp727Glu polymorphism was associated with 2.3% higher BMD in elderly carriers (148). Although the functional consequences of this polymorphism are debated (149), the lower plasma TSH levels in patients carrying the polymorphism could point toward a higher sensitivity of the variant compared to the wild-type TSHR (150;151).

We, therefore, evaluated the independent relation between serum TSH levels and indicators of bone turnover in thyroidectomized patients for differentiated thyroid carcinoma receiving thyroid hormone substitution (chapter 5). In addition, we studied the relationship between the TSHR-Asp727Glu polymorphism and bone as these subjects are not expected to show compensatory lower serum TSH levels if they carry the TSHR-Asp727Glu polymorphism (150;151).

The consequences of *hypothyroidism* on bone metabolism are not clear. Various studies report decreased bone resorption (152-155) or bone formation (152), whereas other studies document no impact on bone turnover (156-158). Furthermore, it is not clear if the effects of hypothyroidism must be attributed to the increased TSH levels or decreased thyroid hormone levels. As mentioned above, TSHR knockout and haploinsufficient mice with normal thyroid hormone levels have decreased bone mass, suggesting that TSH might directly influence bone remodeling (141;143;144). However, other studies question the role of TSH in bone metabolism (159;160). Three studies in humans have investigated the effect of TSH on bone metabolism, but their results were not consistent showing either no impact on bone turnover (161), increased bone formation (162;163) or decreased bone resorption (163).

To document the effects of hypothyroidism on bone metabolism and to discriminate between effects mediated by decreased thyroid hormone levels *versus* those mediated by increased TSH levels, we studied bone metabolism in eleven patients with differentiated thyroid carcinoma (DTC) during short-term thyroxin withdrawal and compared with eleven age-, gender- and BMI-matched DTC patients with increased TSH levels and normal thyroid hormone levels due to rhTSH injections (chapter 6).
Although earlier studies on the role and functional expression of iodothyronine deiodinase enzymes in the skeleton have not revealed unequivocal answers (142;164-167), a recent study reported normal growth in mice with deficiencies in D1 and D2 indicating that D2 may not be critical in skeletal development (168). This was supported by another study, which found that D2 activity is restricted to mature osteoblasts, suggesting a possible role for D2 in mature osteoblast function (169). Because it is difficult to study the role of D2 *per se* on skeletal metabolism in humans, we choose to study the effects of functional D2 polymorphisms on BMD and indicators of bone turnover. Canani *et al*. (118) reported that the maximal velocity of D2 *in vitro* in thyroid and skeletal muscle of homozygous carriers of the Ala^{92} allele was decreased by 3–10-fold. We, therefore, studied the relationship between the functional D2-Thr92Ala polymorphism, BMD and indicators of bone turnover (chapter 7).

V. Glucose metabolism

Thyroid hormone has effects on glucose- and lipid metabolism (13;170). There is a relation between serum thyroid hormone levels and basal and insulin-mediated glucose metabolism in euthyroid subjects with preserved thyroid function (171-173). It has been suggested that T3 regulates insulin response after glucose ingestion in humans (174).
Hyperthyroidism has been associated with impaired glucose tolerance and increased insulin resistance (175-181), predominantly at the level of the liver (182). The pathophysiology has not been completely elucidated, but it has been ascribed to a combination of multiple factors, including diminished pancreatic secretion of insulin (183;184), diminished suppression of glucagon by glucose (185) and increased adrenergic activity (186).
Limited data are available on the consequences of *subclinical hyperthyroidism* on glucose- and lipid metabolism. This issue has been studied only by Yavuz *et al*., who reported a decreased insulin sensitivity index by oral glucose tolerance test in patients with exogenous subclinical hyperthyroidism compared to values after restoration of euthyroidism and compared to controls (187). Regarding lipid metabolism, most studies report no differences in lipid profiles during subclinical hyperthyroidism (188-190), with the exception of 2 studies, that observed decreased total and LDL cholesterol levels (191;192). Franklyn *et al.* reported decreased total cholesterol concentrations only in patients older than 55 years and LDL cholesterol levels were decreased only in patients older than 65 years (193). We therefore performed a prospective placebo-controlled randomized trial to investigate the effects of restoration of exogenous subclinical hyperthyroidism to euthyroidism on glucose- and lipid metabolism (chapter 8).

VI. Autonomic nervous system

The consequences of *hyperthyroidism* on the heart are profound, including tachycardia and/or arrhythmias, increased systolic pressure, increased systolic function, left ventricular hypertrophy and diastolic dysfunction (194-196). It is suggested that these effects are the

Result of direct effects of thyroid hormone on the cardiovascular system and the interaction of thyroid hormones with the sympathetic nervous system (195;197). Hyperthyroidism is associated with a sympathicovagal imbalance, characterized by increased sympathetic activity in the presence of reduced vagal tone, which corresponds with increased urinary excretion of catecholamines (15;16;198). Therefore, the current consensus is that manifestations of altered autonomic nervous system function play a role in the pathophysiology and clinical presentation of thyrotoxicosis.
During *subclinical hyperthyroidism*, cardiovascular effects may also occur, but these are less well known and seemingly less severe. Regular findings during subclinical hyperthyroidism include increased heart rate, supraventricular arrhythmias and abnormalities of LV morphology and function (195;199-201). The consequences of subclinical hyperthyroidism on the autonomic nervous system function are less well defined. Several studies, using measures of heart rate variability, found evidence that in patients with endogenous subclinical hyperthyroidism a reduction of cardiac parasympathetic control is present (18), (200), (202). This is supported by findings on heart rate turbulence by Osman *et al* (203). However, in the study of Goichot (18) no differences in the ratio of low frequency power over high frequency power (LF/HF) were reported in these patients. The LF/HF ratio is commonly used to characterize the balance between vagal and sympathetic influences. To further clarify this issue, we performed a prospective, randomized, placebo-controlled study using heart rate variability to assess the autonomic nervous system in patients with DTC with longer than 10 years exogenous subclinical hyperthyroidism and investigated whether restoration to euthyroidism affects autonomic nervous function (chapter 9).
Hypothyroidism is associated with bradycardia, mild diastolic hypertension, increased peripheral cardiovascular resistance (194;204;205), decreased cardiac output and diastolic dysfunction (194;204;206;207). Hypothyroidism also induces sympathovagal imbalance (17;208;209). Nevertheless, current literature shows inconsistent results with either an increased sympathetic activity (17), a decreased sympathethic modulation (208) or an increased vagal tone (209). We therefore investigated the effects of short-term overt hypothyroidism, 4 weeks after thyroxin withdrawal, and restoration to subclinical hyperthyroidism on the autonomic nerves system (chapter 10).

VII. Quality of life

DTC is associated with an excellent prognosis. This may imply that quality of life in cured DTC patients may be quite normal. However, patients are treated long-term with TSH suppressive thyroxin replacement therapy, reflecting in effect a state of *subclinical hyperthyroidism*, which may impact quality of life (210-212).
Quality of life in cured DTC patients is investigated in a few studies (20;21;213-215). However, these studies are limited by small patient numbers(21;213), limited number of quality of life questionnaires (20;215) or the absence of a healthy control group (20;213;214).
Studies reporting the relation between the level of TSH suppression and quality of life in DTC patients are inconclusive because of small patient numbers, selection of patients with symptoms of hyperthyroidism or selection of patients with a long duration of cure (210;216). For that reason, we investigated quality of life in a large cohort of cured DTC patients compared to controls matched for age, gender and socioeconomic status. In addition, the determinants of quality of life, including serum TSH levels were investigated (chapter 11).
Thyroxin withdrawal resulting in overt *hypothyroidism* may also impact quality of life. It results in fatigue, anorexia, constipation, problems with motor skills and fluid retention. Quality of life during thyroxin withdrawal is also affected by a decreased motivation, productivity and quality of work and by interfering with family and social life (22). In addition, a decreased psychomotor function and an increased fear are reported during thyroxin withdrawal (19;217).

VIII. D2-Thr-92-Ala and thyroxin dose

Several polymorphisms in D2 have been described (118;119;218;219). The functional implications of the *D2-Thr92Ala* polymorphism are inconclusive. One in vitro study found an association with a decreased D2 activity (118) whereas another study found no difference (219). So far no associations between the D2-Thr92Ala polymorphism and serum thyroid hormone levels were documented (151;218;220). A study of Torlontano *et al*. documented that homozygous carriers of the D2-Ala92 allele needed higher dosages of thyroxin in thyroidectomized differentiated thyroid carcinoma (DTC) patients, particular in the group with near-suppressed TSH levels (TSH values between 0.1 and 0.5 mU/L)(221). However, this study had limitations, because actual values of serum TSH levels for wild-type and homozygous groups within the near-suppressed TSH group were not given. It is, therefore, unclear whether TSH levels in both groups were indeed identical, which would be a key finding to ascribe the slight differences in thyroxin dose indeed to the polymorphism. The fact that serum T4 and T3 levels did not differ between the wild-type group and D2-Thr92Ala homozygotes is also remarkable. We, therefore, studied the association between the D2-Thr92Ala polymorphism, thyroid hormone levels and thyroxin dosage (chapter 12).

IX. Outline of this thesis

In chapter 2, we describe the diagnostic and prognostic value of thyroglobulin (Tg) in a homogeneous group of differentiated thyroid carcinoma (DTC) patients with respect to initial therapy, using Tg measurements at 5 defined time-points after diagnosis, in combination with ROC analyses.
In the continuation this thesis, questions about the clinical consequences of exogenous subclinical hyperthyroidism and hypothyroidism on bone metabolism, glucose metabolism, the autonomic nervous system and quality of life in patients with DTC are addressed.
Chapter 3 evaluates the D2 activity and expression of deiodinases 1, 2 and 3 in skeletal muscle samples in DTC patients both during hypothyroidism and thyroxin replacement therapy.
Chapter 4 shows the results of a systematic review describing the effects of TSH suppressive thyroxin therapy on bone mineral density in DTC patients.
In chapter 5, we evaluate the independent relation between serum TSH levels and indicators of bone turnover in DTC patients receiving thyroid hormone substitution.
In chapter 6 we describe a prospective study to investigate the effects of hypothyroidism on bone metabolism and to discriminate between potential effects mediated by decreased thyroid hormone levels versus those mediated by increased TSH levels.
Chapter 7 presents the relationship between the functional D2-Thr92Ala polymorphism, BMD and indicators of bone turnover.
In chapter 8, we investigate the effects of restoration of exogenous subclinical hyperthyroidism to euthyroidism on glucose- and lipid metabolism in a prospective, randomised, placebo-controlled trial.
Chapter 9 describes a prospective, randomized, placebo-controlled study to assess autonomic nervous function in patients with DTC with longer than 10 years exogenous subclinical hyperthyroidism and to investigate whether restoration to euthyroidism affects autonomic nervous function.
In chapter 10 we show the effects of short-term overt hypothyroidism, 4 weeks after thyroxin withdrawal, and restoration to subclinical hyperthyroidism on the autonomic nervous system.
Chapter 11 describes quality of life in a large cohort of cured DTC patients compared to

controls matched for age, gender and socioeconomic status. In addition, the determinants of quality of life, including serum TSH levels were investigated.
In chapter 12, we studied the association between the D2-Thr92Ala polymorphism and thyroid hormone levels and thyroxin dosage

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