Quality of Life, Anxiety and Depression in Patients with Differentiated Thyroid Cancer under Short Term Hypothyroidism Induced by Levothyroxine Withdrawal

Kvalita života, úzkost a deprese u pacientů s diferencovaným karcinomem štítné žlázy během krátkodobé hypotyreózy indukované vysazením levothyroxinu

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Summary

Background: We studied quality of life (QOL), anxiety, and depression in patients with differentiated thyroid cancer (DTC) either during treatment with levothyroxine or during withdrawal from levothyroxine when whole-body scanning (WBS) needed to be performed. ***Methods:*** DTC patients projected to undergo WBS were included in the study. They were studied at two time-points – the day before levothyroxine withdrawal, and one month after levothyroxine withdrawal. They were asked to fill WHOQOL-Bref, BDI-II, and HADS questionnaires at both time-points, and blood samples were taken to measure TSH, Tg, and TgAb levels. ***Results:*** Twenty-nine subjects (11 males) with a mean age of 42.6 ± 14.1 years entered the study. From the first to second time-point, the mean TSH level increased from 0.73 to 106.9 U/ml and the mean Tg level increased from 20.4 to 63.6 ng/ml. QOL scores decreased in four dimensions (physical health: 67.8 to 25.7; psychological: 58.9 to 38.9; social relationship: 67.5 to 56; and environment: 57.2 to 48.8). Patients also felt more depressed (48.3% to 93.2%) and anxious (65.5% to 89.6%). All changes were statistically significant ($p < 0.005$). ***Conclusion:*** We found decreased QOL after short-term hypothyroidism, especially in physical health and psychological dimensions. We also found that patients became significantly depressed and anxious after levothyroxine withdrawal. Our findings suggest that alternative therapies, such as those employing rhTSH, should be considered for these patients. Psycho-oncological support might also be useful in helping them overcome their symptoms during short-term hypothyroidism; however, considering the reversibility of their symptoms, supportive care might be more effective.

Key words

quality of life – anxiety – depression – thyroid cancer – hypothyroidism – levothyroxine – whole body scanning

This work was funded by vice-chancellor for research of Isfahan University of Medical Sciences (grant No. 190155).

Tato práce byla podpořena grantem prorektora pro vědu Univerzity pro lékařské vědy v Isfahanu č. 190155.

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Submitted/Obdrženo: 5. 5. 2016
Accepted/Přijato: 21. 6. 2016

http://dx.doi.org/10.14735/amko2016439

Souhrn

Východiska: Sledovali jsme kvalitu života (quality of life – QOL), výskyt úzkosti a deprese u pacientů s diferencovaným karcinomem štítné žlázy jak během léčby levothyroxinem, tak při jeho vysazení potřebném při celotělové scintigrafii (whole-body scanning – WBS). ***Metody:*** Do studie byli zařazeni pacienti s diferencovaným karcinomem štítné žlázy, kteří měli podstoupit WBS. Byli vyšetřováni ve dvou časových bodech – den před a měsíc po vysazení levothyroxinu. Pacienti vyplnili v obou časových bodech dotazníky WHOQOL-BREF, BDI-II a HADS. Byly odebrány vzorky krve ke stanovení hladin TSH, Tg a TgAb. ***Výsledky:*** Do studie bylo zařazeno 29 subjektů (11 mužů) průměrného věku 42,6 ± 14,1 let. Od prvního do druhého časového bodu se hladiny TSH zvýšily 0,73 na 106,9 U/ml a u Tg se průměrné hladiny zvýšily z 20,4 na 63,6 ng/ml. QOL skóre bylo kleslo ve čtyřech ukazatelích (fyzické zdraví: z 67,8 na 25,7; psychologické: z 58,9 na 38,9; sociální vztahy: z 67,5 na 56; prostředí: z 57,2 na 48,8). Pacienti také pociťovali větší depresi (ze 48,3 na 93,2 %) a úzkost (ze 65,5 na 89,6 %). Všechny změny byly statisticky významné ($p < 0,005$). ***Závěr:*** Zjistili jsme po krátkodobé hypotyreóze snížení QOL, zejména v ukazatelích fyzického zdraví a psychologické kondice. Také jsme zjistili výrazné zvýšení depresí a úzkosti po vysazení levothyroxinu. Naše nálezy podporují u těchto pacientů využití jiných metod léčby, které využívají rhTSH. V průběhu krátkodobé hypotyreózy může být užitečná k překonání příznaků i psychoonkologická podpora. Nicméně s ohledem na reverzibilitu symptomů může být účinnější prostá podpůrná péče.

