OXIDANT-ANTIOXIDANT STATUS IN PATIENTS WITH HYPERTHYROIDISM: EFFECT OF ANTITHYROID TREATMENT

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ABSTRACT

Background and Aim : Hyperthyroidism is a hypermetabolic state associated with increased oxygen consumption that may increase free radical generation, therefore oxidative stress may play a role in the pathogenesis of tissue damage caused by hyperthyroidism. The aim of the present study was to evaluate oxidant-antioxidant status in patients with hyperthyroidism and the effects of antithyroid treatment. *Methods :* We studied 20 untreated newly diagnosed hyperthyroid patients (group I, 14 women and 6 men, 33.2 ± 7.8 years), 16 treated hyperthyroid patients who achieved euthyroidism with antithyroid drug (carbimazole) (group II, 11 women and 5 men, 34.2 ± 9.5 years) and 20 age and sex matched

healthy control subjects. Recorded data included weight, BMI, heart rate, blood pressure, and lipogram. Malondialdehyde (MDA), nitric oxide (NO), reduced glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) were assayed in all patients and controls. Results: Compared with control group, group I patients had an increase in MDA ($P < 0.01$), and NO ($P < 0.01$) and a decrease in GSH ($P < 0.01$), CAT ($P < 0.05$) and SOD ($P < 0.01$). Compared with group II, group I patients had increased MDA and NO ($P < 0.01$) and decreased GSH ($P < 0.01$), CAT ($P < 0.05$) and SOD ($P < 0.01$). Group II patients had increased MDA in comparison to control group ($p < 0.05$), however, NO, GSH, CAT and SOD did not show significant differences between the

two groups. In group I patients, FT4 showed positive correlation with MDA and NO ($r=0.633$, $P=0.003$ & $r=0.580$, $P=0.007$ respectively) and negative correlation with GSH and SOD ($r=-0.490$, $p=0.028$ & $r=-0.559$, $P=0.01$ respectively). Conclusion: Study results reveal an increased oxidative stress indices and decreased antioxidant response parameters in patients with hyperthyroidism. Antithyroid drug treatment can reduce oxidant and increase antioxidant parameters. Oxidant-antioxidant status indices may be useful markers during assessment and in the follow up of therapy in hyperthyroid patients. Antioxidants supplementation along with antithyroid drugs could be beneficial.

INTRODUCTION

Oxidant-antioxidant status in the body depends on the balance between reactive oxygen species (ROS) (such as superoxide anion, hydrogen peroxide and hydroxyl radical) and several defence mechanisms including enzymatic systems and antioxidant compounds (such as superoxide dismutase, "SOD", catalase "CAT" and glutathione "GSH" which cause neutralization or inactivation of free

radicals. ROS are products of physiological process of oxygen consumption and metabolism where few percent of oxygen escape mitochondrial respiratory chain and undergo one electron reaction forming free radicals (1, 2). Excess ROS results in oxidative stress which has a role in the pathogenesis of several disorders through oxidation of molecules leading to tissue injury (3).

Thyroid gland hormones have effects on basal metabolic rate. Hyperthyroidism results in an increased rate of metabolism and oxygen consumption that may enhance ROS production (4, 5) and it was suggested that hyperthyroidism increases oxidative stress in the body (2), which may play a role in hyperthyroidism induced tissue damage. The present study aimed to evaluate the effect of hyperthyroidism and its antithyroid therapy on the oxidant-antioxidant status indicated by certain biochemical markers.

SUBJECTS AND METHODS

The present study included 20 patients with untreated newly diagnosed hyperthyroidism (group I, included 14 women and 6 men with mean age of

33.2±7.8 years), and 16 hyperthyroid patients who achieved euthyroid state with antithyroid drugs and kept on maintenance dose of carbimazole (5-10 mg/day) for a duration ranging from 3.5-18 months, (group II, included 11 women and 5 men with mean age of 34.2±9.5 years). Patients were recruited from inpatient department and outpatient clinic of Diabetes and Endocrinology Unit, Mansoura Specialized Medical Hospital. Patients with hyperthyroidism were presented with diffuse goitre (17 in group I and 14 in group II) and nodular goitre (3 in group I and 2 in group II) as assessed clinically and by thyroid ultrasound. The diagnosis of hyperthyroidism was made on the basis of clinical criteria confirmed by elevated serum FT4, or FT3 above the normal reference range with serum TSH level lower than 0.1 mIU/L (6). Euthyroidism was defined as normal TSH and thyroxine levels. 20 healthy subjects (5 men and 15 women with mean age of 31.9±7.5 years) with normal thyroid function, were regarded as controls. Exclusion criteria included diabetes, smoking, acute or chronic systemic illness, pregnancy, pituitary disorders, other medications and neoplastic diseases.

