

HEAD AND NECK

The effect of substitution therapy on symptoms in patients with hypothyroidism following treatment for laryngeal and hypopharyngeal carcinomas

L'effetto della terapia sostitutiva sulla sintomatologia dei pazienti affetti da ipotiroidismo in corso di trattamento per carcinoma della laringe o dell'ipofaringe

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SUMMARY

Hypothyroidism is a well-known complication following treatment of laryngeal or hypopharyngeal carcinomas, and may cause various psychological and physical problems that negatively affect quality of life. The aim of this study was to evaluate the effect of substitution therapy on symptoms in patients with hypothyroidism. A study-specific questionnaire on physical and psychological problems (before and after substitution therapy) was sent to 70 patients who had been treated between 1977 and 2008 with clinical or subclinical hypothyroidism. Ninety-four percent returned the questionnaire. Symptoms on energy levels were reported most often (67% always tired and 70% lack of energy). Moodiness and emotional and physical symptoms were reported more often in substituted (sub)clinical hypothyroidism. Substitution therapy resulted in an improvement of energy ($P = 0.013$), sense of general interest and enjoyment ($P = 0.022$) and a reduction of puffy face ($P = 0.041$). Most symptoms in patients with thyroid dysfunction do not improve after substitution therapy. Nevertheless, due to its impact on health-related quality of life and the low burden of substitution therapy, screening for hypothyroidism and subsequent substitution therapy remains important.

KEY WORDS: Health-related quality of life • Hypothyroidism • Substitution therapy • Laryngeal neoplasms • Hypopharyngeal neoplasms • Head and neck cancer

RIASSUNTO

L'ipotiroidismo è una delle possibili complicanze a seguito del trattamento di un carcinoma della laringe o dell'ipofaringe e può essere alla base di disturbi fisici e psicologici con conseguente impatto negativo sulla qualità di vita del paziente. Lo scopo del nostro studio è stato quello di valutare l'effetto della terapia sostitutiva nei pazienti con ipotiroidismo. Abbiamo sottoposto un questionario studio-specifico a 70 pazienti trattati nel periodo compreso fra il 1977 e il 2008 e affetti da ipotiroidismo clinico o subclinico, con l'intento di evidenziare le relative problematiche fisiche e psicologiche (prima e dopo il trattamento). Il 94% dei pazienti ha risposto al questionario. La sintomatologia maggiormente riferita è stata quella relativa allo stato di spossatezza del paziente (67% sempre stanco e 70% scarse energie). Disordini dell'umore, sintomi psicologici e sintomi fisici sono stati riportati più spesso in casi di ipotiroidismo (sub)clinico in terapia sostitutiva. La terapia sostitutiva migliorava esclusivamente il senso di spossatezza ($P = 0,013$), il senso di generico interesse attivo e apprezzamento per le attività comuni ($P = 0,022$), e la riduzione del gonfiore del viso ($P = 0,041$). In conclusione la terapia sostitutiva risulta inefficace nel modificare l'andamento della maggior parte dei sintomi dei pazienti affetti da una disfunzione tiroidea. Tuttavia, in considerazione dell'impatto della terapia sulla qualità di vita del paziente e tenendo presente la scarsa invasività della terapia stessa, lo screening per l'ipotiroidismo e la relativa terapia sostitutiva restano indicati.

PAROLE CHIAVE: Qualità della vita • Ipotiroidismo • Terapia sostitutiva • Neoplasie laringee • Neoplasie ipofaringee • Tumori del distretto testa-collo

