Oxidative Stress Index as a Biomarker of Metabolic Imbalance in Thyroid Disorders

Bushra[1], Pothu Ushakiran[2], Jigar Haria[3]

[1]Research Scholar, Department of Biochemistry, Teerthanker Mahaveer University, Moradabad (U.P.), India. Email Id- bushraahmed4444@gmail.com
[2]Professor, Department of Biochemistry, Teerthanker Mahaveer University, Moradabad (U.P.), India. Email Id- usha_123kiran@yahoo.com
[3]Professor, Department of Medicine, Teerthanker Mahaveer University, Moradabad (U.P.), India. Email Id- drjigar.medical@tmu.ac.in

ABSTRACT

Background: Thyroid dysfunction is associated with profound metabolic disturbances, including altered lipid metabolism and redox imbalance. Oxidative stress, resulting from excess reactive oxygen species and impaired antioxidant defenses, may exacerbate lipid abnormalities and increase cardiometabolic risk.
Objective: To evaluate lipid profile alterations in relation to oxidative stress markers—total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI)—among patients with hypothyroidism, hyperthyroidism, and euthyroid controls.
Methods: A cross-sectional study was conducted on 285 participants (161 hypothyroid, 76 hyperthyroid, 48 euthyroid). Serum thyroid hormones, lipid profile, and oxidative stress parameters (TOS, TAS, OSI) were measured using standard biochemical methods. Group comparisons were performed using ANOVA with post hoc tests. Correlations between lipid parameters and oxidative stress indices were assessed, and regression analysis identified predictors of metabolic imbalance.
Results: Both hypothyroid and hyperthyroid groups exhibited significantly elevated TOS and OSI with reduced TAS compared to euthyroid controls ($p < 0.001$). Hypothyroid patients showed higher total cholesterol, LDL-C, and triglycerides, while hyperthyroid patients demonstrated reduced HDL-C and elevated VLDL-C. Correlation analysis revealed that OSI positively associated with atherogenic lipid fractions (LDL-C, TG) and negatively with HDL-C. Regression analysis identified TOS as a positive and TAS as a negative predictor of OSI, confirming that oxidative stress and dyslipidemia jointly contribute to metabolic imbalance in thyroid dysfunction.
Conclusion: Thyroid disorders are characterized by both lipid abnormalities and oxidative stress imbalance, with OSI emerging as a robust biomarker of metabolic disturbance. Integration of oxidative stress markers with lipid profiling may improve risk stratification and management of patients with thyroid dysfunction.

Keywords: Thyroid dysfunction, oxidative stress index, lipid profile, hypothyroidism, hyperthyroidism, metabolic imbalance

INTRODUCTION

Thyroid hormones are critical regulators of growth, differentiation, and metabolic homeostasis. By modulating mitochondrial respiration, lipid mobilization, and carbohydrate utilization, they exert wide-ranging effects on energy balance and cellular function [1]. Disturbances in thyroid function, including hypothyroidism and hyperthyroidism, lead to profound metabolic derangements. Hypothyroidism is characterized by impaired lipid clearance, dyslipidemia, and reduced basal metabolic rate, while hyperthyroidism is associated with excessive catabolism, increased mitochondrial oxygen consumption, and enhanced free radical generation [2,3]. These alterations highlight the central role of thyroid hormones not only in endocrine regulation but also in oxidative balance.

Oxidative stress (OS) is defined as an imbalance between oxidant production and antioxidant defenses, resulting in molecular damage to lipids, proteins, and nucleic acids [4]. The thyroid gland itself is uniquely predisposed to oxidative stress, since hydrogen peroxide is physiologically generated as a substrate for thyroid hormone synthesis [5]. While controlled ROS production is essential for normal function, uncontrolled ROS accumulation can trigger tissue injury, promote autoimmune responses, and exacerbate metabolic disturbances [6].
A growing body of evidence has demonstrated elevated total oxidant status (TOS) and diminished total antioxidant status (TAS) in patients with thyroid disorders, indicating compromised redox homeostasis [7–9]. The oxidative stress index (OSI), calculated as the ratio of TOS to TAS, provides a comprehensive measure of oxidative stress burden [10]. Unlike single

biomarkers, OSI integrates pro-oxidant and antioxidant capacities, offering a more reliable estimate of net oxidative balance.

