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Original Article

Study of oxidant/antioxidant balance and insulin resistance status in both hypo- and hyperthyroid patients: relationship between thyroid hormones and insulin resistance components

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Abstract

This study aimed to determine changes in the oxidant/antioxidant status and evaluate the relationship between thyroid hormones and components of insulin resistance in dysthyroid patients. Our study was conducted on 30 women, including 10 euthyroid, 10 hypothyroidism and 10 hyperthyroid subjects. Glycemia, insulinemia and homeostasis model assessment insulin resistance index (HOMA-IR), lipids (triglycerides, total cholesterol, HDL and LDL cholesterol), thyroid hormones (TSH, FT_3 and FT_4), malondialdehyde levels and antioxidant enzymes activities (catalase, superoxide dismutase and glutathione peroxidase activities) were explored. In the hypothyroid state, IR is characterized by normal plasma glucose, hyperinsulinemia, hyperlipidemia and redox status abnormalities compared to the euthyroid group. TSH levels correlated positively with insulin and HOMA-IR, while FT_4 correlated positively with HOMA-IR and insulin in a hyperthyroid state. Thyroid dysfunctions were characterized by an imbalance of the oxidant/antioxidant system and associated with insulin resistance components.

Keywords: hypothyroidism, hyperthyroidism, insulin resistance, oxidative stress.

Introduction

Insulin resistance (IR) is defined as reduced biological responsiveness to insulin on glucose uptake at the insulin-sensitive target tissues, such as liver, adipocyte and skeletal muscle cells, which creates an imbalance in glucose homeostasis [1, 2] and can lead to various degrees of carbohydrate metabolism disorders like hyperinsulinemia, hyperlipidemia, impaired glucose tolerance, and increased inflammatory markers in plasma [3, 4].

The presence of carbohydrate disorder has been demonstrated in thyroid disease involving either obvious hyperthyroidism or hypothyroidism. The severity of the disease is proportional to the severity of these disorders [5]. Both hypothyroidism and hyperthyroidism have been suggested to be associated with insulin resistance. Furthermore, even variations of thyroid function within normal range might be associated with development and progression of diabetes [6].

Hyperthyroidism has been associated with insulin resistance which has been linked with elevated glucose turnover, increased intestinal glucose absorption, elevated hepatic glucose output and raised free fatty acid concentrations [7]. While clinical hypothyroidism is considered a risk factor for insulin resistance, the pathogenetic mechanism may be related to the dysregulation of the leptin action at the hypothalamic level,

the impaired GLUT4 translocation, and the increase in free fatty acids [8].

In response to converting excessive amounts of free fatty acid and other nutrients into fat, the adipocyte can develop signs of oxidative stress [9], which may play an important role in the pathogenesis of insulin resistance in both hypo- and hyperthyroidism.

A better understanding of the complex relationship between thyroid dysfunction and IR may provide additional treatment targets in the future to prevent the progression of diabetes and its microvascular complication in dysthyroid patients and to reduce the severity of thyroid diseases.

For these reasons, the present study aimed to examine the association between the thyroid hormones and insulin resistance components (glucose, insulin or HOMA-IR values) to investigate the possible relationship between IR and thyroid dysfunction (both hypo- and hyperthyroidism) and to evaluate oxidative stress status in hypothyroidism subjects.

Material and methods

Subjects

The study was conducted and approved by the Ethical Committee of Molecular and Cell Biology Department, Faculty of Nature and Life Sciences, University of Mohammed Seddik Benyahia-Jijel, Algeria, from January to June 2018. The patients visiting the Diabetology and Endocrinology Clinic (Jijel, Algeria) were screened and at each visit, demographic and clinical information, including details of other illnesses, were documented and clinical examinations were carried out. Experiments were performed on twenty patients each (ten) suffering from hypothyroidism (Hpo) and hyperthyroidism (Hpr). A total of ten healthy female volunteers served as controls (Eut: Euthyroid) with normal serum TSH and a normal range of HOMA-IR.

Inclusion and exclusion criteria

All patients with clinical diagnosis and laboratory findings of thyroid disorders (hypothyroidism and hyperthyroidism) for more than three months were included. Study participants were excluded from the study if they had a history of pregnancy and lactation, diabetes, polycystic ovarian disease, liver disorders, renal disorders, congestive cardiac failure or any other systemic illness.

