



## **SYMTHOM ANALYSIS DURING SUBCLINICAL HYPOTHYROIDISM AND HYPOADRENIA**

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### **ABSTRACT**

**Background and Objectives:** By analyzing the existing research, we find that in case of mild subclinical hypothyroidism, patients often may not have any complaints, and if they do, the complaints might be related to another coexisting clinical condition. Such complaints may occur in case of existence of hypoadrenia or so-called "adrenal fatigue syndrome". The goal of the study is to examine the clinical symptoms and their frequency in patients with subclinical hypothyroidism and borderline changes in adrenal stress response hormones — cortisol and DHEA-S and to compare these symptoms with those observed in patients without hypothyroidism but with functional adrenal deviations.

**Materials and methods:** The study included 27 patients who visited the Department of Endocrine Surgery at "Astghik" Medical Center between 2014 and 2022 and were diagnosed with subclinical hypothyroidism and had borderline deviations in adrenal hormones. The patients were split into three groups based on the deviations in adrenal hormone levels. Group I included 21 patients with elevated cortisol levels. Group II included 2 patients with increase in both cortisol and DHEA-S levels. Group III included 4 patients with elevated DHEA-S levels only. A percentage analysis of clinical symptoms was conducted among the patients and compared to the symptoms reported by patients presenting with adrenal hormone deviations only.

**Results:** As a result of the study, the common complaints reported across all groups included: general weakness, anxiety, fatigue, headaches, dizziness, mood decline, palpitations, elevated blood pressure, excessive sweating, muscle tension, shortness of breath, and pigmented spots. When comparing with the complaints of patients presenting solely with hypoadrenia it reveals that the coexistence of subclinical hypothyroidism and hypoadrenia is associated with a higher prevalence of symptoms. In terms of the reproductive system, the two common symptoms observed across the groups were hirsutism and menstrual irregularities.

**Conclusions:** Thus, we conclude that in patients presenting with complaints and subclinical hypothyroidism, the underlying cause of the symptoms may be another condition—specifically, coexisting adrenal fatigue. In this context, the presence of subclinical hypothyroidism may act as an additional stress factor, potentially placing further strain on adrenal function and making the manifestation of symptoms more noticeable.

**Keywords:** subclinical hypothyroidism, hypoadrenia, symptoms.

### **INTRODUCTION**

**Subclinical hypothyroidism (SCH)** is a biochemical condition which is characterized by elevated levels of TSH in the serum in the presence of normal levels of thyroxine (T4) and triiodothyronine (T3) - peripheral thyroid hormones of the thyroid Gland<sup>8</sup>.

SCH can be classified as mild (first-degree) when the upper limit of TSH is up to 9.9 mIU/L, and as more severe (second-degree) when TSH levels are  $\geq 10$  mIU/L. Approximately 80–90% of patients with SCH fall into the first-degree category<sup>2,4,8</sup>.

The most common cause of SCH is autoimmune

thyroiditis, although other causes may also be involved. The manifestations of subclinical hypothyroidism (SCH) may encompass general fatigue, intolerance to cold, weight increase, constipation, along with a decline in mood and quality of life, cognitive abilities, and memory impairment<sup>8, 9</sup>. In individuals diagnosed with subclinical hypothyroidism (SCH), the clinical manifestations are typically less severe compared to those observed in patients suffering from overt hypothyroidism. In cases of first-degree SCH, symptoms may be completely absent, and it is anticipated that both the frequency and intensity of symptoms will escalate as serum TSH levels increase<sup>2, 8</sup>.

However, the relationship between subclinical hypothyroidism and symptom development remains unclear.

Fifteen years ago, in mild cases of the condition (TSH <10 mIU/L), any impact of hypothyroidism on symptom development was not registered, and routine treatment was not recommended. According to most current guidelines, treatment should be initiated when TSH levels exceed 10 mIU/L.

