Evaluation of adrenal reserve in patients with differential thyroid cancer receiving thyroid hormone suppression therapy- case-control comparative study

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Research Article

Keywords: Thyroid cancer, Hyperthyroidism, Thyrotoxicosis, Adrenal insufficiency, ACTH stimulation test

Posted Date: November 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1043425/v1

Abstract

Background

Patients with differentiated thyroid cancer (DTC) are exposed to subclinical exogenous hyperthyroidism for the suppression of thyroid-stimulating hormone (TSH). In this study, we aimed to evaluate the adrenal reserve in DTC patients receiving suppression therapy.

Materials and Methods

The study included 55 DTC patients on suppression therapy and 32 healthy volunteers. Basal serum cortisol of all participants and adrenocorticotropic hormone (ACTH) of the patient group were measured. A standard-dose ACTH test (0.25 mg) was performed in patients with a basal cortisol < 14.5 mcg/dL.

Results

In the patient group, TSH was lower, free thyroxine (fT4) was higher, and free triiodothyronine (fT3) was similar to those of the control group ($p < 0.01$, $p < 0.01$, $p = 0.140$, respectively). The serum cortisol of the patient group was significantly lower than the control group (12.14 ± 5.12 mcg/dL vs 18.00 ± 5.56 mcg/dL, $p < 0.001$). 34 (61.8%) patients with DTC had a basal cortisol < 14.5 mcg/dL. Prolonged TSH suppression (≥ 5 years vs < 5 years) was associated with lower basal cortisol (7.46 ± 2.63 mcg/dL vs 9.48 ± 2.65 mcg/dL, $p = 0.022$). The ACTH stimulation test showed that 2 (5.8%) patients had a cortisol response < 18 mcg/dL. The rate of adrenal insufficiency was 3.6% in DTC patients. A moderate negative correlation was found between ACTH and fT3 of patients with low basal cortisol ($r = -0.358$, $p = 0.038$)

Conclusion

Patients with DTC receiving TSH suppression therapy are at risk for adrenal insufficiency. The duration and severity of suppression might increase this possibility. Dynamic testing with synthetic ACTH can be used to reveal insufficient cortisol response in case of clinical suspicion.

Introduction

Thyroid carcinoma is the most common endocrine malignancy [1]. It is classified as differentiated thyroid cancer (DTC) if it originates from the follicular epithelium [2]. In some patients, DTC treatment involves the long-term administration of a supraphysiological dose of levothyroxine after total thyroidectomy and radioactive iodine (RAI) treatment. [3]. The rationale behind thyroid-stimulating hormone (TSH) suppression is based on data showing that TSH stimulates thyroid cell proliferation and thyroglobulin production [4]. Therefore, TSH suppression prevents the growth of residual neoplastic tissues and ensures the prevention of tumor recurrences [3]. As a result, intermediate and high-risk patients with DTC

may be exposed to iatrogenic thyrotoxicosis for a long time [3]. Many studies have been conducted on the negative effect of hyperthyroidism on the hypothalamic–pituitary–adrenal (HPA) axis [5, 6]. It is suggested that thyrotoxicosis increases the work capacity of the adrenal glands to compensate for the increased cortisol destruction, and causes decreased cortisol response to related stimuli [6, 7]. The enlargement of the adrenal glands detected on computed tomography in hyperthyroid patients was thought to be related to the hyperactivity of the HPA axis [6]. The effect of subclinical iatrogenic thyrotoxicosis on the HPA axis in patients with thyroid cancer has never been studied before. The aim of this study was to evaluate the adrenal reserve in patients diagnosed with thyroid cancer and receiving suppression therapy using levothyroxine.

