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Article

Dysregulation of Thyroid Hormone Equilibrium in Hyperthyroidism: A Prospective Case Control Study of T3, T4 and TSH Dynamics

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Abstract: Hyperthyroidism is a neuroendocrine disorder with dysfunction of the hypothalamic–pituitary–thyroid axis and systemic metabolic acceleration. Although clinically relevant, regional biochemical profiling of thyroid hormone changes has not been well characterized. Objective: To characterize changes in serum concentrations of triiodothyronine (T3), thyroxin (T4), and thyroid-stimulating hormone (TSH) in hyperthyroid patients, and to assess its distribution according to age and sex. In a prospective case–control study from February 2022 to March 2023, a total of 100 subjects (50 hyperthyroid patients (15 men and 35 women) and 50 control sexactly matched forage and within therangeo f25–65years) were comprised. Serum T3, T4 and TSH levels were determined respectively by fluorescence immunoassay (iCHROMA™system). Statistical comparisons were made by one-way ANOVA ($P < 0.05$; $P < 0.01$). The hyperthyroid patients had high endocrine dysfunction with T3 and T4 levels significantly increased and TSH level significantly decreased in the hyperthyroid patients compared to controls ($P \leq 0.01$). Peak prevalence was found in the 40–60-year age group, prompting stratified analysis and indicating age-related susceptibility. In addition, there was also a strong female predominance (64%) underscoring the contribution of biological sex in disease presentation. Such a massive hormonal disturbance indicates a strong inverse relation between an excess of thyroid hormone and the negative modulation of the pituitary by TSH. Here, we describe an identifiable biochemical pattern of hyperthyroidism characterized by increased peripheral thyroid hormone action and feedback suppression of TSH. The results offer regional specific support for demographic determinants of disease distribution and demonstrate the clinical benefit of combined hormone profiling for detection of the disease at an early stage and the possibility of ongoing disease monitoring. These findings help improve diagnostic practices and may also guide endocrine evaluation in specific at-risk groups.

Keywords: Thyroid, Endocrine, Hormones, Pituitary Regulation

Introduction

The thyroid gland is a unique endocrine organ located in the front part of the neck, below the larynx and surrounding the trachea, with the two lateral lobes connected by a central isthmus [1]. The thyroid consists of follicular and parafollicular cells, and mediates metabolic homeostasis by the production and secretion of thyroid hormones that governs a myriad of physiological processes including energy metabolism, growth and cellular differentiation.

Iodine is essential for the production of thyroid hormone, and it is actively transported from the bloodstream into thyroid follicular cells, where it is used for hormone synthesis. Thyroxine (T4) and triiodothyronine (T3) are the main hormones synthesized by the gland, with T4 comprising most of the hormone released into the circulation, while T3 is the metabolically active form [2]. While T4 is secreted in greater amounts, it is converted to T3, but has a much greater metabolic activity at the cellular level [3].

Chronic hyperthyroidism is a clinical syndrome resulting from the overproduction and release of thyroid hormones, and their consequent hypermetabolic effect on multiple organ systems [4]. It is due to dysregulation of the hypothalamic–pituitary–thyroid (HPT) axis causing increased circulating concentrations of T3 and T4 with suppressed levels of thyroid-stimulating hormone (TSH). An imbalance in this tightly controlled feedback loop lies at the heart of disease pathology.

Graves' disease (diffuse toxic goiter) - the most frequent cause of hyperthyroidism in the Western world (an autoimmune disease with production of stimulatory antibodies against the TSH receptor) [5]. Such autoantibodies as thyroid-stimulating immunoglobulins (TSI), thyroid peroxidase (TPO) antibodies and TSH receptor antibodies cause permanent stimulation of the thyroid gland without the usual regulating control of the pituitary gland [6].

Graves’ disease There are significant hereditary factors involved in Graves’ disease, also the sex distribution is highly skewed for females, occurring five times more frequently in females than in males. Environmental and lifestyle factors such as stress, smoking, radiation, some medications, and viral infections are theorized to be involved in triggering the condition in genetically predisposed individuals [5].

Well, although we have undoubtedly made strides to understanding thyroid physiology and autoimmune mechanisms some are still needed, namely, the more precise biochemical characterization of thyroid hormone changes in hyperthyroid patients throughout different demographic groups continues to be warranted. The current study was conducted to determine the serum concentration of T3, T4, and TSH in patients with hyperthyroidism and to correlate their levels with age and gender. Thyroid dysfunction can occur due to different reasons, including iodine excess/deficiency, autoimmune diseases, and inflammation. The major causes of autoimmune-mediated thyroid diseases are immune dysregulation, either hypersecretion as in Graves’ disease or hyposecretion as in Hashimoto's thyroiditis [7]. Thyroid pathophysiology: The fold between genetic susceptibility and environmental triggers elucidated in these conditions.

