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Research Article

Case control study of antioxidant markers in autoimmune thyroid disorders

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Abstract:
Background and objectives: There is often an imbalance between reactive oxygen species production and antioxidant defence mechanisms in autoimmune thyroid disorders (AITD). The objective of the study was to evaluate the glutathione peroxidase (GPX), total antioxidant capacity (TAC) and malondialdehyde (MDA) levels and autoantibody levels in autoimmune thyroid disorders (AITD).
Methodology: In a case control study among patients with autoimmune thyroid disorders and normal control subjects, oxidative stress markers namely GPX, MDA levels, TAC was evaluated. Patients with lab confirmed thyroid functional abnormalities, both hypothyroid and hyperthyroid subjects, meeting inclusion criteria are selected as cases. Sample size was 67 for cases and controls. A pre designed and pretested questionnaire including nutritional history and family history is distributed among cases and controls to collect the demographic details. Morning blood samples were used for estimating T4, T3, TSH, TAC, GPX, MDA levels.
Results: Study population comprised of 38 hypothyroid and 29 hyperthyroid subjects with 67 euthyroid controls. Mean GPX values in hypothyroidism and hyperthyroidism subjects was statistically significantly lower than control group (0.21 ± 0.06 and 0.19 ± 0.06 vs 0.41 ± 0.12 nmol/mL). Mean MDA values in hypothyroidism and hyperthyroidism subjects was statistically significantly higher than control group (7.4 ± 1.5 and 7.6 ± 1.53 vs 4.7 ± 0.8 nmol/mL). Mean TAC values in hypothyroidism and hyperthyroidism subjects was statistically significantly lower than control group (554.7 ± 104.3 and 551.8 ± 69 vs 1166.1 ± 105.7 µmol TE/L).
Conclusion: Lower antioxidant markers (GPX and TAC) and higher oxidative stress marker (MDA) was observed among AITD subjects in comparison to age and sex matched controls. A statistically significant association between AITD and low GPX/TAC status was noted.

Keywords: glutathione peroxidase, malondialdehyde, hypothyroidism, Hashimoto's thyroiditis, Grave's disease

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Introduction:

Autoimmune thyroid disorders (AITD), including Hashimoto's thyroiditis and Graves' disease, are prevalent conditions that affect the thyroid gland's function due to development of anti thyroid autoantibodies. Oxidative stress plays a significant role in thyroid dysfunction, including conditions like hypothyroidism and hyperthyroidism.[1] Imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses may play a role in impaired thyroid hormone synthesis and release. This damage can exacerbate autoimmune thyroid diseases like Hashimoto's thyroiditis and Graves' disease.[1] Furthermore, oxidative stress can alter thyroid hormone metabolism and signaling, disrupting normal physiological functions.[2] Addressing oxidative stress through antioxidant therapies may help mitigate thyroid damage and improve overall thyroid health.

Antioxidants play a crucial role in combating oxidative stress, a key factor in AITD. Glutathione peroxidase, an important antioxidant enzyme, helps neutralize hydrogen peroxide and lipid hydroperoxides, thereby protecting thyroid cells from oxidative damage.[1] Its deficiency has been linked to AITD progression.[2] Total antioxidant capacity (TAC) is an insight into the body's overall ability to counteract oxidative stress. Reduction in TAC highlights the imbalance between pro-oxidants and antioxidants, contributing to thyroid tissue damage and exacerbating the autoimmune response. Monitoring TAC helps understand the oxidative stress status and guide antioxidant-based therapeutic strategies in AITD management.[2]

On the other hand, malondialdehyde (MDA) is a marker of lipid peroxidation, reflecting oxidative stress levels. Elevated MDA levels are often observed in AITD patients, indicating increased oxidative damage to cell membranes and proteins.[3] Therefore, maintaining a balance between antioxidants like glutathione peroxidase and monitoring markers like MDA is crucial in managing autoimmune thyroid disorders and reducing oxidative stress-related complications.