Materials And Methods

Participants

Fifty-five patients with thyroid cancer and 32 healthy volunteers were included. Patient group inclusion criteria were determined as having DTC for at least 1 year and a TSH value of < 0.5 uIU/mL. Exclusion criteria for all participants were having primary or secondary adrenal insufficiency, Cushing syndrome, recent steroid use (last 6 months), history of non-thyroid malignancy, diabetes mellitus, pregnancy, diseases that might affect cortisol-binding globulin level (cirrhosis, nephrotic syndrome), autoimmunity-related diseases (Hashimoto's disease, Graves' disease, celiac disease), and being older than 65 years or younger than 18 years of age. Sociodemographic data, clinical findings, histopathology results, and RAI dose received by the patients were retrieved from the patient files. The total weekly levothyroxine dose was calculated by adding the daily doses of the patients who received varying daily doses of levothyroxine. Local ethical committee approval was obtained, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Laboratory evaluation

Basal cortisol levels of all the participants and adrenocorticotropic hormone (ACTH) levels of the patient group were measured. Blood was taken at 08:00 in the morning for basal cortisol and ACTH measurements. For ACTH measurements, plasma samples were kept in frosted silicon glass tubes containing ethylenediaminetetraacetic acid (EDTA) and stored below − 20°C until transfer. Serum cortisol was measured using an immunometric assay, and intra and interassay coefficients of variability (CVs) were 3.0% and 4.7%, respectively. ACTH was measured using radioimmunoassay; the mean intra and interassay CVs were 3.8% and 7.2%, respectively. Normal levels of cortisol and ACTH defined by the manufacturers were 6.7–22.6 mcg/dl and < 46 ng/L, respectively. Serum TSH, free triiodothyronine (fT3), free thyroxine (fT4), glucose, alanine aminotransferase (ALT), triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured using chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, California and UniCel DXI 800, Beckman Coulter, Brea, California). Normal ranges for serum TSH, fT3, fT4, glucose, ALT, triglyceride, LDL, and HDL were 0.27–4.2 uIU/mL, 1.57–4.71 pg/mL, 0.61–1.12 ng/dL, 70–100 mg/dL, 0–45 U/L, 50–150 mg /dL, < 160

mg/dL, and 45–65 mg/dL respectively. Patients with a cortisol level of < 14.5 mcg/dL were defined to have low basal cortisol, and ACTH stimulation test was performed for suspected adrenal insufficiency in these patients [8].

Adrenocorticotropic hormone stimulation test

It is the standard screening test for the diagnosis of primary adrenal insufficiency. The ACTH stimulation test was performed by the intravenous administration of 0.25 mg ACTH (Synacthen®, Novartis). Cortisol was measured at 0, 30, and 60 minutes after ACTH injection in the morning. If the serum cortisol concentration was ≥ 18 mcg/dL at the 30th or 60th minutes, the diagnosis of primary and secondary adrenal insufficiency was excluded [8–10].

Statistical analysis

All statistical analyses were performed using the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Results of descriptive analyses are presented as mean ± standard deviation for normally distributed variables, median and range (minimum–maximum) for non-normally distributed variables, and number of cases and percentages (%) for nominal variables. Categorical variables were evaluated using the Pearson's chi-square test. Wilcoxon test and paired t-test were used to compare means among non-normally and normally distributed dependent variables, respectively. For non-normally distributed independent variables, Mann–Whitney U and Kruskal–Wallis tests were performed as applicable. Spearman's analysis was used to determine correlations between interval variables that were not normally distributed. The relationship between normally distributed independent variables was examined using the Pearson's correlation test, and the relationship between non-normally distributed independent variables was examined. A p value < 0.05 indicated statistical significance.