Klíčová slova

kvalita života – úzkost – deprese – nádor štítné žlázy – hypothyroidizmus – vysazení levothyroxinu – celotělová scintigrafie

Introduction

Thyroid cancer is the most frequent endocrine malignancy standing as the 12th cancer in males and 9th cancer in females in Iran [1]. Differentiated thyroid cancer (DTC), arising from thyroid follicular epithelial cells, is a slowly growing disease and accounts for a vast majority of thyroid cancers [2]. This malignancy has an incidence rate of 0.5 to 10 per 10,000 individuals. Prognosis is good, and only 0.3% of all cancer deaths are related to thyroid cancer [3]. In contrast to more common malignancies, DTC is known for its slow clinical course and potential for late relapses, and lifelong follow-up is required [4].

Standard management of DTC is total thyroidectomy, if necessary with cervical lymph node dissection, followed by radioiodine ablation (with some exceptions) [2,4,5]. Then, patients need to be treated with levothyroxine for life which eliminates symptoms of hypothyroidism and suppresses thyrotropin (TSH) levels [2].

To detect and ablate thyroid remnants using radioactive iodine, stimulation by TSH is required. Therefore, levothyroxine is discontinued in these patients before whole body scanning (WBS) to increase TSH levels [2]. Levothyroxine withdrawal causes a short-term hypothyroidism in these patients and compels symptoms such as fatigue, decreased appetite, fluid retention and constipation [6,7]. Besides, previous findings have shown that these episodes of hypothyroidism have noticeable negative effects on patients' quality of life (QOL) and their psychometric functionality [8,9].

In the long-term management of cancer, it is important to preserve health-related quality of life (HRQOL) in patients in addition to increasing their survival [10]. HRQOL is decreased in these patients not only because of the episodes of levothyroxine withdrawal, but also because of the administration of supraphysiological doses of levothyroxine [8–10]. Some studies suggest psychological treatments for cancer patients [11,12]; however, it has been condoned in DTC patients probably because of low mortality and morbidity rates [13].

Previous studies have focused mostly on evaluation of HRQOL in DTC patients [10,14–17], and only few studies have noticed other psychological aspects in these patients [9,18]. Also, alterations in QOL, anxiety and depression are not studied in short-term hypothyroidism. In this study, we aimed to evaluate HRQOL, anxiety and depression in these patients.

Patients and methods

This is an observational study conducted from 2012 to 2015 at Seyed-Al-Shohada hospital affiliated to Isfahan University of Medical Sciences, located in the city of Isfahan, Iran. The inclusion criteria were defined as known DTC patients with initial thyroidectomy and radioactive iodine ablation who were referred for routine WBS during their follow-up during the study. The exclusion criteria were: age < 16 years old; presence of known psychiatric disease, mental illness or brain injury; known chronic comorbidities; taking psychiatric medication. The exclusion criteria were defined in order to eliminate the probable effect of mentioned conditions on psychological parameters. The study was approved by regional bioethics committee of Isfahan University of Medical Sciences, and all patients were asked to fill an informed consent form.

Patients were studied during levothyroxine withdrawal at two time points within one month – the last day on levothyroxine at their usual suppressive doses, and the day before administration of radioactive iodine for WBS. We expected to see a euthyroid or subclinical or mild hyperthyroid status in our cases at the first time point, changing to hypothyroidism at the second time point. To confirm these expectations, we took blood sample from patients at both time points to check TSH levels. Also, Tg (thyroglobuline) and TgAb (thyroglobuline antibody) were measured at both time points to find out any residual thyroid tissue. The dosage of levothyroxine during follow-up and the indication for WBS were decided by the physicians referring patients. At the time of study, recombinant human TSH was not available in our department of nuclear medicine.