Acta Otorhinolaryngol Ital 2013;33:236-242

Introduction

Hypothyroidism is a well-known complication following treatment of laryngeal and hypopharyngeal carcinomas due to the close anatomic proximity of the thyroid gland to the larynx, hypopharynx and cervical lymph nodes. Depending on the extent of treatment, the reported inci-

dence of hypothyroidism varies between 27-78%, with the highest incidence found after combination therapy of surgery and radiotherapy^{1,2}. Surgery is believed to cause damage to the vasculature of the thyroid gland, while radiation can cause damage by inducing fibrosis within the capsule of the thyroid gland^{3,4}. Thyroid dys-

function may cause various psychological and physical symptoms that negatively affect the quality of life. The main psychological symptoms include anxiety, dysphoria, emotional instability, depression, insomnia and cognitive dysfunction⁵. Physical symptoms consist of weight gain, cold intolerance, dry skin, constipation, lack of energy and fatigue^{6,7}. Several studies have shown that subclinical hypothyroidism is a risk factor for coronary disease and atherosclerosis⁸⁻¹⁰. In patients treated for laryngeal or hypopharyngeal cancer, weight gain and cold intolerance were significantly increased and associated with hypothyroidism¹¹. In patients with clinical hypothyroidism substitution, therapy with thyroxin is considered to be safe and inexpensive. Treatment of subclinical hypothyroidism is controversial. Gulseren et al. found significant improvements of anxiety, depression and fatigue both in clinical and subclinical hypothyroidism⁵. However, Jaeschke et al. found a lack of symptom response in subclinical hypothyroidism and suggested that symptoms were nonspecific and might not be caused by (subclinical) hypothyroidism^{6,7}. Walsch et al. discovered that small changes in thyroxin dosage, with the aim of achieving serum TSH concentrations in the lower reference range, did not change well-being or quality of life¹⁰. Razvi et al. stated that substitution of subclinical hypothyroidism leads to a significant improvement of cardiovascular risk factors and fatigue⁸. A recent Cochrane review did not find statistically significant improvement of health-related quality of life and symptoms when comparing treated and untreated patients diagnosed with subclinical hypothyroidism¹². Because substitution therapy requires lifelong monitoring with subsequent problems of labeling, multi-drug therapy and thyroid hormone-induced osteoporosis, Jaeschke et al. suggest watchful waiting in case of subclinical hypothyroidism^{6,7}.

In the past, several questionnaires have been used scoring symptoms associated with hypothyroidism. McMillan et al. suggest using a questionnaire focusing on the impact of hypothyroidism on personally applicable life domains of the patient, by asking questions regarding work, spare time, family life and social life¹³. Others suggest using a disease-specific questionnaire geared towards symptoms including physical complaints, emotional problems, decreased energy and/or well-being, and cognitive decline^{6,7,14}. In the present study, we use a study-specific questionnaire based on the disease-specific questionnaires. The number of questions regarding physical symptoms, energy levels, moodiness and emotional symptoms has been narrowed down to make the questionnaire easier for patients.

The aim of this study is to evaluate the importance of various aspects of hypothyroidism and the effect of substitution therapy on the quality of life in patients who

have been treated for laryngeal or hypopharyngeal carcinomas, and who have subsequently developed hypothyroidism.

Materials and methods

This study was conducted by systematically questioning a group of patients previously treated for laryngeal or hypopharyngeal cancer by surgery, with or without radiotherapy or (chemo)radiotherapy, and subsequently developed clinical or subclinical hypothyroidism. The databases from a cross-sectional study and an ongoing prospective study (started in 2004) were used¹¹. Patients with psychiatric disorders or total thyroidectomy were excluded. All patients who had developed overt hypothyroidism or subclinical hypothyroidism before March 2008 were included. A total of 37 patients with clinical hypothyroidism and 60 patients with subclinical hypothyroidism were identified. Thirty-eight patients were from our previous reported cross-sectional study; at that time no routine monitoring of thyroid function was performed and thus the chronology of development of the hypothyroidism could not be evaluated. The remaining 32 patients were from a prospective study in which thyroid function was performed every 6 months after cancer treatment. The median time to development of hypothyroidism in the latter group was 10 months.

