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Correlations between Oxidative Stress and Thyroid Hormone in Subclinical and Overt Hyperthyroid Patients of Nepal

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ABSTRACT

Aim: The main aim of the present study was to correlate the oxidative stress marker with thyroid hormone in subclinical and overt hyperthyroid patients of Nepal which remains unexplored till June 2024.
Methods: A total of 129 patients with hyperthyroidism including subclinical and overt cases were enrolled in this cross-sectional study. Thyroid function parameter (T3, T4, and TSH) and oxidative stress marker including malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase activity and total antioxidant capacity (TAC) in patient were estimated using Chemiluminescent immunoassay and spectrophotometrically, respectively. Utilizing IBM SPSS version 20.0., Chi-square test and Pearson's correlation coefficient were employed for statistical analysis.
Results: Significantly higher level of T3 and T4 were found in overt case when compared subclinical case of hyperthyroidism. In correlation analysis, T3 showed significant positive correlation with MDA (r: 0.487, $p < 0.01$) and SOD (r: 0.623, $p < 0.01$), while significant negative correlation with GPx (r: -0. 834, $p < 0.01$) and TAC (r: -0.672, $p < 0.01$). Similarly, T4 also showed significant positive correlation with MDA (r: 0.438, $p < 0.01$) and SOD (r: 0.559, $p < 0.01$), while significant negative correlation with GPx (r: -0.745, $p < 0.01$) and TAC (r: -0.605, $p < 0.01$). Unlike, TSH showed significant negative correlation with MDA (r: -0.491, $p < 0.01$) and SOD (r: -0. 487, $p < 0.01$), and significant positive correlation with GPx (r: 0.645, $p < 0.01$), GR (r: 0.281, $p< 0.01$) and TAC (r: 0.888, $p < 0.01$). Similar trends of correlations with strong to extreme magnitude between thyroid hormone and stress markers was observed in overt case compared to subclinical case of hyperthyroidism.
Conclusion: oxidative stress amplifies the thyroid hormones highlighting the importance of adjuvant antioxidant in treatment of hyperthyroidism.
Keywords: Oxidative stress, Antioxidant enzyme system, Thyroid hormones, Hyperthyroidism

1. BACKGROUND

Hyperthyroidism is a condition characterized by an overproduction of thyroid hormones and becomes a global threat (1). It is associated with a range of adverse effects, including cardiovascular complications, bone loss, and psychological disturbances (2). Overt hyperthyroidism is

characterized by low or suppressed TSH levels, along with elevated levels of free T4 and/or free T3 (3). Patients with over hyperthyroid disorder typically exhibit symptoms of thyrotoxicosis (4). Likewise, Low serum TSH levels together with normal serum levels of free thyroxine (T4) and triiodothyronine (T3) biochemically characterize subclinical hyperthyroidism (5,6).

Hyperthyroidism causes an increase in cellular oxygen consumption and basic metabolism, enhances intracellular ATP consumption, malfunction in the mitochondrial respiratory chain, and increases reactive oxygen species (ROS) production (7–9). High ROS production cause imbalance between the reactive oxygen species (ROS) and the body's natural antioxidant defense system contribute to oxidative stress. Elevated ROS levels damage cellular components like proteins, lipids, and DNA, potentially contributing to various diseases (7,10,11). Chronic oxidative stress in hyperthyroid patients has been linked to potential long-term health consequences, including increased risk of cardiovascular disease and cancer (12).