All participants underwent full history taking and complete clinical examination. Heart rate was measured by the palpatory method at the radial artery level. Sitting blood pressure was measured with mercury sphygmomanometer twice in the sitting position after 10 minutes of rest, the mean of two measurements was used. Weight and height were measured while wearing light clothing and no shoes. BMI was calculated as weight divided by height squared (kg/m²).

From each participant, 10 ml fasting venous blood sample was withdrawn and divided into: 1) 6.5 ml was collected into plain tube, serum was separated and kept in aliquates at -20°C till the assay of superoxide dismutase activity(SOD) according to Winterbourn et al(1975)(7); catalase activity(CAT) by the method of Chance and Mackley(1955) (8), free T4, free T3 and TSH by electrochemoluminescence immunoassay kit supplied by Roche (6,9,10); total cholesterol (TC), and triglycerides (TG) by enzymatic methods (11,12), and HDL-C by the precipitation method then LDL-C was calculated by Friedewald

equation (13), 2) 1.5 ml was collected into EDTA containing tube used for determination of malondialdehyde (MDA), using thiobarbituric acid to form a complex that can be measured colorimetrically (14), 3) 2 ml was collected into heparin containing tube, used for determination of blood reduced glutathione (GSH),⁽¹⁵⁾ and plasma nitric oxide (NO) by colorimetric assay (16).

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 10. To compare between groups, Chi-square test was used for quantitative data (frequency and proportions) and one way ANOVA test was used for quantitative data (mean $\pm$ SD). To test association between variables, Pearson correlation test was used. P value <0.05 was considered statistically significant.

RESULTS

Control and patient groups were matched as regard age and sex. Group I patients had statistically significant lower body weight (67.1 $\pm$ 7.2 vs 73.2 $\pm$ 7.4, $P<0.05$) lower BMI (23.8 $\pm$ 2.7 vs 26.1 $\pm$ 2.8, $P<0.05$), higher pulse rate (98 $\pm$ 8 vs 80 $\pm$ 8, $P<0.01$),

higher systolic blood pressure (134 $\pm$ 13 vs 119 $\pm$ 9, $P<0.01$), higher FT4 and FT3 and lower TSH, compared with control subjects (table 1).

Group I patients had statistically significant lower body weight (67.1 $\pm$ 7.2 vs 71.9 $\pm$ 6.4, $P<0.05$), lower BMI (23.8 $\pm$ 2.7 vs 25.8 $\pm$ 2.4, $P<0.05$), higher pulse rate (98 $\pm$ 8 vs 83 $\pm$ 7, $P<0.01$), higher SBP (134 $\pm$ 13 vs 123 $\pm$ 9, $P<0.01$), higher FT4 and FT3 and lower TSH compared with group II. No significant difference between group II and control subjects as regard body weight, BMI, pulse rate, blood pressure values or thyroid hormones levels (table 1).

Group I patients showed statistically significant lower total cholesterol (161.3 $\pm$ 14.7 vs 176 $\pm$ 18.3, $P<0.01$), lower LDL-C (90 $\pm$ 13 vs 102 $\pm$ 17, $P<0.05$), lower HDL-C (44 $\pm$ 4.6 vs 50.2 $\pm$ 4.4, $P<0.01$) and higher TG (139.3 $\pm$ 22 vs 114.1 $\pm$ 22.2, $P<0.01$) compared with control subjects. Group I had significant lower total cholesterol (161.3 $\pm$ 14.7 vs 184.4 $\pm$ 18.8, $P<0.01$), lower LDL-C (90 $\pm$ 13 vs 106 $\pm$ 17.5, $P<0.05$), and lower HDL-C (44 $\pm$ 4.6 vs 48.1 $\pm$ 4.1,

$P<0.01$), compared with group II. However, no significant difference between the two patient groups as regard TG levels. Group II had higher TG levels as compared to controls. However, no significant difference between the two groups total cholesterol, LDL-C and HDL-C levels (table 1).

