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Original Article

Biochemistry Section

Evaluation of Serum Cortisol Levels in Patients with Hypothyroidism at a Tertiary Care Hospital, Telangana, India: A Case-control Study

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ABSTRACT

Introduction: Serum Cortisol is a glucocorticoid hormone released from the zona fasciculata layer of the adrenal cortex, which plays an important role in regulation of blood pressure and metabolism. Hypothyroidism causes elevated cortisol levels due to both decreased clearance and negative feedback of cortisol on the hypothalamic pituitary-adrenal axis.

Aim: To investigate the correlation of serum cortisol and with Triiodothyronine (T3), Thyroxine (T4), Thyroid Stimulating Hormone (TSH) and serum cortisol levels in patients with hypothyroidism.

Materials and Methods: Present case-control study was carried out in the Department of Biochemistry, Gandhi Medical College and Hospital, Secunderabad, Telangana, India, July 2022 to August 2022. A total of 60 patients with hypothyroidism (cases) aged between 35-60 years, and 60 controls were selected from Gandhi Medical College and Hospital. Samples were analysed in Siemens Advia centaur XPT. T3, T4, TSH and cortisol levels were estimated by "CLIA" method. Data were statistically analysed using Karl Pearson's correlation test.

Results: In present study, there were five males and 55 females in control group, 23 males and 37 females were in case group. The mean age in cases was 39.39±6.44 years and in control group was 39.38±10.97 years. The mean T4 in subjects cases was 10.74±5.34 ng/mL, as compared to 8.99±2.43 ng/mL, in controls. The mean TSH level in cases was 13.38±20.43 mIU/L, as compared to 3.47±4.20 mIU/L, in controls. The mean cortisol level in cases was 64.88.44±16.25 µg/dL, as compared to 9.55±5.59 µg/dL, in controls. There was significant positive correlation between serum cortisol level and T3 (r=0.12, p-value 0.02), T4 (r=0.12, p-value 0.02), and TSH Levels (r=0.31, p-value 0.01) in case group.

Conclusion: The results of present study showed that serum levels of cortisol were significantly increased in hypothyroidism patients as compared to normal healthy controls.

Keywords: Adrenal cortex, Glucocorticoid hormone, Metabolism, Thyroid hormone

INTRODUCTION

Thyroid is a large endocrine gland located in the neck, attached to the trachea just below the larynx [1]. Thyroxine (T4) and Triiodothyronine (T3) are thyroid hormones, which play an important role in basal metabolism and the functioning of almost all tissues and systems in the body [2]. Hypothyroidism is defined by a decrease in thyroid hormone production and thyroid gland function, leading to metabolism slow down [3]. Thyroid function test evaluate the levels of TSH and T4 in the blood [4,5]. The prevalence of overt hypothyroidism is approximately 1-2% in women and 0.1% in men [6,7].

Hypothyroidism is a condition caused by insufficient production of thyroid hormones. Subclinical hypothyroidism can be defined as a state of high serum Thyroid Stimulating Hormone (TSH) levels with normal serum free thyroxine (T4) levels [8]. Cortisol is a steroid hormone that is released in response to stress and low blood glucose concentration. It was observed by the researchers that hypothyroid patients have elevated cortisol levels [7,9] and the serum TSH level was positively correlated with serum cortisol levels in subclinical hypothyroidism [7]. It was also observed that in the case of primary hypothyroidism (elevated TSH) cortisol was elevated, but in the setting of primarily elevated cortisol, TSH level was suppressed [9].

Hypothyroidism causes elevated cortisol levels, due to decreased clearance of cortisol and negative feedback of cortisol on the hypothalamic pituitary-adrenal axis. T3 and T4, TSH secretion is maintained within relatively narrow limits via a sensitive negative feedback loop in which TSH stimulates the synthesis and release of thyroid hormones. Cortisol by negative feedback mechanism stimulates the synthesis and release of Adrenocorticotropic Hormone (ACTH) [9]. Hypothyroidism is more common in older persons than younger individuals, especially among women, principally due to the rising incidence and prevalence of autoimmune thyroiditis [10].

Demers LM and Spencer CA in their study showed an elevation of serum cortisol level in hypothyroid patients group and positive correlation between TSH and serum cortisol. Authors also suggested that the conversion of T4 to T3 is influenced by adrenal cortisol. High cortisol levels induce a conversion of T4 to an improper form of T3 called reverse T3 (rT3) [3]. Gopalakrishnan A et al., suggested a physiologic feedback loop where lower thyroid function increases serum cortisol. Their result suggested a positive relationship between TSH and serum cortisol also showed high values of cortisol in 12.5% of hypothyroid patients [4].