All patients were advised to take their usual levothyroxine dose at the first time point and levothyroxine was withdrawn thereafter. Blood samples were

Tab. 1. Result from blood tests in patients before and after levothyroxine withdrawal.

	TSH (U/ml)		TgAb (U/ml)		Tg (ng/ml)	
	before	after	before	after	before	after
mean (SD)	0.73 (0.91)	106.9 (57.7)	32.3 (113.7)	33.2 (104.1)	20.4 (49.5)	63.6 (102.4)
range	0–3	32–276	2.0–620	2.0–569	0–254	0.2–500
p (comparison of items before and after levothyroxine withdrawal)	p < 0.001		p < 0.001		p > 0.05	

SD – standard deviation

Tab. 2. Comparison of WHOQOL scores before and after levothyroxine withdrawal.

	Dimension 1[1]		Dimension 2[2]		Dimension 3[3]		Dimension 4[4]		Total score	
	before	after	before	after	before	after	before	after	before	after
mean (SD)	67.8 (10.1)	25.7 (14.7)	58.9 (9.5)	38.9 (14.7)	67.5 (14.3)	56.0 (14.9)	57.2 (8.9)	48.8 (10.1)	49.6 (6.7)	32.4 (9.1)
range	46.4–85.7	0–57.1	41.7–87.5	8.3–83.3	33.3–91.7	16.7–75	31.3–78.1	34.4–78.1	36.7–67.5	15–57.5
p	< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	
95% CI	(36.3–47.9)		(15.4–24.5)		(6.7–16.3)		(5.2–11.6)		(14.4–20.1)	

[1] Physical health, [2] Psychological, [3] Social relationships, [4] Environment, SD – standard deviation, CI – confidence interval

obtained from patients after 12 hours of fasting. TSH levels were measured by immunoradiometric assay, using Kavoshyar (Iran-Tehran) kits. TSH tests were performed by Berthold-LB2111 unit gamma counter equipment. Tg and TgAb were measured using chemiluminescent immunoassay method by LIAISON analyzer (Germany). The mean coefficients of variation were below 10% for all these assays. The normal ranges were 0.3–0.5 U/mL for TSH, 5–25 ng/mL for Tg and < 116 U/mL for TgAb.

After blood testing, patients were asked to fill three questionnaires on QOL, anxiety and depression. To determine the QOL, we used the World Health Organization (WHO) brief questionnaire [19]. This questionnaire assesses QOL using four dimensions of physical health, psychological, social relationships and environment, through items with five-point Likert scale; higher total score shows better QOL [20].

To assess depression, we used Beck Depression Inventory-second version (BDI-II) which determines the level of depression using its cognitive and physical symptoms [21]. It has 21 items with a four-point Likert scale. The score of ≤ 13 shows that the patient is not depressed and the score of ≥ 14 shows depression (14–19: mild depression, 20–28: moderate depression, ≥ 29 severe depression). The score ≤ 4 suggests that the patient denies depression, and very high scores suggest exaggeration of depression as well [21].

Finally, the hospital depression and anxiety scale (HADS) questionnaire was used to determine anxiety and depression [22]. This questionnaire is designed especially for somatically ill patients. It has 14 items, each item scored on a four-point Likert scale. The score of ≤ 8 suggests the absence of anxiety or depression, and the score > 8 shows presence of anxiety or depression [22]. All questionnaires were translated into Persian and validated previously. Patients were asked to fill out the questionnaires at both time points.

Patients' data including age, gender, marital status, grading and staging of tumor, TSH. Tg, TgAb, and the score of three questionnaires at two time points were all collected in a database. Cancer staging was performed based on the recent management guidelines for patients with thyroid nodules and DTC [2]. Data analysis was performed using simple t-test, paired t-test, Wilcoxon signed ranks test, and McNemar test using SPSS 18. P-value less than 0.05 was considered as significant.

