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A Comparison of Short-Term Changes in Health-Related Quality of Life in Thyroid Carcinoma Patients Undergoing Diagnostic Evaluation with Recombinant Human Thyrotropin Compared with Thyroid Hormone Withdrawal

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Context: Thyroid carcinoma requires lifelong monitoring with serum thyroglobulin, radioactive iodine whole body scanning, and other imaging modalities. Levothyroxine (L-T_4) withdrawal for thyroglobulin measurement and whole body scanning increases these tests' sensitivities but causes hypothyroidism. Recombinant human TSH (rhTSH) enables testing without L-T_4 withdrawal.

Objective: Our objective was to examine the impact of short-term hypothyroidism on the health-related quality of life (HRQOL) of patients after rhTSH *vs.* L-T_4 withdrawal.

Design, Setting, and Patients: In this multicenter study, the SF-36 Health Survey was administered to 228 patients at three time points: on L-T_4, after rhTSH, and after L-T_4 withdrawal.

Interventions: Interventions included administration of rhTSH on L-T_4 and withdrawal from thyroid hormone.

Main Outcome Measures: Mean SF-36 scores were compared during the two interventions and with the U.S. general population and patients with heart failure, depression, and migraine headache.

Results: Patients had SF-36 scores at or above the norm for the general U.S. population in six of eight domains at baseline on L-T_4 and in seven of eight domains after rhTSH. Patients' scores declined significantly in all eight domains after L-T_4 withdrawal when compared with the other two periods ($P < 0.0001$). Patients' HRQOL scores while on L-T_4 and after rhTSH were at or above those for patients with heart failure, depression, and migraine in all eight domains. After L-T_4 withdrawal, patients' HRQOL scores were significantly below congestive heart failure, depression, and migraine headache norms in six, three, and six of the eight domains, respectively.

Conclusions: Short-term hypothyroidism after L-T_4 withdrawal is associated with a significant decline in quality of life that is abrogated by rhTSH use. **(*J Clin Endocrinol Metab* 91: 878–884, 2006)**

THYROID CARCINOMA AFFLICTS approximately 25,690 people per year in the United States (1) and is rapidly increasing at a rate of 2% per year (2). The majority of these cases are well-differentiated epithelial papillary and follicular carcinomas. Because of low mortality rates and a moderately high recurrence rate in older series, lifelong monitoring is required (3, 4). Tools for monitoring include serum thyroglobulin measurement and radioactive iodine whole body scanning (WBS), both of which are more accurate during TSH stimulation. However, the generation of an endogenous TSH stimulus by thyroid hormone withdrawal causes symptoms of hypothyroidism and has been shown to impair patients' health-related quality of life (HRQOL) (5). Recom-

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Abbreviations: HRQOL, Health-related quality of life; MCS, mental component summary; PCS, physical component summary; rhTSH, recombinant human TSH; WBS, whole body scanning.

binant human TSH (rhTSH, TSH-α, or Thyrogen) facilitates this testing while patients remain euthyroid on thyroid hormone therapy (6, 7) with a sensitivity for disease detection comparable to traditional thyroid hormone withdrawal (8).

The negative impact of hypothyroidism on HRQOL in general, and in patients with well-differentiated thyroid carcinoma (thyroid carcinoma) undergoing L-T_4 withdrawal in particular, has been established (5, 9, 10). Although other studies have evaluated the QOL in patients with thyroid carcinoma undergoing L-T_4 withdrawal, the clinical impact of hypothyroidism has not been rigorously compared with other common health conditions or explicitly related to its effects on activities of daily living. The purpose of this study was to confirm and extend these findings by comparing the HRQOL of treated thyroid cancer patients sequentially undergoing rhTSH- and thyroid hormone withdrawal-mediated diagnostic testing with the health impairment associated with three other conditions: heart failure, depression, and migraine headache.

Patients and Methods

Study patients

All 229 adult patients with thyroid carcinoma were studied at three time points, as previously described (8): at baseline on L-T_4 suppressive therapy, after rhTSH while on L-T_4 on the day of the WBS, or after withdrawal of thyroid hormone on the day of the WBS with two instruments, the SF-36 Health Survey and the Billewicz scale. Two hundred twenty-six patients completed the study. Informed consent was obtained from all patients, and the protocol was approved by the institutional review board at each site. Two weeks after rhTSH-mediated testing, patients were withdrawn from L-T_4, and after their serum TSH concentration was confirmed to be greater than or equal to 25 mU/liter, 4 mCi (148 MBq) ^{131}I was administered with WBS 48 h later. One hundred seventy-seven (74%) were changed to interim L-T_3 therapy and then withdrawn from it 2 wk before WBS, whereas a minority (26%) were directly withdrawn from L-T_4. All patients were instructed to consume a low-iodine diet before both scans.