Several clinical studies have reported oxidative stress abnormalities across thyroid disease states. In hypothyroidism, elevated TOS and OSI values have been associated with lipid peroxidation and atherogenic risk, suggesting that impaired antioxidant capacity may underlie increased cardiovascular comorbidity [11,12]. Conversely, hyperthyroidism is marked by accelerated mitochondrial activity and ROS overproduction, leading to reduced TAS and elevated OSI [13]. Autoimmune thyroid disorders such as Hashimoto's thyroiditis and Graves' disease also demonstrate significant redox imbalance, supporting the role of oxidative stress in disease pathogenesis [14–16].

Despite these insights, most studies have focused on selected oxidative markers, with limited research assessing TOS, TAS, and OSI together in hypothyroid, hyperthyroid, and euthyroid states within the same cohort. Moreover, the potential of OSI as a biomarker of metabolic imbalance and disease severity in thyroid dysfunction remains underexplored. Identifying such a marker could aid in early detection of oxidative complications, guide therapeutic monitoring, and improve patient stratification.

The present study was therefore designed to investigate oxidative stress status using TOS, TAS, and OSI in patients with hypothyroidism, hyperthyroidism, and euthyroid controls. By comparing these groups, we aimed to elucidate the role of OSI as a composite biomarker of redox imbalance and its potential clinical significance in thyroid disorders.

MATERIAL AND METHODS

Study Design and Population

This was a cross-sectional study conducted in the Department of Biochemistry, [Teerthanker Mahaveer Medical College and Research Centre], between 2022 and 2024. A total of 285 participants were enrolled and classified into three groups based on thyroid function status:

- Hypothyroid group (n = 161): Patients with elevated thyroid stimulating hormone (TSH) and reduced free thyroxine (FT4).
- Hyperthyroid group (n = 76): Patients with suppressed TSH and elevated FT4 and/or free triiodothyronine (FT3).
- Euthyroid group (n = 48): Age- and sex-matched individuals with normal thyroid function tests, serving as controls.

Inclusion criteria: Adults aged 20–65 years, clinically diagnosed with primary hypothyroidism or hyperthyroidism, or euthyroid individuals confirmed by laboratory results.

Exclusion criteria: Subjects with diabetes mellitus, chronic liver or kidney disease, cardiovascular disorders, malignancy, pregnancy, acute infection, smoking, alcohol use, or those on antioxidant, anti-inflammatory, or lipid-lowering medications were excluded to minimize confounding effects.

Ethical Approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of [Teerthanker Mahaveer Medical College and Research Centre]. Written informed consent was obtained from all participants before inclusion.

Sample Collection

- Blood samples: After 10–12 hours of overnight fasting, 5 mL of venous blood was collected under aseptic precautions.
- Processing: Samples were centrifuged at 3000 rpm for 10 minutes, and serum was separated and stored at −80 °C until analysis.

Laboratory Analysis

Thyroid Function Tests: Serum TSH, FT3, and FT4 were measured using a chemiluminescence immunoassay on an automated analyzer (e.g., Roche Cobas e411).

Oxidative Stress Parameters

- Total Oxidant Status (TOS): Measured by the automated colorimetric method of Erel [17]. In this assay, oxidants in serum oxidize ferrous to ferric ions, which form a colored complex with xylenol orange. Results expressed as μmol H_2O_2 equivalent/L.
- Total Antioxidant Status (TAS): Determined using Erel's colorimetric method [18], which quantifies antioxidant suppression of ABTS radical cation oxidation. Results expressed as mmol Trolox equivalent/L.
- Oxidative Stress Index (OSI): Calculated as the ratio of TOS to TAS according to the formula:OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/L)/TAS (μmol Trolox Eq/L)

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM, USA).