Hollowell JG et al., found that significant hypercortisolemia in primary hypothyroidism is primarily due to decreased metabolic clearance of cortisol and a presumptive decrease in the negative feedback effect of cortisol on the hypothalamo-pituitary axis [5]. No such study is conducted in Telangana population also, the findings of present study have a possibility of being helpful in establishing the role of cortisol as additional marker in the diagnosis of hypothyroidism.

Hence, the present study was undertaken to determine the correlation of serum cortisol and TSH, T3 and T4 in patients with hypothyroidism.

MATERIALS AND METHODS

This case-control study was carried out in the Department of Biochemistry, Gandhi Medical College and Hospital, Secunderabad, Telangana, India, over a period of two months, from July 2022 and August 2022. The study was approved by the Human Research Committee review at Gandhi Medical College and Hospital, Musheerabad, Secunderabad as part of a biochemistry research project (Ethical approval no- IEC/GMC/2002/06/06 dated 29th June 2022).

Inclusion criteria: Subjects aged between 30-70 years, with confirmed diagnosis of hypothyroidism, whose cortisol level is more than 25 µg/dL were included as cases. Age and gender matched healthy euthyroid subjects with normal thyroid hormone levels and cortisol level <25 µg/dL was included as controls. Women were randomly assigned to participate during the late luteal phase or follicular phase of their menstrual cycle, because of menstrual phase effects on cortisol levels.

Exclusion criteria: Patients on thyroxin treatment, with history of smoking (in the span of last one year), patients with renal disease, liver disease, cardiovascular disease and diabetes mellitus, any neurological disorders or depression, critically ill patients admitted in intensive care unit, patients with confirmed or suspected cases of pancreatic pathology were excluded. Women with a partial or complete hysterectomy, tubal ligation, history of menstrual irregularities and who were pregnant or lactating within the past 12 months were excluded.

Sample size calculation: Sample size was calculated at 5% level of significance, to maintain power of study at 99% and it comes out to be 60 per group. Therefore, the total sample size for the present study has been calculated to be 120 (60 cases and 60 controls)

Total of 120 subjects were divided into two groups of 60 each:

Cases: 60 subjects with hypothyroidism were enrolled, based on American Thyroid Association (ATA) criteria for the diagnosis of hypothyroidism [11].

Controls: 60 healthy euthyroid subjects with normal thyroid hormone levels and cortisol level <25 µg/dL were enrolled as controls.

Study Procedure

The cases were selected from those attended, the Medicine Outpatient Department (OPD) Gandhi Hospital, Secunderabad. The Investigations were carried out in Biochemistry laboratory, Gandhi Medical College and Hospital, Secunderabad. The subjects were selected based on the medical history obtained from a health proforma and from recent lab reports, established diagnosed cases of hypothyroidism. Demographic data for age and gender were collected from all the study subjects. T3, T4, TSH and cortisol levels were assessed and compared among cases and controls.

After informed consent from patients, 5 mL of venous blood sample was obtained from every volunteer into red tubes. All the blood samples were immediately carried to the biochemistry laboratory. Samples were analysed in Siemens Advia centaur XPT. T3, T4, TSH and serum cortisol were estimated by "CLIA" method.

Normal reference range as per American Thyroid Association (ATA) guidelines [11]:

- T3 - 0.8-2 ng/mL
- T4 - 5.0-11.0 µg/dL
- TSH - 0.4-5.5 mIU/L.
- Serum cortisol - 5-25 µg/dL

STATISTICAL ANALYSIS

The data were statistically analysed using Graph Pad Prism 7.0. The measured parameters were expressed as mean±Standard Deviation (SD). Unpaired t-test was used to compare the groups. Relationship between the variables was assessed by Karl Pearson's correlation test. The p-value of 0.05 or less was considered statistically significant.

RESULTS

The mean age in control group and case group were 39.38±10.97 years and 39.99±6.44 years. There were 23 male and 37 female in case group and five males and 55 females in control group. There was statistically no significant difference was found between both the groups regarding age and gender distribution [Table/Fig-1]. In present study TSH (p-value=0.01), T3 (p-value=0.02), T4 (p-value=0.02) and serum cortisol level (p-value=0.01) were significantly increased in case group as compared to control group [Table/Fig-2].

Parameters	Cases	Controls	p-value
Age (in years) (Mean±SD)	39.99±6.44	39.38±10.97	0.06
Gender distribution	Male-23	Male-5	0.05
	Female- 37	Female-55	

[Table/Fig-1]: Comparison of demographic data among cases and controls.
Unpaired t-test; level of significant p-value <0.05

Parameters	Cases	Controls	p-value
T3 (in ng/mL)	0.98±0.45	0.91±0.22	0.02
T4 (in µg/dL)	10.74±5.34	8.99±2.43	0.02
TSH (in mIU/L)	13.38±20.43	3.47±4.20	0.01
Serum cortisol (in µg/dL)	64.88±16.25	9.55±5.59	0.01

[Table/Fig-2]: Comparison of T3, T4 TSH and serum cortisol among cases and controls.
Unpaired t-test; level of significant p-value <0.05

There was significant positive correlation between serum cortisol level and T3 (r-value=0.12, p-value=0.02), T4 (r-value=0.12, p-value=0.02), TSH level (r-value=0.31, p-value=0.01) in case group [Table/Fig-3].