The baseline characteristics of the 229 patients enrolled in the study have been previously described (Table 1), as have the two regimes of rhTSH preparation employed (8). Of the 229 enrolled patients, 228 patients completed the survey at baseline and on rhTSH, and 225 patients did so after withdrawal from thyroid hormone on the day of the WBS.

TABLE 1. Baseline characteristics of study participants

Patient characteristics	n (%)
Mean age (SD)	47 (16)
Female	148 (65)
Type of thyroid cancer	
Papillary	142 (62)
Follicular	39 (17)
Hurthle cell	8 (3)
Papillary/follicular	40 (18)
Thyroidectomy status	
Total/near total	228 (100)
Hemi	1 (0)
Time since last surgery	
<1 yr	69 (30)
>1 yr	99 (43)
Not reported	61 (27)
Radioiodine ablation	184 (80)
Cumulative ^{131}I activity	
<200 mCi	110 (48)
>200 mCi	72 (32)
Not reported	47 (20)
Time since last ^{131}I	
<1 yr	56 (24)
>1 yr	128 (56)
Not reported	45 (20)

Survey measurements

SF-36 Health Survey. HRQOL was assessed with the SF-36 Health Survey, a well-validated measure of general health status (11, 12) that assesses physical and mental health as perceived by the individual. This self-administered 1-wk-recall version consists of 36 items and assesses eight dimensions (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional health, and mental health), which are aggregated to produce physical and mental component summary measures (PCS and MCS, respectively). All SF-36 scales were scored using norm-based methods that standardize the scores to a mean of 50 and a SD of 10 in the general U.S. population (12–14); higher scores indicate better health.

Billewicz scale. To assess disease-specific morbidity, 14 symptoms and signs of hypothyroidism were assessed using the Billewicz scale, an observer-rated set of clinical findings that have been widely used in studies of hypothyroidism (15).

Analytic protocol

Impact of hypothyroidism on HRQOL. To characterize the impact of hypothyroidism on HRQOL, study participants' SF-36 scores were compared with general U.S. population norms (n = 6742; National Survey of Functional Health Status, which included a representative sample of noninstitutionalized adults in the U.S. matched to U.S. census data on geographical region, age, income, and gender, 1998) (16) as well as to patient norms for three illnesses: heart failure (n = 216), depression (n = 503), and migraine headache (n = 386). All comparisons were statistically adjusted for age, gender, and race. Patient norms for congestive heart failure and depression come from the Medical Outcomes Study (MOS) (11, 17). The severity of the heart failure was scored 1 if a patient had no orthopnea or dyspnea on walking one block or 2 if the patient had one of these symptoms. The average severity score was 1.61 with a SD of 0.49 (18). The severity of the depression was categorized as dysthymia (26.64%), major depression (39.56%), or both (33.80%). Patient norms for migraine come from a sample of the U.S. population using the SF-8 (a well-validated eight-item version of the SF-36). Subjects indicated that they had experienced a severe headache or other migraine symptom in the past 2 wk. These three chronic conditions were chosen for comparison with the hypothyroid state because they each significantly impact either the physical functioning (*e.g.* congestive heart failure) or mental functioning (*e.g.* depression) as measured by the SF-36 health survey. To establish the impact of disease, study HRQOL scores at baseline were compared with normative samples with and without statistical adjustments for the impact of the respective comorbidities on HRQOL scores using linear regression methods. Because similar results were observed in both cases (data not shown), only results obtained without this statistical adjustment are presented here.

Impact of thyroid hormone withdrawal on changes in HRQOL scores. Student's *t* tests were used to determine whether mean scores of two study time points differed between the three groups. Multivariate ANOVA was conducted on the change scores of the eight SF-36 scales at each time interval to determine whether the set of mean scores of two study time points differed overall. Mean changes in SF-36 summary scores (MCS and PCS) after rhTSH *vs.* withdrawal were calculated for patients administered interim T_3 therapy or not, stage of disease (stages 1 and 2 *vs.* 3 and 4) and time since last surgery (less than or greater than 1 yr since surgery).