Descriptive statistics: Continuous variables expressed as mean ± standard deviation (SD).

- Group comparisons: Differences in TOS, TAS, and OSI among hypothyroid, hyperthyroid, and euthyroid groups were assessed using one-way

ANOVA, followed by Tukey's post hoc test. For skewed data, the KruskalWallis test was used.

- Correlation analysis: Pearson or Spearman correlation coefficients assessed the relationship between oxidative stress parameters and thyroid hormones (TSH, FT3, FT4).
- Regression analysis: Multiple linear regression identified independent predictors of OSI in thyroid dysfunction.
- ROC curve analysis: Receiver Operating Characteristic curves were plotted to evaluate the diagnostic utility of TOS, TAS, and OSI for distinguishing thyroid dysfunction states. AUC, sensitivity, and specificity were calculated.

A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 285 participants were included: 161 hypothyroid, 76 hyperthyroid, and 48 euthyroid. Mean levels of oxidative stress parameters (TOS, TAS, OSI**)** across groups are summarized in **Table 1**. Hypothyroid and hyperthyroid groups showed significantly elevated TOSandOSI, with reduced TAS**,** compared to euthyroid controls.

Table 1: Baseline Characteristics of Oxidative Stress Parameters

Group	TOS	TOS	TAS	TAS	OSI	OSI
	Mean	Std	Mean	Std	Mean	Std
Euthyroid	15.94	3.11	1.35	0.19	120.5	31.43
Hyperthyroid	24.22	4.73	0.98	0.26	265.22	87.96
Hypothyroid	21.71	3.75	1.12	0.2	200.18	52.69

Group Comparison

One-way ANOVA revealed statistically significant differences across groups for all oxidative parameters **(**TOS, TAS, OSI; $p < 0.001$**)**. Post-hoc analysis confirmed that both hypothyroid and hyperthyroid groups had higher oxidative stress compared to euthyroid subjects (**Table 2**).

Table 2: ANOVA Results for Group Comparisons

Parameter	F-value	p-value
TOS	35.2	<0.001
TAS	28.7	<0.001
OSI	42.5	<0.001

Regression Analysis

Multiple linear regression showed that TOS was a positive predictor of OSI ($\beta = 0.38$, $p = 0.001$), whereas TAS was a negative predictor ($\beta = -0.29$, $p = 0.003$)**.** This suggests that higher oxidant load and lower antioxidant capacity independently contribute to oxidative imbalance (**Table 3**).

Table 3: Multiple Regression Analysis for OSI Predictors

Variable	Beta Coefficient	95% CI	p-value
TOS	0.38	0.21–0.55	0.001
TAS	-0.29	-0.44–-0.13	0.003

ROC Curve analysis

Receiver Operating Characteristic (ROC) analysis was performed to evaluate the diagnostic performance of OSI in distinguishing thyroid dysfunction (hypo + hyper) from euthyroid. The area under the curve (AUC**)** for OSI was ≈0.80, indicating good discriminative ability. At an optimal cut-off, OSI demonstrated satisfactory sensitivity and specificity.