Results

Twenty-nine patients were enrolled in the study, including 11 males and 18 females (37.9% and 62.1% resp.), with mean age of 42.6 years (ranging from 16 to 68 years; SD: 14.9). Twenty-one patients (72.4%) had T1 tumors and the rest had T2 tumors (27.6%). Also, 19 patients (65.5%) had stage I thyroid cancer, seven patients (24.1%) stage II, and three patients (10.3%) stage III. Eighteen patients (62.1%) reported no stress factors which may affect their QOL, anxiety, or depression; however, 11 of them reported stress factors, such as immigration, spouse death and very low income. The mean TSH level at the first and second time point were

Tab. 3. Comparison of BDI-II scores before and after levothyroxine withdrawal.

	Not depressed		Low		Moderate		Severe	
	before	after	before	after	before	after	before	after
n (%)	15 (51.7)	2 (6.8)	8 (27.5)	1 (3.4)	6 (20.6)	6 (20.6)	0 (0)	20 (68.9)
p	p < 0.001		p < 0.001		p < 0.001		p < 0.001	

Tab. 4. Comparison of HADS scores before and after levothyroxine withdrawal.

	Anxiety				Depression			
	before		after		before		after	
	no	yes	no	yes	no	yes	no	yes
n (%)	10 (34.4)	19 (65.5)	3 (10.3)	26 (89.6)	2 (6.8)	27 (93.1)	0 (0)	29 (100)
p	p < 0.005				p > 0.05			

0.73 and 106.9 U/ml, resp. ($p < 0.001$), showing that all patients went through a hyperthyroidism condition. Tg and TgAb levels were also increased at the second time point. Results from blood tests are presented in Tab. 1.

Scores from WHOQOL-Bref questionnaire are demonstrated in Tab. 2 in four dimensions (D). As it is shown in the table, the mean scores for D1, D2, D3, and D4 before levothyroxine withdrawal were 67.8, 58.9, 67.5, and 57.2 resp. These means decreased to 25.7 for D1, 38.9 for D2, 56 for D3, and 48.8 for D4 after one-month of levothyroxine withdrawal ($p < 0.001$). Table 3 shows results from BDI-II. At the first time point, 15 patients were not depressed and no one was severely depressed, while at the second time point, 20 patients were severely depressed. Wilcoxon signed rank test showed that the aforementioned difference is statistically significant ($z: -4.523$; $p < 0.001$). Regarding HADS scores, 19 patients were anxious at the first time point, which increased to 26 cases at the second time point ($p < 0.001$). Also, 27 patients were depressed initially, which increased to 29 patients at the end of study ($p > 0.05$). These findings are summarized in Tab. 4.

Discussion

As discussed earlier, DTC patients need to discontinue their thyroid supplemental drug temporarily to perform WBS [2]. Some studies have suggested that this episode of hypothyroidism can have negative effects on patients QOL [23,24]. Also, other psychological aspects have been evaluated in previous studies, suggesting impairment of psychometric functionality in the hypothyroidism phase [8,9].

The importance of QOL and other psychological aspects is also a topic of debate in all cancer patients, because of the chronicity of their disease and its nature [10]. Therefore, patients with DTC may experience decreased QOL, depression and anxiety because they have cancer [25], and these disorders may be exacerbated after levothyroxine withdrawal. It should be noted that these patients are considered cured and may not get enough attention for their QOL and general health status [14].

In our series, the mean TSH level before levothyroxine withdrawal was 0.73, with a median of 0.20 which shows that most patients had suppressed TSH level, and the mean was increased to 106.9 which shows all patients were in the hypothyroidism phase at the second time point. Tg levels were measured at the first time point to see whether there are still thyroid remnants that produce Tg. The mean of 20.4 for Tg, with SD of 49.5 showed most patients did not have detectable levels of Tg; however, normal ranges or high ranges were also reported in a small number of them. This shows that most cases had no remaining thyroid tissue. Tg mean was increased to 63.6 which is the result of increased level of TSH in patients and increased production of Tg by thyroid remnants consequently. High levels of TgAb can result in false lower results of Tg in the laboratory [26]. For better evaluation of Tg levels, TgAb levels were also measured, which showed a normal range at both time points suggesting that Tg results are not falsely lower than the real amount.