Content-based interpretation of HRQOL results. To interpret the meaning of changes in HRQOL scores, the content of some SF-36 items per scale was examined. Specifically, item responses of selected items of SF-36 scales that yielded significance were dichotomized to capture, for example, the extent to which patients experienced the following: 1) "limited in moderate activities"; 2) "did not cut down on work or activities due to physical health"; 3) "pain does not interfere with normal work"; 4) "very good to excellent health"; 5) "felt full of pep all or a good bit

of the time"; 6) "health interferes slightly or not at all with social activities"; 7) "did not cut down on work or activities due to emotional problems"; and 8) "happy person all or most of the time."

Results

Impact of hypothyroidism on HRQOL

Before receiving rhTSH, study patients on thyroid hormone therapy were not statistically different from U.S. population norms on four of eight SF-36 scales (physical functioning, vitality, social functioning, and role emotional) as well as the MCS (Table 2). Study patients were significantly above the U.S. norm on two scales (role physical and bodily pain) and for the PCS. Study patients were slightly but significantly below the norm on the general health and mental health scales. After administration of rhTSH, study patients remained significantly below norm on the general health scale, but were not statistically different from the U.S. norm on six of eight SF-36 scales (physical functioning, role physical, vitality, social functioning, role emotional, and mental health) and for MCS (Table 2). In contrast, after thyroid hormone withdrawal, patients scored significantly below the norm on all SF-36 scales and both the MCS and PCS measures (Table 2).

Impact of thyroid hormone withdrawal on changes in HRQOL scores

Study patients' SF-36 scores declined significantly from rhTSH administration to thyroid hormone withdrawal in all eight HRQOL domains as well as the physical and mental summary measures ($P < 0.0001$ for each; Fig. 1). The largest decrease upon withdrawal compared with rhTSH was seen in the role physical score ($P < 0.0001$; Fig. 1). With the exception of the role physical scale, differences on the HRQOL domains that assess some aspect of physical health were smaller than those assessing aspects of mental health (*i.e.* vitality, social functioning, role emotional, and mental health). Both the PCS and MCS scores also declined significantly ($P < 0.0001$ for each; Fig. 1). Scores at baseline on thyroid hormone therapy *vs.* withdrawal from thyroid hormone also declined significantly in all eight HRQOL domains and PCS and MCS ($P < 0.0001$ for each; Fig. 1). In contrast, scores on thyroid hormone therapy *vs.* rhTSH did not significantly differ in seven of eight HRQOL domains and PCS and MCS ($P > 0.05$; Fig. 1). The sole exception was the social functioning domain ($P = 0.009$; Fig. 1).

We also investigated three factors that could impact the significant difference seen in SF-36 scores from rhTSH to withdrawal: use of L-T_3 therapy, time since last surgery, and stage of disease. Analysis of mean change in PCS scores of patients who received L-T_3 *vs.* those were directly withdrawn from L-T_4 revealed a significant difference from rhTSH to withdrawal (-7.62 *vs.* -6.16; $P < 0.0001$ for both) but no impact of L-T_3 therapy ($P = 0.3534$) on outcome. Similarly, analysis mean change in MCS scores of patients who received L-T_3 *vs.* those were directly withdrawn from L-T_4 revealed a significant difference from rhTSH to withdrawal (-11.31 *vs.* -11.86; $P < 0.0001$ for both) but no impact of L-T_3 therapy ($P = 0.7950$) on outcome. Examination of mean change in PCS scores of patients who were less than 1 yr since surgery *vs.* those greater than 1 yr since surgery revealed a significant difference from rhTSH to withdrawal (-6.75 *vs.* -7.52; $P < 0.0001$ for both) but no impact of time since surgery on the result ($P = 0.5961$). Likewise, examination of mean change in MCS scores of patients who were less than 1 yr since surgery *vs.* those greater than 1 yr since surgery revealed a significant difference from rhTSH to withdrawal (-10.62 *vs.* -12.18; $P < 0.0001$ for both) but no impact of time since surgery on the result ($P = 0.4129$). Lastly, investigation of mean change in PCS scores in patients with stage 1 or 2 disease *vs.* stage 3 or 4 disease showed a significant difference from rhTSH to withdrawal (-7.86 *vs.* -11.77; $P < 0.0001$ and $P = 0.0101$) but no impact of stage of disease on outcome ($P = 0.2163$). Additionally, investigation of mean change in MCS scores in patients with stage 1 or 2 disease *vs.* stage 3 or 4 disease showed a significant difference from rhTSH to withdrawal (-5.96 *vs.* -11.84; $P < 0.0001$ for both) but no impact of stage of disease on outcome ($P = 0.9717$). None of these three factors accounted for the significant difference in SF-36 scores of patients after rhTSH *vs.* after withdrawal from thyroid hormone.