Biochemical measurement parameters

After an overnight fasting, blood samples were collected from all participants for measuring biochemical parameters: lipid profile, namely, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL), in addition to levels of glucose and insulin, free triiodothyronine (FT_3), free thyroxine (FT_4) and thyroid stimulating hormone (TSH). Measurements of plasma glucose concentrations were determined using the enzymatic colorimetric method with glucose oxidase. Fasting total cholesterol, triglycerides, and HDL cholesterol levels were measured by enzymatic colorimetry using commercial kits from Spinreact, Spain. LDL cholesterol was calculated for using the equation: LDL=total cholesterol – HDL – (triglycerides/5) [10]. Plasma insulin and TSH were measured by ELISA (a solid phase enzyme-linked immunosorbent assay) using commercially available kits (Menarini Diagnostics, France) and (IBL International, Germany), respectively, FT_4 and FT_3 were determined by chemiluminescent immunometric assays using the Abbott reagent kit, ARCHITECT.

Reference range

For TSH was 0.25–5 mIU/L, FT_3 (4.0–8.3 pmol/L), FT_4 (9.0–20.0 pmol/L). Thyroid function groups were determined as follows: patients were said to be euthyroid if all thyroid hormone levels fell within the reference range. Hypothyroidism was defined as TSH>5. Hyperthyroidism was defined as TSH<0.25 mIU/L. The normal range for fasting insulin was 2.6–24.9 µU/ml.

Anthropometric and blood pressure measurements

Height was measured to the nearest 0.1 cm using a stadiometer, and weight was measured to the nearest 0.1 kg using standard methods. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2) and categorized as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2) and obesity (≥30 kg/m^2) [11, 12]. Blood pressure was measured by an auscultatory method in each subject in a supine position.

Insulin resistance

Insulin resistance was calculated using the homeostasis model assessment insulin resistance [13, 14] (HOMA-IR) according to the following formula: Fasting

glucose (mmol/L) × fasting insulin (µU/mL)/22.5. Insulin resistance was defined as HOMA-IR index ≥2.4 [15].

Biomarkers of oxidative stress in serum

The principle of malondialdehyde (MDA) determination was based on the spectrophotometric measurement of the color occurring during the reaction to thiobarbituric acid with MDA. The concentration of thiobarbituric acid reactive substances was calculated by the absorbance coefficient of the malondialdehyde-thiobarbituric acid complex and expressed in nmol/ml [16, 17].

The catalase activity was estimated according to the method of Clairborne (1985) [18]. The determination of CAT activity depends on the change in absorbance resulting from the decomposition of H_2O_2 by CAT. This change is measured at 240 nm every min for 2 min. Enzyme activity was expressed as a unit per mg of protein.

The measure of superoxide dismutase activity (SOD) was based on the ability of the enzyme to inhibit the auto-oxidation of pyrogallol. The measurement was based on the modified method of Marklund and Marklund (1974) [19]. The reagent consisted of 0.252 M pyrogallol in 0.1 M sodium phosphate buffer (pH 7.4) and the appropriate volume of serum. The reaction was initiated by light illumination, and the oxidation rate was measured with a spectrophotometer at 420 nm. SOD activity is expressed as units/mg of protein. The unit is defined as the amount of the enzyme which caused 50% inhibition of pyrogallol oxidation per min and per mg of protein.

Glutathione peroxidase (GPx) activity was measured by the procedure of Floche and Gunzler (1984) [20]. 1 ml of the reaction mixture, containing 0.3 ml of phosphate buffer (0.1 M, pH 7.4), was prepared; 0.2 ml of GSH (2 mM), 0,1 ml of sodium azide (10 mM), 0.1 ml H_2O_2 (1 mM) and 0.3 ml of serum. After incubation at 37°C for 15 min, the reaction was completed by the addition of 0.5 ml 5% TCA. Tubes were centrifuged at 1,500 × g for 5 min and the supernatant was collected, 0.2 ml of phosphate buffer (0.1 M pH 7.4) and 0.7 ml of DTNB (0.4 mg/ml) were added to 0.1 ml of reaction supernatant. After mixing, absorbance was recorded at 420 nm.

Statistical analysis

Collected data were analyzed using the Statistical Package for Minitab (ver. 15). All data were expressed as means±standard deviation (SD). Student's t-test followed by One-way analysis of variance (ANOVA) was used to compare differences between the study and control groups. Pearson's correlation coefficients were calculated to determine the strength of the associations. A level of $p<0.05$ was considered statistically significant.

