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

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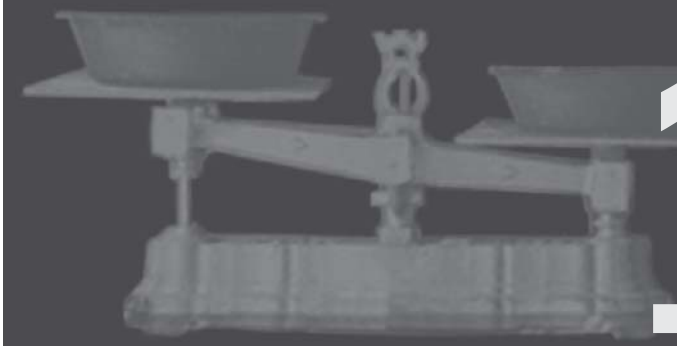

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Quality of Life in Cured patients with Differentiated Thyroid Carcinoma

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Abstract

Objective: This study was performed to evaluate the impact of cured differentiated thyroid carcinoma (DTC) on quality of life. Previous studies on quality of life in patients with DTC were hampered by small patient numbers, limited of quality of life parameters or were uncontrolled.
Design: Cross-sectional case-control study.
Method: We assessed quality of life in 153 cured DTC patients with a median duration of cure of 6.34 years (range 0.3-41.8) and studied the contribution of disease specific, biochemical and social variables, focusing on the degree of TSH suppression. Four validated health-related questionnaires were used (Short Form-36, Multidimensional Fatigue Index-20, Hospital Anxiety and Depression Scale and Somatoform Disorder Questionnaire), including multiple aspects of physical, psychological and social functioning. Patients were compared with 113 controls selected by patients themselves (control group-I), and with 336 pooled age- and gender-matched controls from other Leiden quality of life studies (control group-II).
Results: Patients had significantly decreased quality of life in 11 of 16 subscales when compared with control group-I. Comparison with control group-II, decreased scores in 13 of 16 items were observed. An important independent predictor for quality of life was duration of cure. Quality of life parameters were not influenced by serum TSH levels, both measured at the time of quality of life assessment and measured over time since initial therapy.
Conclusions: Patients cured for DTC have impaired quality of life, independently of TSH level. Quality of life parameters were inversely affected by duration of cure and consequently may be restored after prolonged follow-up.

Introduction

Well-differentiated thyroid carcinoma (DTC) is associated with an excellent medical prognosis, with 10-year survival rates reaching 90-95% (1). Following initial therapy, usually consisting of total thyroidectomy and radioiodine thyroid remnant ablation therapy, most patients used to be treated with high doses of L-thyroxin in order to suppress TSH levels (1). On one hand, the excellent prognosis and the moderate invasiveness of the initial therapy may implicate that quality of life in cured DTC patients may be relatively normal. On the other hand, TSH suppressive thyroxin replacement therapy may lead to a decreased quality of life (2,3,4).
Only a few studies have evaluated quality of life in cured DTC patients (5,6,7,8,9). These studies are limited by small patient numbers (6,7), limited number of quality of life questionnaires (5,9) or the absence of a healthy control group (5,6,8).
Studies that focused on 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 (2,10). Therefore, the aim of the present study was to assess quality of life in a large cohort of cured DTC patients and to investigate the determinants of quality of life, including serum TSH levels. We used four validated, health-related questionnaires and included controls matched for age, gender and socioeconomic status.

Patients and methods

Cured DTC patients, 18-70 years old, were recruited from the outpatient clinic of the Department of Endocrinology of the Leiden University Medical Center. Other medical conditions or drugs that could influence quality of life were not permitted.
Initial therapy consisted of near-total thyroidectomy, followed by postoperative radioiodide ablation therapy with I-131. Cure after initial therapy was defined as the absence of I-131 accumulation at diagnostic 185 MBq scintigraphy, serum Tg concentrations below 2 µg/L after TSH stimulation in absence of Tg antibodies and no other evidence of disease (11). Patients with tumor relapse were only included if they were subsequently cured.
Initially, 157 DTC patients who met these criteria were asked to participate. Four validated questionnaires were sent to their homes together with a list of general questions about level of education, country of origin and marital state. Four patients specifically wished not to participate. Each patient was also asked to provide a control person of comparable sex, age and socio-economic status (friend, neighbour, relative) (control group-I). We received 153 completed questionnaires from patients and 113 questionnaires from controls. To exclude bias in the selection of control group-I, we also compared the patients with a larger cohort of age, gender and socioeconomic status matched healthy controls (n=336) obtained from other quality of life studies performed in our centre (12,13,14,15) (indicated as control group-II).
The study protocol was approved by the medical ethics committee of the Leiden University Medical Centre and written consent was obtained from all patients.