TABLE 2. Impact of hypothyroidism in the three groups compared with U.S. norms

	L-T_4 (N = 228)		rhTSH (n = 228)		Hypothyroid (n = 225)		U.S. norms (n = 6742)		*P* value		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	L-T_4 *vs.* U.S. norm	L-T_4 + rhTSH *vs.* U.S. norm	Hypothyroid *vs.* U.S. norm
SF-36 scales											
Physical functioning	50.06	0.62	50.33	0.60	40.84	0.76	49.35	0.25	0.3	0.13	<0.0001[a]
Role physical	51.15	0.59	50.69	0.61	37.25	0.75	49.77	0.26	0.03[b]	0.16	<0.0001[a]
Bodily pain	53.19	0.64	53.49	0.62	47.08	0.81	49.80	0.26	<0.0001[b]	<0.0001[b]	0.001[a]
General health	48.54	0.64	48.39	0.65	45.26	0.71	49.96	0.26	0.04[a]	0.03[a]	<0.0001[a]
Vitality	51.49	0.66	51.13	0.68	38.33	0.75	50.23	0.26	0.08	0.22	<0.0001[a]
Social functioning	50.25	0.58	49.19	0.62	37.35	0.85	49.90	0.26	0.59	0.29	<0.0001[a]
Role emotional	50.59	0.64	49.96	0.66	36.77	0.89	50.21	0.26	0.59	0.72	<0.0001[a]
Mental health	48.56	0.71	49.15	0.70	39.94	0.84	50.13	0.26	0.04[a]	0.19	<0.0001[a]
SF-36 summary measures											
Physical summary	51.32	0.55	51.32	0.54	44.03	0.65	49.53	0.25	<0.005[b]	<0.005[b]	<0.0001[a]
Mental summary	49.53	0.68	49.14	0.68	37.27	0.82	50.34	0.26	0.26	0.10	<0.0001[a]

[a] All significant changes reflect scores less than the U.S. norm, with the exception of bodily pain and PCS in patients on L-T_4 and L-T_4 plus rhTSH, and role physical in patients on L-T_4.

[b] Exceptions as noted above.

