

Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma

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Abstract

We studied the psychological performance and the quality of life in patients with differentiated thyroid carcinoma, either during treatment with chronic suppressive doses of levothyroxine, or during the withdrawal of levothyroxine needed to perform whole-body scanning with radioactive iodine, with those of appropriate healthy controls.

Eighteen women with differentiated thyroid carcinoma and 18 euthyroid age-matched healthy women were recruited. Patients were studied the day before levothyroxine withdrawal (when in chronic mild or subclinical hyperthyroidism), 4–7 days later (when most patients had normal serum free thyroxine and free triiodothyronine levels), and the day before scanning (when in profound hypothyroidism). Controls were studied at one time point.

When compared with controls, patients presented with impairment of several indexes during chronic suppressive levothyroxine therapy (total score, emotional, sleep, energy and social of the Nottingham Health Profile; mental health, general health and social function of the SF-36, and total score on Wais Digit Span; $P < 0.05$ for all comparisons). Also, quality of life indexes (19 of 21 scores), cognitive tests (6 of 12 scores), and affective and physical symptoms visual mental scales (18 of 19) worsened during profound hypothyroidism ($P < 0.05$ for all comparisons). Quality of life and cognitive performance were almost comparable with those of euthyroid controls when most patients had normal free thyroxine and triiodothyronine levels.

In conclusion, quality of life and psychometric functionality in patients with differentiated thyroid carcinoma is not only affected by withdrawal of levothyroxine but also by long-term treatment with supraphysiological doses of levothyroxine.

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Introduction

Differentiated thyroid carcinoma (DTC) is a frequent endocrine disorder. Mortality rates in DTC patients have fallen significantly in the United States during the last two decades, possibly because of generalized use of initial complete surgical resection and ablation of thyroid remnants using radioactive iodine (Hundahl *et al.* 1998). This practice is frequently followed by chronic suppression of endogenous secretion of thyrotropin (TSH) by administering supraphysiological doses of oral levothyroxine to these patients.

Detection and ablation of thyroid remnants using radioactive iodine requires stimulation by TSH. Levothyroxine withdrawal prior to radioactive iodine whole-body scanning (WBS) is the 'gold-standard' method to obtain these

increased circulating TSH levels before WBS, and is the preferred approach for ablation therapy (Mazzaferri & Kloos 2001). Although the efficacy and safety of this approach has been demonstrated for decades, patients frequently complain of symptoms of profound hypothyroidism resulting from levothyroxine withdrawal. The recent availability of i.m. recombinant human TSH (rhTSH) as a useful method to stimulate radioactive iodine uptake by thyroid remnants (Meier *et al.* 1994, Haugen *et al.* 1999, Robbins *et al.* 2001) has stimulated research into the poor psychological performance and the loss of quality of life (QoL) of patients with DTC during levothyroxine withdrawal.

Several studies have demonstrated impairment in tests measuring QoL and psychometric functionality in patients with DTC during triiodothyronine (Meier *et al.* 1994) or lev-

othyroxine (Dow *et al.* 1997, Haugen *et al.* 1999) withdrawal, compared with these tests when the same patients were taking suppressive doses of triiodothyronine (Meier *et al.* 1994) or levothyroxine (Dow *et al.* 1997, Haugen *et al.* 1999), and when these patients were given rhTSH (Meier *et al.* 1994, Haugen *et al.* 1999).

However, in none of these studies were QoL and psychometric functionality in DTC patients compared with appropriately matched healthy euthyroid controls. For that reason, the extent to which QoL and psychometric functionality worsen during levothyroxine withdrawal is not known and, more importantly, the possibility that QoL and psychometric functionality may be also impaired by the chronic administration of suppressive doses of levothyroxine have not been explored to date.

Materials and methods

Subjects

Eighteen consecutive women with DTC, age 44.3 ± 12.5 years (s.d.), who were referred to the Department of Nuclear Medicine for a routine WBS during follow-up after initial surgery and radioactive iodine ablation, were recruited prospectively. Another patient aged 16 was studied, but her data were not included for the present report because some of the QoL tests used here have not been validated in minors. Patients were studied during levothyroxine withdrawal at three time points: the last day on levothyroxine at their usual suppressive doses, 4–7 days after withdrawal (DeGroot *et al.* 1997), and the day before administering radioactive iodine for scanning. Thyroid function in these patients was expected to change from a state of subclinical or mild hyperthyroidism in the first visit to a situation of normal circulating levels of thyroxine and triiodothyronine at the second visit, ending in a state of profound hypothyroidism at the last visit.

Before the present WBS, 16 of the 18 patients had no evidence of residual thyroid tissue because of undetected serum thyroglobulin levels. Another patient had detectable thyroglobulin levels within the normal range (1.8 ng/ml) and afterwards was given a therapeutic dose of radioactive iodine because of a cervical thyroid remnant. The last patient was told she might need treatment with radioactive iodine depending on the result of the WBS, because her serum thyroglobulin concentration was mildly increased before WBS.

