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Advanced Oxidation Protein Products Levels and Paraoxonase 1 (Arylesterase) Activity in Patients with Thyrodisim

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Abstract

Objectives: The purpose of study was to explore the correlation of advanced oxidation protein products (AOPP), which reflect the oxidation of protein and the oxidative stress status, and the activity of antioxidant enzyme of Paraoxonase (PON1), using its arylesterase activity in patients with thyrodisim.

Methods: The study included 100 women with newly diagnosed thyrodisim were subdivided in two groups according to thyroid hormones levels: hyperthyroidism group (50 female patients, age range 18–60 years); and hypothyroidism group (50 female patients, age range 18–75 years). A control group (30 healthy females, age range 18–70 years) was also included for comparison. Demographic and clinical measurements for all participants were recorded which include: Body mass index (BMI), age, weight, height, lipid profile, vitamin D, thyroid hormones (TSH, T3, and T4, FT3, FT4), AOPP levels, and arylesterase activity.

Results: The serum level of AOPP in hypothyroidism group (71.92 ± 19.04 µmol/L) and in hyperthyroidism group (30.41 ± 4.72 µmol/L) were significantly higher than controls (13.12 ± 2.50 µmol/L) ($P < 0.05$). In contrast, lower aryl esterase activity was found in hypothyroidism (5.03 ± 0.50 U/L), and hyperthyroidism (3.64 ± 0.40 U/L) when compared to control group (6.78 ± 0.62 Ku/L) with significant values ($P < 0.05$).

Conclusions: These results disclosed a significant role of protein oxidation in patients with hypothyroidism as well as the oxidative stress status.

Keywords: Thyroidism, hypothyroidism, hyperthyroidism, advanced oxidation protein products, aryl esterase activity

Introduction

Thyroid gland is a vital organ in the body that plays most important role in the harmony and control of growth as well as the metabolism of the human body.[1] It regulates many modified body functions by secreting continuous amount of thyroid hormones to the blood stream and according to body needs.[2] The main functions of thyroid hormones are controlling blood pressure; regulate body temperature, control metabolism of protein, fat and carbohydrate in all cells, growth hormone secretion, skeletal maturation, heart rate and other functions.[3]

Thyroidism constitutes the main bulk of endocrine diseases that the physicians have to understand during their clinical practice.[4] Thyroidism is associated with either inadequate production (hypothyroidism) or excessive of thyroid hormones (hyperthyroidism).[5]

Elevated levels of reactive oxygen species (ROS) can trigger oxidative stress, resulting in the apoptosis of astrocytes and thyrocytes. This, in turn, increases the likelihood of developing thyroid dysfunction and neurodegenerative conditions. Furthermore, the presence of excessive free radicals increases thyroid thermogenesis causing hyperthyroidism or its excess may cause hypothyroidism by inhibiting iodide uptake.[6] Advanced Oxidation Protein Products (AOPPs), which result from the interaction between oxidants and plasma proteins, are considered reliable markers to estimate the degree of oxidant-mediated protein damage.[7] Most AOPPs are formed due to increased release of myeloperoxidase (MPO) from activated phagocytes.[8] Fibrinogen has been recognized as a key molecule responsible for increased plasma AOPP; although any protein is susceptible to oxidative modification may contribute to increase plasma AOPP concentrations.[9]

The significance of AOPP has been analyzed in numerous diseases as they are widely regarded as easily measurable markers of oxidative stress. Protein oxidation was observed in patients suffering from various diseases such as chronic kidney disease (CKD), rheumatoid arthritis, lupus, cancer, and cardiovascular disease.[10] Higher AOPP levels were observed in patients with hyper uric acid levels due to high triglycerides levels and other endogenous factors.[11] Elevated serum AOPP levels were associated with higher risk of all-cause mortality in hemodialysis patients.[12]

