

## Effect of Short Term Thyroxin Withdrawal on Health Related Quality of Life in Differentiated Thyroid Carcinoma Patients

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### Abstract

**Background:** We aimed to study the HRQL in patients with differentiated thyroid carcinoma (DTC) during hypothyroidism due to thyroxin withdrawal, which is induced routinely for iodine-131 (I-131) whole body scan and ablative treatment.

**Methods:** Between September 2011 and March 2012, eligible patients with DTC who were referred to our institution for diagnostic or therapeutic radioiodine administration under hypothyroid conditions due to thyroid hormone withdrawal were asked to complete the psychological instruments rating their HRQL and psychological status. HRQL was studied using the Short Form (SF-36), Hospital Anxiety and Depression Scale (HADS), Profile of Mood States (POMS), the total mood disturbance (TMD) score, Beck Depression Inventory (BDI). One hundred and forty three hypothyroid patients with DTC (F=101, M=42, age=58.7 yrs) who were also on low-iodine diet were included in this study. Hypothyroidism was induced by withdrawal of thyroxin replacement in all patients.

**Results:** The results of SF-36 showed that the HRQL was significantly impaired in hypothyroid patients during withdrawal of thyroxin (physical component scale:  $44.3 \pm 9.5$ , mental component scale:  $40.8 \pm 10.2$ ,  $p \leq 0.001$ ). Depression scores were in the normal or non-clinically relevant range:  $4.1 \pm 3.8$  on the HADS-Depression and  $8.3 \pm 6.6$  on the Beck Depression Index. However, the mean score of  $28.8 \pm 25.2$  on the POMS TMD was within normal range.

**Conclusion:** HRQL is impaired in hypothyroid patients with DTC during thyroxine withdrawal before I-131 whole body scan and radioiodine therapy.

**Keywords:** HRQL; Thyroxine withdrawal; DTC

### Introduction

In recent years, assessment of mental health in cancer patients has been attracting increasing attention [1,2]. The concept of health-related quality of life (HRQL) covers the patient's perceptions of his or her physical, emotional, social, and cognitive functions and, more importantly, disease symptoms and side effects of treatment. Measurement of HRQL has been accepted as a way to collect more meaningful data about cancer patients' subjective experiences during cancer therapy [2]. At the same time, depression and anxiety have become recognized as the most frequent emotional problems in cancer patients, with an important impact on HRQL [3,4].

Increased thyroid-stimulating hormone (TSH) is needed in patients with differentiated thyroid carcinoma (DTC) before radioactive iodine-131 (I-131) ablation and also I-131 whole body scan (WBS) during follow-up. Most widely accepted method to achieve elevated serum TSH concentrations is to render the patients hypothyroid through withdrawal of thyroxin replacement.

Health Survey Short-Form 36 (SF-36) is used to assess generic HRQL [5]. This generic instrument covers aspects of physical, psychological, and social functioning [6]. The signs and symptoms of hypothyroidism, including cold intolerance, weight gain, constipation, and slowness in movements all contribute to the substantial impact on the patient's ability to perform optimally. The concurrent symptoms of hypothyroidism therefore result in a substantial disruption of the patients' lives and ability to work.

We conducted the present study with three objectives: to characterize HRQL in a group of hypothyroid patients with DTC on thyroid hormone withdrawal; to test correlations between mental and physical HRQL summary scores and between these scores and various demographic, physical and psychological variables; and to identify factors influencing HRQL in this population [7-19].