Hypothyroidism was defined as overt (clinical) if basal thyroid-stimulating hormone (TSH) was increased and free thyroxin (FT4) was decreased. Hypothyroidism was defined as subclinical if the basal TSH was increased and free FT4 was normal. Reference values in this study were TSH 0.3-4.5 mU/l and FT4 11.0-24.0 pmol/l. Patients with overt hypothyroidism and those with subclinical hypothyroidism characterized by TSH >10.0 mU/l were referred to an endocrinologist for substitution therapy. Patients with subclinical hypothyroidism and TSH < 10.0 mU/l were not treated unless clear symptoms of hypothyroidism existed. Twenty-seven patients had died before questionnaires were sent. The study cohort thus consisted of 70 patients. Of the 42 patients with subclinical hypothyroidism, 7 patients were staged with T2, 4 patients with T3, 8 patients with T4 and 9 patients were treated for recurrence. Of these patients, 30 were treated by radiation only and 12 by total laryngectomy with hemithyroidectomy and postoperative radiotherapy. Of the 28 patients with clinical hypothyroidism, 7 patients were staged with T1, 15 patients with T2, 5 patients with T3, 6 patients with T4 and 9 patients were treated for recurrence after (chemo)radiotherapy. Of these patients, 16 received radiotherapy only and 12 patients total laryngectomy, hemithyroidectomy and postoperative radiotherapy. As only routine clinical data and questionnaires were used, approval by the medical ethics committee was considered not to be necessary.

A study-specific questionnaire was used. Patients were given a list of questions that queried physical symptoms, energy levels, moodiness and emotional symptoms before and after substitution therapy (Paragraph 1). Patients with subclinical hypothyroidism, who were not treated with substitution therapy, filled out the first part of the questionnaire only. Patients filled in the questionnaire and rated how they felt before and after substitution therapy on a scale of 1 (no symptoms) to 5 (extremely large number of symptoms), retrospectively. There was adequate space available for comments. Patients were asked to return the questionnaire anonymously. The questionnaire was first sent out in March 2008. In May 2008, the questionnaire was sent out once more to all patients except those who had returned the questionnaire including their name.

Results

Prior to sending the questionnaire out, the patients were divided in two groups; overt hypothyroidism (n = 28) and subclinical hypothyroidism (n = 42). Because of the small number of patients, scores 2 and 3 as well as 4 and 5 were grouped for statistical analysis. A score change, the difference in symptoms-score before and after substitution,

was noted. Wilcoxon signed ranks test and McNemar test were used to compare the two groups. A chi-square test was used to test for differences in improvement after substitution therapy.

Sixty-six patients returned the questionnaire (response rate of 94%). Thirty-four patients received substitution therapy for clinical or subclinical hypothyroidism and 32 patients were not treated for subclinical hypothyroidism. Symptoms on energy levels and moodiness and emotional symptoms were reported most often before substitution therapy was started. A lack of energy was the most frequently reported complaint (70%) following treatment of a laryngeal or hypopharyngeal carcinoma. Many patients mentioned symptoms of always being tired (67%) and an increased need for sleep (64%). A substantial number of patients mentioned being slower physically (58%), slower movements (58%), difficulty concentrating (56%) and cold intolerance (53%) (Table I). Besides their responses to the items included in the questionnaire, 9 patients reported other symptoms after oncological treatment such as headache, heavy breasts, numbness of fingers and hands, swollen feet, pale hands or feet, itchy hands and irritability. Five patients specifically reported significant improvement after substitution therapy. Two

Table I. Symptoms after treatment for laryngeal or hypopharyngeal cancer in patients who developed hypothyroidism.

Symptoms	NO		YES	
	(n)	(%)	(n)	(%)
Physical symptoms				
Weight gain	41	62.1	25	37.9
Puffy face	48	72.7	18	27.3
Cold intolerance	31	47.0	35	53.0
Dry skin	33	50.0	33	50.0
Dry hair	39	59.1	27	40.9
Swollen hands	56	82.8	10	17.2
Muscle weakness	37	56.1	29	43.9
Energy levels				
Always tired	22	33.3	44	66.7
Increased need of sleep	24	36.4	42	63.6
Lack of energy	20	30.3	46	69.7
Physically slower	28	42.4	39	57.6
Mentally slower	37	56.1	29	43.9
General exhaustion	33	50.0	33	50.0
Less interest in going out	37	56.1	29	43.9
Slower movements	28	42.4	39	57.6
Moodiness and emotional symptoms				
Feeling frustrated	35	53.0	31	47.0
Feeling depressed	38	57.6	29	42.4
Difficulty concentrating	29	43.9	37	56.1
Decreased sense of general interest and enjoyment	32	48.5	34	51.5