Results

Baseline characteristics of different study groups

This study included 30 participants, 10 hypothyroid patients, 10 hyperthyroid patients and 10 euthyroid control groups. Table 1 shows the baseline characteristics of different study groups. There were no significant differences ($p>0.05$) among the three groups in the mean of age (Eut: 43.8±3.9; Hpo: 40.0±4.7; Hpr: 42.3±6.5) and the mean of diastolic blood pressure (Eut: 7.55±0.19; Hpo: 7.45±0.37; Hpr: 7.17±0.48), while the systolic blood pressure of hyperthyroid subjects was significantly higher than in the control group. There was a statistically significant increase in weight and BMI in the hypothyroid group compared to the control group ($P<0.0001$).

Table 1: Baseline characteristics of different study groups.

Characteristic	Euthyroid (n=10)	Hypothyroid (n=10)	Hyperthyroid (n=10)
Age (years)	43.8±3.9	40.0±4.7	42.3±6.5
Body weight (kg)	59.57±1.3	79.5***±3.3	60.2±4.8
BMI (kg/m²)	23.86±0.41	2.47***±1.6	24.37±2.3
Blood pressure (mmHg)			
Systolic	11.30±0.3	11.36±0.36	13.16##±0.4
Diastolic	7.55±0.19	7.45±0.37	7.17±0.48

Note: Values are given as mean with their standard error. Significance of differences: between (Eut) and (Hpo): (*** – $p<0.001$); between (Eut) and (Hpr): (## – $p<0.01$).

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Table 2: Lipid parameters in euthyroid, hypothyroid and hyperthyroid states.

Lipid parameters	Euthyroid (n=10)	Hypothyroid (n=10)	Hyperthyroid (n=10)
Total cholesterol (g/L)	1.35±0.12	1.86**±0.11	1.84#±0.18
Triglyceride (g/L)	0.74±0.08	1.11±0.21	1.04±0.18
HDL cholesterol (g/L)	0.55±0.091	0.50±0.39	0.54±0.09
LDL cholesterol (g/L)	0.77±0.19	1.14**±0.37	1.07#±0.48

Note: Values are given as mean with their standard error. Significance of differences: between (Eut) and (Hpo): (** – p<0.01); between (Eut) and (Hpr): (# – p<0.05).

Lipid parameters

In comparison with control subjects, total and LDL-cholesterol means were found to be significantly higher in hyperthyroid (P<0.05) and hypothyroid patients (P<0.01), while HDL cholesterol and triglycerides did not show significant difference (P>0.05) (Table 2).

Insulin resistance components

Mean HOMA-IR was significantly higher in the hypothyroid (P<0.01) and the hyperthyroid patients (P<0.05) as compared to Eut subjects, whereas insulin levels were significantly higher in the Hpo group (P<0.05) when compared to control group. There were no significant differences in fasting plasma glucose levels among the three groups (Figure 1).

Thyroid function parameters

TSH concentration was significantly higher in Hpo group (P<0.05) and lower in Hpr group (P<0.01) as compared to the control group. In comparison, the FT_4 concentration of hyperthyroid patients was significantly higher than in the control group (P<0.05), but we could not find any significant differences in FT_3 among the three groups (Figure 2).

Oxidative stress markers

Among serum MDA leveles, CAT, SOD and GPx activities were significantly increased in hypothyroid patients (p<0.05, p<0.05, p<0.05, and p<0.01, respectively) and hyperthyroid subjects (p<0.05, p<0.05, p<0.01, and p<0.01, respectively), compared with euthyroid controls (Figure 3).

Correlation between thyroid function parameters and insulin resistance markers in Hpo and Hpr groups

In hypothyroid state, we found that TSH levels correlated positively with: insulin (r=0.557; p=0.048) and HOMA-IR (r=0.59; p=0.043), while in hyperthyroid state FT_4 levels correlated positively with: HOMA-IR (r=0.84; p=0.036) and insulin (r=0.77; p=0.073) (Table 3).

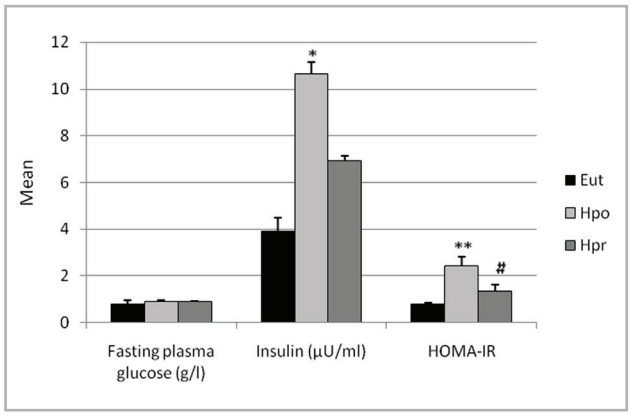

Figure 1: Glycaemia, insulinemia and HOMA-IR in euthyroid, hypothyroid and hyperthyroid states. Values are given as mean with their standard errors. Significance of differences: between (Eut) and (Hpo): (* – p<0.05; ** – p<0.01); between (Eut) and (Hpr): (# – p<0.05).