The guidelines set forth by the European Thyroid Association (ETA) advocate for treatment in cases of more severe manifestations of the condition. In cases of milder forms, when repeated TSH measurements are within the range of 5–10 mIU/L and symptoms indicative of hypothyroidism are present, the administration of levothyroxine may be considered. Should there be no observable symptomatic improvement within 3–4 months following the normalization of TSH, it is advisable to cease treatment. This determination is inherently difficult, as the symptoms associated with hypothyroidism are nonspecific, and the choice to initiate or withhold treatment should be tailored to the treated individual<sup>3</sup>.

By analyzing the existing literature, we find that in cases of not expressed subclinical hypothyroidism, patients often may not have any complaints, and if they do, the complaints might be related to another coexisting clinical condition.

However, patients with subclinical hypothyroidism sometimes present with a range of complaints—particularly general weakness, fatigue, anxiety, and fluctuations in blood pressure that appear to be unrelated to subclinical hypothyroidism itself and may instead have a different etiology.

Referring to the existing literature, we can suggest that similar symptoms can occur in cases of vitamin deficiencies, depression, and a condition not yet widely recognized by endocrine associations—hypoadrenia, or so-called "adrenal fatigue syndrome".

These conditions may coexist with subclinical hypothyroidism, and the true underlying cause of the symptoms may be one of them.

As we have previously studied the condition of hypoadrenia and its clinical manifestations, and how they are spread out in statistics<sup>1, 7</sup>, it was decided to also check adrenal function in patients with subclinical hypothyroidism in order to determine whether these complaints might be associated with functional suppression of the adrenal glands.

Below is presently discussed the concept of "Adrenal Fatigue Syndrome" .

Dr. James L. Wilson, after reviewing the knowledge base accumulated over the past 100 years regarding hypoadrenia, adopted and further developed the theory of hypoadrenocorticism, renaming it as *Adrenal Fatigue Syndrome (AFS)*<sup>5</sup>.

The adrenal fatigue, basing on the author's words, is one of the most widespread yet rarely diagnosed syndromes of the past 50 years. The latter believes that adrenal fatigue is a manageable condition and that energy levels can be restored.

According to Wilson, hypoadrenia (adrenal fatigue) develops when an individual is exposed to significant stressors—such as the loss of a loved one, intense workloads, infections, emotional stress, absence of relaxation, fears, poor nutrition, surgical interventions, and etc<sup>5</sup>.

In this case, the adrenal glands begin to function in a stress mode, entering the "alarm phase" according to Selye, during which their function is already impaired; only after this the exhaustion phase comes up. When a person enters a second or third stress situation without recovering from the first, the adrenal glands become even more depleted. Clinical signs of adrenal fatigue appear: difficulty waking up in the morning, constant fatigue that doesn't go away with sleep, dizziness upon standing, mild depression, scattered thoughts, vague memory, low productivity, expressed premenstrual syndrome, salty food preference, and the need to put great effort to complete daily tasks. Decrease in sexual desire and stress tolerance may also be observed.

According to Dr. Michael Lam<sup>6</sup>, "Adrenal Fatigue Syndrome" appears to be the body's normal neuroendocrine response to stress. With this syndrome, the adrenal glands remain structurally unchanged. Medical historians might refer to this syndrome as a severe form of the General Adaptation Syndrome. On the other hand, modern endocrinologists may consider the term "non-adrenal illness syndrome" more adequate (similar to the term "non-thyroidal illness syndrome").

The cause of Adrenal Fatigue Syndrome (AFS) is considered to be stress, which can be physical, chemical

(such as exposure to toxins and heavy metals), or emotional. Amongst other contributing factors we could mention illnesses, infections, chronic pain, and surgeries. The symptoms include: progressive weakness and lack of energy, needing significant effort to perform daily tasks, reduced ability to cope with stress, tendency to gain weight and inability to lose it, decreased libido, dizziness, memory impairment, needing coffee to start the day upon waking up, sweets and salty food, irregular menstrual cycles, expressed premenstrual syndrome, mild depression, nervous tension, heart palpitations, and more. By analyzing the existing literature and our own on-hand research data, we decided to include patients with subclinical hypothyroidism in the study—those who had complaints and were under chronic stress—and to also examine their adrenal hormone levels, assuming that hypoadrenia might be the underlying cause of their symptoms.

