

Differentiating Graves' Disease from Subacute Thyroiditis Using Ratio of Serum Free Triiodothyronine to Free Thyroxine

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Disclaimers

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ABSTRACT

Background: Graves' disease and subacute thyroiditis are common causes of hyperthyroidism that share overlapping clinical features, making differentiation challenging. Accurate diagnosis is crucial for appropriate management to prevent adverse outcomes.

Objective: To differentiate Graves' disease from subacute thyroiditis using the ratio of serum free triiodothyronine (FT3) to free thyroxine (FT4).

Methods: This prospective observational study was conducted at the Department of Diabetes, Endocrinology, and Metabolic Diseases, Hayatabad Medical Complex, Peshawar, from November 2023 to May 2024. A total of 248 patients diagnosed with Graves' disease (n = 158) or subacute thyroiditis (n = 90) were included. Clinical, biochemical, and imaging data were collected, and the FT3/FT4 ratio was calculated. Data were analyzed using SPSS v25, with independent samples t-tests and ROC curve analysis performed.

Results: The mean FT3/FT4 ratio was significantly higher in Graves' disease (4.5 ± 0.8) compared to subacute thyroiditis (2.1 ± 0.5), $p = 0.001$. An FT3/FT4 ratio >3.0 had a sensitivity of 87% and specificity of 85%, with an AUC of 0.92.

Conclusion: The FT3/FT4 ratio is a reliable diagnostic tool for differentiating Graves' disease from subacute thyroiditis, offering high sensitivity and specificity.

INTRODUCTION

Thyroid disorders, including Graves' disease and subacute thyroiditis, are common endocrine conditions that can lead to significant clinical consequences if not accurately diagnosed and managed. Both disorders often present with hyperthyroidism, making differentiation between them challenging due to overlapping clinical manifestations and laboratory findings (1).

Graves' disease is an autoimmune disorder characterized by the presence of thyroid-stimulating immunoglobulins that provoke excessive production of thyroid hormones, leading to symptoms of hyperthyroidism. Conversely, subacute thyroiditis is an inflammatory condition of the thyroid gland, often following a viral infection, which results in the release of preformed thyroid hormones, thus also presenting as hyperthyroidism in its early stages (2). This clinical overlap necessitates a precise diagnostic approach to effectively distinguish between these two conditions, as they require different management strategies (3).

Traditionally, the diagnosis of Graves' disease and subacute thyroiditis relies on a combination of clinical assessment, biochemical markers, and imaging studies.

The radioiodine uptake test (RAIU) is frequently employed to differentiate the two conditions, with Graves' disease typically showing increased uptake and subacute thyroiditis demonstrating reduced uptake due to the destruction of thyroid tissue (4).

However, RAIU may not be universally available and has limitations, particularly in certain patient populations such as pregnant or breastfeeding women, and in cases where

the results are inconclusive (5). Recent studies have suggested that the ratio of serum free triiodothyronine (FT3) to free thyroxine (FT4) could serve as a valuable diagnostic tool in distinguishing these conditions. This ratio reflects the relative production and release patterns of these hormones, which differ significantly between Graves' disease and subacute thyroiditis (6).

In Graves' disease, a higher FT3/FT4 ratio is observed due to increased turnover and conversion driven by thyroid-stimulating immunoglobulins, whereas subacute thyroiditis typically presents with a normal or slightly elevated ratio because of the non-stimulatory release of stored hormones (7).

The FT3/FT4 ratio has emerged as a promising diagnostic marker due to its ease of measurement and potential applicability in settings where RAIU and other advanced diagnostic tools may be less accessible. Despite its potential, the use of this ratio in clinical practice has been limited, partly because previous studies involved small sample sizes and lacked robust validation (8). The current study aims to address this gap by evaluating the diagnostic utility of the FT3/FT4 ratio in a larger cohort, thereby providing more definitive evidence for its use in routine clinical settings.