The indication for the WBS (rhTSH was not available in Spain at the time of the study), as well as the degree of suppression of endogenous TSH secretion and the doses of levothyroxine used during follow-up, were decided by the physicians referring these patients, and were not influenced by any of the authors of the study. None of the patients was taking any drug known to affect thyroid hormone metabolism other than levothyroxine sodium. Patients were taking the latter at a TSH-suppressing dose of 170 ± 22 µg/day.

Eighteen healthy female volunteers served as euthyroid controls. These women were recruited from healthy relatives of the patients or of hospital colleagues, and were of similar age (43 ± 15.3 years), ethnic, social and cultural background, academic degrees and current professional occupations compared with the patients. The controls were not taking any drugs known to influence thyroid function.

None of the patients or controls was taking psychotropic drugs or was under psychotherapy, or had a previous history of central nervous system alterations, mental disabilities or psychological disorders.

The ethics committee of the Hospital Ramón y Cajal approved the study, and written informed consent was obtained from all the patients and controls or their legal representatives.

Study protocol

Patients and controls reported to the metabolic testing unit on the morning after a 12 h fast. Patients were advised to take their usual levothyroxine dose just after waking up and before reporting to the hospital on the day of the first visit, and levothyroxine was withdrawn thereafter. Evaluation was repeated in the patients after 4–7 days (second visit, mean \pm s.d. 5.4 ± 1.0 days after levothyroxine withdrawal), and the day before WBS was performed (third visit, mean \pm s.d. 30.3 ± 4.5 days after levothyroxine withdrawal). Controls were evaluated only at one time point.

Serum samples were obtained for determination of TSH, free thyroxine (FT4) and free triiodothyronine (FT3) using commercial immunochemiluminescence assays (Immulite 2000; Diagnostic Products Corporation, Los Angeles, CA, USA). The mean coefficients of variation were below 10% for all these assays. The normal ranges were 0.4–4.0 µU/ml for serum TSH, 0.8–1.9 ng/dl for FT4, and 1.8–4.2 pg/ml for FT3 as reported by the Central Laboratory of Hospital Ramón y Cajal. Whole blood, serum and 24 h urine samples were obtained, and several tests of cardiovascular performance and body composition were performed for future studies regarding the influence of thyroid hormones on the function of several organs and body systems. Sampling was performed in the same sequence in patients and controls, to avoid any possible influence on psychometric testing. After blood testing and echocardiography, patients and controls had a small breakfast, and then an independent evaluator performed a battery of cognitive, affective and QoL tests, assessing the following areas: (i) Clinical hypothyroidism was evaluated by the Zulewski score (Zulewski *et al.* 1997), which is virtually equivalent to the Billewicz index of clinical hypothyroidism (Billewicz *et al.* 1969) used in previous studies (Meier *et al.* 1994, Haugen *et al.* 1999). (ii) Cognitive function was assessed by three standard tests (Table 1): the Digit Symbol Substitution Test that measures psychomotor

Table 1 Methodological description of cognitive tests

Description	Scoring system
<p>Digit Symbol Substitution Test It has a code table at the top of the page in which digits 1 to 9 are arranged in numerical order, and beneath each digit is a nonsense symbol. Below are rows of pairs of squares, the upper of which contains a number, the lower of which is blank. With the code table available, the subject is allowed 90 s to write in each blank square the symbol paired with that digit in the code table. In order to measure the effect of psychomotor speed in this test, the symbol-copy task modification was also performed. This involves merely copying the symbols used in the original task, without pairing them with digits. Two other scores are given: the raw number of copies performed in 90 s, and the difference between the number of copies and the number of correct symbol-digit pairs completed in the first 90 s.</p>	<p>The raw score is the number of correct entries completed in 90 s. This score measures psychomotor performance. The lower the difference between copies and correct pairs, the better the global result.</p>
<p>Digit Span Test It measures immediate auditory attention by asking the subject to repeat spoken numbers with increasing numbers of digits. Then, the subject is asked to repeat the numbers in reverse order, measuring mental flexibility.</p>	<p>Three scores are given: correct forward repeats, correct backward repeats and total correct repeats.</p>
<p>Visual Scanning Test It measures distractibility and visual inattentiveness. The subject is asked to find a particular symbol within a paper with a matrix of symbols, of which 60 are correct.</p>	<p>The time needed to complete the test, the omissions and the errors are scored.</p>

performance (Wechsler 1981) and psychomotor speed (Kaplan *et al.* 1991); the Digit Span Test that measures immediate auditory attention (Wechsler 1981, Wechsler & Kaufman 1999); and the Visual Scanning Test, which measures distractibility and visual inattentiveness (Weintraub & Mesulam 1985). (iii) Auto-administered questionnaires were used to assess mood, affective state, physical symptoms and QoL (Table 2): Visual Analogical Mental Scales (VAMS), the Profile of Mood States (POMS), which measures depression and affective state (McNair *et al.* 1992), and the Nottingham Health Profile (NHP) and the SF-36

Health Survey (SF-36), which are modern and widely validated tools to assess QoL (Alonso *et al.* 1990, 1994, 1998, Garratt *et al.* 1993, Bullinger *et al.* 1998). Finally, an objective estimation of central and peripheral nervous system performance was obtained. Ankle reflexes were measured by using a reflexometer (Cardioline; Elettronica Trentina, Cavareno, Trento, Italy), and visual (VEP) and brainstem auditory evoked potential (BAEP) were also evaluated following The International Federation of Clinical Neurophysiology Recommendations (Celesia & Brigell 1999, Pratt *et al.* 1999).

