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# Study the effect of thyroid disorder on Paraoxygenase -1, Malondialdehyde (MDA) and reduced Glutathione (GSH) in a sample of Iraqi patients

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## ABSTRACT

Paraoxonase-1 (PON-1), it is an antioxidant enzyme that associate with high-density lipoproteins, plays a crucial role in mitigating lipid peroxidation. Three paraoxonase forms (PON-1, 2, and 3), with PON-1 synthesized in the liver and transported with HDLs in the plasma. This study aimed to estimate the levels of paraoxonase-1, malondialdehyde (MDA), and reduced glutathione (GSH) in the sera of patients with thyroid dysfunction that include 50 patients; 25 with hypothyroidism and 25 with hyperthyroidism which compared with 25 healthy controls in a study conducted between May and July 2023, utilized the enzyme-linked immunosorbent assay (ELISA) for PON-1, the thiobarbituric acid (TBA) method for MDA, and Ellman's method for GSH which revealed that there is a significant reduction in PON-1 activity and GHS levels in both hypothyroid and hyperthyroid groups compared to controls, with a significant increase in MDA levels in the hyperthyroid and hypothyroidism groups which indicates that thyroid dysfunction influences oxidative stress markers (MDA and GSH) and PON-1 activity, which can be used as a potential biomarker for early diagnosis or as a therapeutic target for monitoring thyroid dysfunction's clinical status.

**Keywords:** paraoxonase-1, malondialdehyde, lipid peroxidation, glutathione, thyroid

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## INTRODUCTION

The average growth and development of bodily organs rely on the presence of thyroid hormones produced by the thyroid gland. However, when the thyroid becomes excessively active and releases excessive T3 and T4 hormones into the bloodstream, a condition called thyrotoxicosis occurs[1]. On the other hand, hypothyroidism is the opposite condition, where the thyroid fails to produce adequate amounts of hormones. Primary hypothyroidism is a thyroid dysfunction that occurs when the defect resides in the thyroid. In contrast, secondary hypothyroidism is caused by a defect outside the thyroid glands, related to an abnormality in the hypothalamic-pituitary-thyroid axis[2]. Moreover, iodine deficiency resulting from ingesting an inadequate amount of iodine in the diet can also cause hypothyroidism, which affects the production of the thyroid hormone. Hypothyroidism can be also caused by certain medications such as lithium. Globally, the deficiency of iodine can be considered the most common cause of hypothyroidism[3]. Previous studies have demonstrated significant variations in T3, T4, and TSH levels during different thyroid states with different oxidative stress markers' levels, indicating an assumed relationship between thyroxin levels and oxidative stress[4,5]. Several animal studies have shown increased lipid peroxidation and malondialdehyde (MDA) in patients with overt hypothyroidism[6,7].

Additionally, dyslipidemia was consistently linked with the peroxidation of lipids in hypothyroidism[8, 9]. Other studies reported that protein carbonylation (PCO) was identified as a measure of oxidative damage to proteins in patients with overt hypothyroidism[10,11]. lipid peroxidation considered as a catalyst for the creation of protein carbonyls which may prove the link between the oxidative stress and thyroid dysfunction[12,13]. This process is intensified by elevated levels of thyroid-stimulating hormone (TSH), which triggers oxidative stress in cases of hypothyroidism[5,14]. However, there is a lack of comprehensive research regarding oxidative stress in cases of subclinical hypothyroidism, with conflicting reports on whether or not there is a change in oxidative stress and lipid peroxidation compared to control groups[8,15]. Interestingly, there is also a shortage of information regarding the levels of protein carbonyls in the subclinical hypothyroidism group. Recent interest in studying oxidative stress in thyroid disorders has emphasized the role of thyroid hormones in regulating antioxidant activity[16].

Reduced glutathione (GSH) has a crucial function in scavenging free radicals and inhibiting lipid peroxidation, as it acts as a detoxifier for hydrogen peroxide ($H_2O_2$) through the enzyme glutathione peroxidase (GPx)[17]. Superoxide radicals

undergo dismutation by the superoxide dismutase enzyme that also serves as an antioxidant enzyme due to its role in scavenging the superoxide radicals[18]. In hypothyroidism, the GSH level has been inadequately reported[5,18]. A few controversial findings reported different results in that some of the studies demonstrated an elevation in the activity of SOD, CAT7, and GPx [5,19]. In contrast, other studies reported a decline in the activities of SOD, CAT, and GPx enzymes[16,20]. In contrast, no alteration was reported in the activities of SOD, CAT7, or GPx21 in overt hypothyroidism patients. To our best knowledge, GSH evaluation and antioxidant enzymes in subclinical hypothyroidism patients have hardly been reported. In most research, the obtainable literature on oxidative stress in hypothyroidism, contrasting with most other studies, focuses on overt hypothyroidism patients. Therefore, the present study aimed to evaluate the markers of lipid peroxidation and antioxidant defense code by measuring MDA, GSH, and enzymes such as PON1 in the patients' group compared to controls.