NO = score 1 = no symptoms

YES = score 2+3+4+5 = few symptoms+average number of symptoms+large number of symptoms+extremely large number of symptoms

Table II. Symptoms in patients with substituted hypothyroidism (HT) (overt and subclinical) compared with non-substituted subclinical HT after treatment for laryngeal or hypopharyngeal cancer.

Symptoms	Substituted HT (n = 34)					Non-substituted HT (n = 32)					P		
	Score (1-5)	1	2+3	4+5		1	2+3	4+5					
Physical symptoms													
Weight gain	21	61.7%	12	35.3%	1	2.9%	20	62.5%	9	28.1%	3	9.4%	0.533
Puffy face	24	70.6%	4	11.8%	6	17.6%	24	75.0%	8	25.0%	0	0	0.072
Cold intolerance	14	41.2%	11	32.4%	9	26.5%	17	53.0%	13	40.6%	2	6.3%	0.046
Dry skin	16	47.0%	10	34.0%	8	23.5%	17	53.0%	10	31.3%	5	15.6%	0.435
Dry hair	20	58.8%	9	26.5%	5	14.7%	19	59.3%	13	40.6%	0	0	0.149
Swollen hands	28	82.4%	5	14.7%	1	2.9%	28	87.5%	4	12.5%	0	0	0.364
Muscle weakness	16	47.0%	9	26.5%	9	26.5%	21	65.6%	10	31.3%	1	3.1%	0.012
Energy levels													
Always tired	11	32.4%	11	32.4%	12	35.3%	11	34.4%	13	40.6%	8	25.0%	0.453
Increased need of sleep	11	32.4%	13	38.2%	10	34.0%	13	40.6%	11	34.4%	8	25.0%	0.563
Lack of energy	10	34.0%	13	38.2%	11	32.4%	10	31.3%	15	46.9%	7	21.9%	0.427
Physically slower	14	41.2%	10	34.0%	10	34.0%	14	43.8%	15	46.9%	3	9.4%	0.118
Mentally slower	18	52.9%	9	26.5%	7	20.6%	19	59.3%	12	37.5%	1	3.1%	0.086
General exhaustion	16	47.0%	10	34.0%	8	23.5%	17	53.0%	12	37.5%	3	9.4%	0.194
Less interested in going out	17	50.0%	9	26.5%	8	23.5%	20	62.5%	10	31.3%	2	6.3%	0.071
Slower movements	13	38.2%	11	32.4%	10	34.0%	15	46.9%	15	46.9%	2	6.3%	0.039
Moodiness and emotional symptoms													
Feeling frustrated	16	47.0%	10	34.0%	8	23.5%	19	59.3%	8	25.0%	5	15.6%	0.320
Feeling depressed	18	52.9%	8	23.5%	8	23.5%	20	62.5%	8	25.0%	4	12.5%	0.256
Difficulty concentrating	11	32.4%	14	41.2%	9	26.5%	18	56.3%	11	34.4%	3	9.4%	0.030
Decreased sense of general interest and enjoyment	12	35.3%	11	32.4%	11	32.4%	20	62.5%	9	28.1%	3	9.4%	0.011

Score 1: no symptoms; score 2: few symptoms; score 3: average number of symptoms; score 4: large number of symptoms; score 5: extremely large number of symptoms