Study parameters

Primary study parameters were the outcomes of the four health related questionnaires and the contribution of patient characteristics (age, gender, educational level, marital status), disease specific characteristics (initial TNM stage, recurrent disease, duration of cure), treatment (extent of surgery, radioiodine therapy and additional treatments) and biochemical parameters (serum free T4, T3 and TSH levels) to quality of life.

The influence of TSH on quality of life was investigated both by evaluation of serum TSH levels at time of the survey (expressed as continuous variable or stratified as 'profoundly suppressed' (<0.1 mU/l), 'moderately suppressed' (<0.4 mU/l) and 'unsuppressed' (>0.4 mU/l) and by summary TSH parameters over time since initial therapy for each patient. Summary TSH parameters over time were the mean, 25th, 50th and 75th percentiles and the percentage of profoundly suppressed, suppressed and unsuppressed TSH values from all available unstimulated TSH measurements since initial therapy.

Quality of life questionnaires

Short-form-36 (SF-36)

The SF-36 questionnaire comprises 36 items and records general well-being during the previous 30 days (16), subdivided in 8 health concepts. Scores are expressed on a 0–100 scale, and higher scores are associated with a better quality of life.

Multidimensional Fatigue Index-20 (MFI-20)

The MFI-20 comprises 20 statements (5 dimensions) to assess fatigue, which are measured on a five-point scale (17). Scores vary from 0-20; higher scores indicate greater fatigue.

Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 items pertaining to anxiety and depression. Scores for the anxiety and depression subscale range from 0 to 21, and values for the total score range from 0-42. Higher scores indicate more anxiety or depression (18).

Somatoform disorders questionnaire (SDQ)

All somatoform disorders mentioned in classification DSM-III were comprised in this questionnaire (19). The total score varies from 0-51 for women and 0–55 for men. The total score expresses the extent of physical complaints that were present in the previous week.

Assays

Serum free thyroxin (FT4, normal range 10-24 pmol/L) and TSH levels (normal range 0.4-4.5 mU/L) were measured by electrochemoluminescentic immunoassay using a Modular Analytics E-170 system (Roche, Almere, The Netherlands).

Statistical analysis

SPSS for Windows, Version 12.0 (SPSS Inc., Chicago, IL. USA) was used to perform all analyses. Data are expressed as mean ± SD unless indicated otherwise. As dependent variables, we calculated delta scores between each patient and age and gender matched Leiden-controls by subtracting age and gender specific means of the controls from patient scores for all questionnaire subscales. Stepwise univariate linear regression analysis was used to identify independent variables for quality of life. Differences were considered statistically significant at $p<0.05$.

Results

One hundred and fifty three patients (28 males, 125 females, age 49±13 years, 127 papillary- and 27 follicular carcinomas) were analyzed. Tumor stages were T1-3 M0 in 131, T4 in 18 and M1 in 4 patients. Median duration of cure was 6.3 years (range 0.3-41.8). At the time of the survey, median TSH was 0.1 mU/L (range 0.005-6.8) and FT4 was 22.4±4 pmol/L. An average of 15 unstimulated TSH measurements per patient was obtained since initial therapy. Summary parameters of TSH over time per patient were: mean 0.4 mU/L (range 0.1-3.4), median 0.05 mU/L (range <0.005 - 2.18); proportions of profoundly suppressed values: 58% (range 0 –100) and moderately suppressed values: 80% (range 0-100%). The slope of TSH values was -0.0001 mU/year (range -0.004-0.000 mU/year), indicating that the TSH levels were reasonably stable. Mean dose of L-thyroxin was 183 ± 51 µg/day.

Quality of life in DTC patients and controls

Quality of life scores in patients were significantly reduced in 11 of the 16 items assessed when compaired to control group-I. According to the SF-36 questionnaire, patients had significantly worse scores on social functioning and general health perception. All MFI-20 subscales and HADS subscales were affected in DTC patients. The SDQ total score was also significantly worse than in control group-I. Comparison of the patients with control group-II (12,13,14,15) showed similar results: 13 of 16 quality of life parameters differed significantly between patients and controls (Table 1).

Determinants of quality of life

Marital status, country of birth, initial TNM-stage, total activity of I-131, tumor recurrence, L-thyroxin dose, post-surgical hypoparathyroidism, and serum FT4-level did not affect any of the questionnaire items.