## METHODOLOGY

### Subjects

This study comprised Fifty patients with thyroid disorders (25 patients with hypothyroidism and 25 with hyperthyroidism) who recruited from an endocrine clinic in Al-Imamain Al-Kadhimain Medical City from May-July 2023. The patient group were compared with 25 age and sex matched healthy subjects who represent the control group.

### Inclusion criteria

Patients with multinodular enlargement of the thyroid gland upon examination with a history of exaggeration of previous symptoms like weight loss, fatigue, and difficulty in swallowing.

### Exclusion criteria

Patients who are currently undergoing treatment for autoimmune disorders, pregnant women, and individuals with conditions such as diabetes mellitus, rheumatoid arthritis, renal impairment, and liver diseases are not eligible for participation in the present study.

### Blood sampling

Patients and control participants were subjected to blood sample collection, where 7 milliliters of blood were obtained using serum separator. The sera were isolated and promptly stored at a temperature of -20 °C until they were analyzed.

**Paraoxygenase -1 activity measurement**

The activity of paraoxygenase -1 was determined quantitively by using an ELISA kit supplied by AVISCERA BIOSCIENCE INC and the procedure performed according to the manufacturer instructions.

**Thyroid function test**

Enzyme immunoassay and colorimetry (Accu-Bind VAST KITS) were used to quantify T3, T4, and TSH levels. Each sample was tested twice, with measurements showing a difference of less than 10%. The average value was then determined and utilised for statistical analysis.

**Serum MDA measurement**

The levels of MDA in the serum were evaluated using the thiobarbituric acid (TBA) method developed by Buege and Aust[22]. Malondialdehyde, which is produced by the degradation of polyunsaturated fatty acids, functions as a valuable indicator of peroxidation reactions. The Buege and Aust (1978) method utilizing thiobarbituric acid to quantify MDA levels, as it undergoes a reaction with thiobarbituric acid resulting in the formation of a pink color. Measurements of absorbance were conducted at a wavelength of 532 nm.

**Estimation of reduced glutathione**

The concentration of reduced glutathione (GSH) was measured using Ellman's technique, as described by Ellman in 1959[23]. To do this experiment, 1.0 ml of plasma was combined with 0.5 ml of Ellman's reagent, which contains 19.8 mg of 5.5-dithiobisnitrobenzoic acid (DTNB) in 100 ml of 0.1% sodium nitrate. Additionally, 3.0 ml of phosphate buffer with a concentration of 0.2 M and a pH of 8.0 was added. Afterwards, the intensity of light absorption was determined at a wavelength of 412 nm.

**Statistical analysis**

The data obtained in the current study were analyzed statistically by using the Statistical Package for the Social Sciences (SPSS) software 26. Continues variables were expressed as mean ± standard deviation (SD) and all statistical comparisons were made by student t-test and Analysis of variance (ANOVA) test with the using of post-hoc Tukey test to assess the difference between each two groups within more than two groups with $P \leq 0.05$ was considered statistically significant.

## RESULTS and DISCUSSION

The results of this study showed decreases in the level of paraoxygenase -1 activity in hypothyroidism compared with hyperthyroidism and healthy controls, and statistical analysis showed a significant difference ($p<0.01$) between whole patients and the control group, as shown in Table 1 and Figure 1. Moreover, in a similar manner to that obtained with PON-1, GSH levels in patients with hypothyroidism were significantly lower than that in patients with hyperthyroidism and also than that in controls, it also demonstrated that the levels of GSH in whole patients were significantly lower than that in controls. On the other hand, the results obtained in the current work elucidate that the patients with hyperthyroidism and hypothyroidism had significantly higher levels of MDA than the healthy controls, as shown in Table 1 and Figures 1&2.