By analyzing the FT3/FT4 ratio alongside traditional diagnostic markers such as thyroid-stimulating immunoglobulin levels and RAIU, this study seeks to establish a more practical and accessible approach for differentiating Graves' disease from subacute thyroiditis, thereby facilitating timely and appropriate therapeutic interventions for patients with hyperthyroidism (9).

MATERIAL AND METHODS

This prospective observational study was conducted at the Department of Diabetes, Endocrinology, and Metabolic Diseases, Hayatabad Medical Complex, Peshawar, from November 2023 to May 2024. The study included 248 patients who were newly diagnosed with hyperthyroidism and met the inclusion criteria, which required patients to be over 18 years of age with confirmed hyperthyroidism based on suppressed serum thyroid-stimulating hormone (TSH) levels and elevated serum free triiodothyronine (FT3) and/or free thyroxine (FT4) levels. Patients were required to have complete clinical and laboratory data, including thyroid function tests, thyroid autoantibodies, and thyroid imaging, and a definitive diagnosis of either Graves' disease or subacute thyroiditis based on clinical presentation and laboratory findings. Patients with a history of thyroid surgery, radioactive iodine treatment, previous antithyroid drug therapy, or other causes of hyperthyroidism, such as toxic multinodular goiter or toxic adenoma, were excluded, as were those with incomplete clinical or laboratory data.

Data were collected retrospectively from medical records and included demographic information such as age and gender, the presence and duration of symptoms, and details of clinical assessments including the presence of hyperthyroid symptoms, neck pain, tenderness over the thyroid, and accompanying constitutional symptoms. Laboratory data included measurements of serum TSH, FT3, and FT4 levels using immunoassay tests, and thyroid-stimulating immunoglobulin (TRAb) levels were assessed to aid in the diagnosis of Graves' disease. For patients diagnosed with Graves' disease, a positive TRAb and increased RAIU were expected, while subacute thyroiditis was characterized by low or normal TRAb levels and decreased RAIU. The FT3/FT4 ratio was calculated by dividing each patient's serum FT3 level by their FT4 level, following the methods established by Li et al., which have been suggested as valuable for differentiating between Graves' disease and subacute thyroiditis (1).

Ethical approval for the study was obtained from the Institutional Review Board of Hayatabad Medical Complex, Peshawar, and the study adhered to the principles outlined in the Declaration of Helsinki. All patient data were anonymized to maintain confidentiality, and the

retrospective nature of the study design waived the need for informed consent. Data analysis was performed using SPSS version 25. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables, such as age and hormone levels, were expressed as mean \pm standard deviation, and categorical variables, such as gender distribution and symptom prevalence, were presented as frequencies and percentages. Independent samples t-tests were employed to compare the mean FT3/FT4 ratios between patients with Graves' disease and those with subacute thyroiditis, with statistical significance set at a p-value of less than 0.05. The diagnostic performance of the FT3/FT4 ratio was evaluated using receiver operating characteristic (ROC) curve analysis to calculate sensitivity, specificity, and the area under the curve (AUC) to assess the ratio's ability to differentiate between the two conditions (2). The study aimed to validate the FT3/FT4 ratio as a practical and reliable tool for differentiating Graves' disease from subacute thyroiditis, potentially providing a more accessible diagnostic alternative in clinical settings where advanced diagnostic tests such as RAIU are not readily available. By establishing clear diagnostic criteria and robust statistical analysis, this study sought to contribute valuable evidence to the clinical management of hyperthyroid patients, ensuring appropriate and timely treatment interventions based on accurate diagnosis (3).

RESULTS

A total of 248 patients were included in the study, comprising 158 diagnosed with Graves' disease and 90 with subacute thyroiditis. The mean age of patients with Graves' disease was 42.5 ± 10.2 years, while those with subacute thyroiditis had a mean age of 39.8 ± 11.5 years. The gender distribution indicated a higher prevalence in females across both conditions, with 102 females and 56 males in the Graves' disease group, and 62 females and 28 males in the subacute thyroiditis group. Patients with Graves' disease reported a longer duration of symptoms, averaging 8.2 ± 3.5 weeks, compared to 6.5 ± 4.1 weeks in those with subacute thyroiditis. Thyroid pain was significantly more common in subacute thyroiditis (72%), whereas ophthalmopathy was predominantly observed in Graves' disease (45%).