Hyperthyroidism is characterized by a marked gender difference from an epidemiological perspective, with approximately 5 times as many women as men being affected. Current estimates suggest a global prevalence of ~1.3% in the general population,4 increasing to 4–5% among women of older age5 [8]. Less-obviously (or less directly) referable to risk, smoking has also been a hit — among many others! Graves disease is the most common cause in younger populations, while toxic nodular goiter is the most prevalent cause in older populations [9].

The anatomy of the thyroid gland is a highly vascularised gland located in the anterior neck region, between the 5th cervical and 1st thoracic vertebrae. The thyroid gland is located deep to the infrahyoid muscles and has two lobes connected by a narrow isthmus. In adults, the gland weighs about 15–20 g with dimensions depending on age, sex, and physiological condition [10], [11]. The unique follicular architecture and its rich associated vascular supply are vital for optimal hormone production and delivery systemically.

Thyroid hormone secretion is regulated by the hypothalamic–pituitary–thyroid (HPT) axis, a tightly controlled negative feedback system. Thyrotropin (T3) hormone is secreted from a gland known as the pituitary, in response to hypothalamic stimulation of thyrotropin-releasing hormone (TRH) [12]. High circulating concentrations of T3 and T4 inhibit the hypothalamus and pituitary, creating hormonal

homeostasis. Disruption of this regulatory axis —either as part of autoimmune stimulation, causing Graves-disease hyperthyroidism, or as part of autonomous production by a thyroid nodule or TSH-secreting pituitary tumor—leads to overproduction and clinical hyperthyroidism [13].

Thyroid hormone synthesis is one of the most complex biological processes which is a dependent upon iodine and involves, at the molecular level, iodide uptake, oxidation and organification in thyroid follicular cells. The MIT and DIT which incorporate the iodine into the tyrosine residues of thyroglobulin, and these will subsequently couple to form T3 and T4 [14]. Although most of the hormone in circulation is T4, peripheral deiodination converts T4 to the more biologically active T3. Most importantly, only unbound (free) levels of these hormones is biologically active, and any change in protein binding, or hormone production can trigger thyrotoxicosis [12].

Graves' disease, thyroiditis, excessive exogenous thyroid hormone intake, and autonomous thyroid nodules are some of the causes of hyperthyroidism. More rarely, hormone-secreting tumors, as well as iodine-induced hyperthyroidism, after an iodinated contrast agent used for imaging studies are also responsible [15]. This heterogeneity of these underlying causes reinforces the requirement for a detailed biochemical and clinical assessment.

There are multiple risk factors important in the development of hyperthyroidism, which include being female, older age, family history, and thyroid autoimmune disease. More variables like gestation, viral pathogens and dietary iodine fluctuations may also influence risk [16], [17]. Variations due to ethnicity and diet (especially iodine-rich diets) have been proposed to account for the distribution of the disease.

From a clinical point of view, hyperthyroidism occurs as a hypermetabolic state with weight loss in the face of increased appetite, heat intolerance, palpitations, nervousness, and fatigue. During the physical examination, the patient may also be found to have tachycardia, warm and moist skin, fine hair, lid lag, and possibly goiter and gynecomastia [12], [18]. These manifestations represent the multimodal systemic burden of excess thyroid hormone on various organ systems.

Thyroid hormones are essential for normal growth, development and metabolic homeostasis. Together, T3 and T4 affect skeletal maturation, rate of energy expenditure, and cellular differentiation in many tissues [19]. Indeed, whilst everyone knows that a lack of thyroid hormone results in hypothyroidism and consequently, developmental defects, too much thyroid hormone generates a clinical picture of hyperthyroidism defined by an increased metabolic rate and global physiological disturbances [20], [21].

Since there is not only high clinical burden of hyperthyroidism which global epidemiology and since thyroid hormones are central in maintaining physiological homeostasis, clear and meticulous characterization of their alterations are warranted. Hence, the present study aimed to evaluate the biochemical profile of T3, T4, and TSH and the association of these parameters with demographic variables among hyperthyroid patients.

Materials and Methods

Study design and participants

Setting: Out-of-hospital diagnostic laboratories from February 10, 2022 to March 1, 2023 Design: A prospective case–control study One hundred participants consisting of 50 patients with hyperthyroidism and 50 apparently healthy subjects were included. Participants were aged between 25 and 65. Hyperthyroidism was diagnosed clinically, and subsequently diagnosed by lab determination of thyroid hormone levels by qualified clinicians. Patients were assigned to patient and control groups for comparative evaluation.