The aim of this research is to study the clinical symptoms and the frequency of their occurrence in patients with subclinical hypothyroidism and borderline deviations in adrenal stress-response hormones—cortisol and DHEA-S—and to compare those symptoms with the clinical symptoms of patients

with adrenal functional abnormalities but without hypothyroidism.

**MATERIAL AND METHODS**

In the frames of the research overall 27 patients were included who visited the Department of Endocrine Surgery at “Astghik” Medical Center between 2014 and 2022 suffering from subclinical hypothyroidism and borderline changes in adrenal hormones. All patients were female, with an average age of  $30.6 \pm 8.8$  years.

The patients presented complaints characteristic of hypoadrenia, such as difficulty waking up in the morning, general weakness, getting tired instantly, anxiety, palpitations, headaches, blood pressure (BP) fluctuations, menstrual cycle irregularities, hirsutism, and so on parallelly having functional deviations in cortisol (CORT) and DHEA-S levels, along with an increase in TSH up to 10 mIU/L. The normal reference ranges for these hormones in the blood are presented in Tab 1.

**Table 1. Normal range for Cortisol, DHEA-S and TSH in blood**

Index		Reference
Cortisol (CORT)		171-536 nmol/L
Thyreotropin (TSH)		0,27-4.0 mU/L
DHEA-S	Female	4,02-11,0 mcmol/L
	Male	1,2-8,98 mcmol/L

The increase and decrease of adrenal hormones — cortisol and DHEA-S —used to be considered different phases of the same pathological process. Hormone overproduction is viewed as the adrenal alert or resistance phase in response to stress, while underproduction of the latter is regarded as the adrenal exhaustion phase that occurs during stress overcoming.

Based on deviations in hormone levels, the patients were categorized into three groups. Group I included 21 patients who had an increase in TSH levels up to 10 mIU/L, along with an elevation in cortisol only among the adrenal hormones. Group II consisted of 2 patients with a TSH increase up to 10 mIU/L, accompanied by increased levels of both cortisol and DHEA-S. Group III included 4 patients who had a TSH increase up to 10 mIU/L, along with an elevation in DHEA-S only. (See Table 2)

**Table 2. Division of the patients according to the nature of their hormonal deviation**

Index		Subgroup		
		I (n=21)	II (n=2)	III (n=4)
Nature of hormonal deviation	CORT	↑	↑	N
	DHEA-S	N	↑	↑
	TSH	↑	↑	↑

A detailed medical history was collected from all the patients included in the research, during which all complaints were inquired, and for each complaint in the pre-prepared complaints questionnaire, a "yes" or "no" mark was placed. Specifically, the presence of the following complaints was assessed: general weakness, easy fatigability, anxiety, palpitations, weight gain, weight loss, depressed mood, headaches, dizziness, excessive sweating, sensation of suffocation, hair loss on the head, muscle tension, insomnia, increased blood pressure, decreased blood pressure, joint pain, spinal pain, shortness of breath, hand tremors, sensitivity to cold, numbness in the hands, fears, pigmented spots. In women of reproductive age, disorders of the reproductive system were also assessed, including the presence of hirsutism, menstrual cycle irregularities or absence of menstruation, menstrual pain, and the presence of breast pain. The duration of the complaints was inquired—month, year, or decade. Attention was paid to the presence and duration of past exposure to stress (month, year, or continuous stress—chronic stress). The presence of other diseases, hereditary factors, and infectious diseases experienced in early childhood was also inquired.