Oxidative stress resulting from high ROS and free radical has proven to play a significant role in hyperthyroidism therefore could offer new avenues for the prevention and management of hyperthyroidism and its associated health risks. Several oxidative stress markers have been proposed for the evaluation of oxidative stress, including malondialdehyde (MDA), total antioxidant capacity (TAC), glutathione peroxidase (GPx), and superoxide dismutase (SOD) (13). Clinical manifestations of hyperthyroidism are well-studied while the underlying mechanism particularly the role of oxidative stress is an ongoing area of research. Uncovering the mechanisms contributing to hyperthyroid pathophysiology can help to develop better diagnostic tools and potential therapeutic targets. Therefore, this study aims to determine the oxidative stress marker and thyroid hormone in subclinical and overt hyperthyroid. Furthermore, this study analyses the cause-and-effect relationship between oxidative stress and hyperthyroidism including subclinical and overt causes implementing correlation statistics.

2. MATERIALS AND METHODS

2.1. Study Design: An observational cross-sectional strategy was employed to collect the data on thyroid function parameters and oxidative stress markers concurrently. The research was conducted at the Chitwan Medical College and Teaching Hospital, Bharatpur, Chitwan, Nepal, from July 2023 to April 2024.

Ethical approval was taken from the Institutional Review Committee of Chitwan Medical College and Teaching Hospital (Reference number 2078/79-231). At first informed consent was sought from each patient willing to participate and agreed to give blood sample for the investigation in the study.

2.2. Sample size: A total of 129 clinically diagnosed hyperthyroid patients, including both subclinical and overt cases, were included adopting convenience sampling technique. The sample size was calculated based on a 95% confidence level and a 5 % margin of error, considering a 9 % prevalence rate of hyperthyroid disorders a study conducted at Kathmandu University (7).

2.3. Inclusion and exclusion criteria: Patients of age above 15 years who diagnosed with hyperthyroidism and gave their consent were included in the study. Likewise, Patient with abnormal dietary habits such as chronic smoking, tobacco intake, alcoholism, and on medications known to interfere with thyroid hormone function and pregnant and lactating women were excluded from the study.

2.4. Data collection methods: The data collection method integrates self-report

measures through a comprehensive questionnaire and objective assessments through laboratory and clinical procedures. Self-report measures involve administering a structured questionnaire in paper format during hospital visits. Objective assessments include clinical examinations by medical specialists as well as laboratory testing for thyroid function parameters and oxidative stress markers. A proforma is used to record the data gathered from methods, ensuring accuracy and validation through the signatures of health professional.

2.5. Biochemical analysis

Venous blood (5 ml) was collected from each patient via vein puncture and dispensed in sodium citrate vial and plain vial. Afterward, the blood samples were processed to isolate serum and non-hemolyzed plasma for the analysis of oxidative stress markers and thyroid hormones. Thyroid profile (free T3, free T4, and TSH) levels were measured by chemiluminescent immunoassay (Siemens ADVIA Centaur XP analyzer) (14). Malondialdehyde (MDA), total antioxidant capacity (TAC), glutathione peroxidase (GPx) activity and superoxide dismutase (SOD) activity were measured spectrophotometrically adopting the method described previously (15,16). All the parameters were estimated following the standard protocol as manufacturer's guideline.

3. STATISTICAL ANALYSIS

All laboratory data were displayed in table as mean ± standard deviation. Using a SPSS version 21.0 software, statistical analysis including Chi-square and Pearson's correlation coefficient (r) was measure to establish relationships between oxidative stress markers and thyroid function parameters. A p-value with two tails less than 0.05 was deemed statistically significant.

4. RESULTS

4.1. Demographic characteristics of participants

Table 1 summarizes the demographic characteristics of enrolled hyperthyroid patients including sub-clinical and overt hyperthyroidism. The sub-clinical hyperthyroidism group had a higher percentage of females (58.8%) than the overt group (41.2%), revealing non-statistically significant ($p = 0.195$). With respect to age distribution, the majority of patients were of 31- 45 years with sub-clinical (62.0%) and overt (38.0%), showing no significant difference in age distribution ($p < 0.525$). A substantial proportion of patients showed the normal BMI values of 18.5 to 24.9, comprising sub-clinical (31.1 %) and overt case (23.5 %). Interestingly, second-grade obesity (BMI: 35-39.9) were not found in any hyperthyroid patient as shown in Table 1.