Group I patients had statistically significant higher malondialdehyde (MDA) (3.58 ± 1.32 vs 1.26 ± 0.5 , $P<0.01$), higher nitric oxide (NO) (35.78 ± 8.18 vs 14.1 ± 3.7 , $P<0.01$), lower reduced glutathione (GSH) (1.84 ± 0.65 vs 5.17 ± 1.41 , $P<0.01$), lower catalase (CAT) activity (0.0551 ± 0.016 vs 0.069 ± 0.019 , $P<0.05$), and lower superoxide dismutase activity (SOD) (37.15 ± 6.61 vs 54.11 ± 4.85 , $P<0.01$) compared with control subjects. Group I patients had statistically significant higher MDA (3.58 ± 1.32 vs 1.82 ± 0.74 , $P<0.01$), higher NO (35.78 ± 8.18 vs 19.13 ± 3.4 , $P<0.01$), lower GSH (1.84 ± 0.65 vs 4.93 ± 1.12 , $P<0.01$), lower SOD

(37.15 ± 6.61 vs 51.9 ± 4.36 , $P<0.01$) and lower CAT (0.0551 ± 0.016 vs 0.0669 ± 0.018 , $P<0.05$) compared with group II patients. Group II in comparison to control group showed significantly higher MDA (1.82 ± 0.74 vs 1.26 ± 0.5 , $P<0.05$), however, no significant difference between group II and control subjects as regard NO, GSH, CAT and SOD values (table 2).

In group I, TSH showed negative correlation with MDA ($r=-0.645$, $P=0.002$), negative correlation with NO ($r=-0.537$, $P=0.015$), positive correlation with GSH ($r=0.449$, $P=0.047$) and positive correlation with SOD ($r=0.463$, $P=0.04$). There was positive correlation of FT4 with MDA and NO ($r=0.633$, $P=0.003$ & $r=0.580$, $P=0.007$ respectively) and negative correlation of FT4 with GSH and SOD ($r=-0.490$, $P=0.028$ & -0.559 , $P=0.01$ respectively). FT3 correlated positively with MDA and NO ($r=0.580$, $P=0.007$ & $r=0.454$, $P=0.044$ respectively) (table 3).

Table (1): Characteristics of the studied groups.

	Control group (n=20)	Hyperthyroid patients	
		Untreated (group I, n=20)	Treated (group II, n=16)
Male/female	5/15 (25/75)	6/14 (30/70)	5/11 (31.3/68.8)
Age (years)	31.9±7.5	33.2±7.8	34.2±9.5
Weight (kg)	73.2±7.4	67.1±7.2 ^a ^b	71.9±6.4
BMI (kg/m ²)	26.1±2.8	23.8±2.7 ^a ^b	25.8±2.4
Duration of therapy (months)	-	-	3.5-18
Goitre: Diffuse	-	17	14
Nodular	-	3	2
Pulse (beat/min)	80±8	98±8 ^a ^b	83±7
SBP (mmHg)	119±9	134±13 ^a ^b	123±9
DBP (mmHg)	76±6	73±8	77±6
FBS (mg/dl)	88.6±12	94±13	91±10
TC (mg/dl)	176±18.3	161.3±14.7 ^a ^b	184.4±18.8
TG (mg/dl)	114.1±22.2	139.3±22 ^a	145±21.9 ^a
HDL-C (mg/dl)	50.2±4.4	44±4.6 ^a ^b	48.1±4.1
LDL-C (mg/dl)	102±17	90±13 ^a ^b	106±17.5
FT4 (ng/dl)	1.4±0.27	2.61±0.35 ^a ^b	1.58±0.3
FT3 (pg/ml)	2.83±0.77	4.6±1.4 ^a ^b	2.9±0.83
TSH (mIU/L)	2.26±0.8	0.035±0.027 ^a ^b	2.1±0.75

^ap Compared to control, ^bp compared to group II

* P<0.05

** P<0.01

Table (2): Levels of oxidant-antioxidant status markers in patients with hyperthyroidism and in control group

	Control group (n=20)	Hyperthyroid patients	
		Group I (n=20)	Group II (n=16)
MDA (nmol/ml packed cells)	1.26±0.5	3.58±1.32 **ab	1.82±0.74 *a
NO (μmol/L)	14.1±3.7	35.78±8.18 **ab	19.13±3.4
GSH (mmol/L cells)	5.17±1.41	1.84±0.65 **ab	4.93±1.12
CAT (Ku/g protein)	0.0690±0.019	0.0551±0.016 *ab	0.0669±0.018
SOD (U/g Hb)	54.11±4.85	37.15±6.61 **ab	51.9±4.36

^ap Compared to control, ^bp compared to group II

* P<0.05

** P<0.01

Table (3): Correlation of TSH and thyroid hormones with oxidative stress markers in patients with hyperthyroidism.