Paraoxonase (PON1) is an enzyme synthesized mainly by the liver that is carried into the circulation bound to high-density lipoproteins (HDL). It can be internalized in peripheral cells and, thus, its protein expression is practically ubiquitous in almost all tissues. The enzyme is a lipoperoxide hydrolase that degrades lipoperoxides in lipoproteins and cells, and participates in the subject's innate immune.[13]

The PON1 has many hydrolysis activities of substrates such as organophosphate triesters, aryl esters, cyclic carbamates, glucuronides, estrogen esters, and thiolactones while its "natural" substrates are assumed to be lactones.[14] Experiments with PON1-knockout mice have indicated that the absence of PON1 leads to an increase in endothelial adhesion molecules and oxidative stress, confirming this enzyme's role in preventing the onset of atherosclerosis.[15]

A clinical study suggested that the serum antioxidant activity of PON1 (arylesterase activity) is an important factor in protecting from oxidative stress and lipid peroxidation in cardiovascular diseases (CAD).[11]

The enzymatic functions of PON1 may be influenced by various environmental factors, such as the presence of certain elements. For instance, dietary lipids and lipid peroxidation products can lead to a reduction in both PON1 activity and gene expression.[16] Our goal was to examine oxidative stress status according to the level of AOPPs and PON1 and their association with thyroidism.

Experimental Part

Subjects

In this case-control study, 100 women with previously untreated thyrodisim, aged 18 to 75, were participated. A control group was selected for comparison consisted of thirty healthy females (aged 18–70 years). Patients were chosen from Al-Imameen Al-Kazimin Medical Hospital in Baghdad, which ran from October 2021 through the end of January 2022. Pregnant women, smokers, people with acute or chronic inflammatory diseases, diabetes mellitus (T2DM or T1DM), chronic or hereditary diseases, and family history made up the exclusion criteria. A formed consent was taken from all participants. The study approval was obtained from the scientific and ethical committee.

Anthropometric Measurements

Body mass index (BMI) was calculated after measurement the standing height by stadiometer, and weight using precision scales by the following equation: weight in (kg)/height² in (meter).

Collection of Blood Samples

After an overnight fast, 5 ml of venous blood from each participant was taken, allowed to clot at room temperature for 10 minutes, and centrifuged at 3000 rpm for 10 minutes before being used for analysis; the separated serum was kept in Eppendroff tubes at –20°C.

Determination of Thyroid Hormones, Lipid Profile and Vitamin D Levels

Thyroid profile included Triiodothyronine (T3), Thyroxine (T4), Thyrotropin (TSH), Free T3 (fT3), Free T4 (fT4) as well as Vitamin D level were measured by Cobas Roshe / Hitachi. Total cholesterol and high-density lipoprotein cholesterol (HDL-c) were measured using an enzymatic method (Hitachi, Germany).

The Friedewald's equation is used to calculate low-density lipoprotein cholesterol (LDL-C), which states that LDL-C is equal to total cholesterol minus (HDL-C plus triglycerides/5), while (triglycerides/5) was used to calculate VLDL.

Determination of Advanced Oxidation Protein Products (AOPP)

The AOPP comprise several chromophores, including pentosidine, carbonyls, and proteins cross-linked by dityrosine, which shows absorbance at a wavelength of 340 nm.[17] Determination of AOPP was based on spectrophotometric detection according to Kalousov et al. and the AOPP concentration was expressed in chloramines-T equivalents.[18]

Determination of PON-1 Arylesterase Activity

Arylesterase activity was determined according to Shen et al. 2014, using phenyl acetate as substrate.[19] PON-1 activity was measured in 100 mM Tris-HCl buffer (pH 8.0) containing 4 mM phenyl acetate substrate and 2 mM $CaCl_2$. The absorbance was monitored spectrophotometrically at 270 nm. Enzyme activity was calculated with a molar extinction coefficient of 1310 M^{-1} cm^{-1}. One unit of arylesterase activity hydrolyzed 1 µmol of phenyl acetate per minute.