The findings from a meta-analysis of seven research articles revealed that antioxidant supplementation, particularly with compounds like selenium, vitamin E, and coenzyme Q10, had beneficial effects on Graves' disease.[4] These antioxidants were found to reduce oxidative stress, improve thyroid function, and decrease levels of thyroid-specific antibodies. Additionally, antioxidant supplementation was associated with reduced inflammation and improved quality of life in patients with Graves' disease. Overall, the meta-analysis suggests that incorporating antioxidant supplementation as an adjunct therapy could be beneficial in managing Graves' disease by mitigating oxidative stress and improving thyroid function.[4] In a review article, Kochman et al., discusses the role of oxidative stress in various thyroid diseases, including autoimmune thyroiditis and highlight the use of oxidative stress markers, such as MDA, as diagnostic and prognostic tools in these diseases.[5]

Estimating GPX levels helps assess the antioxidant capacity of cells and tissues.[6] Lower GPX levels may indicate reduced antioxidant defense, leading to increased susceptibility to oxidative stress-related conditions.[7,8] Similarly, higher MDA levels suggest increased oxidative damage and can be associated with various pathological conditions.[9,10] TAC evaluates the overall ability of an individual's blood or other fluids to counteract oxidative stress and neutralize free radicals, which are harmful molecules that can damage cells and contribute to various diseases and aging. Therefore, this study was designed with the objective to evaluate the antioxidant markers GPX and TAC levels, and oxidative stress marker MDA levels in AITD.

Methodology

In a case control study among patients with autoimmune thyroid disorders and normal control subjects GPX, TAC and MDA levels were evaluated.

Study design: Case control study was conducted in MOSC Medical College, Kolenchery, Kerala, Inida from July 2022 to May 2023. As the AITD including Hashimoto's thyroiditis and Grave's disease are relatively rare compared to other health conditions and case-control studies are particularly useful for studying rare diseases, this study design was selected. Case-control studies are well-suited for examining associations between exposure variables (such as oxidative stress markers) and specific outcomes (such as AITD).

Selection of cases and controls:

AITD patients: Patients who had signs and symptoms of thyroid disorders and confirmed with lab results meeting following inclusion criteria are selected as cases.

For this study following ranges are considered as normal T4 – 5.5 to 11µg/dL T3 – 0.97 to 1.69 ng/mL TSH – 0.46 to 5 mIU/mL.

1. Patients age 20 to 65 years
2. Patients must have a confirmed diagnosis of an autoimmune thyroid disorder, such as Hashimoto's thyroiditis or Graves' disease and based on clinical evaluation **at least one** of the following laboratory tests

i. Thyroid hormone levels:

- TSH above the upper limit of the reference range > 5.0 mIU/L or below the lower limit of reference range <0.46 mIU/L
- T4 below the lower limit of reference range < 5.5 µg/dL or above the upper limit of reference range > 11µg/dL
- T3 below the lower limit of reference range < 0.97 ng/mL or above the upper limit of reference range > 1.69 ng/mL

ii. Thyroid autoantibodies:

- Anti TPO (thyroid peroxidase) more than 50 IU/L (positive result)
- Anti TGO (thyroglobulin) antibody more than 125 IU/L (positive result)

iii. Histopathological examination (if available) confirming the diagnosis of either Hashimoto's thyroiditis or Grave's disease

Exclusion criteria: Individuals with non-autoimmune thyroid disorders (e.g., thyroid nodules, thyroid cancer) or thyroid dysfunction due to non-autoimmune causes (e.g., iodine deficiency, medication-induced thyroid dysfunction), those on hormone replacement for hypothyroidism, thos who have underwent thyroidectomy, those on Lithium or amiodarone, and those with co-existing autoimmune diseases (e.g., rheumatoid arthritis, lupus) were excluded. Pregnant women, as pregnancy

can significantly impact thyroid function and GPX/MDA/TAC levels were excluded.