TSH levels measured at the time of the assay (both continuous and stratified) and summary TSH values over time appeared not to be a significant independent predictor for quality of life. Post-hoc power calculation revealed sufficient power (all items > 0.9) to draw this conclusion.

A longer duration of cure was correlated with better scores on SF-36 social functioning (standardized β=0.21, p=0.030), role limitations due to physical problems (β=0.17, p=0.049), general health perception (β=0.32, p=0.001), MFI-20 general fatigue (β= -0.17, p=0.035), physical fatigue (β= -0.24, p=0.003) and mental fatigue scores (β=-0.17, p=0.038). We calculated the duration of cure needed for the quality of life scores to reach the normal range of all healthy subjects (Figure 1). The 95% CI intervals of quality of life scores only included 0 (no difference between quality of life of patients and controls) after a relatively long duration of cure (approximately 12 to 28 years for SF-36 respectively MFI-20).

Discussion

The purpose of this study was to evaluate quality of life in a large cohort of cured DTC patients using multiple quality of life parameters and a matched healthy control group. We found that quality of life scores assessed by the majority of subscales are reduced in patients previously treated for DTC, compared to controls. Although our observations are in line with other studies on quality of life in DTC patients (5,9,6,7,8), our study includes a higher numbers of patients, uses more quality of life questionnaires and uses matched control groups.

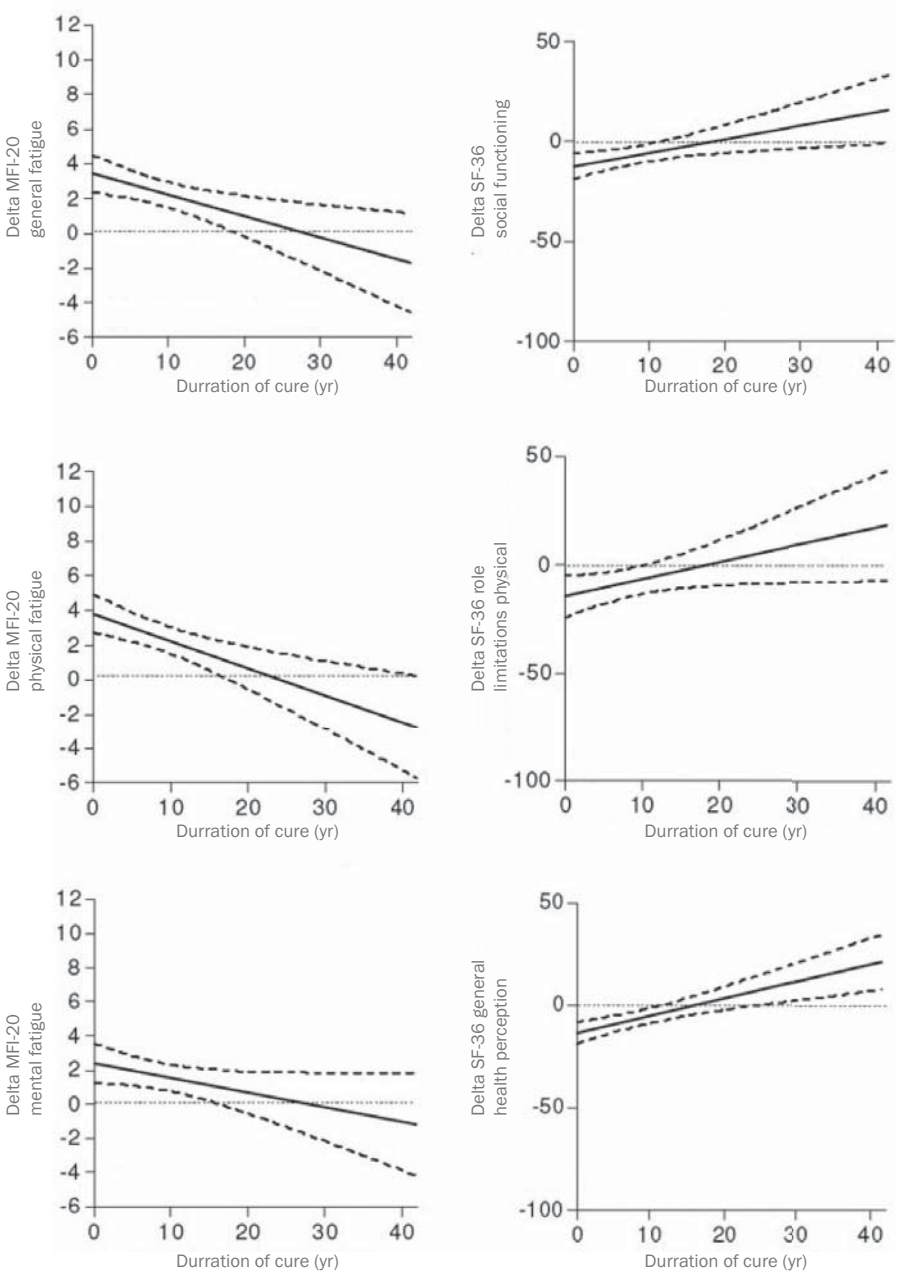
Table 1: Quality of life in patients treated for DTC compared with controls selected by patients themselves (Control Group I) and age and gender matched controls from other Leiden quality of life studies (Control Group II) (12,13,14,15). Data shown are mean ± SD.