Statistical Analysis

Results are expressed as means ± SD for the comparison of non-parametric variables in both groups. The parametric variables of patients and control groups were compared by using ANOVA test (unpaired student *t*-test). Correlation between parameters was assessed by Pearson correlation analysis. Statistical analysis was performed with SPSS 26 statistical software. A *P* value for significance was set at 0.05.

Results

Clinical characteristics of the patients and control groups are described in Table 1 which revealed non-significant difference in age, and height, when compared with control group, while significant higher levels in weight and BMI of hyperthyroidism group and hypothyroidism than those of control groups were observed.

Lipid profile showed different significant levels in the two patients groups when compared with those of control group. A significant ($P < 0.05$) higher TC, LDL-C, and TG levels was found in hypo and hyperthyroidism when compared with control group. Vitamin D showed non-significant differences ($P > 0.05$) between all groups.

Thyroid stimulating hormone was significantly higher in hypothyroidism group (8.45 ± 3.76 µIU/ml) than controls (2.43 ± 0.96 µIU/ml) which were in turn significantly higher than hyperthyroidism group (0.50 ± 0.56 µIU/ml). In contrast, patients in hyperthyroidism group demonstrated higher level of T3, T4 and FT3 (2.34 ± 1.10 nmol/L, 13.37 ± 2.57 µg/dl and 3.96 ± 0.55 pmol/L, respectively) than either controls (1.25 ± 0.30 nmol/L, 9.6 ± 1.08 µg/dl and 3.48 ± 0.28 pmol/L, respectively) or hypothyroidism group (0.37 ± 0.11 nmol/L, 3.16 ± 0.99 µg/dl and 3.01 ± 1.07 pmol/L) with significant differences between the three group. Although FT4 was slightly higher in hyperthyroidism group than controls and hypothyroidism group, the differences were not significant (Table 2).

The mean serum level of AOPP in hypothyroidism group was (71.92 ± 19.04 µmol/L) which was significantly higher than hyperthyroidism group (30.41 ± 4.72 µmol/L) or controls (13.12 ± 2.50 µmol/L) as shown in Table 3 and Figure 1.

In contrast, lower aryl esterase activity was observed in hyperthyroidism (3.64 ± 0.40 U/L) or hypothyroidism (5.03 ± 0.50 U/L) compared to control group (6.78 ± 0.62 U/L), as shown in Table 4 and Figure 2.

Correlation of AOPP and Aryl Esterase with other Variables

Pearson's correlation was used to explore the possible correlation of AOPP and aryl esterase with other variables in hyperthyroidism, hypothyroidism and control groups.

Table 1. **Mean ± SD of age, weight, height, BMI, lipid profile, and vitamin D in hypothyroidism, hyperthyroidism, and control groups**

Variables	Controls ($n = 30$)	Hypothyroidism ($n = 50$)	Hyperthyroidism ($n = 50$)	*P*- value
Age (years)	34.32 ± 12.56	39.1 ± 14.01	34.93 ± 12.76	0.320
Weight (Kg)	63.96 ± 3.78	*77.66 ± 11.08[a]	*68.0 ± 9.11[a]	**0.000**
Height (cm)	162.85 ± 7.72	160.26 ± 7.86	163.83 ± 7.47	0.186
BMI (Kg/m^2)	23.58 ± 1.38	*30.37 ± 3.69[a]	*31.44 ± 3.25[a]	**0.000**
TC (mg/dl)	146.86 ± 17.0	*231.93 ± 26.1[a]	*204.20 ± 21.4[a,b]	**0.000**
TG (mg/dl)	92.66 ± 16.55	*123.06 ± 46.77[a]	*120.05 ± 41.43[a]	**0.006**
HDL-C (mg/dl)	53.59 ± 9.10	52.36 ± 10.78	52.82 ± 11.14	0.903
LDL-C (mg/dl)	102.41 ± 14.57	*171.27 ± 8.54[a]	*143.78 ± 8.96[a]	**0.018**
VLDL (mg/dl)	24.35 ± 8.49	25.68 ± 9.16	26.86 ± 5.62	0.484
Vit D (ng/ml)	28.66 ± 6.99	25.24 ± 7.05	26.29 ± 8.26	0.211

**P* value < 0.05. The small liters refer to presence of significance between groups; a: significant when compared with control, b: significant when compared between hypo and hyper.