	TSH		FT4		FT3	
	r	p	r	p	r	p
MDA	-0.645 **	0.002	0.633**	0.003	0.580**	0.007
NO	-0.537*	0.015	0.580	0.007	0.454*	0.044
GSH	0.449*	0.047	-0.490*	0.028	- 0.319	0.17
CAT	0.201	0.395	-0.252	0.284	- 0.052	0.827
SOD	0.463	0.04	-0.559**	0.01	- 0.350	0.130

* Correlation is significant at P<0.05

** Correlation is significant at P<0.01

DISCUSSION

Reactive oxygen species (ROS) are produced in the body during the process of oxygen utilization, low levels of ROS are necessary for biological processes. However, excess amount and/or inadequate neutralization of ROS by antioxidant defence systems may result in oxidative stress which has been implicated in the pathogenesis of several disorders (3, 17). High concentrations of thyroid hormones may change oxygen metabolism and stimulate the production of free radicals (4). So the study of oxidant-antioxidant status in patients with hyperthyroidism has gained increased interest in recent years.

In the present study, patients with untreated hyperthyroidism exhibited lower body weight and BMI, increased heart rate and higher systolic blood pressure when compared to control subjects and treated hyperthyroid patients. Weight loss, increased heart rate and systolic hypertension are known manifestation of hyperthyroidism which can be changes after control of thyroid function (18-21).

This study revealed decreased levels of TC, LDL-C and HDL-C and increased TG levels in patients with untreated hyperthyroidism as compared to control subjects. TC, LDL-C and HDL-C levels were increased in patients with treated hyperthyroidism than in untreated cases, this in agreement with the results of Sewerynek et al. (22). Such lipid changes in hyperthyroidism can be explained by enhanced lipolysis and delivery of fatty acids to the liver associated with increased TG synthesis and secretion (23, 24), changes in the activity of enzymes involved in HDL-C particle remodeling (25) and enhanced cholesterol clearance caused by thyroid hormones effect on LDL receptor gene expression (26-28).

Hyperthyroidism is a hypermetabolic state that is associated with increased oxygen consumption. It was found that thyroid hormone acceleration of oxygen consumption leads to elevation of superoxide radical and hydrogen peroxide generation at mitochondrial or microsomal sites, as well as nitric oxide by nitric oxide synthase (4). Excess production of these

free radicals induce oxidation of biomolecules in addition to the formation of lipid peroxides leading to DNA damage, cell injury or death (1, 29).

Elevated lipid peroxidation products may be useful as markers of oxidative stress during hyperthyroidism (30). One of the compounds originating in the process of lipid peroxidation is malondialdehyde (MDA). The present study revealed increased levels of MDA and NO in untreated hyperthyroid patients as compared to controls and treated hyperthyroid (table 2), which confirmed the results of other authors who found increased free radicals generation indices, lipids peroxides or MDA in patients with hyperthyroidism (30-33). In this study, MDA and NO in untreated hyperthyroid were correlated with the changes in thyroid hormones (table 3), which can be supported by the previous finding of a relation between both NO and lipid peroxides and free thyroxine (34,35). These data indicated increased free radical production and lipid peroxidation during hyperthyroidism which is related to thyroid status.