Results

The patient group consisted of 50 (90.9%) women and 5 (9.1%) men and the control group consisted of 27 (84.4%) women and 5 (15.6%) men (p = 0.357). The mean age of the patient group was 44.27 ± 10.81 years, and the mean age of the control group was 42.65 ± 13.79 years (p = 0.546). Histopathological diagnosis was papillary thyroid cancer in 51 (92.7%) and follicular thyroid cancer in 4 (7.3%) patients. The median disease duration was 33 months (12–107 months), mean levothyroxine dose was 949.72 ± 182.09 mcg/week, and RAI dose was 114.45 ± 32.80 mci. There was no difference between the groups in terms of body mass index (kg/m²), fasting glucose, ALT, triglyceride, LDL, HDL, and fT3 levels (*Table-1*). In the patient group, TSH was significantly lower and free T4 was significantly higher compared to those of the control group (p < 0.001 for each) **(***Table-1***).** DTC patients had significantly lower cortisol than control group (12.14 ± 5.12 mcg/dL vs 18.00 ± 5.56 mcg/dL, p < 0.001) The mean ACTH level of the patient group was 21.49 ± 11.77 ng/L. 34 (61.8%) patients had a basal cortisol level of < 14.5 mcg/dL (low basal cortisol), whereas 21 (38.2%) had a basal cortisol level of ≥ 14.5 mcg/dL (normal basal cortisol). Rate of patients with low basal cortisol was higher in the patient group compared to the control group (p = 0.006). ACTH stimulation test performed in the patients with low basal cortisol showed a mean

cortisol level of 11.78 ± 4.27 mcg/dL at the 0th minute, 23.73 ± 5.96 mcg/dL at the 30th minute, and 27.48 ± 6.42 mcg/dL at the 60th minute. There were 2 (5.8%) patients with a cortisol response of < 18 mcg/dL at the 30th and 60th minutes (*Table-2*). Of all the patients with DTC, the rate of unresponsiveness to the ACTH stimulation test was 3.6%.

Among patients with low basal cortisol, those with a < 5-year duration of suppression had significantly higher basal cortisol compared to those with a ≥ 5-year duration of suppression (9.48 ± 2.65 mcg/dL vs 7.46 ± 2.63 mcg/dL, p = 0.022). The mean basal ACTH level did not differ with regard to disease duration (17.42 ± 7.79 ng/L in those with < 5 years and 14.71 ± 6.12 ng/L in those with ≥ 5 years supression, p = 0.320) (*Table-3*). In patients with low cortisol, basal cortisol and ACTH were not correlated with levothyroxine weekly dose and exposed RAI dose (*Table-4*). In addition, no correlation was found between basal cortisol level and TSH, fT4, and fT3 levels. While basal ACTH was not correlated with TSH and fT4 levels, a moderate negative correlation was found between basal ACTH and fT3 (r = − 0.358, p = 0.038)

Discussion

Studies examining the effect of elevated thyroid hormone levels on adrenal reserve focus on patients with Graves' disease or endogenous hyperthyroidism [6, 11–16]. To the best of our knowledge, no study has been conducted on the effect of TSH suppression therapy on the adrenal reserve in patients with DTC. This is the first study in the literature showing this relationship. Few studies on the adverse effects of iatrogenic thyrotoxicosis on the HPA axis were conducted using animal models but these effects are not yet evaluated in humans [5, 17]. In the present study, we initially screened our participants with a morning basal cortisol measurement. Different results have been presented for morning basal cortisol levels in patients with hyperthyroidism. In a study by Mishra et al., patients with endogenous hyperthyroidism were found to have a basal cortisol level similar to that of the individuals in the control group [11]. In contrast, Nascif et al. found it to be higher compared to that of the controls [16]. In another study, basal cortisol levels of patients were lower in the hyperthyroid phase compared to those in the euthyroid phase [6]. In the present study, basal serum cortisol of patients with DTC was significantly lower than those of the control group. In addition, rate of patients with low basal cortisol was significantly higher in the patient group than in the control group. The reason for lower cortisol in our patient group might be longer duration of suppression in our study compared to previous studies. Supporting our study, Tsatsoulis et al showed that steroidogenesis was not increased and even significantly suppressed in case of chronic administration of high-dose thyroxine in thyroidectomized male rats [14].

We think that the results of our patient group reflect the chronic effects of thyrotoxicosis on the adrenal glands. Consistent with this opinion, we found that the basal cortisol level was significantly lower in patients whose suppression treatment duration exceeded 5 years. Although serum ACTH was lower in patients with a longer disease duration, this finding was not statistically significant. Prolonged suppression periods were also shown to be associated with thyroid storm due to reduced adrenocortical reserves [18]. This is explained by the fact that when hyperthyroidism becomes chronic, the adrenal

glands work at maximum capacity to keep up with the increased metabolic destruction of cortisol, depleting their reserves [5].