Table 2. **Mean ± SD of thyroid hormones levels in hypothyroidism, hyperthyroidism, and control groups**

Variables	Controls ($n = 30$)	Hypothyroidism ($n = 50$)	Hyperthyroidism ($n = 50$)	*P*- value
TSH (µlU/ml)	2.43 ± 0.96	*8.45 ± 3.76[a]	*0.50 ± 0.56[a,b]	**0.001**
T3 (nmol/L)	1.25 ± 0.30	*0.37 ± 0.11[a]	*2.34 ± 1.10[a,b]	**0.001**
T4 (µg/dl)	9.6 ± 1.08	*3.16 ± 0.99[a]	*13.37 ± 2.57[a,b]	**0.001**
FT3 (pmol/L)	3.48 ± 0.28	*3.01 ± 0.17[a]	3.96 ± 0.55	**0.001**
FT4 (ng/dl)	1.24 ± 0.19	1.21 ± 0.82	1.52 ± 1.15	0.285

**P* value < 0.05. The small liters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

Table 3. Mean ± SD of AOPP in hypothyroidism, hyperthyroidism, and control groups

Variables	Controls ($n = 30$)	Hypothyroidism ($n = 50$)	Hyperthyroidism ($n = 50$)	*P*- value
AOPP (µmol/L)	13.12 ± 2.50	*71.92 ± 19.04[a]	*30.41 ± 4.72[a,b]	**0.001**

**P* value < 0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

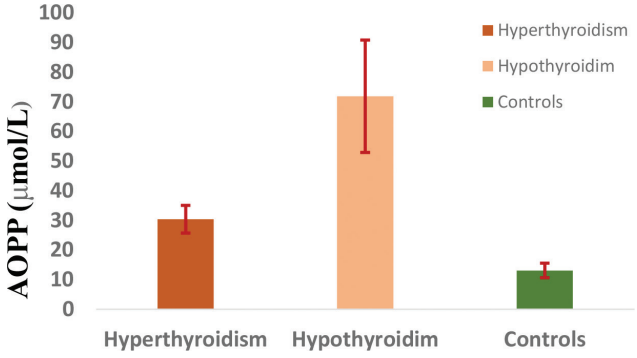

Fig. 1 **Mean serum level of AOPP in the three groups.**

In Control Group

The AOPP demonstrated a positive correlation significantly with height ($r = 0.429$, $P = 0.023$) and a negative correlation significantly with FT3 ($r = -0.422$, $P = 0.025$). Aryl esterase, on the other hand, showed a negative correlation significantly with each of BMI ($r = -0.401$, $P = 0.034$) and HDL ($r = -0.384$, $P = 0.044$) as shown in Table 5, Figure 3.

In Patients Group with Hyperthyroidism

The AOPP showed a negative correlation significantly with FT3 ($r = -0.359$, $P = 0.049$). Aryl esterase, on the other hand, a negative correlation significantly was found with vitamin D ($r = -0.363$, $P = 0.048$) as shown in Table 6, Figure 4.

In Patients Group with Hypothyroidism

The AOPP showed negative correlation significantly with TG ($r = -0.353$, $P = 0.050$), while, aryl esterase showed non-significant correlation with any variable, as presented in Table 7, and Figure 5.