**Objective examination and instrumental investigations:** Body weight and height were measured, and the Body Mass Index (BMI) was calculated. Palpation of the thyroid gland was performed, the presence of hand tremor was assessed, pulse rate and blood pressure were measured. In women, signs of hyperandrogenism were evaluated: the presence of hirsutism in androgen-dependent zones according to the race- and ethnicity-specific Ferriman-Gallwey hirsutism scale, as well as the presence of acne. All patients underwent electrocardiography (ECG).

**Ultrasound examination:** All patients underwent ultrasound examination of the thyroid gland and adrenal glands; in women, ultrasound of the ovaries and uterus was also performed. In all patients, thyroid gland hormones (TSH, Free T4) prolactin, total testosterone, cortisol, and DHEA-S were assessed. The study included those patients who had abnormalities in one or both of the hormones produced by the zona fasciculata and zona reticularis of the adrenal cortex—CORT (cortisol) and DHEA-S—as hormones of the adrenal layers that respond to stress and adrenocorticotrophic hormone (ACTH), as well as an increase in TSH up to 10 mIU/L. Hormonal examinations were performed by the electrochemiluminescence method using the Roche Elecsys 2010 analyzer.

*Organic diseases of the adrenal glands were excluded as follows:* Cushing's syndrome was excluded using the dexamethasone suppression test—1 mg of dexamethasone was administered orally at 23:00, and cortisol levels were measured at 08:00 in the following morning. The cortisol level was below 50 ng/mL, in accordance with international guidelines for Cushing's disease exclusion. The functional nature of hyper-DHEA-S-aemia was also denied by dexamethasone administration, as DHEA-S levels were suppressed the day after receiving dexamethasone. The functional nature of hypo-DHEA-S-aemia is confirmed through dynamic monitoring, when hormone levels restore was registered. No cases of functional hypocortisolaemia were recorded, and a Synacthen test was not required. Hormone samples were collected between 8:00 and 8:30 in the morning. During the two days prior, patients had refrained from physical activity, consumption of sugary foods, and caffeine. Special attention was paid to the presence of stress, to avoid attributing any detected hypercortisolaemia to an acute stress response.

### RESULTS

In Group I, cortisol levels ranged from 542.6 to 1225 nmol/L (reference range: 171–536 mcmol/L), ( $703.4 \pm 121.2$ ). TSH levels ranged from 4.3 to 10.2 mIU/L (reference range: 0.27–4.0 mIU/L), ( $6.3 \pm 1.4$  mIU/L). Cushing's syndrome was ruled out in all patients of Group I based on the results of the dexamethasone suppression test: 1 mg of dexamethasone was administered orally at 23:00, and cortisol levels measured the following morning were below 50 nmol/L.

In Group II — the group with elevated cortisol and DHEA-S levels — cortisol levels were 626.5 and 799 nmol/L, while DHEA-S levels were 12.9 and 19.4 mcmol/L (reference range: 4.02–11.0 mcmol/L); TSH levels were 5.36 and 4.35 mIU/L (reference range: 0.27–4.0 mIU/L).

In Group III, where only DHEA-S levels were elevated, the DHEA-S values ranged from 11.3 to 13.6 mcmol/L (reference range: 4.02–11.0 mcmol/L), with a mean of  $12.3 \pm 1.02$  mcmol/L; TSH levels in this group ranged from 4.09 to 10.0 mIU/L (reference range: 0.27–4.0 mIU/L), ( $5.6 \pm 2.1$  mIU/L).

We conducted only a descriptive analysis of the complaints and objective data of patients in Groups I and III presented in decreasing order, as the number of patients in the groups was small.

In Group I, the analysis of symptoms in patients with elevated cortisol and TSH levels is presented in Table 3.

Table 3. Symptoms of patients in Group I – by number and percentage.