Table 2 Methodological description of QoL tests

Description	Scoring system
<p>SF-36 Health Survey (SF-36) Modern and widely validated tool to assess QoL. Auto-administered test of 36 items that measure general health, physical function, role-physical, pain, vitality, social function, role-emotional and mental health.</p>	<p>Higher scores indicate better performance, with the exception of pain category.</p>
<p>Nottingham Health Profile (NHP) Widely validated test to assess QoL. Is an auto-administered test of 38 items; each has to be answered as 'yes' or 'no'. Results are grouped into six categories of QoL (energy, pain, emotional, sleep, social and mobility).</p>	<p>Higher scores indicate worse performance. Result of the test can be used as the total score or as the scores of the six categories separately.</p>
<p>Profile of Mood States (POMS) Auto-administered test that measures depression and affective states, and consists of 65 items, each of a distinct subjective feel, graded from 0 to 4.</p>	<p>Scores for six aspects of mood are obtained.</p>
<p>Visual Analogical Mental Scales (VAMS) Each scale consists of a 100 mm-length line that joins a pair of phrases such as 'as sad as possible' and 'as happy as possible'. The subject is asked to place a mark at the point best corresponding to his or her state at that time.</p>	<p>Measurement (in mm) of the marks from the beginning of the line generates a score for each VAMS.</p>

Statistical analysis

Data are expressed as means \pm s.d. The normal distribution of the variables was analyzed using the Kolmogorov–Smirnov test. Logarithm or square root transformations were applied to ensure normality whenever possible. The values of the patients during the three visits were compared by repeated-measures ANOVA, or Friedman two-way ANOVA by ranks, as appropriate. After Friedman analysis, comparisons between visits 1, 2 and 3 were performed using repeated Wilcoxon signed rank tests applying the Bonferroni correction to the level of significance.

The comparisons of the values of the patients at each visit with the controls were performed by one-way ANOVA followed by Dunnett's test, or by Kruskal–Wallis one-way ANOVA by ranks followed by Mann–Whitney tests, depending on the distribution of the variables. After a significant Kruskal–Wallis test was obtained, the identification of the particular visit, or visits, which were different compared with the controls was made using separate Mann–Whitney tests. Because no comparisons were made between visits, no correction was applied to the level of significance. An α value of 0.05 was chosen as the level of statistical significance with the exceptions described above. Statistical analyses were performed using SPSS for Macintosh, Version 10 (SPSS Inc., Chicago, IL, USA).

Results

Thyroid hormone function during levothyroxine withdrawal

As expected from chronic treatment with supraphysiological doses of levothyroxine, the mean serum thyroid hormone levels were in the mild hyperthyroid range at visit 1 (15 of 18 patients had increased FT4 levels, whereas all the patients had suppressed TSH levels, and only two had increased FT3 concentrations (Fig. 1)).

At visit 2, mean TSH levels were in the lower limit of the normal range, whereas mean serum FT4 and FT3 were within the normal range. Sixteen of 18 patients still had decreased TSH levels, but their FT4 and FT3 levels were within the normal range except in one patient who still had minimally increased FT4 levels. When considering patients as a group, at visit 2 patients presented with lower mean TSH and FT3 levels compared with euthyroid controls (Fig. 1).

At visit 3, all the patients presented with increased serum TSH and low serum FT4 and FT3 levels (Fig. 1). When considering patients as a group, mean serum TSH was increased, and mean FT4 and FT3 levels were decreased, compared with controls and with respect to the normal range established in the Central Laboratory of Hospital Ramón y Cajal.

The Zulewski score of clinical hypothyroidism was comparable with those of euthyroid controls at visits 1 and 2,

increasing above the normal range and compared with the controls at visit 3 (Fig. 1).

QoL tests

Changes in QoL tests are detailed in Table 3. Only three of the 21 variables included in the NHP, SF-36 and POMS were different in patients at visit 2 compared with euthyroid control women (energy and social of NHP and general health of SF-36).

On the contrary, 8 of the 21 scores were abnormal in patients at visit 1 – total score, energy, emotional, sleep and social scores of the NHP, and the scores of mental health, social function and general health of the SF-36 – when compared with controls. Also worse results were observed at visit 1 compared with visit 2 (when serum FT4 and FT3 were within the normal range in most patients) in scores such as pain of NHP, and the depression-dejection, anger-hostility, and vigor-activity scores of the POMS. Finally, as expected from previous studies by others, 19 of the 21 variables worsened markedly at visit 3 (profound hypothyroidism) compared with euthyroid controls.

Thus, a biphasic pattern of changes was observed, because the results worsened when the patients had mild or subclinical hyperthyroidism and when they were markedly hypothyroid, both when compared with the moment when most of the patients had normal plasma FT4 and FT3 levels, and when compared with the euthyroid controls.