**Table 1.** The anthropometric and biochemical variables among the three studied groups

| Parameters | Control | Hypothyroidism | Hyperthyroidism | P(ANOVA)-(T-Test) |
|---|---|---|---|---|
| NO. | 25 | 25 | 25 | ..... |
| Age (yrs) (Mean± SD) | 41.35 ± 7.08 | 43.89 ± 6.38 | 42.87 ± 7.66 | NS |
| BMI (Kg/m²) (Mean± SD) | 29.81 ± 6.55 | 26.86 ± 5.17 | 24.88 ± 4.37 | Patients x Controls: P ≤ 0.01 hyper x hypo: p ≤ 0. 05 |
| PON1 (U/ml) (Mean± SD) | 378.93 ± 39.33 | 179.84 ± 18.53 | 269.38 ± 17.88 | Patients x Controls: P ≤ 0.001 hyper x hypo: p ≤ 0. 05 |
| MDA (µmol/l) (Mean± SD) | 0.57 ± 0. 35 | 1.29 ± 0.83 | 1.18 ± 0.66 | Patients x Controls: P ≤ 0.001 hyper x hypo: p ≤ 0. 05 |
| GSH (mmol/l) (Mean± SD) | 3.88 ± 0.17 | 1.37 ± 0.13 | 2.19 ± 0.31 | Patients x Controls: P ≤ 0.001 hyper x hypo: p ≤ 0. 05 |
| T3 (ng/ml) (Mean± SD) | 1.18 ± 0.07 | 0.29 ± 0.03 | 3.58 ± 0.17 | Patients x Controls: P ≤ 0.01 hyper x hypo: p ≤ 0. 05 |
| T4(ng/ml) (Mean± SD) | 8.08 ± 0.57 | 3.88 ± 0.11 | 11.99 ± 1.07 | Patients x Controls: P ≤ 0.01 hyper x hypo: p ≤ 0. 05 |
| TSH (ng/ml) (Mean± SD) | 4.18 ± 0.38 | 15.72 ± 1.31 | 0.27 ± 0.09 | Patients x Controls: P ≤ 0.01 hyper x hypo: p ≤ 0. 05 |

