Evaluation of Adrenal Reserve in Patients with Differentiated Thyroid Cancer Receiving Thyroid Hormone Suppression Therapy- case-control Comparative Study

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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. 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 < .001). A total of 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 = .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 = .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. It is classified as differentiated thyroid cancer (DTC) if it originates from the follicular epithelium. In some patients, DTC treatment involves the long-term administration of a supraphysiological dose of levothyroxine after total thyroidectomy and radioactive iodine (RAI) treatment. The rationale behind thyroid-stimulating hormone (TSH) suppression is based on data showing that TSH stimulates thyroid cell proliferation and thyroglobulin production. Therefore, TSH suppression prevents the growth of residual neoplastic tissues and ensures the prevention of tumor recurrences. As a result, intermediate and high-risk patients with DTC may be exposed to iatrogenic thyrotoxicosis for a long time. Many studies have been conducted on the negative effect of hyperthyroidism on the hypothalamic–pituitary–adrenal (HPA) axis. 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. 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. 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 as follows: DTC patients who were receiving thyroid hormone suppression therapy and had a stable response for more than 6 months were included. Patients with other endocrine or systemic diseases, patients with a history of adrenal dysfunction, and patients who had undergone adrenal gland surgery were excluded. Healthy volunteers were recruited from the university staff and students. They were excluded if they had a history of endocrine or systemic diseases, had been exposed to any endocrine or systemic diseases, or had undergone any surgical procedures in the adrenal gland region. All participants provided informed consent before the study. The study was approved by the local ethics committee.
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, infection, 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 variation (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 total cortisol was measured using an enzyme-linked immunosorbent assay (ELISA) technique ([DRG Instruments GmbH, Marburg, Germany]). Serum ACTH was measured using ELISA technique ([DRG International Inc., USA]). 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, 0.85–1.78 ng/dL, 70–100 mg/dL, 0–45 U/L, 50–150 mg/dL, <160 mg/dL, and 45–65 mg/dL respectively. The sensitivity of using a morning basal serum cortisol level of ≥10 mcg/dL as a criterion for adrenal insufficiency is 62% and the specificity is 77%.8 However, a basal serum cortisol level above 14.5 mcg/dL is indicative of a robust HPA axis.9,10 In our study, a threshold basal serum cortisol level above 14.5 mcg/dL was considered normal in both the patient and control groups. A value between 10 and 14.5 mcg/dL was established as the gray zone for basal serum cortisol levels. Participants in the gray zone underwent ACTH stimulation testing, depending on whether complaints such as weakness and fatigue were present. Since the participants in the gray zone in the healthy control group did not have any complaints, the synacthen test was not performed on them.8–10

**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.11–13

**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 < .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 = .357). The mean age of the patient group was 44.3 ± 10.8 years, and the mean age of the control group was 42.7 ± 13.8 years (p = .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 949.7 ± 182.1 mcg/week, and RAI dose was 114.5 ± 32.8 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 < .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 < .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 = .006). ACTH stimulation test conducted only in those patients with DTC who had basal cortisol level of <14.5 mcg/dL and complaints of weakness and fatigue (n=34) 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 = .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 suppresion, p = .320) (Table 3). In patients with low cortisol, basal cortisol and ACTH were not correlated with levothyroxine weekly dose and exposed RAI dose. In addition, no correlation was found between basal cortisol level and TSH and fT3 levels. While basal ACTH was not

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**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**              | 44.3 ± 10.8                                     | 42.7 ± 13.8                 | 0.546 |
| **Gender**           |                                                 |                             |       |
| Female               | 50 (90.9%)                                      | 27 (84.4%)                  | 0.357 |
| Male                 | 5 (9.1%)                                        | 5 (15.6%)                   |       |
| **BMI (kg/m²)**      | 27.0 ± 3.8                                      | 25.8 ± 3.8                  | 0.138 |
| **Fasting glucose (mg/dl)** | 91.2 ± 9.4                                     | 94.03 ± 11.01               | 0.229 |
| **ALT (U/L)**        | 19.49 ± 9.19                                    | 21.50 ± 12.33               | 0.251 |
| **LDL (mg/dl)**      | 143.23 ± 87.16                                  | 122.34 ± 54.11              | 0.172 |
| **Triglyceride (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.