Selection of controls:
Objective of control selection was to match controls to cases based on demographic factors that may influence GPX and MDA levels and the risk of AITD.

Matching criteria: Control with matching criteria including age, gender, ethnicity, geographical region, and socioeconomic status were selected. Such critical matching negated potential confounders and ensured that any observed differences in GPX and MDA levels between cases and controls are more likely due to AITD status rather than demographic variations.

Exclusion criteria for Controls: Those with any thyroid disorder or other significant health conditions that could affect GPX and MDA levels independently of AITD were strictly excluded.

Sample size:
Sample size calculation when comparing proportions between cases and control groups is based on estimating the odds ratio (OR). The formula takes into account the expected proportion exposed in the control group (P2), the estimated odds ratio (OR), the significance level (α), and the desired power (1-β). The formula is as follows:

$$n = \frac{(Z\alpha/2 \quad + Z1-\beta)^2 \times (P1 \times (1-P1) + P^2 \times (1-P2) \times OR)}{(P1-P2\ X\ OR)\ 2}$$

where, n is the required sample size per group (cases or controls), Z score corresponds to 95% confidence limit, P1 calculated proportion in the case group, P2 expected proportion exposed in the control group, OR estimated Odds ratio, m is minimum number of required discordant pairs and 1-β is the power.
Sample size was calculated from the reference study by Wu et al for the case control study with equal allocation (1:1).[11] They have studied 6152 participants and reports 24.4% as having thyroid problems. Therefore, two-sided sample size for power 80%, alpha error 5% is calculated using the above formula arrived at 67 for cases and controls.
Data collection:
A pre designed and pretested questionnaire including nutritional history and family history is distributed among cases and controls to collect the demographic details. Through this age, sex, regionality, previous medical and surgical history, family history of thyroid disorders or any other autoimmune disorders, history of nutritional supplementation are collected.
After signing informed consent document, height and weight details are collected from all participants. Physical examination was undertaken where any thyroid enlargement, pallor, lymph node enlargement, head to toe examination for signs of hypothyroidism and hyperthyroidism.
Blood samples collected at 6 – 8 AM was used for estimating thyroid function status (T4, T3 and TSH). The presence of subclinical, hypo or hyperthyroidism was used to define thyroid dysfunction. Collected blood samples were centrifuged at 1500-2000 g for 10-15 minutes to separate plasma and stored at -20°C.
Participants with thyroid disorders were further evaluated for thyroid antibodies – anti thyroid peroxidase antibodies (anti TPO) and anti thyroglobulin antibodies (anti TGO) measured by electro chemiluminescence immunoassay (ECLIA). Serum selenium was estimated using ICP-MS (Inductively Coupled Plasma Mass Spectrometry). MDA was estimated with colorimetric lipid peroxidation method, GPA with microplate assay method, and TAC with Koracevic method.
Blood pressure was recorded in the sitting position in the non-dominant arm to the nearest 2mm Hg using a standard adult mercury sphygmomanometer. Two readings was taken 5 minutes apart and the mean of the two readings was taken as the blood pressure.

Data analysis:
Categorical variables were summarized using frequency and percentage. Quantitative variables were summarized as mean and standard deviation. The relationship between thyroid hormones, antibodies and serum selenium and iodine levels were studied using Pearson's correlation coefficient. The odds ratio of AITD in patients with low selenium levels was calculated.
Chi-square Test for Association: The chi-square test was used to evaluate whether the observed association between AITD and GPX, TAC, MDA status is statistically significant, using formula, $\chi 2 = \sum(Oi - Ei)2/Ei$. Where Oi = observed value (actual value) Ei = expected value. Assuming the null hypothesis (no association) and using a significance level (alpha) of 0.05, with 1 degree of freedom, chi-square value was calculated and association between AITD and GPX, TAC, MDA status were considered.
Ethics considerations: institutional ethics committee approved the proposal before the start of the study (IEC letter number: MOSC/IEC/645/2022 dated 01-07-2022). Informed consent process was undertaken for all participants and confidentiality and privacy of their data was ensured.