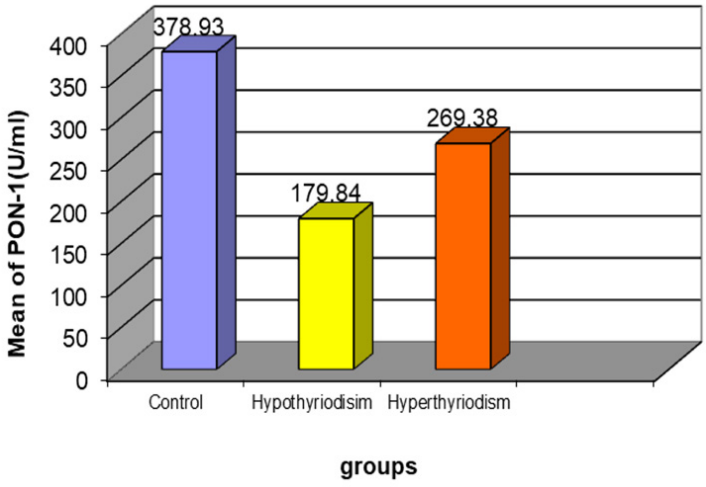


**Figure 1.** Levels of PON-1 in thyroid dysfunction patients in comparison with controls

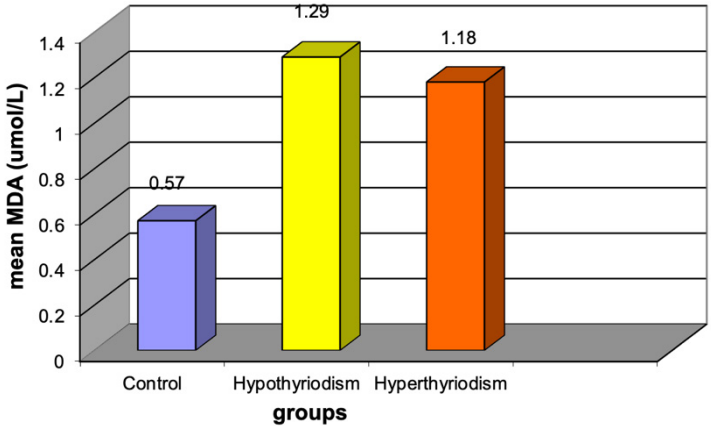


**Figure 2.** Levels of MDA in thyroid dysfunction patients in comparison with controls

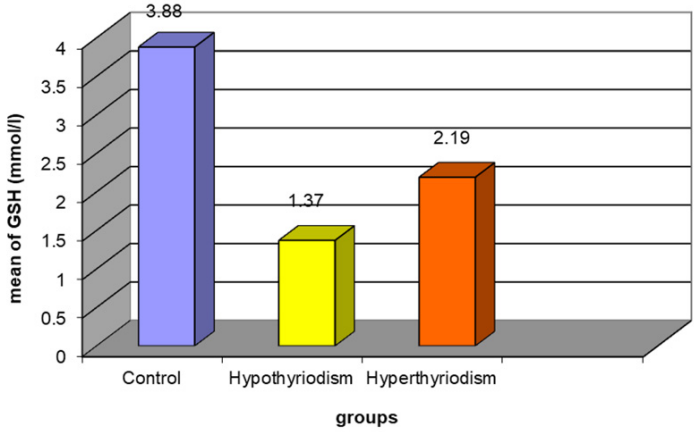


**Figure 3.** Levels of GSH in thyroid dysfunction patients in comparison with controls

The regulation of antioxidants by thyroid hormones is a crucial aspect, as these hormones have been found to promote the generation of free radicals within mitochondria[24]. Additionally, research indicates that thyroid hormones can exhibit a prooxidant effect on specific cells[25]. Notably, hyperthyroidism has been associated with increased oxidative stress and subsequent damage to lipids and genomic DNA in the aortic wall[26]. In the present study, patients diagnosed with hyperthyroidism or hypothyroidism showed a decrease in serum paraoxonase-1 (PON-1) activity. Existing literature on PON-1 activity in hypothyroidism has shown conflicting results[27-30]. Some studies reported decreased PON-1 activity and increased oxidative stress in patients with subclinical hypothyroidism[27,29], which aligns with our findings. However, the differences between our healthy control group and hypothyroidism patients were significantly higher than in previous studies[27,29], indicating that PON-1 activity could be a potential biomarker for assessing cardiovascular risk in subclinical hypothyroidism. It's worth noting that other studies found no difference in PON-1 activity between control groups and hypothyroidism patients[28,30], possibly due to genetic variations. Similarly, we observed a notable decrease in PON-1 activity among hyperthyroid patients compared to the control group. This finding is consistent with research by Azizi et al. who also reported a significant reduction in PON-1 activity in both hyperthyroid and hypothyroid patients[32]. Another study showed that PON-1 activity decreases in hyperthyroid patients but returns to normal levels after achieving euthyroidism[33,34]. Moreover, the decrease in PON-1 activity in hyperthyroidism may be due to the heightened generation of free oxygen radicals, potentially leading to oxidative damage[31].

The current investigation also focused on measuring serum MDA levels as an indicator of lipid peroxidation. Both hyperthyroidism and hypothyroidism patients exhibited significantly higher blood MDA levels compared to healthy individuals ($p<0.001$). However, hyperthyroidism patients had lower serum MDA levels compared to hypothyroidism patients ($p<0.05$), though still significantly higher than the control group. These findings align with other research that has demonstrated increased lipid peroxidation products in hyperthyroid tissues and increased MDA concentrations in patients with hypothyroidism, indicating oxidative damage[35-37]. Research conducted by Sewerynek et al. has demonstrated that the ratio of CD/MDA is lower in hyperthyroid patients compared to the control group[38] and another research findings suggest a significant increase in lipid peroxidation during hyperthyroidism[39].

In terms of glutathione (GSH), both hyperthyroidism and hypothyroidism patients showed a significant decrease in GSH levels compared to the control group. This decrease in GSH may be attributed to the accumulation of free radicals caused by oxidative stress associated with hyperthyroidism and the changes or modifications caused by both hyperthyroidism and hypothyroidism[40]. Previous research has shown that hyperthyroidism, with its high metabolism, leads to increased production of free radicals and oxidized fats. The differences in antioxidant levels between the study groups could also be related to body mass index, indicating lower antioxidant levels in both hyperthyroidism and hypothyroidism patients compared to the control group[41]. These results were in agreement with the results obtained in the current work. The reason is related to the hormones in the gland, oxidation of the thyroid gland's physiological state, as well as the dose and length of thyroid treatment for stress, doesn't work by speeding up the metabolism; instead, it has an effect based on how oxidation works[42]. The reason lies in the state of the gland hormone and the fact that there are a number of oxidative stress effects on the physiological state of the thyroid gland, in addition to the dose and duration of thyroid treatment for stress, not through stimulation of the metabolism process, but whose effect depends on the mechanics of oxidation. The study showed that toxic multinodular goitres with hyperthyroidism had higher levels of oxidative stress markers and increased activities of SOD and CAT, whereas their plasma GPx and GR activities were lower compared to the control group[43].

The results of the present work revealed that there was a significant elevation in the levels of MDA with a significant decrease in GSH levels and PON-1 activity in both hyperthyroidism and hypothyroidism patients compared to healthy individuals. This underscores the importance of considering effective antioxidant therapy, particularly augmenting PON-1 activity, as a potential therapeutic approach for individuals with hyperthyroidism and hypothyroidism.

## STATEMENT OF ETHICS

The study received approval from the Scientific-Ethical Committee College of Science, Mustansiriyah University in November 2023, Number 7134.

## CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared by the authors.

## AUTHOR CONTRIBUTIONS

Design – Hamidy AA, Abdul Jabbar NA, Shnawer NJ; Acquisition of data – Hamidy AA; Analysis of data – Abdul Jabbar NA, Shnawer NJ; Drafting of the manuscript – Hamidy AA, Abdul Jabbar NA, Shnawer NJ; Critical revision of the manuscript – Hamidy AA, Abdul Jabbar NA; Statistical analysis – Hamidy AA; Technical or financial support – Hamidy AA, Abdul Jabbar NA, Shnawer NJ; Supervision – Abdul Jabbar NA, Shnawer NJ.

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