Cognitive tests

Cognitive performance in patients was similar to that of euthyroid controls at visit 2. Some cognitive tests were worse at visit 1 when compared with that of controls (total score of the Wais Digit Span), and with the moment when most of the patients had normal plasma FT4 and FT3 levels at visit 2 (pairs of the Wais Digit Symbol). Cognitive tests were even worse at visit 3, with a significant impairment of the Wais Digit Span, and the memory, attention, problem solving and clumsiness VAMS (Table 4). The impairment in these VAMS at visit 3 was also evident when comparing these variables with the results obtained in the patients at visits 1 and 2. Therefore, as occurred with QoL tests, a biphasic pattern of changes suggests that both excess and deficiency of thyroid hormones may have detrimental effects on cognitive performance of patients with DTC.

Affective and physical symptoms of VAMS

Most of the abnormalities in affective and physical symptoms of VAMS appeared in DTC patients at profound hypothyroidism (Table 5), when 18 of 19 scores presented worse results compared with euthyroid controls, and 16 of these

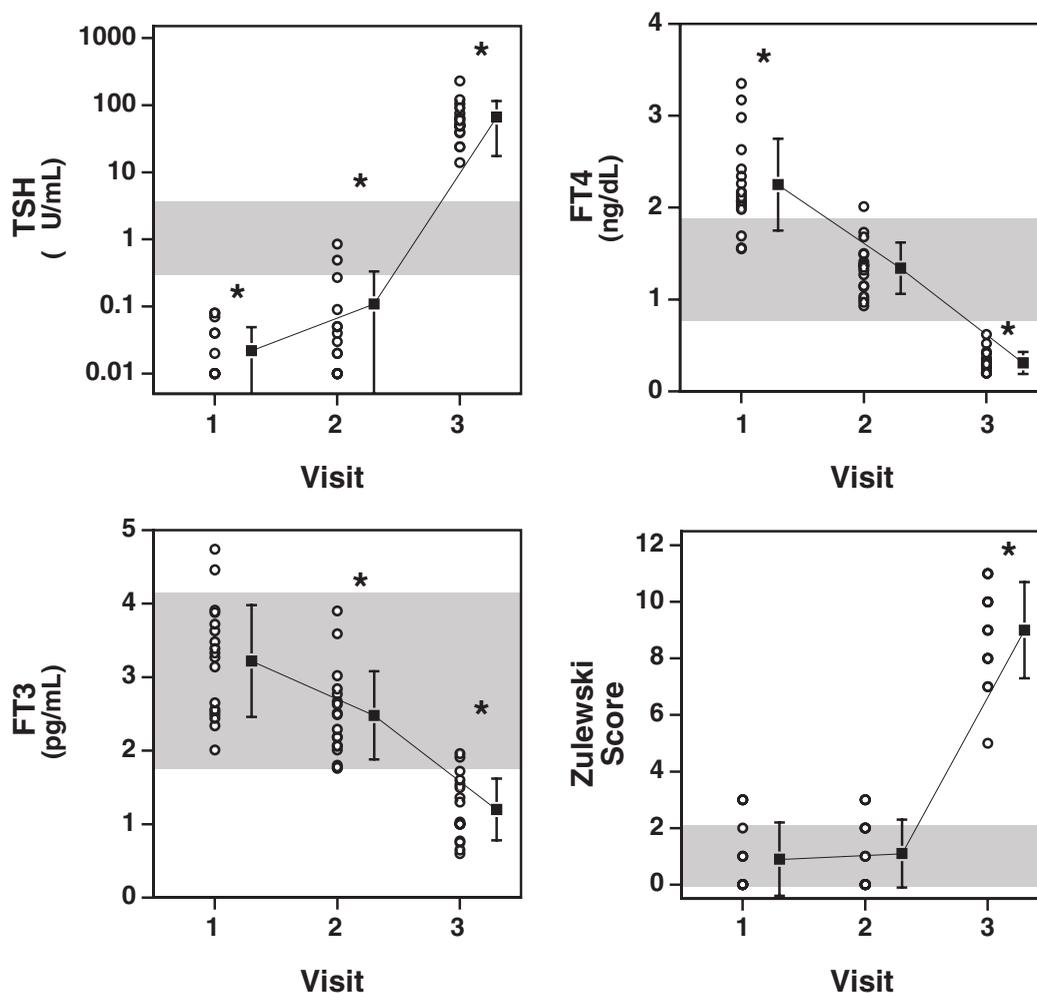


Figure 1 Clinical and biochemical indexes of thyroid hormone function during levothyroxine withdrawal in women with differentiated thyroid carcinoma compared with healthy euthyroid women. Data are means \pm s.d., and the dot scattergram shows the individual data. The shaded areas represent the normal ranges for serum thyroid hormone levels as reported by the Central Laboratory of Hospital Ramón y Cajal, and the normal range for the Zulewski score (Zulewski *et al.* 1997). Statistically significant differences between visits 1, 2 and 3 were observed in serum TSH, FT4 and FT3 levels, with $P < 0.05$ for all the comparisons. The Zulewski score was increased at visit 3 compared with visits 1 and 2 with $P < 0.001$, whereas no difference was observed between visits 1 and 2. The means \pm s.d. of euthyroid control women were: serum TSH 1.87 ± 0.84 μ U/ml, serum FT4 1.29 ± 0.13 ng/dl, serum FT3 3.42 ± 0.79 pg/ml and Zulewski score 0.5 ± 0.8 . * $P < 0.05$ compared with euthyroid controls.

abnormal results at visit 3 were also worse compared with visits 1 and/or 2 (Table 5). In addition to the abnormalities found at hypothyroidism, VAMS of sadness, depression, nausea, blurred vision and dizziness at visit 2 showed worse results compared with euthyroid controls (Table 5).