Questionnaire	Patients (n=153)	Control group I (n=113)	P (patients vs. control group-I)	Control group II (n=336)	P (patients vs. control group-II)
Age	49.10	48.08	0.522	49.99	0.496
M/F	28/125	19/94	0.754	67/269	0.672
SF-36					
Physical functioning	83.70±21.02	88.27±16.78	0.052	87.77±17.14	0.040
Social functioning	81.09±24.90	87.39±20.01	0.037	88.06±19.28	0.007
Role limitations due to physical problems	75.35±40.04	81.42±34.36	0.194	83.38±32.43	0.035
Role limitations due to emotional problems	83.22±35.43	84.66±31.82	0.734	85.93±30.21	0.422
Bodily pain	82.74±21.70	84.78±18.93	0.426	85.17±19.24	0.216
General health perception	65.59±20.48	71.45±18.43	0.027	71.34±18.79	0.007
Change in health	52.15±18.37	55.18±18.19	0.185	54.77±18.64	0.105
MFI-20					
General fatigue	11.03±4.72	8.11±3.35	<0.001	8.60±4.01	<0.001
Physical fatigue	9.95±4.93	6.65±2.64	<0.001	7.60±3.69	<0.001
Reduced activity	8.79±4.15	6.85±3.30	<0.001	7.18±3.57	<0.001
Reduced motivation	8.64±3.76	6.67±2.79	<0.001	7.26±3.53	<0.001
Mental fatigue	9.53±4.50	7.93±3.60	0.002	7.92±3.31	<0.001
HADS					
Anxiety	5.69±3.95	4.14±3.15	<0.001	4.21±3.21	<0.001
Depression	3.61±3.08	2.37±2.52	<0.001	2.86±2.99	0.011
Total	9.30±6.30	6.51±4.92	<0.001	7.07±5.39	<0.001
SDQ					
SDQ total	5.92±6.20	1.66±2.51	<0.001	1.65±2.50	<0.001

Longer duration of cure was associated with better scores on different quality of life items. This finding is in line with studies by Dagan *et al* (7) and Crevenna *et al* (5), but this is the first study to quantify the predicted duration of affected quality of life in relation to duration of cure. After a long duration of cure, approximately 15 to 20 years (MFI-20 respectively SF-36) the 95% confidence intervals of 6 of the 16 quality of life subscales included a normal score (Figure 1).

In our study, quality of life was not influenced by TSH levels at the time of the survey and by TSH levels over time since initial therapy, although it can be objected that generic questionnaires were used. Other studies on the effects of subclinical hyperthyroidism on well-being have yielded inconclusive results. Most of these studies have been performed in patients with endogenous subclinical hyperthyroidism (3) who cannot easily be compared with DTC patients or contained selected patients with DTC (2).

Figure 1 Differences between age- and gender-matched controls and patients for the quality-of-life parameters plotted against duration of cure; linear regression line and 95% confidence interval are shown (standardized B and significance of linear regression analysis). The horizontal line represents the value for quality-of-life parameters where there is no difference between patients and the means of age- and gender-matched controls



Comparison of DTC survivors to survivors of other cancer types is complicated because of the many differences between the several cancer types. A large study (20) revealed that DTC survivors had similar quality of life as patients with breast cancer, worse than survivors of melanoma or colorectal cancer but better than hematological malignancies. Despite cure, excellent prognosis and moderate aggressive treatment, DTC patients have an evident decrease in quality of life that may only be restored after years of follow-up. The findings of our study have therefore implications for the approach of the cured DTC patients: attention for the psychological well-being of the patient and availability of professional support may be important aspects in follow-up.

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