### Material and Methods

Between September 2011 and March 2012, 143 thyroidectomized and hypothyroid patients with DTC were included in this cross-sectional study. All participants provided written, informed consent. All eligible patients who were referred to our institution for diagnostic or ablative radioiodine administration under hypothyroid conditions induced by thyroid hormone withdrawal were asked to complete

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psychological instruments rating their HRQL and psychological status. Any history of psychological illness were not seen in the past among these patients. Levothyroxine replacement was discontinued 2-4 weeks before radioiodine administration. The duration of withdrawal was determined by the result of serum TSH measurements. In accordance with local radiation protection regulations, the patients who ingest radioiodine with an activity higher than 30 m Ci were hospitalized while all other patients who underwent I-131 whole body scan during follow-up were included in this study as outpatients. On the first day, before any medical assessments and ingestion of radioiodine, the patients completed the psychological instruments described below to test HRQL and psychological status. Health Survey Short form-36 (SF-36) measures 4 domains in the area of physical health: physical functioning, physical role limitation, bodily pain and general health perception, and 4 domains in the area of mental health: emotional role limitation, vitality, mental health and social functioning. The Hospital Anxiety and Depression Scale (HADS) to assess depression and anxiety, we used the HADS, a 14-item questionnaire that is particularly suitable for somatically ill patients. As recommended by Zigmond and Snaith, we grouped our patients according to their subscale scores as non-cases (0-7 score), as borderline cases (8-10 score) or as definite cases (11-21 score) [19]. Beck Depression Inventory (BDI) 21-item questionnaire instrument was used to assess depression, specifically, its cognitive and physical symptoms. Each item was scored on a 4-point scale, with higher scores indicating greater severity. Total scores on the instrument of  $\leq 10$  reflect normal mood variation, and those of  $\geq 11$  indicating increasing degrees of clinical depression [20].

Profile of Mood States (POMS) 65-item scale was used to assess overall psychological distress and specific mood states. The patients were asked to describe their mood over the previous week with adjectives rated from 0 (not at all) to 4 (extremely) [21]. The instrument contains six subscales originally derived from factor analytic studies: fatigue-inertia, depression-dejection, vigor-activity, confusion-bewilderment, tension-anxiety, and anger-hostility. To capture the patient's overall psychological status on the POMS, we used the total mood disturbance (TMD) score, which is the sum of the five negative mood state subscales, minus the vigor subscale. The validity and reliability of the POMS have been confirmed in patients with various malignancies [22]. Data were analyzed using SPSS (Statistical Package for the Social Sciences) for Windows, version 13.0. For between-group comparisons, continuous variables were evaluated using the Student t-test. Correlations between findings were tested by calculation of Pearson's correlation coefficient. Demographic (age, gender, education level, relationship status), physical (serum TSH value), and psychological factors (HADS-D, HADS-A scores, TMD) were tested as independent variables. Differences were considered statistically significant when the p-value was  $<0.05$ . The Institution Ethics Committee approved the study protocol.

## Results

Table 1 shows the demographic, clinical, and laboratory data. The total sample consisted of 143 patients with DTC, 42 (29.3%) men and 101 (70.7%) women, who ranged in age from 21 to 82 years. The mean age of all participants was 58.7 years (SD 11.2). In terms of marital status, 119 (83.2%) patients were married, 24 (16.8%) were living alone at the time of study participation. Histopathological diagnosis included papillary carcinoma (80.4%) and follicular carcinoma (19.6%). All patients under thyroid hormone withdrawal were biochemically hypothyroid (free T4, free T3 or both were below normal range). Their mean serum TSH concentration on the day of study entry was 63 m U/L (range: 25-128 m U/L). The mean time since the diagnosis of thyroid

<b>All patients</b>	143
<b>Age</b>	
Years: Mean (SD)	58.7 (11.2)
<b>Gender</b>	
Female	101 (70.7%)
<b>Education</b>	
No qualification	23 (16%)
$\leq 5$ years	68 (47.5%)
5-8 years	29 (20.2%)
9-12 years	6 (4.1%)
University degree	17 (11.8%)
<b>Relationship status</b>	
Marital	119 (83.2%)
Living alone	24 (16.8%)
<b>Employment status</b>	
Full time/part time	51 (35.6%)
Unemployed	12 (8%)
Retired	9 (6%)
Homemaker	71 (49.6%)
<b>Histology</b>	
Papillary carcinoma	115 (80.4%)
Follicular carcinoma	28 (19.6%)
<b>Time from diagnosis (months)</b>	10.2 $\pm$ 28.3

Table 1: Patients' Characteristics.

carcinoma was 10.2 (SD 28.3) months. Most patients in the present study reported various symptoms of hypothyroidism (Table 2). Even the least common complaints were reported by just under a quarter of patients, while the most frequent symptoms were reported by more than 60% of patients. The most common symptoms included impaired performance of physical activities and problems with daily activities as a result of deteriorated physical health, bodily pain and emotional problems. Physical complaints were similar in both gender.