Ankle reflex relaxation time, VEPs and BAEPs

The ankle reflex relaxation time increased significantly at visit 3 compared with visits 1 and 2, and compared with euthyroid controls, in agreement with the profound hypothy-

roidism of these patients. The changes in thyroid hormone levels resulted in several changes in VEPs, because latency increased, and amplitude decreased at visit 3 compared with visits 1 and 2. However, no differences with controls were found. Finally, BAEPs did not change during levothyroxine withdrawal (Table 6).

Discussion

Most studies performed to date have evaluated the impact of thyroid hormone withdrawal before WBS on QoL and

Table 3 Quality of life tests during levothyroxine withdrawal in women with differentiated thyroid carcinoma compared with healthy euthyroid women. Data are means ± s.d.

	Patients (n = 18)			Controls (n = 18)
	Visit 1	Visit 2	Visit 3	
Nottingham Health Profile				
Total	7.6 ± 6.2*	6.8 ± 6.5	14.4 ± 5.3*‡	3.1 ± 3.4
Emotional	12.8 ± 10.0*	9.9 ± 9.8	16.8 ± 11.2*†	4.1 ± 5.0
Sleep	7.2 ± 7.4*	4.9 ± 6.5	12.0 ± 6.0*‡	2.6 ± 4.9
Energy	3.5 ± 7.0*	4.3 ± 6.5*	13.0 ± 8.9*‡	0.0 ± 0.0
Pain	7.1 ± 12.4†	6.4 ± 11.2	14.0 ± 10.8*†	3.6 ± 5.9
Mobility	10.3 ± 12.0	10.4 ± 11.8	23.9 ± 11.6*‡	7.1 ± 10.0
Social	3.9 ± 8.0*	3.9 ± 8.0*	6.9 ± 8.6*‡	0.0 ± 0.0
Profile of mood states				
Tension-anxiety	13.0 ± 7.4	10.2 ± 4.7	14.1 ± 7.4†	9.4 ± 4.1
Depression-dejection	7.9 ± 5.4†	5.8 ± 5.6	11.8 ± 7.7*†	5.1 ± 7.3
Anger-hostility	11.2 ± 6.5†	8.6 ± 4.7	11.6 ± 7.4	9.8 ± 4.9
Vigor-activity	18.6 ± 2.9†	17.2 ± 3.5	12.5 ± 5.0*‡	19.9 ± 5.3
Fatigue-inertia	6.1 ± 5.7	6.6 ± 4.9	16.9 ± 8.2*‡	6.0 ± 4.1
Confusion-bewilderment	7.1 ± 4.6	6.9 ± 4.0	11.6 ± 6.1*‡	6.7 ± 3.9
SF-36 Health Survey				
General health	16.6 ± 4.1*	17.0 ± 4.2*	15.6 ± 4.2*	19.6 ± 2.0
Mental health	21.3 ± 3.4*	22.3 ± 4.1	19.0 ± 4.3*†	23.7 ± 2.0
Physical function	26.2 ± 5.7	26.2 ± 5.4	20.4 ± 4.9*‡	28.2 ± 2.1
Role-physical	7.7 ± 0.8	7.3 ± 1.3	4.7 ± 1.3*‡	7.8 ± 0.5
Role-emotional	5.4 ± 1.1	5.7 ± 0.6	4.2 ± 1.3*‡	5.8 ± 0.5
Social function	9.0 ± 1.2*	9.2 ± 1.5	6.7 ± 1.9*‡	9.7 ± 0.7
Pain	9.3 ± 2.1	9.5 ± 2.1	7.1 ± 1.6*‡	9.5 ± 1.2
Vitality	16.7 ± 4.1	16.3 ± 3.6	11.4 ± 3.6*‡	18.1 ± 1.5

*P < 0.05 compared with euthyroid controls.

†P < 0.05 for the comparison with visit 2.

‡P < 0.05 for the comparisons with visits 1 and 2.

Table 4 Cognitive tests during levothyroxine withdrawal in women with differentiated thyroid carcinoma compared with healthy euthyroid women. Data are means ± s.d.