Table 4. **Mean ± SD of Aryl esterase in hypothyroidism, hyperthyroidism, and control groups**

Variables	Controls ($n = 30$)	Hypothyroidism ($n = 50$)	Hyperthyroidism ($n = 50$)	*P*- value
Aryl esterase (U/L)	6.78 ± 0.62	*5.03 ± 0.50[a]	*3.64 ± 0.40[a,b]	**0.001**

**P* value < 0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

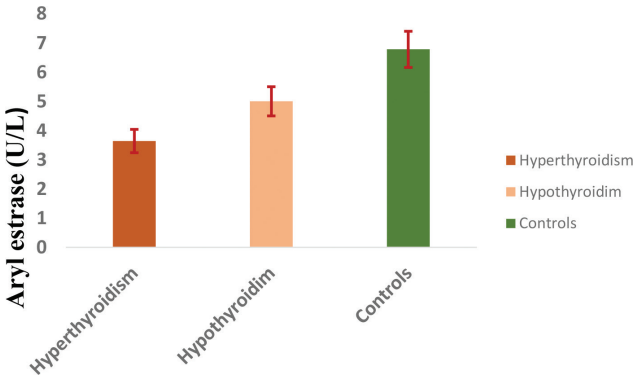

Fig. 2 **Mean serum level of aryl esterase in the three groups.**

Table 5. **Pearson correlation of AOPP and aryl esterase activity with other variables of control group**

Variables	AOPP		Aryl esterase	
	r	*P*-value	*R*	*P*-value
Age	–0.006	0.974	–0.114	0.565
Weight	0.310	0.109	–0.179	0.361
Height	**0.429**	**0.023**	–0.227	0.245
BMI	–0.034	0.864	**–0.401**	**0.034**
TSH	0.295	0.127	0.161	0.414
T3	–0.185	0.347	0.303	0.117
T4	0.306	0.133	0.260	0.181
FT3	**–0.422**	**0.025**	–0.044	0.824
FT4	–0.134	0.496	0.004	0.986
TC	–0.061	0.758	0.056	0.779
TG	0.266	0.179	0.267	0.179
HDL-c	0.176	0.369	**–0.384**	**0.044**
LDL-c	0.212	0.280	0.009	0.966
VLDL	0.204	0.299	–0.058	0.770
Vit. D	–0.016	0.758	–0.268	0.168
Aryl esterase	0.076	0.700	–	–