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	Graves' Disease (n = 158)	Subacute Thyroiditis (n = 90)	Total (n = 248)
Age (years, mean \pm SD)	42.5 \pm 10.2	39.8 \pm 11.5	41.5 \pm 10.8
Gender (Male/Female)	56/102	28/62	84/166
Duration of Symptoms (weeks)	8.2 \pm 3.5	6.5 \pm 4.1	7.6 \pm 3.9
Thyroid Pain (%)	10%	72%	34%
Ophthalmopathy (%)	45%	5%	30%

The diagnostic analysis revealed that the mean FT3/FT4 ratio was significantly higher in patients with Graves' disease (4.5 ± 0.8) compared to those with subacute thyroiditis (2.1 ± 0.5), with a p-value of 0.001, indicating strong statistical significance. An FT3/FT4 ratio greater than 3.0 was observed in 87% of Graves' disease cases, but only in 15% of subacute thyroiditis cases. The diagnostic performance of the

FT3/FT4 ratio demonstrated high sensitivity and specificity, with values of 87% and 85%, respectively, and an area under the curve (AUC) of 0.92.

Further analysis showed that the mean TRAb levels were markedly higher in Graves' disease patients (12.3 ± 5.8). The distribution of FT3/FT4 ratio values further distinguished the two conditions.

Table 2: Diagnostic Performance of FT3/FT4 Ratio

Diagnostic Parameter	Graves' Disease (n = 158)	Subacute Thyroiditis (n = 90)	Total (n = 248)
Mean FT3/FT4 Ratio (\pm SD)	4.5 \pm 0.8	2.1 \pm 0.5	-
FT3/FT4 Ratio > 3.0 (n, %)	137 (87%)	14 (15%)	151 (61%)
Sensitivity (%)	87%	-	-
Specificity (%)	-	85%	-
Area Under the Curve (AUC)	0.92	-	-
Positive Predictive Value (PPV)	90%	-	-
Negative Predictive Value (NPV)	-	82%	-

In Graves' disease patients, 47% had ratios in the 4.0 - 4.9 range, and 23% had a ratio of 5.0 or more compared to those with subacute thyroiditis (1.2 \pm 0.8), with a p-value of 0.001.

Similarly, the mean RAIU was significantly elevated in Graves' disease (45 \pm 12%) compared to subacute thyroiditis (6 \pm 3%), also with a p-value of 0.001.

Table 3: Correlation of FT3/FT4 Ratio with Other Diagnostic Markers

Diagnostic Marker	Graves' Disease (n = 158)	Subacute Thyroiditis (n = 90)	p-Value
TRAb Levels (mean \pm SD)	12.3 \pm 5.8	1.2 \pm 0.8	0.001
RAIU (%)	45 \pm 12	6 \pm 3	0.001
FT3/FT4 Ratio (mean \pm SD)	4.5 \pm 0.8	2.1 \pm 0.5	0.001

Conversely, subacute thyroiditis patients predominantly had lower FT3/FT4 ratios, with 50% falling below 2.0 and 34% in the 2.0 - 2.9 range. Very few Graves' disease patients

had ratios below 2.0 (1%), while none of the subacute thyroiditis patients had a ratio of 5.0 or higher.

Table 4: Distribution of FT3/FT4 Ratio Values by Diagnosis

FT3/FT4 Ratio Range	Graves' Disease (n = 158)	Subacute Thyroiditis (n = 90)	Total (n = 248)
< 2.0	2 (1%)	45 (50%)	47 (19%)
2.0 - 2.9	5 (3%)	31 (34%)	36 (15%)
3.0 - 3.9	40 (25%)	10 (11%)	50 (20%)
4.0 - 4.9	75 (47%)	4 (4%)	79 (32%)
\geq 5.0	36 (23%)	0 (0%)	36 (14%)

The results underscore the FT3/FT4 ratio as a highly effective diagnostic tool for distinguishing Graves' disease from subacute thyroiditis, with clear demarcations in ratio values that align with the respective pathophysiological mechanisms of each condition. This finding supports the integration of the FT3/FT4 ratio into routine clinical practice to enhance diagnostic accuracy and guide appropriate treatment strategies for hyperthyroid patients.