	Patients (n = 18)			Controls (n = 18)
	Visit 1	Visit 2	Visit 3	
Wais Digit Symbol				
Pairs	50.6 ± 19.5†	54.8 ± 19.3	52.1 ± 21.1	47.1 ± 15.3
Copies	87.8 ± 14.7	89.0 ± 11.6	87.9 ± 12.9	85.2 ± 13.9
Difference	37.3 ± 14.8	34.1 ± 15.1	35.8 ± 17.5	37.9 ± 11.0
Wais Digit Span				
Forward	7.4 ± 2.2	7.8 ± 2.5	6.7 ± 2.2*‡	8.7 ± 2.2
Backwards	5.5 ± 2.5	5.9 ± 2.2	5.2 ± 2.6	6.9 ± 2.3
Total	12.9 ± 4.4*	13.7 ± 4.5	11.8 ± 4.4*‡	15.6 ± 4.3
Davis Visual Scanning				
Time	99.7 ± 49.2	86.3 ± 41.7	92.7 ± 38.8	82.9 ± 27.2
Items found	58.6 ± 1.8	58.7 ± 1.3	59.0 ± 1.5	58.3 ± 2.3
Cognitive Visual Analogical Mental Scales				
Memory	59.3 ± 26.2	60.0 ± 28.7	41.7 ± 24.6*‡	62.1 ± 22.3
Attention	63.8 ± 22.6	59.2 ± 26.7	35.3 ± 19.4*‡	61.8 ± 19.1
Problem solving	72.1 ± 20.1	62.4 ± 29.0	44.2 ± 18.6*‡	69.9 ± 20.2
Clumsiness	24.7 ± 22.7	28.8 ± 28.9	57.8 ± 26.5*‡	25.8 ± 18.2

*P < 0.05 compared with euthyroid controls.

†P < 0.05 for the comparison with visit 2.

‡P < 0.05 for the comparison with visits 1 and 2.

Table 5 Affective and physical symptoms tests during levothyroxine withdrawal in women with differentiated thyroid carcinoma compared with healthy euthyroid women. Data are means \pm s.d.

	Patients (n = 18)			Controls (n = 18)
	Visit 1	Visit 2	Visit 3	
Affective Visual Analogical Mental Scales				
Sadness	22.7 \pm 22.2	15.9 \pm 16.2*	34.6 \pm 25.3*†	5.2 \pm 5.3
Confusion	20.0 \pm 25.0	19.6 \pm 21.9	37.5 \pm 27.9*‡	7.9 \pm 8.3
Irritability	15.9 \pm 22.5	11.1 \pm 12.8	42.6 \pm 29.6*§	7.9 \pm 11.0
Anxiety	27.4 \pm 25.6	27.1 \pm 24.4	44.4 \pm 30.5*§	17.9 \pm 27.3
Anger	7.3 \pm 12.5	8.3 \pm 15.1	24.8 \pm 26.4*§	2.6 \pm 4.5
Fear	16.3 \pm 20.7	16.3 \pm 19.9	26.2 \pm 26.0*	3.3 \pm 4.8
Energy	57.7 \pm 14.8	53.8 \pm 24.6	32.0 \pm 23.6*§	61.9 \pm 20.7
Depression	19.0 \pm 25.4	17.3 \pm 17.1*	39.9 \pm 26.7*§	3.2 \pm 4.9
Tension	22.4 \pm 21.4	18.2 \pm 17.4	38.7 \pm 24.6*§	12.0 \pm 12.9
Happiness	66.1 \pm 20.9	68.6 \pm 21.3	51.1 \pm 18.8*§	71.3 \pm 14.7
Agitation	19.4 \pm 19.5	23.8 \pm 21.7	35.4 \pm 24.0*‡	18.8 \pm 21.0
Tiredness	27.3 \pm 27.2	35.4 \pm 26.8	70.4 \pm 22.0*§	29.7 \pm 23.1
Physical Symptoms Visual Analogical Mental Scales				
Feeling cold	13.2 \pm 24.5	23.1 \pm 24.6	32.7 \pm 30.3*‡	15.8 \pm 27.1
Nausea	8.7 \pm 19.3	20.2 \pm 27.0*	23.8 \pm 31.0*‡	0.9 \pm 1.6
Blurred vision	7.4 \pm 13.2	10.5 \pm 12.9*	25.4 \pm 29.0*§	2.4 \pm 5.8
Sleep	14.4 \pm 22.7†	25.0 \pm 23.1	36.7 \pm 28.1*‡	11.6 \pm 14.3
Feeling hot	18.3 \pm 24.0	26.4 \pm 28.2	22.3 \pm 18.1	26.4 \pm 26.5
Clear minded	56.7 \pm 29.2	49.9 \pm 31.5	40.6 \pm 22.1*	63.8 \pm 29.2
Dizzy	9.9 \pm 18.3	11.9 \pm 17.3*	27.2 \pm 29.6*§	3.3 \pm 8.0

P* < 0.05 compared with euthyroid controls.†*P* < 0.05 for the comparison with visit 2.‡*P* < 0.05 for the comparison with visit 1.§*P* < 0.05 for the comparison with visits 1 and 2.Table 6** Ankle reflex relaxation time, visual evoked potentials, and brainstem auditory evoked potentials during levothyroxine withdrawal in women with differentiated thyroid carcinoma compared with healthy euthyroid women. Data are means \pm s.d.