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**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 | 8.1 | 11.7 |
| Cortisol (mcg/dl)    | 23.0 | 14.3 |
| ACTH (ng/L)          |       |        |
| Cortisol response after ACTH stimulation test | 8.3 | 4.8 |
| 0. min cortisol (mcg/dl) | 14.2 | 14.8 |
| 30. min cortisol (mcg/dl) | 17.1 | 17.6 |
| 60. min cortisol (mcg/dl) |       |        |

ACTH: adrenocorticotropic hormone.
correlated with TSH levels, a moderate negative correlation was found between basal ACTH and fT3 \( (r = -0.358, p = .038) \)

**Discussion**

Studies examining the effect of elevated thyroid hormone levels on adrenal reserve focus on patients with Graves’ disease or endogenous hyperthyroidism.\(^6\)\(^7\)\(^14\)\(^18\) 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.\(^5\)\(^19\) To the best of our knowledge, only one study was conducted about the effect of TSH suppression therapy on the HPA-axis function in patients with DTC.\(^20\) Chrisoulidou et al.\(^20\) assessed the HPA axis with the corticotropin-releasing hormone (CRH) test. In our study, we assessed the HPA axis differently by performing the ACTH stimulation test with more participants. 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.,\(^14\) patients with endogenous hyperthyroidism were found to have a basal cortisol level similar to that of the individuals in the control group. In contrast, Nascif et al.\(^7\) found it to be higher compared to that of the controls. In another study, basal cortisol levels of patients were lower in the hyperthyroid phase compared to those in the euthyroid phase.\(^6\) Chrisoulidou et al.\(^20\) found that basal cortisol measurements were similar in the patient and control groups, and also assessed the HPA axis as normal. 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.\(^17\) showed that steriodogenesis was not increased and even significantly suppressed in case of chronic administration of high-dose thyroxine in thyroidectomized male rats.

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.\(^21\) 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.\(^1\) 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.\(^5\) Goswami and Kochupillai\(^6\) found that ACTH and cortisol response were significantly lower in patients with high serum fT3 levels. 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.\(^5\)\(^22\) Agbaht and Gullu\(^15\) found that the cortisol cycle increased as serum thyroid hormone levels increased.

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.\(^23\) 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.\(^24\) Accordingly, we can estimate that patients with DTC receiving suppression therapy are at

**Table 3.** Comparison of basal cortisol and adrenocorticotropic hormone levels according to the duration of thyrotophin 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
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.\textsuperscript{15} Mishra et al.\textsuperscript{14} reported that inadequate cortisol response was observed in 34.5% of the hyperthyroid patients who had been evaluated with 250 mcg ACTH and 48.3% of the patients who had been evaluated with 1 mcg ACTH. Tsatsoulis et al.\textsuperscript{17} showed that adrenal cortisol responses to low-dose ACTH stimulation were reduced after dexamethasone administration in patients with severe thyrotoxicosis. Goswami and Kochupillai\textsuperscript{6} evaluated the patients in hyperthyroid and euthyroid phases and obtained a 22% subnormal response to 250-mcg ACTH in the hyperthyroid phase. 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.\textsuperscript{25,26} 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.\textsuperscript{27} However, we used 250 mcg ACTH stimulation test for this purpose since it is still the standard test recommended by Endocrine Society Clinical Practice Guideline.\textsuperscript{23} Another limitation of our study is not measuring the corticosteroid-binding globulin (CBG) adjusted free cortisol. Previous studies show that although CBG-level increase after treatment of apparent thyrotoxicosis compared to pre-treatment, total cortisol level did not change at all or is only slightly affected.\textsuperscript{14,28} In our patient group, thyrotoxicosis was subclinical level, and we suggest that not measuring the CBG adjusted free cortisol level may not be a significant limitation on our study results. 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.

**Disclosure Statement**

The authors declare no relevant conflicts of interest.

**Funding**

The author(s) reported there is no funding associated with the work featured in this article.

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**Consent For Publication**

Patients signed informed consent regarding publishing their data.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Muhammet Cuneyt Bilginer], [Abbas Ali Tam], [Sevgul Faki], [Nagihan Bestepe], [Fatma Dilek Dellal], [Didem Ozdemir], [Oya Topaloglu], [Reyhan Ersoy] and [Bekir Cakir]. The first draft of the manuscript was written by [Muhammet Cuneyt Bilginer] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Data availability statement**

Data available on request from the authors https://doi.org/10.21203/rs.3.rs-1043425/v1

**Ethical Approval**

The study protocol was approved by Ankara Yıldırım Beyazıt University and complied with the principles of the Declaration of Helsinki (Number 2017/120).
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