DISCUSSION

The differentiation between Graves' disease and subacute thyroiditis remains a critical challenge in clinical endocrinology due to the overlapping clinical and biochemical presentations of hyperthyroidism in these conditions. This study demonstrated that the FT3/FT4 ratio is a highly sensitive and specific diagnostic tool for distinguishing between Graves' disease and subacute thyroiditis, with a mean ratio significantly higher in Graves' disease patients compared to those with subacute thyroiditis. This finding aligns with previous research, which has also highlighted the potential of the FT3/FT4 ratio as a practical and accessible marker for differentiating these two conditions (1). The higher FT3/FT4 ratio in Graves' disease can be attributed to the increased thyroid hormone turnover and thyrotropin-stimulated synthesis driven by thyroid-stimulating immunoglobulins, whereas subacute thyroiditis, being a destructive thyroiditis, leads to a more

uniform release of stored hormones, resulting in a lower or near-normal ratio (2).

The current study's diagnostic performance metrics, including a sensitivity of 87% and specificity of 85% for the FT3/FT4 ratio, provided robust support for its clinical utility, especially in settings where more complex and resource-intensive diagnostic modalities such as RAIU may not be feasible. Previous studies have reported similar findings, reinforcing the utility of the FT3/FT4 ratio in clinical practice, particularly in distinguishing cases of thyrotoxicosis where RAIU is contraindicated or unavailable (3). The study further substantiated these findings by correlating the FT3/FT4 ratio with traditional diagnostic markers such as TRAb levels and RAIU, which were significantly different between the two conditions, thereby confirming the ratio's diagnostic reliability (4).

Despite its strengths, this study had some limitations that need consideration. One of the key limitations was its observational design, which inherently restricts the ability to establish causality between the FT3/FT4 ratio and the differentiation of Graves' disease from subacute thyroiditis. Additionally, the study relied on retrospective data collection, which may have introduced selection bias and limited control over confounding variables. The study population was also restricted to a single center, which may affect the generalizability of the findings to broader or more diverse populations. Furthermore, although the FT3/FT4

ratio proved effective, it remains essential to consider that it may not entirely replace other diagnostic approaches but rather serve as a complementary tool, particularly in clinical scenarios where rapid and less invasive methods are preferred (5).

The findings of this study suggest that integrating the FT3/FT4 ratio into routine diagnostic workflows could significantly enhance the accuracy of differentiating Graves' disease from subacute thyroiditis, potentially reducing diagnostic delays and improving patient outcomes through more tailored therapeutic interventions. Given its simplicity and cost-effectiveness, the FT3/FT4 ratio could be particularly valuable in resource-limited settings where access to advanced diagnostic tests is restricted. However, further research is recommended to validate these results in larger, multicenter cohorts and to explore the potential of integrating the FT3/FT4 ratio with other novel biomarkers for a more comprehensive diagnostic approach (6). Additionally, future studies could investigate the role of the FT3/FT4 ratio in monitoring disease progression and response to treatment, thereby expanding its clinical utility beyond initial diagnosis.

In conclusion, the study confirmed the FT3/FT4 ratio as a valuable diagnostic tool with high sensitivity and specificity for differentiating Graves' disease from subacute thyroiditis. By incorporating this ratio into standard diagnostic practices, clinicians can achieve a more accurate and timely diagnosis, facilitating appropriate management strategies for patients with hyperthyroidism. The study's findings underscore the need for continued exploration of simple yet effective diagnostic tools in endocrinology to optimize patient care and resource utilization (7).

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