Inclusion and exclusion criteria

Patients included those who presented with clinical features consistent with hyperthyroidism (palpitations, heat intolerance, nervousness, irritability, weight loss, tremors, goiter) with biochemical confirmation [22]. The control group included healthy age-matched individuals, who had no clinical signs of thyroid disorders and no history of endocrine diseases or use of thyroid medications, and were recruited from relatives and volunteers from local community for the study. We excluded those with

known chronic systemic diseases, patients already receiving treatment for thyroid dysfunctions, and conditions which would interfere with assessment of thyroid function.

Clinical assessment

All participants underwent a structured clinical evaluation, which consisted of detailed medical history and physical examination. Demographic information and pertinent clinical information—age, sex, history, and associated symptoms—were systematically abstracted [23], [24].

Sample collection and preparation

Prior to treatment activity, 5 mL of venous blood was drawn under sterile conditions with the consent of every participant. After cleaning the skin with 70% ethanol, blood was collected using sterile 21-gauge syringes. Samples were collected in specific tubes with serum separator gel and centrifuged. Specimens were assigned an individual code for tracking purposes to reduce analytical error [25], [26].

Biochemical analysis

According to the manufacturer (Boditech, South Korea), serum levels of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were measured by fluorescence immunoassay (FIA) on the iCHROMA™ system.

T3 and T4 Measurement: The assay was quantitated via competitive immunodetection, where the concentration of analyte is inversely correlated with the fluorescence signal intensity.

TSH Measurement: TSH levels were measured in a sandwich immunodetection assay, using the intensity of fluorescence as a linear indicator of the concentration of TSH present in the sample.

All assays were carried out in a standard laboratory under the same conditions to be analytical accurate and reproducible.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) v.25 was used in data analysis. Results were presented as mean ± SD. One-way analysis of variance (ANOVA) was used to compare between groups. Statistical significance was assigned at $P < 0.05$ and highly significant at $P < 0.01$ (Daniel, 1999).

Results

A total of 100 participants were included in this study, comprising 50 patients diagnosed with hyperthyroidism and 50 healthy controls.

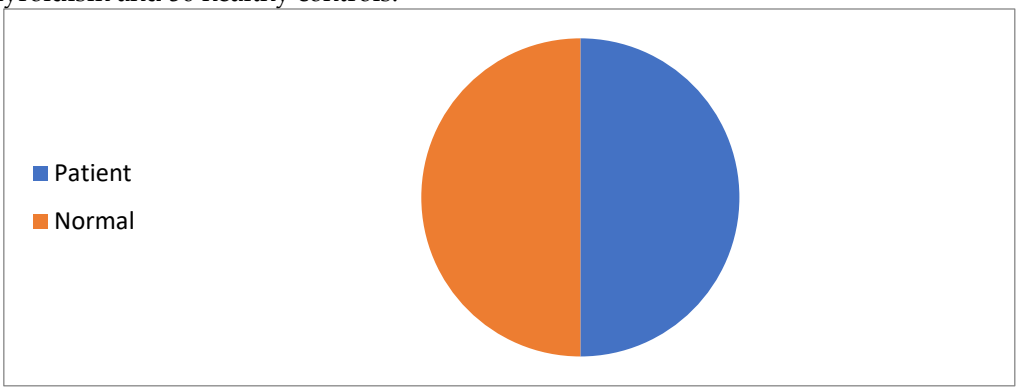

Figure 1. The number of patients group with hyperthyroidism and control group without any signs of hyperthyroidism.

Age Distribution

The distribution of participants according to age is presented in Table 1. The highest proportion of hyperthyroidism cases was observed in the 40–60-year age group (40%), followed by 20–30 years (32%) and 30–40 years (28%). A statistically significant difference was observed between patient and control groups ($P = 0.001$).

Table 1. Age distribution of patients and controls

Age group (years)	Patients (n=50)	Controls (n=50)
20–30	16 (32%)	13 (26%)
30–40	14 (28%)	15 (30%)
40–60	20 (40%)	22 (44%)

P = 0.001 (**highly significant)

Gender Distribution

As shown in Table 2, hyperthyroidism was more prevalent in females (64%) compared to males (36%).

Table 2. Gender distribution in hyperthyroid patients

Gender	Number (n=50)	Percentage (%)
Female	32	64%
Male	18	36%

Biochemical Parameters

Serum Triiodothyronine (T3)

Serum T3 levels were significantly higher in hyperthyroid patients compared to controls (P = 0.001). The mean difference was 0.31 nmol/L (95% CI: 0.09 to 0.53), indicating a moderate effect size (Cohen's d = 0.56).

Table 3. Comparison of T3 level in patients with hyperthyroidism and control group

Parameter	Group	Mean ± SD (nmol/L)	Mean Difference	95% CI	Effect Size (d)	P-value
T3	**Patients**	0.96 ± 0.75	0.31	0.09 to 0.53	0.56 (moderate)	0.001**
	Control	0.65 ± 0.21				

Serum Thyroxine (T4)

T4 levels were markedly elevated in hyperthyroid patients (P = 0.001). The mean difference was 13.8 nmol/L (95% CI: 1.93 to 25.67), with a very large effect size (Cohen's d = 4.57), indicating a strong separation between groups.