4.2. Thyroid function and oxidative stress marker plasma concentration

Table 2 showed the significant differences in clinical marker between subclinical and overt hyperthyroidism. Notably, the thyroid hormone level, T3 (3.24±0.62 vs. 8.58±4.27, $p<0.001$) and T4 (1.23±0.241 vs. 3.23±2.03, $p<0.001$) in subclinical vs. overt cases, respectively, revealing a marked elevation of thyroid hormone in the overt hyperthyroidism. However, the TSH levels (0.13±0.11 vs. 0.02±0.03, $p<0.001$) in subclinical vs. overt cases indicating the significantly suppression of plasma TSH in overt hyperthyroidism. Oxidative stress markers exhibited contrasting patterns, like MDA levels (7.89±0.97 vs. 8.03±0.96, $p<0.001$) in subclinical vs. overt cases, suggesting a high oxidative stress in overt hyperthyroidism. Conversely, antioxidant enzyme activities, including GPx (6.60±0.53 vs. 5.88±1.08, $p<0.001$), and TAC (362.78±48.94 vs. 310.10±37.34, $p<0.001$) were significantly lower in the overt hyperthyroidism, indicating a compromised endogenous antioxidant enzymes system. Meanwhile, GR enzyme

activities (2.38±1.14 vs. 3.82±1.15, p<0.001), were found to be elevated in overt hypothyroidism.

4.3. Correlation between oxidative stress and thyroid function parameter

Correlation matrix displayed in Table 3 demonstrated a significant association between oxidative stress markers and thyroid function measures. Thyroid hormone T3 and T4 showed moderate to strong positive correlation with stress marker such as MDA and SOD, while strong negative correlation with GPx and TAC. However, TSH revealed the significant negative correlation with MDA and SOD, and positive correlation with GPx, GR, and TAC. These significant correlations suggest a complex interplay between thyroid function and oxidative stress in hyperthyroidism.

Table 4 represents the correlation analysis between oxidative stress markers and thyroid function parameters in subclinical and overt hyperthyroidism. In subclinical cases, T3 and T4 showed moderate to weak positive correlation with Stress marker like MDA and SOD, reflecting a significant association in increasing thyroid hormone plasma concentration. Conversely, TSH revealed a significant negative correlation with MDA and SOD. Likewise, T4 and TSH revealed significant figures towards weak negative and extreme positive correlation, respectively with GPx, GR and TAC of subclinical hyperthyroid patient.

In overt cases, T3 and T4 showed an extreme to strong positive correlation with oxidative stress markers like MDA and SOD, indicating a significant association with high T3 and T4 level in blood plasma of overt hyperthyroid patient. However, T3 and T4 revealed an extreme to strong negative correlation with GPx, GR and TAC, suggesting the significant associated between antioxidant activity and low thyroid hormone level. Similarly, TSH possess weak positive to negative correlation with the antioxidant markers, highlighting nonsignificant association.

Table 1: Demographic characteristics of sub-clinical and overt hyperthyroid patients.

Parameters	**Thyroid disorder frequency**		
	Subclinical hyperthyroidism	**Overt hyperthyroidism**	**p value**
	n (%)	n (%)	
Sex			
Female (85)	50 (58.8 %)	35 (41.2 %)	0.195
Male (44)	31 (70.45 %)	13 (29.55 %)	
Age (years)			
15-30	17 (53.1 %)	15 (46.9 %)	0.525
31-45	31 (62.0 %)	19 (38.0 %)	
46-60	16 (66.7 %)	8 (33.3 %)	
61-75	16 (76.2 %)	5 (23.8 %)	
76 and above	1 (50.0 %)	1 (50.0 %)	
Total	81 (62.8 %)	48 (37.2 %)	
Body mass index Category (Kg/m2)			
Under weight (< 18.5)	12 (14.81)	5 (10.41)	
Normal weight	37 (45.67)	28 (58.33)	
(18.5 - 24.9)			
Overweight	15 (18.51)	8 (16.66)	
(25 - 29.9)			
First grade obesity	17 (20.98)	7 (14.5)	
(30 - 34.0)			
Second grade obesity	0 (0.0)	0 (0.0)	

Table 2: Biochemical markers of hyperthyroidism and oxidative stress in subclinical and overt hyperthyroid patients.