<i>Patients with subclinical hypothyroidism and high levels of cortisol (n = 21)</i>		
<i>Symptom</i>	<i>Absolute quantity</i>	<i>Relative quantity (%)</i>
General weakness	19	90,5
Anxiety	19	90,5
Getting tired easily	18	85,7
Headaches	16	76
Mood decline	15	71,4
Palpitations	14	66,7
Dizziness	11	52
Feeling of suffocation	11	52
Blood pressure increase	11	52
Numbness of the hands	11	52
Insomnia	10	47,6
Excessive sweating	9	42,8
Scalp hair loss	9	42,8
Weight gain	8	38
Muscle tension	8	38
Spinal pain	8	38
Blood pressure decrease	7	33,3
Joint pain	7	33,3
Shortness of breath	7	33,3
Pigmented spots	7	33,3
Hand tremor	6	28,5
Sensitivity to cold	4	19
Weight loss	1	4,7
Fears	1	4,7

By analyzing the table and comparing it with the results of our previous study [N.B. Beglaryan, 2018], we observe that in both cases of patients without hypothyroidism and those with hypothyroidism combined with hypercortisolemia, the three main complaints are: general weakness (72.6% and 90.5%, respectively), anxiety (90.4% and 90.5%, respectively), and easy fatigability (70.2% and 85.7%, respectively); however, these three symptoms are more frequently observed in patients with coexisting hypothyroidism.

Among patients with hypercortisolemia combined with hypothyroidism, almost all symptoms are observed more frequently—by approximately 10%— with the exception of fears (9.5% and 4.7%, respectively) and weight loss (13%

and 4.7%, respectively), which are registered in fewer cases. Meanwhile, cold intolerance, palpitations, decreased blood pressure, and hand tremors are observed at nearly the same frequency.

Aside from that, reproductive system related symptoms were also more expressed in this same group (see Table 4).

**Table 4. Reproductive system dysfunctions in Group I patients - by number and percentage.**

<b>Reproductive disorders in Group I patients with hypothyroidism and hypercortisolemia (n = 21)</b>		
<b>Symptom</b>	<b>Absolute quantity</b>	<b>Relative quantity (%)</b>
Hirsutism	6	28,5
Menstrual cycle irregularity	6	28,5
Pain in breasts	4	19
Absence of menstruation/ Amenorrhea	1	4,7
Painful menstruation	1	4,7
Facial acne	0	0

Comparing the reproductive system related symptoms in patients with hypercortisolemia with and without hypothyroidism, we observe the opposite pattern: the main symptoms are about 10% more frequent in the group without hypothyroidism. Specifically, hirsutism occurred in 28.5% and 38.9%, respectively; menstrual cycle disorders in 28.5% and 37.7%, respectively; painful menstruation in 4.7% and 20.8%, respectively; while the presence of breast pain was almost the same — 19% and 20.8%, respectively.

The number of patients in the other two groups is small; however, we will analyze the symptoms of patients in the third group (see Table 5).

**Table 5. Symptoms of patients in the third group — by number and percentage.**

<b>Patients with elevated level of DHEA-S accompanied with hypothyroidism (n = 4)</b>		
<b>Symptom</b>	<b>Absolute quantity</b>	<b>Relative quantity (%)</b>
Anxiety	4	100
General weakness	3	75
Getting tired easily	3	75
Mood decline	3	75
Palpitations	2	50
Headaches	2	50
Dizziness	2	50
Excessive sweating	2	50
Increased blood pressure	2	50
Joint pain	2	50
Feeling of suffocation	1	25

Muscle tension	1	25
Shortness of breath	1	25
Cold intolerance	1	25
Numbness in hands	1	25
Pigmented spots	1	25
Weight gain	0	0
Weight loss	0	0
Scalp hair loss	0	0
Insomnia	0	0
Decreased blood pressure	0	0
Spinal pain	0	0
Hand tremor	0	0
Fears	0	0

When comparing the complaints of patients with elevated DHEA-S levels, with and without hypothyroidism, we observe that — despite the small number of patients — the top three complaints remain the same: anxiety (100% and 73.3%, respectively), getting tired easily (75% and 86.7%, respectively), and general weakness (75% and 66.7%, respectively).

The incidence of the remaining complaints is comparable, with the exception of certain symptoms that were not observed in the group with hypothyroidism, such as: weight gain, spinal pain, insomnia, low blood pressure, hand tremors, and weight loss.