In case of exogenous subclinical hyperthyroidism, serum fT3 levels usually lie in the middle of the reference limits, and an increased fT3 level during levothyroxine therapy is considered to be indicative of overt iatrogenic hyperthyroidism [4]. fT3 is thought to be the best parameter to monitor TSH suppression therapy in patients with DTC [4]. In our study, we found a significant negative correlation between basal ACTH and fT3 levels. In other words, we found that as fT3 increased in patients, serum ACTH level was further suppressed. This result supports the view that besides the duration of the hyperthyroid state, its severity may also be an important factor in determining the functional capacity of the adrenal glands [5]. Goswamin et al. found that ACTH and cortisol response were significantly lower in patients with high serum fT3 levels [6]. In addition, it was suggested that in case of experimentally induced hyperthyroidism, changes in the HPA function become more pronounced as the severity of thyroid dysfunction increases [5, 19]. Agbaht K et al. found that the cortisol cycle increased as serum thyroid hormone levels increased [13].

In the present study, we performed the 250-mcg-standard, high-dose ACTH stimulation test to screen for adrenal insufficiency in patients with thyroid cancer based on the Endocrine Society Clinical Practice Guideline [20]. We found that the rate of patients having an inadequate cortisol response in the ACTH test was 5.8%, and the rate of adrenal insufficiency was 3.6% among all the patients. The prevalence of secondary adrenal insufficiency is estimated to be between 150–280/million [21]. Accordingly, we can estimate that patients with DTC receiving suppression therapy are at a higher risk for adrenal insufficiency compared to the general population. In a study evaluating a heterogeneous group in terms of hyperthyroidism in Turkey, 10% of the patients showed an inadequate response in the ACTH stimulation test [12]. Mishra et al. reported that inadequate cortisol response was observed in 34.5% of the hyperthyroid patients evaluated with 250 mcg ACTH and 48.3% of the patients evaluated with 1 mcg ACTH [11]. Tsatsoulis et al. showed that adrenal cortisol responses to low-dose ACTH stimulation were reduced after dexamethasone administration in patients with severe thyrotoxicosis [14]. Goswamin et al. evaluated the patients in hyperthyroid and euthyroid phases and obtained a 22% subnormal response to 250-mcg ACTH in the hyperthyroid phase [6]. We believe that our study group is not suitable for comparison with other studies in the literature in terms of the rate of adrenal insufficiency. This is because the patient group and duration of illness in our study are different from those in other studies. Accompanied autoimmune adrenalitis was reported in 5.7% of patients with Graves' disease [22, 23]. However, it is difficult to say whether this is purely because of the hyperthyroid status or concomitant adrenal insufficiency due to autoimmunity. In the present study, we eliminated this problem by not including those with a history of Graves' and autoimmune thyroid diseases.

In conclusion, patients with DTC receiving suppression therapy are at a risk for adrenal insufficiency. In addition, it should be kept in mind that the findings of thyrotoxicosis may mask the findings of adrenal insufficiency. This possibility increases as the duration of suppression therapy and the severity of

thyrotoxicosis increases. Furthermore, dynamic testing should be performed in stress conditions with an emphasis on the HPA axis and in cases of clinical suspicion.

Limitations

The main limitation of this study is its single-center design. Furthermore, we screened the control group only using basal cortisol measurements. The cortisol level of these healthy volunteers was above 10 mcg/dl and there was no clinical finding suggestive for adrenal insufficiency. Therefore, we did not measure ACTH levels and perform ACTH stimulation test in this group. In addition, it is suggested by some authors that this dose of ACTH is supraphysiological and 1 mcg ACTH should be used for the diagnosis of adrenal insufficiency [24]. However we used 250 mcg ACTH stimulation test for this purpose since it is still the standart test recommended by Endocrine Society Clinical Practice Guideline [20]. Performing subgroup analyses with a larger patient group and comparing different test protocols might help to clarify effect of suppression treatment on adrenal reserve in DTC patients.