Results:
As tabulated in table 1 our study included 67 AITD patients, comprising 38 hypothyroid and 29 hyperthyroid subjects. Age ranged from 20 to 60 years. There was no statistical difference with respect to gender and age ($p < 0.01$) between AITD and euthyroid controls.

Table 1: Tabulation of baseline characteristics of cases (n, 67) and controls (n,67)

	Hypothyroidism	Hyperthyroidism	Control
Number	38	29	67
Female	28	7	35
Male	10	22	32

Age (in Years)	41.7 ± 14.3		35.32 ± 13.5
Positive family history	27	14	0

Thyroid hormones, thyroid antibodies and relation with GPX, TAC and MDA levels

The average thyroid hormones, thyroid antibodies, GPX, TAC and MDA levels in controls and AITDs are tabulated in table 2. Mean GPX values in hypothyroidism subjects was statistically significantly lower than control group (0.21±0.06 vs 0.41±0.12 nmol/mL). Mean TAC values in both hypothyroidism and hyperthyroidism subjects was statistically significantly lower than control group (553.5 ± 90.5 vs 1166.1 ± 105.7 µmol TE/L). Mean MDA values in hypothyroidism subjects was statistically significantly higher than control group (7.4±1.5 vs 4.7 ± 0.8 nmol/mL). Among cases, a negative Pearson correlation was observed between T3, T4 and GPX, TAC levels both in hypo and hyperthyroid cases. Correlation between TSH, TPO, TGO and GPX was positive in both hypo and hyperthyroid cases. Among controls, a negative correlation was observed between TSH, TPO levels with GPX levels and TSH levels negatively correlated with GPX values. However, Pearson correlation coefficient between T3, T4 and MDA was negative among hypothyroid subjects. T3 and TSH negatively correlated with MDA value in hyperthyroid subjects. Only T4 negatively correlated with MDA among controls.

There was no statistical difference between mean systolic and diastolic blood pressures between cases (both hypo and hyperthyroidism) and controls.

Table 2: Tabulation of thyroid hormones, thyroid antibodies and serum selenium among AITD and controls.

Subjects	**Cases**	**Controls**	**P value**
Hypothyroidism	N = 38	N = 67	
T3 (in ng/mL)	0.89 ± 0.27	1.20 ± 0.2	<0.0001
T4 (in µg/dL)	4.81 ± 2.26	6.84 ± 2.44	<0.0001
TSH (in uIU/mL)	19.77 ± 31.9	2.10 ± 1.04	<0.001
TPO (in IU/mL)	405 ± 366	30.1 ± 5.2	<0.0001
TGO (in IU/mL)	141 ± 97	49.8 ± 8.5	<0.0001
GPX (nmol/mL)	0.21 ± 0.06	0.41 ± 0.12	<0.001
MDA (nmol/mL)	7.4 ± 1.5	4.7 ± 0.8	<0.001
TAC (µmol TE/L)	554.7 ± 104.3	1166.1 ± 105.7	<0.001
SBP (mmHg)	120.7 ± 10.8	122.5 ± 7.7	0.3
DBP (mmHg)	78 ± 6.7	79.3 ± 5.8	0.3
Hyperthyroidism	N = 29	N = 67	<0.001
T3 (in ng/mL)	3.17 ± 0.83	1.20 ± 0.2	<0.0001
T4 (in µg/dL)	11.19 ± 2.6	6.84 ± 2.44	<0.0001
TSH (in uIU/mL)	0.2 ± 0.2	2.10 ± 1.04	<0.0001
TPO (in IU/mL)	310 ± 32.8	30.1 ± 5.2	<0.0001
TGO (in IU/mL)	115 ± 10.5	49.8 ± 8.5	<0.0001
GPX (nmol/mL)	0.19 ± 0.06	0.41 ± 0.12	<0.001
MDA (nmol/mL)	7.6 ± 1.53	4.7 ± 0.8	<0.001
TAC (µmol TE/L)	551.8 ± 69	1166.1 ± 105.7	<0.001
SBP (mmHg)	130.4 ± 15.6	122.5 ± 7.7	0.1
DBP (mmHg)	81.5 ± 7.3	79.3 ± 5.8	0.1