	Patients (n = 18)			Controls (n = 18)
	Visit 1	Visit 2	Visit 3	
Ankle Reflex Relaxation Time (ms)	177 \pm 2	179 \pm 2	251 \pm 2*†	174 \pm 2
Visual Evoked Potentials				
P-100 latency (left, ms)	101.4 \pm 8.9	102.3 \pm 9.9	104.9 \pm 9.8†	104.9 \pm 5.9
P-100 latency (right, ms)	101.0 \pm 9.8	102.4 \pm 9.7	104.9 \pm 9.6†	105.0 \pm 6.1
P-100 amplitude (left, μ V)	8.6 \pm 4.0‡	7.0 \pm 2.9	5.6 \pm 2.6†	6.9 \pm 3.0
P-100 amplitude (right, μ V)	8.5 \pm 3.0‡	7.4 \pm 3.0	6.6 \pm 3.3§	6.7 \pm 2.5
Brainstem Auditory Evoked Potentials				
I latency (left, ms)	1.74 \pm 0.1	1.76 \pm 0.2	1.73 \pm 0.1	1.70 \pm 0.1
I latency (right, ms)	1.75 \pm 0.2	1.79 \pm 0.2	1.77 \pm 0.2	1.67 \pm 0.1
III latency (left, ms)	3.87 \pm 0.3	3.87 \pm 0.2	3.83 \pm 0.2	3.78 \pm 0.2
III latency (right, ms)	3.81 \pm 0.2	3.85 \pm 0.2	3.80 \pm 0.2	3.74 \pm 0.1
V latency (left, ms)	5.72 \pm 0.2	5.73 \pm 0.3	5.75 \pm 0.3	5.69 \pm 0.2
V latency (right, ms)	5.71 \pm 0.3	5.75 \pm 0.4	5.73 \pm 0.3	5.68 \pm 0.2
I–V interlatency (left, ms)	3.98 \pm 0.2	3.98 \pm 0.3	4.02 \pm 0.3	3.99 \pm 0.1
I–V interlatency (right, ms)	3.96 \pm 0.2	3.97 \pm 0.3	3.96 \pm 0.2	4.17 \pm 0.7
I–III interlatency (left, ms)	2.08 \pm 0.1	2.11 \pm 0.2	2.11 \pm 0.2	2.08 \pm 0.1
I–III interlatency (right, ms)	2.06 \pm 0.1	2.06 \pm 0.2	2.04 \pm 0.1	2.07 \pm 0.1
III–V interlatency (left, ms)	1.90 \pm 0.1	1.87 \pm 0.2	1.91 \pm 0.2	1.91 \pm 0.1
III–V interlatency (right, ms)	1.90 \pm 0.2	1.91 \pm 0.2	1.93 \pm 0.2	1.94 \pm 0.1

**P* < 0.05 compared with controls.†*P* < 0.05 for the comparison with visits 1 and 2.‡*P* < 0.05 for the comparison with visit 2.§*P* < 0.05 for the comparison with visit 1.

psychometric functionality in patients with DTC, as compared with the moment when the patients were taking suppressive doses of triiodothyronine (Meier *et al.* 1994) or levothyroxine (Dow *et al.* 1997, Haugen *et al.* 1999), and compared with the use of rhTSH for stimulating thyroid remnants before WBS (Meier *et al.* 1994, Haugen *et al.* 1999). Implicit in these studies was the assumption that QoL and psychometric functionality of DTC patients during chronic suppressive therapy with levothyroxine is satisfactory, and mostly equivalent to those of healthy individuals. Yet, because none of these studies included a control group of healthy individuals, the possibility that chronic suppressive therapy with levothyroxine may actually impair QoL and psychometric functionality, as has been described for endogenous subclinical hyperthyroidism (Biondi *et al.* 2000), was not contemplated.

Our present results suggest, for the first time, that chronic replacement therapy with suppressive doses of levothyroxine impairs QoL and psychometric functionality in DTC patients. Compared with controls, the total score, emotional, sleep, energy and social scores of the NHP, mental health, social function and general health scores of the SF-36, and total Wais Digit Span scores were impaired at visit 1, when the patients had subclinical or mild hyperthyroidism induced by supraphysiological levothyroxine doses. And because most of these abnormalities were reversed partially or completely when the patients achieved normal serum thyroid hormones concentrations on visit 2, our results suggest that these abnormalities were actually related to the excess in thyroid hormone levels present at visit 1. In conceptual agreement, others have reported that QoL is not affected in women receiving non-suppressive doses of oral levothyroxine (Petersen *et al.* 1990).

The previous studies of QoL in DTC patients cited above (Meier *et al.* 1994, Haugen *et al.* 1999) showed a consistent worsening of QoL during withdrawal of thyroid hormone. Meier *et al.* (1994) used the POMS and found that 94% of patients with DTC experienced increased fatigue during thyroid hormone withdrawal, and 89% experienced decreased vigor and activity. Haugen *et al.* (1999) employed the SF-36 health survey and found that many of the parameters evaluated worsened also after levothyroxine withdrawal when compared with treatment with rhTSH. Dow *et al.* (1997) used a specific test for measuring QoL in patients with DTC during levothyroxine withdrawal (the QoL-thyroid scale), as well as a test for the evaluation of functionality in cancer patients (FACT-G), in a series of 34 patients with DTC. Evaluation of these patients started 3 weeks after levothyroxine withdrawal and ended 4 weeks after resumption of levothyroxine treatment (Dow *et al.* 1997). However, because Dow *et al.* did not measure serum thyroid hormone levels throughout the study, the conclusion that the changes in the variables measured were dependent on changes in

thyroid hormone concentration is based on assumptions rather than on actual data.