	Cases			Controls		
Parameters	T3	T4	TSH	T3	T4	TSH
r-value	0.12	0.12	0.31	0.14	0.02	0.34
p-value	0.02	0.02	0.01	0.03	0.02	0.01

[Table/Fig-3]: Correlation of cortisol with T3, T4 and TSH among cases and controls.
Karl Pearson's correlation test; level of significant p-value <0.05

DISCUSSION

Hypothyroidism is caused by inadequate function of the thyroid gland itself (primary hypothyroidism), inadequate stimulation by TSH from the pituitary gland (secondary hypothyroidism), or inadequate release of thyrotropin-releasing hormone from the brain's hypothalamus (tertiary hypothyroidism) [12]. The present study consisted of 120 participants with 60 controls and 60 patients of hypothyroidism. If hypothyroidism patients present with high serum cortisol the TSH, T3 and T4 can serve as a novel marker for the prediction of the risk of diseases. In present study, the mean serum cortisol level in hypothyroid group was 64.88±16.25 µg/dL, where mean serum cortisol level in controls was 9.55±5.59 µg/mL, showing a statistically significant increase in serum cortisol levels in hypothyroid group as compared to the healthy controls. This is in accordance with the previous similar studies [3-5].

In present study there was hypercortisolemia in hypothyroid patients, this findings is consistent with a study by Iranmanesh A et al., they found significant increase in serum cortisol level in primary hypothyroidism. This change in serum cortisol primarily may be due to decreased metabolic clearance of cortisol and a presumptive decrease in the negative feedback effect of cortisol on the hypothalamo-pituitary axis [6]. In present study, there was an elevation of cortisol level in hypothyroid patients and positive correlation between TSH and cortisol, which is in the line with the findings of previous similar study by Ali SS and Dhelal AKJ [8]. An explanation for the above mentioned changes in cortisol levels is that, overt hypothyroidism causes elevation of cortisol by reducing peripheral disposal and blunting feedback of cortisol on the hypothalamic-pituitary-adrenal axis, another explanation for positive relationship between TSH and cortisol as elucidated in a previous study is that hypothyroidism is associated with subtle metabolic stress which could be imposing an effect on the Adrenocorticotropic hormone-adrenal axis leading to an increase in release and production of stress hormone (cortisol) [4,5].

In present study, there was a significant positive correlation between serum cortisol level and T3, T4 and TSH level in healthy controls also. Similarly, Kimberly NW et al., conducted a cross-sectional study on 54 healthy adults and found a positive relationship between TSH and cortisol that is maintained down to a TSH level of 2.5 mIU/L (but not below) in apparently healthy young individuals [9] also, in a study. Walter KN et al., found a positive relationship between TSH and cortisol in apparently healthy young individuals [13]. This relationship may be physiological rather than pathological and the explanation for this positive relationship found between TSH and cortisol in healthy controls was that thyroid hormone production is associated with subtle metabolic stress which could be imposing an effect on the adrenocorticotropic hormone-adrenal axis leading to an increase in release and production of stress hormone cortisol [8].

In present study, serum cortisol level was elevated in the hypothyroidism as compared to the control group. Also, the level of TSH, T3 and T4 levels were in correlation with increased serum cortisol levels. So, screening of TSH and must be done in patients with hypothyroidism to decrease the incidence of metabolism, mental functions, energy level, and bowel movements.

Limitation(s)

The main limitation was that thyroid function tests only measure the total or free T4 and/or T3 and TSH serum concentrations in peripheral blood. They do not measure the effect of the hormone on target organ. Also, serum cortisol can be increased in stress condition, which was not measured in present study.

CONCLUSION(S)

Based on the findings of present study, it can be clearly stated that, serum levels of cortisol significantly increased in hypothyroidism patients as compared to normal healthy controls. Also, there was a significant positive correlation between serum cortisol and thyroid profile. Keeping in consideration with the study, it can be concluded that, subclinical hypothyroidism with early diagnosis and treatment may prevent the onset of overt hypothyroidism. These results, along with similar reports suggest that, the study of these parameters in hypothyroidism may help in better understanding the aetiopathogenesis of hypothyroidism and may act as additional markers of this condition. All the patients suffering from hypothyroidism can be investigated for serum cortisol, as additional markers.

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