Declarations

Funding No funding was received for conducting this study.

Compliance with ethical standards

Conflict of interest The authors declare no relevant conflicts of interest.

Ethical approval The study protocol was approved by Ankara Yıldırım Beyazıt University and complied with the principles of the Declaration of Helsinki

Consent for publication Patients signed informed consent regarding publishing their data.

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Tables

Table-1: Comparison of demographic features and biochemical measurements between patients with differentiated thyroid cancer and healthy control group.

	Differentiated thyroid cancer patients (n=55)	Healthy control group (n=32)	*p*
Age	44.27±10.81	42.65±13.79	0.546
Gender			
Female	50 (90.9%)	27 (84.4%)	0.357
Male	5 (9.1%)	5 (15.6%)	
BMI (kg/m²)	27.02±3.75	25.79± 3.82	0.138
Fasting glucose (mg/dl)	91.2 ±9.46	94.03± 11.01	0.229
ALT (U/L)	19.49±9.19	21.50±12.33	0.251
Trigliserid (mg/dl)	143.23±87.16	122.34± 54.11	0.172
LDL (mg/dl)	111.29±30.14	114.38 ±46.38	0.707
HDL (mg/dl)	59.59±29.03	52.03 ±13.98	0.597
fT3 (pg/mL)	3.29±0.55	3.13± 0.40	0.140
fT4 (ng/dL)	1.87±0.32	1.23 ±0.20	**<0.001**
TSH (uIU/mL)	0.07±0.11	2.11±1.00	**<0.001**
Basal cortisol (mcg/dl)	12.14±5.12	18.00±5.56	**<0.001**
Low basal cortisol (<14.5 mcg/dL)	34 (61.8%)	10 (31.3%)	**0.006**
ACTH (ng/L)	21.49±11.77	-	-

BMI: body mass index, ALT: alanine aminotransferase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, fT3:free triiodothyronine, fT4: free thyroxine, TSH: Thyroid-stimulating hormone, ACTH: adrenocorticotropic hormone

Table-2: Clinical and laboratory features of two differentiated thyroid cancer patients who did not respond to the adrenocorticotropin stimulation test

	Case-1	Case-2
Age (year) / Gender	59 / Female	47 / Female
The duration of suppression (months)	43	40
Basal hormone levels		
Cortisol (mcg/dl)	8.1	11.7
ACTH (ng/L)	23.0	14.3
Cortisol response after ACTH stimulation test		
0. min cortisol (mcg/dl)		
30. min cortisol (mcg/dl)	8.3	4.8
60. min cortisol (mcg/dl)	14.2	14.8
	17.1	17.6

ACTH: adrenocorticotropic hormone

Table 3: Comparison of basal cortisol and adrenocorticotropic hormone levels according to the duration of thyrotrophin suppression in differentiated thyroid cancer patients with a basal cortisol level of <14.5 mcg/dL

	All patients (n=34)	Duration of suppression <5 years (n=22)	Duration of suppression ≥5 years (n=12)	*p*
Basal cortisol (mcg/dL)	8.95±2.76	9.48±2.65	7.46±2.63	**0.022**
Basal ACTH (ng/L)	16.75±7.39	17.42±7.79	14.71±6.12	0.320

ACTH: adrenocorticotropic hormone

Table 4: Correlation between basal cortisol and adrenocorticotropic hormone levels, and clinical features and thyroid functions in differentiated thyroid cancer patients with a basal cortisol level of <14.5 mcg/dL

	Cortisol		ACTH	
	r	*p*	*r*	*p*
Levothyroxine weekly dose	-0.153	0.388	0.272	0.120
RAI dose	0.023	0.896	0.276	0.114
TSH	0.122	0.494	0.050	0.777
fT4	0.282	0.106	0.208	0.237
fT3	0.268	0.125	**-0.358**	**0.038**

ACTH: adrenocorticotropic hormone, RAI: radioactive iodine, TSH: thyroid-stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine,