Short-term hypothyroidism after Levothyroxine-withdrawal in patients with differentiated thyroid cancer: clinical and quality of life consequences

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Abstract
Acute hypothyroidism induced by thyroid hormone withdrawal in patients with differentiated thyroid cancer during monitoring for remnant or metastatic disease, seriously affects multiple organs and systems, and especially in severe cases can impair quality of life. Indeed, it may induce untoward cardiovascular effects and can be hazardous in patients with underlying cardiovascular disease, particularly in the elderly. Moreover, acute hypothyroidism deranges the lipid profile and exacerbates neuropsychiatric illness. The introduction of recombinant human TSH (rhTSH) as a diagnostic and therapeutic tool in the care of patients with thyroid cancer has widened the scope of disease management. The use of rhTSH prevents derangement of various systems at approximately equivalent societal costs to that of withdrawal and promotes compliance while preserving the patient’s normal daily functioning and productivity. Its reliability allied with its safety render this compound a valid alternative in the monitoring of patients with differentiated thyroid carcinoma as well as providing an alternative therapeutic procedure whenever LT4-withdrawal may be hazardous or in cases of patient non-compliance.

Introduction
The incidence of differentiated thyroid cancer (DTC) is on the increase worldwide though the statistics may simply reflect enhanced detection of subclinical disease rather than an actual increase (1). The most widely established treatment consists of total thyroidectomy and ablation of any thyroid remnant with radioiodine (131I), followed by thyroid-stimulating hormone (TSH) suppressive treatment with levothyroxine (LT4) (2). In recent years, the development of more effective treatment and the introduction of new follow-up modalities of DTC have led to modifications in follow-up management in relation to the clinical spectrum of the disease (3–5).

The traditional follow-up of DTC, which is designed to detect persistent or recurrent disease, entails evaluation of the tumor marker thyroglobulin (Tg), neck ultrasonography and, in some cases, total body scan with 131I. A high level of TSH improves the sensitivity of Tg monitoring and is required to stimulate sufficient radioiodine uptake for diagnostic imaging or therapy (6). This can be obtained either by prolonged withdrawal of thyroid hormone treatment or by injections of recombinant human TSH (rhTSH; TSH-α; Thyrogen®) (7–10). The standard procedure is to withdraw LT4 therapy in order to stimulate endogenous TSH, thereby inducing short-term hypothyroidism. According to the consensus of European Thyroid Association and the guidelines of American Thyroid Association for patients undergoing radioiodine therapy or diagnostic testing, LT4 can be withdrawn for at least 3 weeks, or alternatively LT3 can be administered for 2 weeks followed by LT3-withdrawal for 2 weeks (11, 12). Both procedures result in serum TSH levels higher than 30 mU/l in about 90% of patients. However, although this protocol prevents long-term hypothyroidism, it restricts patient’s daily functioning. rhTSH being less restricting in this respect (10, 13).

Long-standing hypothyroidism has profound effects on multiple organs and systems: it exacerbates neuropsychiatric illness and cardiovascular disease, negatively influences lipid metabolism, and increases atherosclerotic risk, though these changes are usually reversible via achievement of euthyroidism (14–16). In contrast, there is a paucity of data on the effects of short-term hypothyroidism induced by LT4-withdrawal on metabolism, possibly due to the reversibility of these results and to the variability of LT4-withdrawal protocols.

With the increasing awareness that various degrees of long-term hypothyroidism contribute significantly to the morbidity resulting from dyslipidemia, and
cardiovascular and neuropsychiatric disease, we have reviewed the data on the implications of short-term hypothyroidism after thyroidectomy in patients with DTC during LT4-withdrawal for diagnostic purposes.

**Cardiovascular effects of short-term hypothyroidism**

Thyroid hormone deficiency is known to seriously affect the cardiovascular system (17). Both subclinical and overt hypothyroidism have been associated with normal/depressed systolic function, left ventricular diastolic dysfunction at rest, systolic and diastolic dysfunction during effort, increased peripheral vascular resistance, and impaired endothelial function (18, 19). The similar pattern of these cardiovascular abnormalities in subclinical and overt hypothyroidism suggests that there is a continuum in cardiovascular effects related to thyroid hormone deficiency and also that a lesser degree of thyroid hormone deficiency may induce severe cardiovascular abnormalities. Moreover, cardiovascular function was found to be impaired not only in long-standing but also in short-term hypothyroidism (20–29).

However, it should be underlined that it is difficult to evaluate data about the effects of short-term hypothyroidism on the cardiovascular system, because the protocols used differ among the various studies, and in some cases severe hypothyroidism was induced by LT4-withdrawal. Furthermore, many studies have evaluated the cardiovascular effects of acute hypothyroidism during LT4-withdrawal in patients with DTC as compared with controls and/or with the same patients evaluated during TSH-suppressive therapy with levothyroxine. Compared with results obtained after 6 months of TSH-suppressive therapy, echocardiographs recorded during acute and severe hypothyroidism (40 days after total thyroidectomy) showed abnormalities, similar to those of chronic hypothyroidism, namely, prolongation of the QT interval and flattening and inversion of the T waves (20). In acutely induced hypothyroidism, heart rate at rest was reported to be normal when compared with controls, but it was found significantly lower at rest and during exercise when compared with the same patients during TSH-suppressive therapy (21, 22).

A reduced preload was reported in patients with short-term hypothyroidism as documented by reduced left ventricular end-diastolic volume (22). Short-term hypothyroidism may worsen diastolic function as a result of altered calcium handling induced by thyroid hormone deficiency. Left ventricular mass was higher in DTC patients after 5 weeks of LT4-withdrawal than during TSH-suppression: this increase was attributed to the presence of early interstitial myxedema (23). Compared with controls, diastolic dysfunction, defined by ventricular filling, was altered in patients with short-term hypothyroidism as documented by Doppler-echocardiographs (24). The magnitude of mitral valve flow velocity curves at both the early phase (E wave) and the maximal late flow (A wave) was decreased during thyroxine withdrawal in young- and middle-aged patients with DTC (24). Additionally, isovolumic relaxation time was reported to be significantly increased during acute hypothyroidism (25), and radionuclide ventriculography with simultaneous right catheterization confirmed a lower peak filling rate (26). Thus, a reduced ejection fraction during effort was documented by radionuclide ventriculography (26).

Recent data support an increase in afterload during short-term hypothyroidism (6 weeks after LT4-withdrawal) with a consequent increased prevalence of hypertension in the same patients evaluated during LT4-suppressive therapy (27). This was recently corroborated in a study of cardiovascular function evaluated by ambulatory blood pressure monitoring, in 19 patients with DTC, in which night-time systolic, mean, and diastolic blood pressures were higher during short-term hypothyroidism versus controls and versus the same patients under TSH-suppressive treatment (21). During the hypothyroid state, adrenaline, nor-adrenaline, and cortisol were increased, probably due to their reduced clearance (28). Moreover, there would seem to be no relation between tissue sensitivity to catecholamine and thyroid status, because patients with short-term hypothyroidism had a normal response to adrenaline infusion (28).

In conclusion, adverse cardiovascular effects have been reported during acute hypothyroidism, namely, electrocardiographic abnormalities, reduced heart rate at rest and during exercise, impaired left ventricular diastolic function, impaired systolic function during effort, increased systemic vascular resistance with a reduced cardiac output, and a reduced cardiac efficiency. There is clear evidence that young- and middle-aged patients with short-term hypothyroidism may have a reduced exercise capacity and an increased prevalence of hypertension. This finding provides a plausible explanation for the worsening of hypertension, heart failure, and coronary heart disease in patients with short-term hypothyroidism and preexisting heart disease, especially in elderly patients. Therefore, rhTSH can preferably be applied for diagnostic procedures in patients who have a higher risk of adverse cardiovascular effects. Furthermore, it must also be pointed out that alterations of cardiovascular function in short-term hypothyroidism are less well tolerated because they occur in patients that are usually exposed to the effects of mild thyroid hormone excess induced by TSH-suppressive therapy (21, 29).

In another study, positron emission tomography with $^{11}$C acetate and magnetic resonance imaging was used to investigate myocardial oxidative metabolism and its relation to cardiac function and geometry in ten patients with severe acute hypothyroidism (30). In this study, cardiac oxygen consumption was lower after LT4-withdrawal ($4.3 \pm 9$ days) compared with the values detected $40 \pm 13$ days after LT4-replacement.
therapy. The increase in afterload can account for the finding that the hypothyroid myocardium was energy-inefficient and the decrease in cardiac work in short-term hypothyroidism was more pronounced compared with the decrease in oxygen consumption (30).

Finally, in thyroidectomized patients with DTC taking anticoagulants, an inverse correlation between TSH and international normalized ratio after LT4-withdrawal has been recently reported, indicating that more frequent monitoring of the anticoagulation parameters and sometimes adjustment of the therapy with coumarin derivates might be required in hypothyroid patients (31).

Effects on lipids

In overt hypothyroidism, elevated levels of cholesterol and low density lipoprotein cholesterol (LDL-C) and quantitative changes that enhance its susceptibility to oxidation have been well documented (32, 33). Therefore, hypothyroidism constitutes a severe atherogenic condition. In a recent study, serum cholesteryl ester transfer protein (CETP) concentration, a crucial enzyme for the inverse cholesteryl transport, was reduced in short-term hypothyroidism, but the enzyme activity was normal (34). Additionally, the size distribution of high density lipoprotein (HDL) was altered with significant lower proportions of large-sized HDL2b and HDL2a in patients before than during LT4 therapy (34). No correlations were observed between CETP and HDL or LDL in treated or untreated patients, in contrast to the negative correlation between CETP and HDL and to the positive one between CETP and LDL in normal subjects. These findings may indicate a disconnection between the changes in lipoprotein parameters and the serum CETP levels in short-term hypothyroidism. Restoration of euthyroidism by LT4 therapy usually corrects these lipid abnormalities. Though these lipid alterations are mostly reversible on restoration of euthyroidism and have no impact on recovery outcome, they should be avoided in patients with diffuse atherosclerosis and/or cardiovascular disease.

Finally, elevated levels of homocysteine (hct), a cardiovascular risk factor, were found increased in two studies with 17 and 16 patients respectively with severe hypothyroidism after withdrawal of thyroid hormone (35, 36). A strong association was detected between creatinine, cholesterol, and hct levels, suggesting that these changes are partly due to alterations in renal function (36). The elevated hct levels significantly decreased after correction of hypothyroidism.

Affective disorders and cerebral blood flow in short-term hypothyroidism

A definite link has been established between thyroid dysfunction and mood disorders, and it has been reported that patients hospitalized with hypothyroidism have a higher risk of readmission with depression than controls (37). Thyroid dysfunction-induced mood changes may be partly due to cerebral blood flow (CBF) abnormalities, as demonstrated in patients with transient hypothyroidism studied with 131I-MIBG/123I-MIBG SPECT versus normal controls (38). Regional CBF alterations have been detected in the bilateral parietal lobes and in the bilateral occipital lobes, which extended to the prefrontal cortices as hypothyroidism worsened. However, these results were partly disputed in a study that correlated regional CBF and glucose metabolic activity, evaluated with the positron emission tomography 18F-labeled 2-deoxy-2-fluoro-D-glucose method, with the mental state of ten patients affected by severe hypothyroidism (TSH: 109.83 ± 40.25 mU/l) (39). That study identified a global but not regional reduction of CBF and glucose metabolic activity which may reflect a direct effect of thyroid failure on the overall brain activity. This inconsistency with other studies was explained by the authors as the result of the suddenly induced massive hypothyroidism that affects overall, not regional, brain activity. The reduction is unlikely to have been due to increased vascular resistance alone, since glucose metabolism was also impaired. This condition might be clinically reflected in the observed slowing of psychomotor function in patients rather than in their states of clinical depression (39). This mental state was interpreted as resulting from the abruptly induced deficiency of thyroid hormone, which led to the incapacity of brain cells to extract an adequate amount of oxygen and glucose from the blood.

Quality of life

Since there is no single definition of quality of life (QoL), we would suggest the definition proposed by the WHO. Thus, the term QoL is defined as an individual’s perception and expectation of a certain standard of excellence as regards his/her social and cultural environment (40). QoL accounts for every positive or negative aspect of life at physical, emotional, social, and cognitive level. Over the last few years there has been an increasing focus on the QoL of patients with thyroid cancer and several studies have reported impaired QoL with respect to thyroid carcinoma (13, 41). In 34 subjects with DTC undergoing thyroid hormone withdrawal in preparation for scanning procedures, significant changes at both physical and psychological levels were identified with a disease-specific rating scale (13). The patients routinely reported overwhelming fatigue, anorexia, problems with motor skills, constipation, and fluid retention, all of which inevitably resulted in impaired QoL (13). They also presented diminished motivation, as well as decreased productivity and quality of work. Moreover, the study revealed that thyroid hormone withdrawal has deleterious effects, not
only on the patients themselves, but also on their family and social life. In summary, the inability to perform customary household tasks and forced disengagement from participation in social activities severely disrupts the patient’s daily functioning.

A psychometric study recently evaluated QoL in 61 patients with DTC by means of a self-rating questionnaire (KSQ) and the Hamilton Depression Scale (HDS) (42). Both scales, KSQ and HSD, were significantly higher in patients than in controls, whereas HDS was significantly higher in female than in male patients.

Recently, the results were published of a 13-item survey aiming to elucidate the clinical, QoL, and pharmacoeconomic effects of hypothyroidism by comparing societal costs of withdrawal with rhTSH (43). About 92% of the patients who participated in the study had symptomatic and 85% had multisymptomatic disease, whereas half the patients needed medical support. Societal costs were calculated to be approximately 25% less for rhTSH as compared with LT4-suppression. Nevertheless, the strength of this study could have further been increased by the use of a specific and well-validated questionnaire (including the content validity), like the one used by Dow (13).