Table 4. Comparison of T4 level in patients with hyperthyroidism and control group

Parameter	Group	Mean ± SD (nmol/L)	Mean Difference	95% CI	Effect Size (d)	P-value
T4	**Patients**	18.9 ± 42.76	13.8	1.93 to 25.67	4.57 (very large)	0.001**
	Control	5.1 ± 2.08				

Serum Thyroid-Stimulating Hormone (TSH)

TSH levels were lower in patients compared to controls; however, the difference showed high variability. The mean difference was −2.5 μIU/mL (95% CI: −9.44 to 4.44), with a small effect size (Cohen's d = −0.14).

Table 5. Comparison of TSH level in patients with hyperthyroidism and control group

Parameter	Group	Mean ± SD (μIU/mL)	Mean Difference	95% CI	Effect Size (d)	P-value
TSH	**Patients**	16 ± 18.5	−2.5	−9.44 to 4.44	−0.14 (small)	0.001**
	Control	18.5 ± 16.82				

Discussion

The current study shows a biochemical profile associated with hyperthyroidism, showing increased serum levels of T3 and T4 hormones with decreased circulating concentrations of thyroid-stimulating hormone (TSH). These results are consistent with the well known pathophysiology of hyperthyroidism caused by dysregulation of the hypothalamic–pituitary–thyroid (HPT) axis leading to the disruption of normal hormonal feedback loops [27], [28]. The addition of an effect size analysis augments the understanding of the magnitude and clinical significance of these differences at beyond just statistical significance. The between-group difference in serum T3 levels had a moderate effect size (Cohen's d = 0.56) and provides a biologically relevant difference between patients and controls. Even slight increases in T3 level may play an important role in the hypermetabolic manifestations of hyperthyroidism as T3 is considered the most biologically active thyroid hormone [3].

Serum T4 levels, on the other hand, showed a very large effect size (Cohen's d = 4.57), indicating high discriminatory power to distinguish between hyperthyroid patients and healthy individuals. This is in line with previous studies that have consistently demonstrated high T4 levels as a feature of hyperthyroidism [29]. The significant variation in T4 values, on the other hand, could be due to the variability in disease duration, severity, or physiology, and T4 should still be interpreted in the context of other hormones.

TSH was also statistically significant but with a small effect size (Cohen's d = −0.14) and a confidence interval crossing zero, indicating a lack of practical significance. The differences may be attributed to the degree of pituitary responsiveness or disease stage in each patient. As also observed for TSH (also an extremely sensitive parameter), a single measurement of fT4 or fT2 may vary in relation to feedback mechanisms and individual endocrine vascular dynamics [28].

This demographic finding aligns with previous literature. The higher female predominance for hyperthyroidism (64%) is in accordance with previous reports where this gender diversity is attributed to an increased tendency for autoimmune disorders in women and the role of hormonal factors [30], [31]. Also, the higher incidence in the 40-60-year-old age group corresponds to the age detected demographic fluctuations in thyroid function and regulation [32], [33].

Finally, the use of effect size measures increases the interpretability of study results since they provide an estimate of the strength of associations (in addition to P-values). Although statistical significance supports differences, effect size gives an objective perspective on the magnitude of the difference, which is vital for clinical significance and translational importance in endocrine diseases. The study therefore concludes that the combined assessment of hormones (T3, T4 and TSH) is essential for the diagnosis and evaluation of hyperthyroidism. This enhances the combined data, adding a layer of sensitivity to the analysis and presents additional scope of the underlying hormonal changes within this condition.

Conclusion

We offer a detailed biochemical and demographic assessment of hyperthyroidism with much more abnormality in thyroid hormone levels. Regardless, hyperthyroid patients showed increased serum concentrations of triiodothyronine (T3) and thyroxine (T4), with reduced thyroid-stimulating hormone (TSH), in accordance with HPT axis dysregulation. Notably, effect size analysis showed that T4 had the highest discriminatory power between hyperthyroid individuals and controls, followed by T3, and TSH has a small to negligible effect size even though it was statistically significant. The results emphasize the importance of interpreting effect size both in addition to and instead of p-value to advance the clinical relevance. In terms of demographics, hyperthyroidism predominated in the female sex and 40–60 years' age group, again consistent with hormonal and age-related factors contributing to disease susceptibility. In conclusion, this study highlights the need for integrated hormonal profiling (T3, T4, and TSH) to increase diagnostic accuracy and facilitate clinical evaluation of hyperthyroidism. These findings provide region-specific evidence for the role of biochemical assessment for endocrine disorders.

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