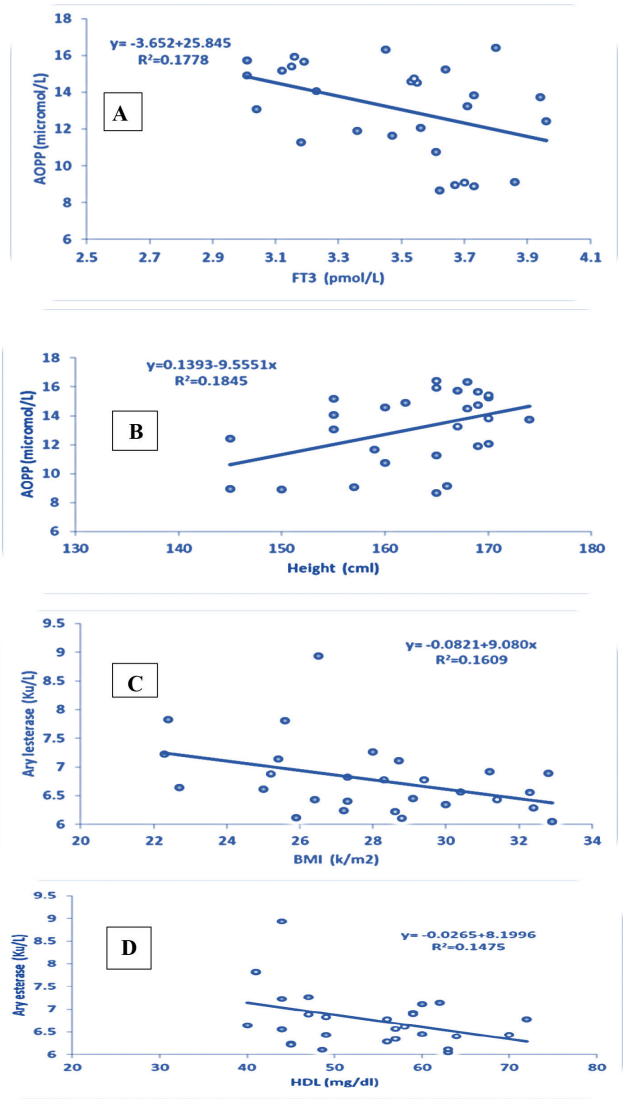

Fig. 3 **Scatter plot and regression line between A: height and AOPP, B: FT3 and AOPP, C: BMI and Arylesterase, D: HDL and Arylesterase in control group.**

Discussion

Thyroid hormones play major roles in cell growth, development, and metabolism. Considerable research supports a relationship between the thyroid hormones and pathophysiology of various thyroidism types. Notably, both hyperthyroidism and hypothyroidism appear to be associated with oxidative stress in animal and human diseases, indicating involvement of the thyroid hormone in disease progression.[20]

The lower vitamin D levels may be due to poor nutrition or inadequate sunlight exposure, which in turn increases susceptibility to autoimmune thyroid disorders. Our result was in agreement with that of a study by Rasool et al.[6]

Sarsat et al. provided information on AOPP, claiming that they are able to trigger the synthesis of inflammatory cytokines in neutrophil leukocytes and monocytes, and seem to act as inflammatory mediators.[21]

Despite a high frequency of overweight and obese subjects in this study, no correlation was found between AOPP and BMI. This finding is consistent with the study conducted by Codoñer-Franch et al. in obese children, where no correlation was found between AOPP and anthropometric measurements (BMI, WC).[22]

Table 6. **Pearson's correlation of AOPP and aryl esterase activity with other variables of patients with hyperthyroidism**

Variables	AOPP		Aryl esterase	
	r	*P*-value	*R*	*P*-value
Age	0.101	0.595	–0.020	0.917
Weight	–0.041	0.813	–0.009	0.962
Height	0.092	0.630	–0.023	0.902
BMI	–0.230	0.221	0.231	0.220
TSH	0.101	0.597	–0.026	0.893
T3	0.051	0.789	–0.191	0.312
T4	0.157	0.409	–0.063	0.741
FT3	**–0.359**	**0.049**	–0.070	0.713
FT4	0.010	0.958	–0.124	0.515
TC	0.228	0.225	–0.117	0.539
TG	–0.079	0.679	–0.113	0.551
HDL-c	–0.002	0.993	0.014	0.943
LDL-c	–0.193	0.306	–0.074	0.699
VLDL	–0.097	0.612	0.011	0.954
Vit. D	0.082	0.665	**–0.363**	**0.048**
Aryl esterase	–0.183	0.333	–	–

Table 7. **Pearson correlation of AOPP and aryl esterase activity with other variables of patients with hypothyroidism**

Variables	AOPP		Aryl esterase	
	R	*P*-value	*R*	*P*-value
Age	–0.021	0.911	–0.183	0.343
Weight	–0.016	0.933	0.080	0.672
Height	–0.102	0.590	–0.100	0.599
BMI	0.062	0.746	0.171	0.367
TSH	0.094	0.621	0.050	0.794
T3	–0.678	0.347	0.185	0.327
T4	0.280	0.134	–0.079	0.687
FT3	–0.185	0.328	0.119	0.531
FT4	0.146	0.385	0.269	0.151
TC	–0.020	0.915	0.125	0.510
TG	**–0.353**	**0.050**	0.109	0.566
HDL-c	0.170	0.370	0.085	0.665
LDL-c	0.043	0.819	0.201	0.288
VLDL	–0.292	0.117	0.020	0.915
Vit. D	–0.196	0.300	–0.222	0.238
Aryl esterase	0.243	0.195	–	–