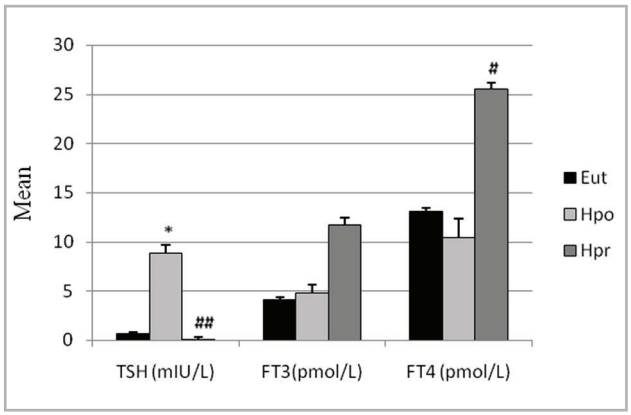

Figure 2: Thyroid hormones profile in dysthyroidism participants and control group. Values are given as mean with their standard errors. Significance of differences: between (Eut) and (Hpo): (* – p<0.05); between (Eut) and (Hpr): (# p<0.05; ## – p<0.01).

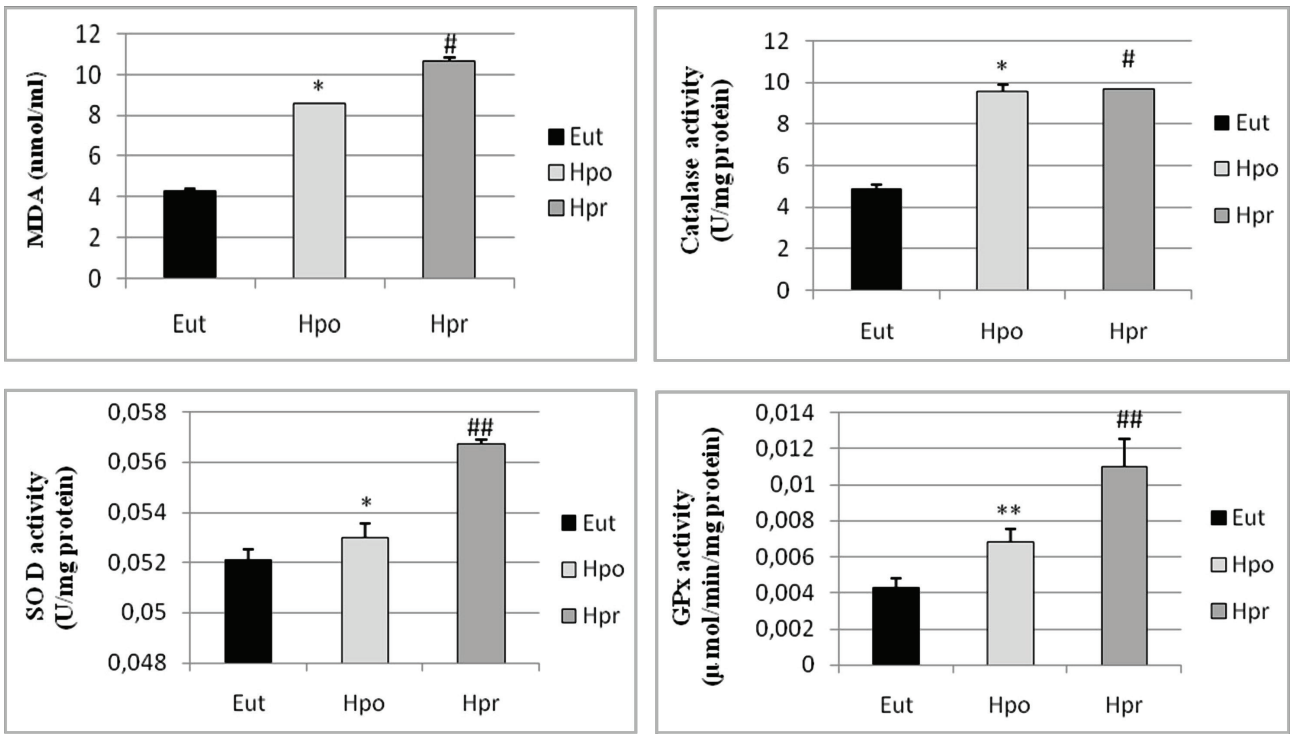

Figure 3: Malondialdehyde levels and antioxidant enzymes activities in euthyroid, hypothyroid and hyperthyroid patients, Values are given as mean with their standard errors, Significance of differences: between (Eut) and (Hpo): (* – p<0,05; ** – p<0,01); between (Eut) and (Hpr): (# – p<0,05; ## – p<0,01),

Discussion

In the present study, we analyzed the relationship between insulin resistance and thyroid disorders in both hyper and hypothyroid female subjects.