In summary, the results of all these studies accord in indicating severe impairment in QoL of patients with DTC when short-term hypothyroidism was induced, whereas considerable improvement is achievable when rhTSH testing is used in the management of the disease. However, one could comment that the methodology used in all the fast studies is lacking of the validity content that was provided in only one study (13). Therefore, further randomized studies comparing LT4-withdrawal and rhTSH using validated, disease-specific QoL questionnaires as outcome measures.

All relevant studies into the effects of short-term hypothyroidism on various systems are categorized according to whether they comprise a randomized controlled study, a longitudinal study, or clinical case studies (Table 1). They were rated using the modified criteria from the US Preventive Services Task Force as they have been recently published in the Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer by the American Thyroid Association Task Force (12, 49). The most studied parameters are categorized into four domains: 1) Physical complaints, 2) Health-related QoL, 3) Cognitive function, and 4) Psychometric function, and are evaluated in DTC patients before diagnostic whole-body scan, during short-term hypothyroidism, and on TSH-suppressive LT4 treatment compared with healthy controls matched for age, sex, height, and weight (50).

SF-36 scores above those for patients with heart failure, depression, and migraine. In contrast, the scores after LT4-withdrawal were calculated significantly below the norms of heart failure, depression and migraine, once again indicating severe impairment of QoL after LT4-withdrawal that can be abrogated by rhTSH (48).

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thyroxine withdrawal for monitoring in patients with DTC induced a reduction of IL-18, sL-2R and the percentage of natural killer cells in peripheral blood as compared with thyroxine-suppressive treatment, thus indicating that thyroid hormone modulates the cell-mediated immune response (51).

Short-term hypothyroidism after thyroid hormone withdrawal can significantly prolong both gastric half-emptying time and emptying rate, as has been reported in 22 patients with DTC (52). The disturbed gastrointestinal (GI) peristalsis results in delayed absorption of glucose from the GI-tract and reduced hepatic glucose transport, leading to a decrease in fasting glucose level. The alternative use of rhTSH

The recent introduction of rhTSH for monitoring of thyroid cancer patients, in preparation for ablation of thyroid remnant or for metastatic disease, represents a valid alternative to the short-term hypothyroid state and a model that checks for presence of thyroid cancer (3–5). It has been established that the combination of rhTSH-stimulated Tg with neck ultrasound (providing a diagnostic sensitivity of 96.3%) offers high diagnostic accuracy in detecting persistent disease in low risk patients, while it inhibits the implications of short-term induced hypothyroidism (5, 9, 10). Its use is particularly recommended for older patients suffering from heart disease, arterial hypertension, severe arteriosclerosis, anemia, and psychic disorders where LT4-withdrawal can be life-threatening. Despite the fact that most reported observations and references represent reversible effects, short-term induced hypothyroidism should be avoided in the above-mentioned cases as well as in those patients who, due to their working and social obligations, tolerate with difficulty any impairment of their QoL. Furthermore, its administration was not accompanied by measurable effects on heart rate, rhythm, left ventricular morphology, or systo-diastolic function (53). Additionally, an asymptomatic decrease in systolic and mean blood pressure was observed during rhTSH administration, whereas there was no effect on heart rate variability (HRV), suggesting that rhTSH does not influence the sympathovagal control of HRV when applied in patients with normal heart function (54). On this basis, rhTSH administration is clinically safe and may have beneficial effects on the vascular system by reducing arterial blood pressure and increasing circulating nitric oxide (55). Moreover, in postmenopausal, but not in premenopausal women, monitored for DTC, rhTSH administration acutely decreases the serum C-telopeptides of type-1 collagen and increases serum bone alkaline phosphatase levels, but does not affect osteoprotegerin production (56). Thus, an acute increase in serum TSH concentration leads to a marked inhibition of bone resorption.

Finally, when patients are rendered hypothyroid, there is achievement of a decreased residence time of radioiodine in the remnants and increased radiation exposure overall, as compared with the euthyroid state (57). In a study calculating the red marrow absorbed dose of high therapeutic doses of radioiodine 131I administered after rhTSH application, it was found that the bone marrow dose remained constantly below the safety level of 2 Gy (58). Therefore, the use of rhTSH may reduce the exposure of various organs to radioiodine and consequently diminish the complications rate.

Our review supports the use of rhTSH more extensively in DTC patients, since it prevents the derangement of various systems and promotes compliance, while ensuring in a safe and reliable way the quality of life in all patients.

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**Table 1** Study description and level of evidence of several articles describing the implications of short-term hypothyroidism on various systems.

<table>
<thead>
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<th>Author</th>
<th>Number of patients</th>
<th>Duration of withdrawal</th>
<th>Study description</th>
<th>Level of evidence</th>
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A, strongly recommend; B, recommend.

*Two weeks LT3.
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