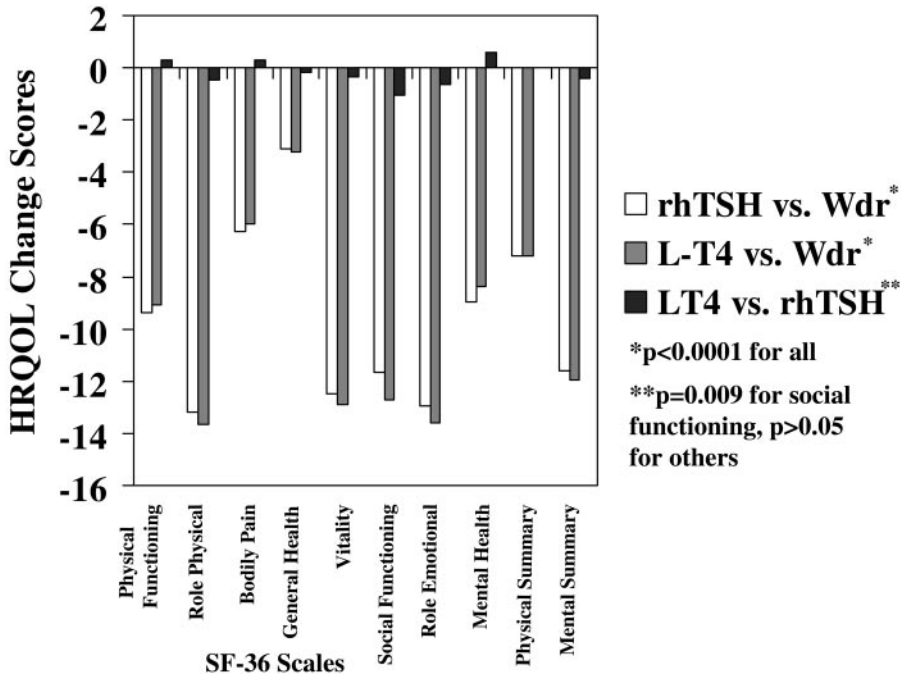

FIG. 1. Impact of thyroid hormone withdrawal on changes in HRQOL scores. Change in mean SF-36 scores from 1) rhTSH *vs.* withdrawal (Wdr) (*white bars*; *, $P < 0.0001$ for all), 2) baseline on L-T_4 *vs.* withdrawal (*gray bars*; $P < 0.0001$ for all), and 3) baseline on L-T_4 *vs.* rhTSH (*black bars*; **, $P = 0.009$ for social functioning scale; otherwise, $P > 0.05$).

Content-based interpretation of HRQOL results

Individual item responses in the physical functioning scale showed that more patients had significantly greater limitations in activities of daily living in the withdrawal phase than in the other two study phases. For example, 73% of patients were limited when climbing several flights of stairs after withdrawal, whereas only 41 and 39%, respectively, were limited at baseline on L-T_4 or after rhTSH (supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Other physical functioning questions yielded similar responses. Item responses for the role physical and role emotional scales also indicated greater limitation when patients were withdrawn from thyroid hormone than during the other two study phases. For example, 74% of patients had difficulty performing work because of physical health after withdrawal, whereas only 18 or 21% felt this way on medication at baseline or after rhTSH. Similar results were seen on the mental health and vitality scales, with more limitations after thyroid hormone withdrawal. Less of a difference was seen in the general health scale questions. Overall, more limitation on the physical functioning, role physical, role emotional, social functioning, and bodily pain scales was seen upon L-T_4 withdrawal *vs.* the other phases.

HRQOL in hypothyroidism compared with three other medical conditions: heart failure, depression, and migraine headache

Study patients on thyroid hormone at baseline scored above the heart failure norm for physical functioning, role physical, and general health scales as well as on the PCS; they were not significantly different on the remaining HRQOL measures (Table 3 and Fig. 2). Similarly, after rhTSH administration, study patients' scores were above the heart failure norm in the same three of eight SF-36 domains as well as the PCS; they were not significantly different from the heart failure norm in the other HRQOL measures (Table 3 and Fig. 2). In contrast, after thyroid hormone withdrawal, study patients' scores were significantly below the heart failure norm on six of eight SF-36 domains and remained at or above the congestive heart failure norm on only two scales, general health and physical functioning (Table 3). On the component summary scales, study patients' scores were significantly below the heart failure norm on the MCS and at the norm on the PCS (Fig. 2).

In comparison with the congestive heart failure, depression, and migraine headache norms, study patients on thyroid hormone at baseline scored above the norm in all SF-36 domains and the component summary scores (Table 3 and Fig. 2). After rhTSH, participants' scores remained above the depression norm in all SF-36 domains and on the component summaries (Table 3 and Fig. 2). After thyroid hormone withdrawal, study patients' scores were below the depression norm in physical functioning, role physical, and vitality scales and PCS; above in bodily pain, general health, and mental health scales and MCS; and not different in the social functioning and role emotional scales (Table 3 and Fig. 2).

When study patients on baseline thyroid hormone or after receiving rhTSH were compared with the general population migraine norms, their SF-36 scores were above the migraine norm in all 10 HRQOL measures (Table 3 and Fig. 2). In contrast, after thyroid hormone withdrawal, study patients' scores were below the migraine norm in physical functioning, role physical, vitality, social functioning, role emotional, and mental health scales as well as MCS; they were not significantly different on the remaining two scales, bodily pain and general health, and PCS (Table 3 and Fig. 2).