In all domains of SF-36, hypothyroid patients with DTC reported significantly reduced HRQL, i.e. DTC patients scored significantly lower for physical health (PCS) ( $p \leq 0.001$ ) and mental health (MCS) ( $p \leq 0.001$ ). In these study, mean  $\pm$  SD depression scores were in the normal or non-clinically relevant range:  $4.1 \pm 3.8$  on the HADS-Depression and  $8.3 \pm 6.6$  on the Beck Depression Index. According to the cut off criteria of the HADS-D, 13 patients (9%) were identified as borderline depression cases and another 12 (8.3%) as definite depression cases for a probable prevalence of clinical depression of 17.3%. In contrast, anxiety scores for the overall study population exceeded the borderline levels (mean  $\pm$  SD HADS-A score of  $8.4 \pm 2.6$ ). On the HADS-A, fifty two patients (36.3%) were identified as borderline anxiety cases and 36 patients (25.1%) as definite anxiety cases for an overall probable prevalence of anxiety of 61.4%. In total, 88 patients (61.4%) suffered from psychological distress documented by the HADS-D, the HADS-A, or both. However, the mean  $\pm$  SD score,  $28.8 \pm 25.2$  on the POMS TMD, which incorporates measurements of fatigue-inertia, confusion-bewilderment, anger-hostility and vigor-activity as well as depression and anxiety was within normal range.

## Discussion

Hypothyroidism is accompanied by a variety of complaints including fatigue, sleep disorders, dry skin, constipation and cold intolerance affecting negatively patients' physical well-being and functioning [7]. Furthermore, neurological and psychiatric disturbances

Hypothyroid Symptoms	DTC patients (N=143)
Fatigue	91 (63.6%)
Constipation	61 (56.6%)
Dry skin	49 (34.2%)
Weight gain	38 (26.5%)
Cold intolerance	31 (21.6%)
Impaired mental activity	27 (18.8%)

**Table 2:** Patients reported various symptoms of hypothyroidism.

due to hypothyroidism such as psychomotoric slowing, depression and anxiety have been studied [3,8,9]. DTC is associated with good prognosis; 10- and 20-year survival rates are 90% and 60%, respectively [10]. However, up to 20% of these patients develop local recurrence and locoregional lymph node metastasis, and up to 13% distant metastases within decades after the initial diagnosis [11]. Therefore long-term follow-up is required in these patients to detect persistent or recurrent disease or metastasis at an early stage. Both radioiodine whole-body scan and serum thyroglobulin measurement, the two main procedures commonly used for the detection of recurrence and metastasis during follow-up depend on elevated serum thyroid-stimulating hormone concentrations to optimize their sensitivity. Thyroxin withdrawal for 2-4 weeks is the common method to achieve elevated TSH, but, recently, recombinant human TSH (rhTSH) injection is also used for this purpose when logistically feasible. The patients suffer from severe hypothyroid symptoms during the thyroxin withdrawal period. rTSH injection while the patient continues to receive daily thyroxin dose maintains sufficiently elevated serum TSH levels without causing hypothyroidism. For optimal, reliable radioiodine ablation and whole body scan, serum TSH level is desired to exceed 30 m U/L.