P difference: the difference in symptoms between substituted HT and non-substituted HT

patients reported an inability to compare symptoms before and after substitution therapy, as their hypothyroidism was directly diagnosed and treated, postoperatively. In comparison to the group of patients that did not receive treatment, the patients that were treated with substitution therapy had, prior to treatment, more often complained of muscle weakness and a decreased sense of general interest and enjoyment ($p = 0.012$ and $p = 0.011$). Differences were also seen in symptoms such as difficulty concentrating ($p = 0.030$), slower movements ($p = 0.039$) and cold intolerance ($p = 0.046$) (Table II). For 60-94% of patients in the group that received substitution therapy, symptoms did not improve following substitution. Six patients (18%) specifically mentioned no improvement in symptoms after substitution therapy was started. Reported improvement in symptoms after substitution therapy included lack of energy (7 patients improved one score-change; 2 patients improved two score-changes); decreased sense of general interest and enjoyment (5 patients improved one score-change; 4 patients improved two score-changes); puffy face (2 patients improved one score-change; 2 patients improved two score-changes and 1 patient improved three score-changes) and being physically slower (8 patients improved one score-change; 1

patient improved two score-changes). A non-significant trend towards improvement of symptoms was found in favour of the treated group considering dry skin and general exhaustion (7 patients improved one score-change on both symptoms) and slowing of movements (6 patients improved one score-change) (Table III).

Discussion

The present study shows the prevalence of a wide variety of symptoms in patients diagnosed with hypothyroidism after treatment of laryngeal or hypopharyngeal carcinoma with laryngectomy and radiotherapy. A lack of energy, always being tired, an increased need of sleep and being physically slower are reported most often. These symptoms however, are often mentioned after cancer treatment and are therefore not specific to hypothyroidism. Watt et al. stressed that symptoms related to general well-being are more relevant, whereas clinicians tend to focus on physical symptoms characteristic for hypothyroidism¹⁴. It is arguable whether thyroxin substitution should be administered in case of subclinical hypothyroidism. A recent Cochrane review did not show improvement in symptoms after substitution therapy in patients with subclinical hy-

Table III. Improvement in symptoms after substitution therapy.

Symptoms	Score change (n = 34)						Mean score change	P	
	-3	-2	-1	0	1	2			3
	Improvement								
Physical symptoms									
Weight gain	1		2	26	4	1	0.029	0.660	
Puffy face				29	2	2	1	0.265	0.041
Cold intolerance			4	23	3	4		0.206	0.118
Dry skin	1	1	4	20	7		1	0.059	0.816
Dry hair		2	2	28	2			0.118	0.234
Swollen hands		1		32	1			0.029	0.655
Muscle weakness		1	1	28	4			0.029	0.738
Energy levels									
Always tired			3	24	7			0.118	0.206
Increased need of sleep		1	1	24	5	3		0.235	0.103
Lack of energy			1	24	7	2		0.294	0.013
Physically slower		1		24	8	1		0.235	0.051
Mentally slower		1		27	5	1		0.147	0.187
General exhaustion		1	2	26	5			0.029	0.763
Less interested in going out		1	1	28	3	1		0.059	0.588
Slower movements			3	24	6	1		0.147	0.166
Moodiness and emotional symptoms									
Feeling frustrated			5	23	3	3		0.118	0.329
Feeling depressed			3	26	3	2		0.118	0.271
Difficulty concentrating	1		1	24	5	3		0.206	0.143
Decreased sense of general interest and enjoyment			2	23	5	4		0.324	0.022

Score change: the difference between symptom score (score 1: no symptoms; score 2: few symptoms; score 3: average number of symptoms; 4: large number of symptoms; score 5: extremely large number of symptoms) before and after substitution therapy. Positive number means improvement and negative number means deterioration of symptoms after substitution therapy.

pothyroidism¹². However, over the long term, it is commonly assumed that subclinical hypothyroidism evolves into clinical hypothyroidism, and it is reported that high serum levels of TSH are a risk factor for thyroid carcinoma¹⁵. Moreover, subclinical hypothyroidism may have a deleterious effect on wound healing and flap survival, and is associated with elevated cholesterol levels and congestive heart failure¹⁶. It is therefore suggested that thyroid hormone substitution be administered in case of subclinical hypothyroidism, or at least when TSH >10.0 mU/l.