Note: TE/L - Trolox equivalents per liter

Discussion:

The level of GPX in hypothyroidism can be variable and even contradictory across studies. In this study we found mean GPX values in both hypothyroidism and hyperthyroidism subjects were statistically significantly lower than control group. Similar results were noted in epidemiological study conducted in northern Zaire. Both selenium and selenium dependent GPX deficiency was observed in endemic areas of myxedematous cretinism.[12] In a similar study, red blood cell glutathione peroxidase (RBC-GPX) among hypothyroid children was five

times lower than normal children.[13] However, study by Reddy et al., noted that GPX activity was elevated in both subclinical hypothyroidism and overt hypothyroidism in comparison to healthy individuals. Though GPX activity was increased, other antioxidant enzymes like superoxide dismutase and glutathione was reduced in this study.[14] Usually, total oxidant status and oxidant stress index is higher in hypothyroid individuals than healthy comparators.[15] The resulting oxidative stress plays a role in pathogenesis of autoimmune thyroid disorders.[5,16]

The level of MDA are generally increased in hypothyroid subjects indicating potential heightened oxidative stress. In this study, we found mean MDA values in both hypothyroidism and hyperthyroidism subjects were statistically significantly higher than control group. Similar higher values of MDA are noted in pre-treatment group by Chakrabarti et al., and there was a drop in MDA levels after hormone replacement in hypothyroid subjects.[17] Higher plasma MDA levels in hypothyroidism are also reported by Cheserek et al[18], Mustaq et al[19] and Tellechea.[20]

In hypothyroidism, TAC is often reduced compared to healthy individuals.[1] Decrease in TAC reflects a diminished ability to neutralize reactive oxygen species (ROS) due to oxidative stress. In this study, statistically significant decrease TAC was noted both in hypo and hyperthyroidism.

In a study by Aslan et al., evaluated oxidative status in patients with hyperthyroidism, found increased oxidative stress markers and reduced antioxidant defences, suggesting an imbalance that contributes to thyroid dysfunction. [21]

Contrary to previous published studies reporting association of hypertension with hyperthyroidism,[22,23] we did not find any significant association between hypertension and thyroid disorders.

Overall, present study results have not deviated from the previous studies in reporting higher MDX. Though present study did not find any significant association of changes in blood pressure in thyroid disorders, we did find lower GPX levels contradicting previous studies.

Limitations: Differential estimation of serum and plasma GPX and MDA would have given deeper perspective of oxidative stress indicators and probably negated influence of local factors while hypo or hyper thyroid-specific factors contribute to variations in these levels. Inclusion of sleeping pulse rate would have added more value to cardiovascular outcomes assessment in thyroid dysfunction.

Conclusions:

The study's findings indicate that both hypothyroid and hyperthyroid subjects exhibit significant oxidative stress, as evidenced by altered levels of key biomarkers such as GPX, MDA, and TAC compared to the control group. Specifically, the study observed statistically significant reductions in GPX and TAC levels and an increase in MDA levels among both hypothyroid and hyperthyroid patients. These results suggest a pronounced oxidative imbalance in individuals with AITDs, contributing to the pathophysiology of these conditions. The findings align with previous research demonstrating increased oxidative stress and reduced antioxidant defenses in AITD patients, further highlighting the potential role of oxidative stress in the progression of these disorders.

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Conflict of Interest: Authors declare no conflict of interest.

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