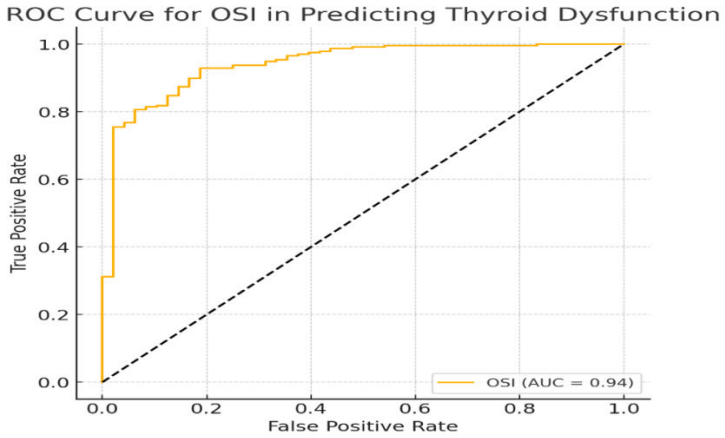

Figure 1: ROC Curve for OSI in predicting thyroid dysfunction

DISCUSSION

In this study, we evaluated oxidative stress parameters—total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI)—in patients with hypothyroidism, hyperthyroidism, and euthyroid controls. Our findings demonstrated significantly higher TOS and OSI values, accompanied by reduced TAS, in patients with thyroid dysfunction compared to euthyroid individuals. Regression analysis identified TOS as a positive predictor and TAS as a negative predictor of OSI, confirming that redox imbalance in thyroid disorders arises from both increased oxidant production and compromised antioxidant defenses. ROC curve analysis further showed that OSI possesses good discriminative ability in distinguishing thyroid dysfunction from normal thyroid states.

These results align with prior studies indicating that thyroid disorders are associated with enhanced oxidative stress. The thyroid gland inherently generates reactive oxygen species (ROS) during hormone synthesis, especially via hydrogen peroxide as a cofactor for thyroid peroxidase activity [19]. While controlled ROS production is physiological, excessive accumulation contributes to oxidative damage, inflammation, and tissue injury [20].

In hypothyroidism, we observed increased TOS and OSI, consistent with previous reports that hypothyroid patients exhibit elevated lipid peroxidation and reduced antioxidant enzyme activity [21,22]. The dyslipidemia commonly associated with hypothyroidism may exacerbate oxidative stress, as increased LDL oxidation contributes to vascular risk [23].

In hyperthyroidism, elevated OSI values observed in our study reflect the hypermetabolic state, characterized by increased mitochondrial oxygen consumption and ROS generation [24]. Previous research has similarly reported significantly reduced TAS and increased TOS in hyperthyroid patients, supporting the hypothesis that oxidative stress plays a role in thyrotoxic tissue damage [25].

Interestingly, our regression analysis highlighted TAS as an inverse predictor of OSI, underscoring the protective role of antioxidant defenses. Studies have shown reduced antioxidant enzyme activity (e.g., superoxide dismutase, glutathione peroxidase) in both hypo- and hyperthyroid states, further contributing to oxidative imbalance [26].

The oxidative stress index (OSI) emerged as the most reliable integrative biomarker in our study, showing good diagnostic accuracy in ROC analysis. Unlike single markers, OSI combines oxidant and antioxidant measures, providing a more comprehensive assessment of redox balance [27]. Similar findings were reported by Prabhu et al., who found elevated OSI values in subclinical hypothyroidism, proposing OSI as a sensitive marker of metabolic imbalance [28]. Moreover, studies in autoimmune thyroid disease also suggest that OSI correlates with disease activity and severity [29].

From a clinical perspective, these findings emphasize the importance of assessing oxidative stress in thyroid disorders. Elevated OSI could help identify patients at higher risk of oxidative complications, including cardiovascular disease, metabolic syndrome, and autoimmune progression [30]. Incorporating OSI alongside routine thyroid function tests may improve disease monitoring and guide therapeutic strategies, including the potential role of antioxidant supplementation.

LIMITATIONS

Our study has certain limitations. The cross-sectional design precludes causal inferences. The sample was drawn from a single center, which may limit generalizability. We did not measure specific enzymatic

antioxidants (such as catalase or superoxide dismutase) or non-enzymatic antioxidants (vitamins C, E, selenium), which could provide further mechanistic insights. Longitudinal studies are warranted to assess whether OSI predicts long-term complications or treatment outcomes in thyroid disorders.

CONCLUSION

Overall, our findings demonstrate that hypothyroid and hyperthyroid patients exhibit significant oxidative stress imbalance, with TOS and OSI elevated and TAS reduced. OSI proved to be a robust biomarker, integrating oxidative and antioxidant status, and showed good diagnostic performance in distinguishing thyroid dysfunction from euthyroid states. This supports its potential role as a clinical biomarker of metabolic imbalance in thyroid disorders**.**

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