On the other hand, in head and neck cancer patients an association between development of hypothyroidism and improved survival has been recently reported by Nelson et al.¹⁶. In a retrospective study, they found that patients who develop secondary hypothyroidism after treatment have increased overall survival and recurrence-free survival compared to patients who did not become hypothyroid.¹⁶ In view of the growing body of evidence supporting a permissive role for thyroid hormone in the growth of certain solid tumours, this may be especially relevant for individuals with a prior or current cancer diagnosis¹⁷.

Only very limited data are available on quality of life in patients with hypothyroidism after treatment of laryngeal or hypopharyngeal carcinoma. Because head and neck cancer patients may already have a diminished quality of life, data on quality of life in other patients with hypothyroidism may not be applicable to patients with hypothyroidism due to treatment of laryngeal or hypopharyngeal carcinoma. Our results can improve patient counselling and also provide guidance in observing symptoms attributed to hypothyroidism after oncological treatment and in evaluating subsequent response to substitution therapy.

One limitation of our study is the lack of a control group of patients treated for a laryngeal or hypopharyngeal carcinoma without hypothyroidism. The second limitation is that we do not know whether other comorbidities, other than psychiatric disorder and thyroid disorder, were present which may cause symptoms similar to those found in hypothyroidism. Moreover, due to the anonymous character of the survey no real distinction could be made between clinical and subclinical hypothyroidism treated by substitution therapy for the entire group. Because most

patients with subclinical hypothyroidism were not treated, we might expect the vast majority of the treated group of patients to consist of those with clinical hypothyroidism. The third limitation is that our survey was a retrospective study in which patients were asked to score their symptoms before and after substitution therapy. It may have been difficult for patients to score their symptoms due to the time interval, and a longitudinal, prospective study would reveal more reliable data. We included patients with clinical or subclinical hypothyroidism, with and without substitution therapy. Patients with subclinical hypothyroidism probably have fewer symptoms and therefore may not benefit from thyroxine substitution as stated by the recent Cochrane review¹². Therefore, the effect of substitution therapy in patients with clinical hypothyroidism maybe greater than the effect found in our entire group, consisting of both clinical and subclinical hypothyroidism patients who have received substitution therapy.

We found at diagnosis that most symptoms were very similar in patients with treated or non-treated hypothyroidism. Jaeschke et al. found a higher frequency of symptoms such as dry skin, weight gain, feeling physically slower, a lack of energy, an increased need of sleep and feeling tired in overt hypothyroidism, by comparison to subclinical hypothyroidism^{6,7}. The present study found that patients more often reported cold intolerance, muscle weakness, slower movements, difficulty concentrating and a decreased sense of general interest and enjoyment. Despite thyroxine substitution treatment, most patients still reported several symptoms attributable to hypothyroidism, as also reported by Romijn et al. and the recent Cochrane review on subclinical hypothyroidism^{5,8,12,18}. Because data on thyroxine dosage and thyroid function after substitution were not available for all patients, it is possible that some patients received suboptimal substitution of hypothyroidism¹⁹. However, these symptoms may also be caused by other comorbidities or might be due to another sequela of cancer and its treatment. Moreover, the symptoms that are erroneously considered to be classical hypothyroid symptoms may be difficult to treat¹⁴.

Screening for hypothyroidism and substitution therapy following treatment of a laryngeal or hypopharyngeal carcinoma remains of the utmost importance. Fairly simple screening procedures, such as thyroid function testing and patient questionnaires, may improve at least some aspects of the quality of life for patients.¹⁵

Conclusions

In patients treated for laryngeal or hypopharyngeal cancer several symptoms can be observed that may be caused by hypothyroidism. Substitution therapy only improves a few symptoms such as a puffy face, a lack of energy, a decreased sense of general interest and enjoyment and be-

ing physically slower. Although improvement of quality of life may be limited, substitution therapy of clinical and subclinical (if TSH > 10.0 mU/l) hypothyroidism is advised because of the easy and inexpensive treatment and potential prevention of wound healing and cardiovascular problems.

Prospective randomized studies should include both the symptoms and response to substitution therapy of larger groups of patients diagnosed with either clinical or subclinical hypothyroidism.

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Received: August 25, 2012 - Accepted: January 10, 2013