TABLE 3. HRQOL in hypothyroidism compared with three other medical conditions: heart failure, depression, and migraine headache

SF-36 scales	Heart failure (n = 216)		Depression (n = 503)		Migraine (n = 386)		*P* value							
							vs. heart failure			*vs.* depression			*vs.* migraine headache		
	Mean	SE	Mean	SE	Mean	SE	L-T_4	rhTSH	Hypothyroid	L-T_4	rhTSH	Hypothyroid	L-T_4	rhTSH	Hypothyroid
Physical functioning	40.61	2.66	44.24	0.54	44.83	1.10	$<0.001^b$	$<0.001^b$	0.93	$<0.0001^b$	$<0.0001^b$	$<0.001^a$	$<0.0001^b$	$<0.0001^b$	$<0.005^a$
Role physical	42.79	2.35	40.13	0.59	44.95	1.14	$<0.001^b$	$<0.001^b$	0.03^a	$<0.0001^b$	$<0.0001^b$	$<0.005^a$	$<0.0001^b$	$<0.0001^b$	$<0.0001^a$
Bodily pain	52.34	2.45	44.80	0.58	45.66	1.16	0.74	0.65	0.04^a	$<0.0001^b$	$<0.0001^b$	0.02^b	$<0.0001^b$	$<0.0001^b$	0.31
General health	40.27	2.28	40.92	0.55	45.86	1.05	$<0.001^b$	$<0.001^b$	0.04^b	$<0.0001^b$	$<0.0001^b$	$<0.0001^b$	0.03^b	0.04^b	0.63
Vitality	47.17	2.27	41.87	0.52	47.38	1.11	0.07	0.09	$<0.001^a$	$<0.0001^b$	$<0.0001^b$	0.0001^a	$<0.005^b$	$<0.005^b$	$<0.0001^a$
Social functioning	49.78	2.68	38.85	0.61	45.40	1.19	0.87	0.83	$<0.0001^a$	$<0.0001^b$	$<0.0001^b$	0.15	$<0.0005^b$	$<0.005^b$	$<0.0001^a$
Role emotional	47.36	2.96	36.22	0.68	44.99	1.01	0.28	0.39	$<0.001^a$	$<0.0001^b$	$<0.0001^b$	0.62	$<0.0001^b$	$<0.0001^b$	$<0.0001^a$
Mental health	51.09	2.26	34.16	0.61	45.66	1.28	0.29	0.41	$<0.0001^a$	$<0.0001^b$	$<0.0001^b$	$<0.0001^b$	0.05^b	0.02^b	$<0.0005^a$

Scores reflect significant changes where the L-T_4, rhTSH, or hypothyroid group is less than the respective chronic condition (*e.g.* heart failure, depression, or migraine headache) or greater than the chronic condition (see below).

[a] Scores less than the respective chronic conditions.

[b] Scores greater than the respective chronic conditions.

FIG. 2. Comparison of mean SF-36 component summary scores in study patients *vs.* three chronic diseases. Study patients' mean SF-36 physical (A, *top*) and mental (B, *bottom*) component summary scores on thyroid hormone (*bars with dots*), after rhTSH (*light gray bars*), or after withdrawal from thyroid hormone (*black bars*) in comparison with U.S. adult general population norm or three chronic diseases: congestive heart failure (*diagonal lines*), depression (*horizontal lines*), and migraine (*vertical lines*). *, $P < 0.0001$; **, $P < 0.05$ in comparison with withdrawal from thyroid hormone.

Clinical correlation with Billewicz score

All of the signs and symptoms of hypothyroidism, including cold intolerance, weight increase, constipation, hoarseness, paresthesia, dry skin, deafness, slow movements, periorbital edema, and bradycardia, were significantly increased in the withdrawal phase but not after rhTSH ($P < 0.001$ for all). There was a strong negative correlation of PCS and MCS scores with total Billewicz scores (r = −0.466 and −0.504, respectively; $P < 0.0001$ for both).

Discussion

The SF-36 scores when these thyroid cancer patients were taking thyroid hormone at baseline were at or above the U.S. general adult norm in six of eight categories, with the exception of modestly lower scores on the general health and mental health domains. This perception of a decrease in general and mental health has been seen in other studies of