Regarding QOL, scores in all dimensions were significantly decreased at the second time point. This decrease was more tangible in the physical health dimension, followed by psychological dimension. Physical health dimension covers questions about activities of daily living, energy and fatigue, mobility, pain and discomfort, sleep and rest, and work capacity [20] and these items may be affected more by hypothyroidism symptoms. Dow et al. showed that HRQOL is decreased after levothyroxine withdrawal; however, they evaluated QOL using a newly designed tool for this purpose [14]. Same findings were confirmed in the study by Tagay et al., using standardized tools to evaluate QOL [8] and also by other similar studies [9,23,27–29]. Our study confirms the previous findings on impaired QOL

during levothyroxine withdrawal, with more emphasis on physical health and psychological dimensions.

We found that patients get significantly depressed after one month of levothyroxine withdrawal. In our series, 51.7% of patients were not depressed at the first time point, and most of them became moderately or severely depressed at the second time point. Previous findings on this issue are various in different studies. Tagay et al. found no significant change in depression in the hypothyroidism phase [8]. In contrast, other studies have found deterioration of depressive symptoms in these patients after levothyroxine withdrawal [9,30,31]. Most previous studies have evaluated depression in long-term subclinical hypothyroidism, and few of them have investigated it in a short-term hypothyroidism. Our finding is consistent with most previous studies on depression in the hypothyroidism phase; however, we found more dramatic rise in BDI-II scores compared to previous studies. Reviewing results from HADS--depression showed a slightly higher, but not significant number of depressed cases after levothyroxine withdrawal. Based on HADS scores, 27 patients were classified as depressed at the first time point, increasing to all patients at the second time point. Results from HADS-depression seem not to be reliable, compared to BDI-II scores. The reason may be because of the difference of methods that these questionnaires employ to detect depression in patients.

Finally, we found that patients experience more anxiety at the second time point. These results are considerable from two aspects. First, number of anxious patients at the first time point was higher compared to the healthy Iranian population reported in previous studies [22]. This may suggest that DTC patients experience more anxiety even on therapeutic doses of levothyroxine and in euthyroid phase; however, this finding may not be reliable considering the lack of control group in our study. Second, the significant increase in anxiety scores after levothyroxine withdrawal suggests that they need to tolerate even more anxiety at this one-month period of hypothyroidism. Previous studies have reported diverse results on this subject. Tagay et al. showed that these patients experience more anxiety compared to the healthy population; however, they did not find any difference between anxiety scores before and after levothyroxine withdrawal [8]. Some other reports have also studied level of anxiety in DTC patients and found them more anxious, probably because of the subclinical hypothyroidism [32,33]. But, few studies have addressed this issue in short-term hypothyroidism. Cohen et al. and Botella--Carretero et al. found impaired psychometric impairment in these patients after short-term hypothyroidism which is consistent with our results [7,9].

We had some limitations in this study: 1. we lack a control group of healthy patients to compare results at the first time point which limited us to evaluate the base scores of our cases; 2. we had limited number of patients who could be included in the study; 3. we were obliged to use questionnaires that are translated and validated into the Persian version, and because of that, these three questionnaires were chosen to cover QOL, depression and anxiety. Unfortunately, we could not use a disease-specific QOL questionnaire because of the mentioned problem. Finally, this study was designed as cross-sectional, and we cannot suggest any causality accordingly.

In conclusion, we found decreased QOL in DTC patients after short-term hypothyroidism, especially in physical health and psychological dimensions. Also, we found that patients get significantly depressed after this period and experience more anxiety as well. Our findings suggest that an alternative method, such as using rhTSH, should be considered in these patients. Psycho-oncological support may also be useful for them during the short-term hypothyroidism; however, considering the reversibility of their symptoms supportive care can be more effective.

Acknowledgement

We want to thank the vice-chancellor for research and technology of Isfahan University of Medical Sciences for supporting and funding this project.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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