Biochemical markers	Subclinical hyperthyroidism	Overt hyperthyroidism
	Mean ± SD	Mean ± SD
T3 (pgm/ml	3.24±0.62	8.58±4.27
T4 (ngm/ml)	1.23±0.241	3.23±2.03
TSH (µIU/ml)	0.13±0.11	0.02±0.03
MDA (µmol/L)	7.89±0.07	8.03±0.96
SOD (U/gm P/mL)	21.67±2.13	21.93±6.40
GPx (U/mg of Hb)	6.60±0.53	5.88±1.08
GR (U/gm Hb)	2.38±1.14	3.82±1.15
TAC (µmol/L)	362.78±48.94	310.10±37.34

Table 3: Correlation matrix of oxidative stress markers and thyroid function parameters in hyperthyroid patients

Oxidative stress marker	Thyroid function parameter		
	T3	T4	TSH
MDA	0.487**	0.438**	-0.491**
SOD	0.623**	0.559**	- 0.487**
GPx	- 0.834**	- 0.745**	0.645**
GR	-0.013	-0.035	0.281**
TAC	-0.672**	- 0.605**	0.888**

***Correlation is significant at the 0.05 level (2-tailed).**
****Correlation is significant at the 0.01 level (2-tailed).**

Table 4: Correlation analysis of oxidative stress markers and thyroid function parameters in Subclinical and overt hyperthyroid patients of Nepal

Oxidative stress marker	Subclinical hyperthyroidism			Overt hyperthyroidism		
	T3	T4	TSH	T3	T4	TSH
MDA	0.598**	0.483**	-0.697**	0.956**	0.797**	-0.284
SOD	0.149	0.266*	- 0.999**	0.998**	0.795**	-0.175
GPx	-0.13	-0 .251*	0.997**	-0.997**	- 0.797**	0.188
GR	-0.125	-0.273*	0.918**	-0.996**	-0.819**	0.172
TAC	-0.18	-0.288**	0.985**	-1.00**	-0.802**	0.178

***Correlation is significant at the 0.05 level (2-tailed).**
****Correlation is significant at the 0.01 level (2-tailed).**

5. DISCUSSIONS

Oxidative stress ideally reflects the imbalance between the biological pro-oxidant/ free radicals and antioxidant defense system (10). Over production of reactive oxygen species and free radicals overlaps the detoxification capacity of endogenous antioxidants defense system (superoxide dismutase, glutathione peroxidase and catalase) which cause damage to lipids, proteins, and DNA and also contributes to the pathogenesis of several diseases especially thyroid disorders (7,11) . Several previous studies have reported the profound impact of thyroid hormone on oxidative stress like increase in ROS production as a result of elevated metabolic rate and mitochondrial respirations in hyperthyroid patients (7–9). However, the biochemical associations between the oxidative stress and thyroid hormone remains unestablished especially in Nepalese hyperthyroid populations therefore the present study aimed to explored the correlation for the first time.

Subclinical hyperthyroidism is characterized by suppressed serum TSH level with normal T3, T4 and absence of obvious thyroid symptoms (5,6). while, the elevated T3, T4 differentiate the overt case from subclinical case of hyperthyroidism (3). Likewise, the current study has demonstrated the showing the significant elevation in serum T3 and T4 concentrations and depression in TSH level thereby satisfying the previous studies (6).