A study in 36 patients with DTC showed that the HRQL scores were lower than those in a control group of healthy individuals [12]. However, when these patients become euthyroid by the initiation of thyroxin supplementation, the HRQL scores were the same with those of control group except for the general health functional scale, which continued to be lower in the patients with DTC [12]. In another study of 150 consecutive patients with DTC on levothyroxine, SF-36 HRQL functional scores were statistically similar between the DTC patients and sex- and age matched healthy controls in all SF-36 functional areas except role emotional and vitality. Of interest, the SF-36 physical role, mental health and social functioning scores were significantly lower in a subgroup of patients who had been diagnosed with DTC within 1 year of study entry than in controls [13]. This finding suggested an HRQL improvement in DTC patients with time since the initial diagnosis of DTC. Hence, the length of thyroxine replacement in a given study population could influence the HRQL findings. However, subgroup analyses in our study population did not support this finding. One reason may be that, in our study, the mean time interval since the initial diagnosis of DTC (10.2. months) was too short to disclose this relation. Our study examines quantitatively via numerous standardized self-rating instruments the physical complaints, HRQL, depression, anxiety, and their interrelationships in a large group of patients with DTC during thyroxin withdrawal period. Remarkably, the decline in psychosocial HRQL was more pronounced in our hypothyroid patients with DTC than that was reported in patients with other malignancies [14,15]. For example, patients with non-thyroid cancers undergoing diagnostic or therapeutic procedures (e.g., laparoscopic staging for prostate cancer or lumpectomy for breast cancer) that presumably are similarly stressful as WBS or radioiodine treatment of DTC showed a similarly reduced physical HRQL, but a much better psychosocial HRQL compared to our patient population [16]. The severity of depressive symptoms in

our patients was in the normal range of healthy reference populations [17,18]. In addition, the depression case prevalence as defined by HADS criteria was comparable with the reference populations [19]. The lack of an abnormal degree of depression in the present study was confirmed by the mean POMS depression and Beck Depression Inventory scores, both of which fell into the “not clinically relevant” range [12,20]. This finding is in compliance with previously reported results in a similar group of patients [3]. The association between long-term thyroid hormone deficiency and clinical depression, even when the hypothyroidism is subclinical, is well known and well documented: clinical depression occurs in >40% of chronically hypothyroid patients [20,21]. Our observations suggest that the association between short-term hypothyroidism and depression is less clear in patients with DTC.

Chronic hypothyroidism, even in the mild form is associated with neurocognitive dysfunction including memory loss and depression [22]. Previous studies on hypothyroid subjects have indicated serious psychiatric symptoms affecting the patient’s quality of life. Euthyroid and hyperthyroid subjects do not differ significantly in their general health questionnaire scores from subclinical or clinical (overt) hypothyroid subjects. In contrast, hypothyroid patients show a significantly higher HRQL impairment [3,7,23]. Hypothyroidism increases the risk for mood deterioration by about seven-fold [24]. Thus, hypothyroidism represents a widely underestimated functional condition that may severely affect mental health. In our group of patients, mood disturbance as measured by the POMS TMD and anxiety as measured by the HADS-A were significant independent effects of short term hypothyroidism. Demographic or somatic variables however did not significantly affect mental HRQL.

In contrast to thyroid hormone deficiency, TSH values in our hypothyroid patients showed no significant impact on HRQL, depression, anxiety, mood disturbance or physical symptoms. A similar absence of correlation between TSH concentration and depression or bodily complaints were previously observed by other researchers in patients with long- as well as short-term hypothyroidism [25-28]. This lack of correlation could be in part due to variations in TSH secretion: in the course of its circadian rhythm, peak and concentrations differ by approximately 50% [26] while in our patients all blood samples were drawn between 9 and 11 hour a.m. as a standard procedure. In a study, it has been shown that diurnal rhythmicity of TSH secretion was abolished in a cohort of patients with short-term severe primary hypothyroidism [27].

The limitation of this study is the lack of a control group. Also, our study design did not allow us to have a control group from patients who did not undergo I-131 whole body scan or remnant ablation treatment.

In conclusion, our study showed that HRQL was reduced in patients with DTC during thyroid hormone withdrawal which was needed for diagnostic or therapeutic procedures.

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