Glutathione (GSH), catalase (CAT) and superoxide dismutase are antioxidants that protect the body against free radical induced oxidative stress injury (36). In the present study reduced GSH levels, SOD and CAT activity were lower in patients with untreated hyperthyroidism in comparison to healthy control subjects and treated hyperthyroid. SOD, CAT and GSH in untreated hyperthyroid were correlated to TSH and thyroid hormones (table 3), this indicates diminished antioxidative response in hyperthyroidism which is related to thyroid status, these findings can be explained by the regulatory effect of thyroid hormones on the activity of antioxidant enzymes (37). Moreover, transcriptional activation of respiratory genes by thyroid hormone causes high production of ROS and consequent antioxidant depletion (38-40). There is controversy regarding the level and activity of antioxidant markers in hyperthyroidism. In agreement with our results, previous studies revealed a decrease in SOD⁽⁴¹⁾, CAT and GSH⁽⁴²⁾ in patients with hyperthyroidism versus controls. However, some authors found no difference in SOD (30) and catalase activity (2)

between hyperthyroid and control groups. While others observed an increase in SOD and catalase activity in hyperthyroid patients (31,43), and consider this a compensatory response against increased peroxidation products in the body, thereby protects the cells against oxidative damage.

In this study, hyperthyroid patients treated with carbimazole had oxidative stress markers levels which did not significantly differ from control values except for MDA which was slightly higher than control value. In agreement, other researchers reported normalization of oxidative stress parameters in hyperthyroid patients who become euthyroid after antithyroid drug therapy (31, 39). This indicates that treatment with antithyroid drugs may help to decrease the imbalance in oxidant-antioxidant status, suggested mechanisms for this include a decrease of thyroid hormones levels and a possible antioxidant effect of carbimazole. However, it was suggested that carbimazole does not act as a free radical scavenger (44), also antioxidant supplementation in the

treatment of hyperthyroidism is justified (45).

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الملخص العربي

حالة المؤكسدات ومضادات الأكسدة في مرضى زيادة إفراز الغدة الدرقية وتأثرها بالعلاج المضاد للغدة الدرقية

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الهدف من الدراسة :

• تسبب زيادة إفراز الغدة الدرقية تغيرات في معدل الأيض وإستهلاك الأكسجين مما قد يؤثر على توليد الشقوق الحرة التى لها تأثير مدمر على الأنسجة. وتهدف الدراسة الى تقييم مستوى المؤكسدات ومضادات الأكسدة فى مرضى زيادة إفراز الغدة الدرقية وتأثير العلاج المضاد للغدة الدرقية على ذلك.

المرضى وطريقة البحث :

• ضمت الدراسة مجموعتين من مرضى زيادة إفراز الغدة الدرقية، المجموعة الأولى مكونه من ٢٠ مريضاً قبل العلاج ، والثانية مكونه من ١٦ مريضاً تم علاجهم بواسطة دواء مضاد للغدة الدرقية (كاربيمازول) كما ضمت الدراسة ٢٠ شخصا من الأصحاء كمجموعة ضابطة. وقد خضع المرضى والمجموعة الضابطة للفحص الإكلينيكي الشامل والتحليل الطبية التى شملت هورمونات الغدة الدرقية ونسبة الدهون بالدم وعوامل التأكسد (بروكسيدات الدهون و نيتريك أوكسيد) ومضادات الأكسدة (إنزيم الكاتيليز وإنزيم سوپراوكسيد ديسميٹيز والجلوتاثيون).

النتائج :

• تبين وجود زيادة فى نسبة المألونديالدهيد (ناتج بروكسيدات الدهون) والنيتريك أوكسيد وانخفاض فى نشاط إنزيم الكاتيليز والسوبر أوكسيد ديسميٹيز ونسبة الجلوتاثيون فى مرضى

زيادة إفراز الغدة الدرقية الذين لم يعالجوا عند مقارنتهم بالمجموعة الضابطة والمرضى الذين تم علاجهم بالكاريمازول، كما لوحظ وجود علاقة بين مؤشرات الضغط التأكسدي وهورمونات الغدة الدرقية.

خلاصة البحث :

• مرضى زيادة إفراز الغدة الدرقية لديهم ارتفاع فى نسبة المؤكسدات وانخفاض فى مضادات الأكسدة الذى له علاقة بوظائف الغدة الدرقية، مما قد يعرضهم للتأثير المدمر للضغط التأكسدي كما أن العلاج المضاد للغدة الدرقية يقلل من المؤكسدات ويزيد نشاط مضادات الأكسدة ولذا فإن قياس مؤشرات الضغط التأكسدي أثناء تقييم ومتابعة هؤلاء المرضى، واستخدام مضادات الأكسدة كعلاج بجانب الأدوية المضادة للغدة الدرقية قد يؤدي الى نتيجة أفضل فى تلك الحالات .