Malondialdehyde (MDA) is a key marker of oxidative stress level in biological system (17). In hyperthyroid patients, over production of ROS leads to the lipid peroxidation which in turn increases the by-product malondialdehyde level in blood plasma (8). The current study revealed a significant positive correlation with thyroid hormone T3 and T4 in both subclinical and overt cases, which was found to consistence with several previous studies (17,18) and also contrary to the non-significant negative correlation reported by Cheng et al. (9). In fact, overt cases showed profound increase in MDA level, which could be the intense alternation in metabolic rates leading to the high free radical/ROS release especially H_2O_2 and nitric oxide, and lipid peroxidation (8,17,18). This finding highlights the immense stress level in over hyperthyroid case compared to subclinical cases.

Biological antioxidant enzyme including superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase minimizes the free radicals in human tissues via preventing the production and inactivating free radicals (18–22). SOD upregulated the dismutation of superoxide anion radical into hydrogen peroxide and molecular oxygen (18,20). Likewise, GPx reduces the H2O2 concentration via detoxifications (20). Additionally, GPx also prevents lipid peroxidation via transforming the lipid peroxide to alcohols (18). The current study revealed the significant positive correlation of SOD with T3 and T4 in subclinical and overt cases, which was found to be parallel with several previous studies (19,22,23). Especially, strong-extreme positive correlation between SOD and thyroid hormone (T3 and T4), revealed a significant induction of SOD and inhibition of GPx activity in overt hyperthyroidism. Previously, Andryskowski et al. and komosinska et al. reported a significant increase in GPx level in hyperthyroidism (19,22) while Bednarek et al. (24) revealed the contrary result supporting our findings.

Glutathione function as a buffer against intracellular oxidation processes. High ROS production leads to formation of dimer including two oxidized glutathione molecules. Glutathione reductase (GR) reverses the oxidized form to reduced form of glutathione thereby lowered its reactivity (20). Reduced glutathione in serves as intracellular antioxidant via neutralizing several free radicals and ROS especially hydroxy radical, peroxynitrite and singlet oxygen (17). In the current studies GR level were found to have significant negative correlations with T3 and T4 in both subclinical and overt case of hyperthyroid, favoring the several previous reports showing the lower level of GR I hyperthyroidism (22,24).

Total antioxidant capacity (TAC) is a key indicator representing the overall ability of body including endogenous antioxidant enzymes and exogenous antioxidant compounds to neutralize oxidation processes (20). Several previous studies have demonstrated the decrease in TAC in body fluid of hyperthyroid patient (10,19,21,22). Likewise, our studies also revealed the significant negative correlation between TAC and thyroid hormone (T3 and T4). However, the correlation was found to be extreme to perfect in overt case compared to subclinical cases suggesting the intense depletion of antioxidants especially in overt hyperthyroid patients. Therefore, exogenous antioxidant supplements like Vit E, tocopherol, ascorbic acid, flavonoids and polyphenolic compounds reinforce the antioxidant defense system to combat the oxidative stress related to subclinical and overt hyperthyroidism (10,17,21).

6. CONCLUSIONS

The present investigation and correlation analysis elucidated complex associations between thyroid function parameters and oxidative stress markers among hyperthyroid patients of Nepal for the first time. Notably, T3 and T4 exhibited positive correlations with oxidative stress markers,

while thyroid-stimulating hormone (TSH) showed dual associations. Therefore, antioxidant supplements may be a novel strategy in therapeutic regimen of hyperthyroidism to combat the consequences of oxidative stress.

Abbreviations

T3: Tri-iodothyronine
T4: Tetra-iodothyronine
TSH: Thyroid-stimulating hormone
BMI: Body mass index
ROS: Reactive oxygen species
MDA: Malondialdehyde
TAC: Total antioxidant capacity
GPx: Glutathione peroxidase
SOD: Superoxide dismutase

Data Availability

The data used to support the study are included in this article

Declaration by Authors

Ethical Approval: Approved

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