The complaints regarding reproductive system in this same group are as follows (see Table 6):

**Table 6. Reproductive system disorders in patients of the Group III — by number and percentage.**

<i>Reproductive disorders in Group III (n =4)</i>		
<i>Symptom</i>	<i>Absolute quantity</i>	<i>Relative quantity (%)</i>
Hirsutism	3	75
Dysmenorrhea	2	50
Facial acne	1	25
Absence of menstruation	0	0
Painful menstruation	0	0
Pain in breasts	0	0

By comparing the symptoms related to reproductive system in women with high DHEA-S levels, both with and without hypothyroidism, we observe that in both groups, hirsutism ranks first (75% and 58.3%, respectively). Menstrual cycle disorders are present in 50% of cases in both groups. Among patients with hypothyroidism, facial acne is observed in 25%, while in the group without hypothyroidism, multifollicular ovaries are found in 16.7%.

**DISCUSSION**

The following section presents an analysis of the percentage distribution of symptoms observed in patients only in Groups I and III. Discussing those symptoms which are seen in 40% of cases or more we notice:

Group I: general weakness, anxiety, getting tired easily, headaches, mood decline, palpitations, dizziness, feeling of suffocation, increased blood pressure, numbness in hands, insomnia, excessive sweating, hair loss on the scalp.

Group III: anxiety, general weakness, getting tired easily,

mood decline, palpitations, headaches, dizziness, excessive sweating, increased blood pressure, joint pain.

The general complaints include overall weakness, anxiety, getting tired easily, headaches, dizziness, mood decline, palpitations, increased blood pressure, and excessive sweating.

Of course, the number of patients in this study is lower than in the previous study [N.B. Beglaryan, 2018]. However, by comparing the results of these two studies, it becomes clear that when subclinical hypothyroidism is combined with hypoadrenia, the symptoms appear at a higher percentage.

Considering the complaints that occur with a frequency of 20–40% in Groups I and III, it is noteworthy that in Group I, the symptoms include weight gain, muscle stiffness, spinal pain, decreased blood pressure, joint pain, shortness of breath, pigmented spots, and hand tremors

Meanwhile In Group III, the commonly reported symptoms are a feeling of suffocation, muscle tension, shortness of breath, cold sensitivity, numbness in the hands, and pigmented spots.

The general complaints are muscle tension, shortness of breath, and pigmented spots. As we can see, the symptoms that occur with a frequency of 20–40% in this group are fewer than in patients with only functional adrenal deviations, because nearly all complaints in that group occur at a higher percentage.

Analyzing the reproductive system–related symptoms, it can be noted that these occur in 20% or more of the cases. For instance, in Group I, the symptoms include hirsutism, menstrual cycle disorders, and breast pain. In Group III, the symptoms are hirsutism, menstrual cycle disorders, and facial acne. As we can see, the two common reproductive system-related complaints in both groups appear to be hirsutism and menstrual cycle disorders, which also coincide with the symptom frequency observed in patients from the previous study.

Thus, we conclude that borderline deviations in adrenal hormone levels cause symptoms regardless of whether they appear independently or in combination with hypothyroidism. Moreover, when combined with hypothyroidism, the severity of the symptoms increases. According to the literature, subclinical hypothyroidism may not cause any symptoms<sup>2,8</sup>.

## CONCLUSION

To sum up, the findings suggest that in patients who present with complaints and have subclinical hypothyroidism, the cause of the symptoms may lie elsewhere—specifically, in concurrent hypoadrenia.

The presence of subclinical hypothyroidism may act as an additional stress factor, which in turn can further strain adrenal function, thereby intensifying the manifestation of symptoms.

## DECLARATION

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### Competing and conflicting Interests

The authors report there are no competing interests to declare.

### Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committees (REC) of the Faculty of Dentistry, Cairo University, Egypt on 28/5/2024 with approval number 26524.

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