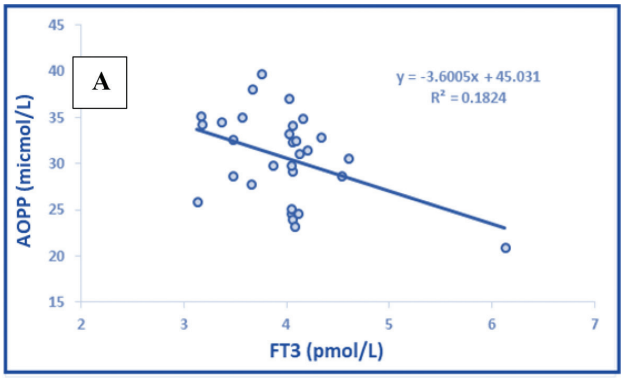

Fig. 4 **Scatter plot and regression line between: A: FT3 and AOPP, B: vitamin D and aryl esterase in patients with hyperthyroidism.**

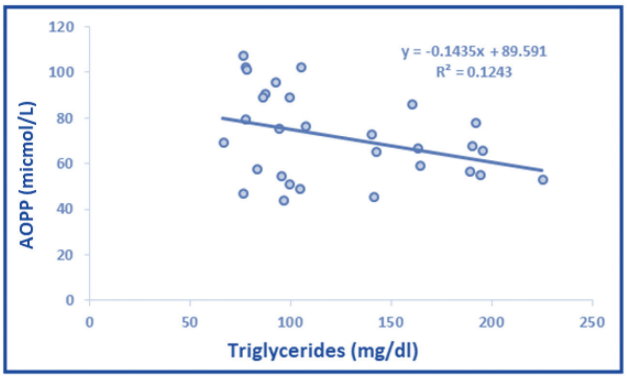

Fig. 5 **Scatter plot and regression line between triglycerides and AOPP in patients with hypothyroidism.**

Our study showed a negative association between TG and AOPP in patients with hypothyroidism, which could be attributed to a combination of metabolic changes as explained by the study of Diana et al.[23]

Hyperlipidemia is associated with oxidative stress and inflammation.[24] Liu et al.[25] have reported that AOPP are an important component of the complex interaction between inflammation and oxidative stress with the atherogenic process. The formation of AOPP is mediated by hypochlorous acid (HClO) arising from the action of myeloperoxidase, the same compound that promotes oxidation of LDL-C (Ox-LDL).[26,27]

PON1 offers several benefits, including enhancing HDL cholesterol-mediated efflux from macrophages, safeguarding LDL from oxidation by reducing lipid peroxide levels, hindering ox-LDL uptake by macrophages, which ultimately prevents macrophage foam cell formation, and inhibiting macrophage cholesterol biosynthesis.[28] PON1 antioxidant activity is inversely correlated to carotid intima-media thickness. The hydrolytic lactonase, arylesterase, and paraoxonase activities of PON1 are all inactivated under oxidative stress, and epidemiological evidence shows that low serum PON1 activity is associated with many pathological diseases.[11,29]

Our study was in contract with a study by Azizi et al.[30] who found significant lower PON1 activity in both

hyperthyroidism and hypothyroidism patients that lead them to conclude that the observed increased LDL-C oxidation in thyroid dysfunction, at least to some extent, can be attributed to reduced PON1 activity.

Low PON-1 activity in this study may be due to high BMI and dyslipidemia as supported by previous study that illustrated a link between low-HDL-PON activity and membrane peroxidation in obese and dyslipidemia patients.[31] A significant detrimental effect of overt hypothyroidism on the antioxidant PON-1 serum levels compared to normal healthy controls was observed.[32]

Conclusion

In conclusion, AOPP concentrations were observed to increase while the PON1 activity decreases in both types of thyroidism that indicates the presence of oxidative stress. The fact that AOPP increased could be attributed to metabolic changes such as being overweight, obesity, and hypertriglyceridemia.

Therefore, AOPP could be considered a good indicator and a therapeutic target by appropriate dietary supplementation of antioxidants.

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Conflict of Interest

The writers declare that there are no discorded of interest regarding the publication of this paper.

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