thyroid cancer patients (19–21). These findings did not significantly change with rhTSH administration to prepare for diagnostic testing, except that the mental health score was no longer significantly below the norm. In contrast, after thyroid hormone withdrawal for testing, patients scored below this norm in all eight areas. In general, the mental health domain scores had the largest declines after medication withdrawal. Patients' age, gender, and stage of disease (stages 1 and 2 *vs.* stages 3 and 4) did not account for the difference in SF-36 scores after rhTSH compared with after withdrawal from thyroid hormone. Similarly, examination of time since surgery (less than or greater than 1 yr) did not affect the outcome. Lastly, we were unable to detect an effect of interim L-T_3 therapy on the decline in HRQOL scores seen after thyroid hormone withdrawal, as measured 2 wk after thyroid hormone withdrawal. Although it is likely that patients had higher HRQOL while taking T_3, our study design did not permit us to define the duration of hypothyroid symptoms. Recent studies have shown that interruption of L-T_4 therapy for 3 wk can adequately raise the TSH to permit diagnostic testing in the majority of patients (22–24); however, there have not been any direct comparisons of this regimen with interval L-T_3 therapy and rhTSH with respect to HRQOL. One limitation of the study was that the order of the scans was not randomized. It would have been inappropriate to perform the withdrawal scan first, because a patient who required radioiodine therapy based on the results of the study would have had to undergo withdrawal twice. That is, they would have had a withdrawal scan, restarted L-T_4, undergone rhTSH-stimulated scanning, and then withdrawn again from thyroid hormone to receive treatment.

To gain a better understanding of the limitations in the activities of daily living that occur in acutely hypothyroid individuals after withdrawal from thyroid hormone, we examined some of the significant SF-36 item responses in detail by dichotomizing the responses. As expected, we found limitations on both the physical and mental domains. This analysis highlights the fact that even some patients on suppressive replacement L-T_4 doses have limitations on many of these scales at baseline. Thus, the treating physicians can better understand the clinical consequences for patients when they recommend diagnostic testing using withdrawal from thyroid hormone.

The postoperative L-T_4-treated state was at or above the norm for QOL in the three other chronic medical conditions (heart failure, depression, and migraine headache) used for comparison, both in patients on thyroid hormone at baseline and after rhTSH administration. Minimal, if any, side effects such as nausea, fatigue, or headache were seen in patients after rhTSH; however, withdrawal of thyroid hormone led to the aggravation of patients' comorbidities, as previously seen (8). After thyroid hormone withdrawal, however, patients' QOL deteriorated to the extent that their scores became lower than these three chronic disease norms in most scales. This relative decline in QOL did not occur after rhTSH in preparation for diagnostic testing. Another limitation of our study is that the norms from three chronic illnesses have limitations in their use as comparisons. For example, the age, gender, or severity of their illnesses may have been different from that of our thyroid cancer patients. These analyses were adjusted for age and gender, so these factors do not account for the decline in QOL after L-T_4 withdrawal. These limitations do not change the fact that our patients had a marked and rapid decline in QOL, from average or even better than the average to much worse than these diseases.

Although the Billewicz scale is a highly investigator-dependent tool, these results confirmed a significant difference in prevalence of symptoms and signs of hypothyroidism in study patients between their periods on T_4 at baseline and after rhTSH *vs.* after withdrawal from thyroid hormone. There was a strong negative correlation between the Billewicz total scores and the PCS and MCS scores. These results confirm that patients with more symptoms and signs of hypothyroidism have decreased QOL.

Our findings are consistent with other smaller studies of QOL in thyroid cancer patients. In a study of 18 female patients with thyroid carcinoma before and after L-T_4 withdrawal, Botella-Carretero *et al.* (20) found worsening in 19 of 21 QOL scores, six of 12 cognitive tests, and 18 of 19 affective and physical symptom scores. This group also observed that patients on chronic suppressive L-T_4 therapy had significantly worse SF-36 scores on the mental health and general health scales, a finding we confirmed, and a decrease in social function, which was not seen in our study (20). Crevenna *et al.* (19) examined the QOL in asymptomatic thyroid cancer patients on L-T_4 suppression with no evidence of disease and found that there were significant deficits in the 51 patients who were within 1 yr after diagnosis in four SF-36 domains: vitality, role physical, role emotional, mental health, and social functioning. In this study, only vitality and role emotional remained significantly decreased later than 1 yr after diagnosis. In contrast, in our study, the duration since primary treatment did not affect the change in SF-36 scores after rhTSH or thyroid hormone withdrawal.

In conclusion, the diagnosis of thyroid cancer alone in this large series had minimal impact on QOL when patients were on thyroid hormone at baseline or after rhTSH preparation for diagnostic testing. In contrast, there was a dramatic decrease in QOL after thyroid hormone withdrawal, the magnitude of which was significantly worse than the previously documented impacts of heart failure, depression, and migraine headache on QOL. This decline in QOL after withdrawal from thyroid hormone can be abrogated by the use of rhTSH to facilitate diagnostic testing.

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