Our present study confirms and expands these results, with the additional advantage of having compared the results of the patients with a control group of healthy women, allowing us to determine the magnitude of the marked deterioration of these variables when compared with euthyroid controls.

Psychometric performance has also been studied during levothyroxine withdrawal. Burmeister *et al.* (2001) recently studied 13 DTC patients before and during thyroid hormone withdrawal with a battery of cognitive tests, showing delayed recall of verbal information, which was also significant when compared with a small group of three euthyroid controls. Patients also complained of worsening in memory, concentration, thinking, alertness and motivation, whereas the Wais Digit Symbol Test showed no differences throughout levothyroxine withdrawal (Burmeister *et al.* 2001). Other authors have shown an alteration in concentration capacity that could also explain a worse state of cognition at this moment (Dow *et al.* 1997). Furthermore, hypothyroidism in non-demented adults has been previously found to worsen cognition (Osterweil *et al.* 1992) and even subclinical hypothyroidism has been associated with some degree of memory alteration (Baldini *et al.* 1997). In agreement, we also found a worsening of recalling verbal information during profound hypothyroidism, as the Wais Digit Span Test reflects auditory attention and learning.

Of note, when most of the patients in our present study had serum FT4 and FT3 within the normal range at visit 2, their overall QoL and the test of psychometric functionality were mostly comparable with those of control euthyroid women. However, despite the fact that serum FT4 and FT3 were within the normal range in most of the patients, some of the NHP, SF-36 and affective and physical visual scales scores had worse results in DTC patients also at visit 2 compared with the controls. We hypothesize that these particular results might be related to the fears and expectancies of DTC patients regarding the final diagnosis after WBS, or to the fact of having a malignant disease, although in most of the patients studied here recurrences of thyroid cancer were actually unexpected given their undetected serum thyroglobulin levels.

Yet the explanation may be that, although most of the patients presented with normal FT4 and FT3 serum concentrations at visit 2, the mean FT3 levels of these patients was lower than those of euthyroid controls. Bunevicius *et al.* (1999) recently reported that combined levothyroxine plus triiodothyronine replacement therapy for primary hypothyroidism improves the POMS and other psychometric tests compared with levothyroxine alone and hypothesized that this improvement was related to the increase in triiodothyronine levels observed during combined therapy. However, we have demonstrated that thyroidectomized rats infused with a wide range of levothyroxine doses maintain normal cerebral cortex

triiodothyronine despite wide fluctuations in thyroid hormone levels (Escobar-Morreale *et al.* 1995). Based on the excellent homeostasis of brain triiodothyronine concentrations in thyroidectomized rats treated with levothyroxine, we do not believe that the mild decrease in the mean serum FT3 concentrations observed in our group of DTC patients at visit 2, compared with the euthyroid controls, exerted any influence in the QoL and psychometric tests studied here, especially when serum FT4 levels were completely normal at this visit.

Finally, other indexes of central and peripheral nervous system such as the ankle reflex relaxation time and VEPs were sensitive to the changes in thyroid hormone status. The ankle reflex relaxation time increased at visit 3 compared with previous visits and with controls, reflecting the profound hypothyroidism at this visit. The decrease in serum thyroid hormones during levothyroxine withdrawal was paralleled by significant lengthening in the latency, and a decrease in amplitude of VEPs, in agreement with previous studies (Osterweil *et al.* 1992, Tamburini *et al.* 1998). On the contrary, we have not found any change in BAEPs during levothyroxine withdrawal. Di Lorenzo *et al.* (1995) reported abnormal results in as many as 25% of hypothyroid patients but these abnormalities did not improve after 5 or more months on levothyroxine therapy, casting doubt upon the causative role of thyroid hormone deficiency on these abnormal BAEPs. In agreement with our present results, other authors have shown that short-term hypothyroidism has no effect on BAEPs (Osterweil *et al.* 1992).

In summary, our present results demonstrate a marked deterioration in QoL and psychometric functionality in patients with DTC during levothyroxine withdrawal. These results indicate that the detection of recurrences of DTC by WBS should be routinely based on the administration of rTSH for the stimulation of thyroid remnants, instead of using withdrawal of thyroid hormone replacement therapy.

But more importantly, our results suggest that even during long-term replacement therapy with levothyroxine, these patients have abnormalities in QoL and psychometric performance that might be related to the supraphysiological doses of levothyroxine used to suppress the endogenous secretion of TSH. Although these abnormalities are much milder than those occurring during withdrawal of levothyroxine, patients may suffer them for much longer periods, even for a lifetime. If confirmed by future studies in larger series of patients with DTC, the worsening of QoL and psychometric performance observed during TSH-suppressive therapy with levothyroxine should stimulate research into novel strategies for long-term treatment of patients with DTC. Among others, establishing evidence-based criteria for a more precise grading of the degree of suppression of endogenous TSH, and the duration of TSH-suppressive therapy, needed to prevent recurrences, as well as the development of new drugs such as thyroid hormone analogues with preferential specificity for pituitary thyrotropes or TSH-receptor

antagonists, would benefit the QoL and psychometric functionality of patients suffering this prevalent type of cancer.

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