In our data, hyperthyroidism status was characterized by low TSH, high FT_3 and FT_4 levels while hypothyroidism patients showed elevated TSH concentration and normal range of FT_3 and FT_4.

In the current study, we selected HOMA-IR as the evaluation index of IR. Our results showed a state of IR in the hypothyroid state compared to the healthy controls. Increased insulin resistance in hypothyroidism has been attributed to impaired translocation of GLUT-4 insulin receptors present in skeletal muscle and adipose tissue [21]. Furthermore, the development of IR leads to many metabolic abnormalities; in hypothyroid participants. IR regrouped obesity, hyperinsulinemia

Table 3: Correlation between thyroid function parameters and insulin resistance markers in Hpo and Hpr groups.

	Hypothyroidism		Hyperthyroidism	
	r	P	R	P
Glycemia Vs				
TSH	-0.206	0.511	0.312	0.609
FT_3	-0.040	0.913	0.509	0.382
FT_4	0.452	0.190	0.408	0.496
Insulin Vs				
TSH	0.557*	0.048	-0.133	0.831
FT_3	-0.240	0.505	-0.013	0.984
FT_4	0.289	0.450	0.770	0.073
HOMA-IR Vs				
TSH	0.592*	0.043	-0.063	0.919
FT_3	-0.124	0.751	0.099	0.874
FT_4	-0.467	0.205	0.842*	0.036

Note: * – P<0.05.

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and dyslipidemia with elevated triglycerides and cholesterol levels, while in hyperthyroid participants, hypercholesterolemia and blood pressure disturbance was observed.

BMI was elevated in the hypothyroid group compared to the euthyroid group. This fact supports the theory that obesity and particularly its visceral component should be considered the primary source of inflammatory cytokines (TNF-α, CRP, IL-1, IL-6) that contribute to local and systemic inflammation, hepatic lipotoxicity, oxidative stress, which affect insulin signaling in target cells (and binding of insulin to its receptor) leading to IR and its systemic consequences [22].

In our study, the IR state was characterized by a normal range of glycemia and raised levels of insulinemia as compared to the healthy subjects.

Our results are consistent with the results of Purohit (2012), Purohit and Sharma (2014), who reported that hyperinsulinemia of hypothyroid patients was significantly associated with dyslipidemia characterized by raised total cholesterol, triglycerides and cholesterol-rich lipoproteins [23, 24].

Total cholesterol and LDL-cholesterol were significantly raised in Hpo and Hpr groups compared to Eut control, whereas the HDL- cholesterol level was lower. Some reports have also suggested that even high serum TSH values may affect serum lipids and increases the incidence of lipid metabolism disorders, which might be followed by weight gain in women. In hypothyroidism, dyslipidemia is mainly due to increased cholesterol synthesis and decreased degradation, with elevated serum levels of total cholesterol and LDL- cholesterol [25].

In this study, oxidative stress was found to be increased in both hyper and hypothyroidism due to elevated plasma lipids an altered lipid metabolism caused by thyroid dysfunction [26].

Plasma MDA is an important biomarker of oxidative damage to lipids. We observed a marked increase in MDA in the two groups compared with euthyroid controls, indicating increased oxidative stress. Thus, lipid oxidation may not have been directly caused by thyroid dysfunction but was enhanced by the presence of elevated plasma cholesterol and LDL secondary to hypo- and hyperthyroidism [27].

In our study, an antioxidant state in dysrthyroidism has shown significantly increased activity of intracellular oxygen radical scavenging enzymes: SOD, CT and GPx, compared to healthy subjects. We suggest that the two alterations are a sign of functional changes induced by radical overproduction and an increase in the biosynthesis of antioxidant enzymes [28, 29].

Results of the present study revealed that TSH is positively correlated with insulin (r=0.575) and HOMA-IR (r=0.592) in hypothyroid patients. On the other hand, FT_4 is positively associated with insulin (r=0.770) and HOMA-IR (r=0.842) in hyperthyroid patients. This confirms the view that the effects of thyroid hormone can be insulin agonists, as established in the muscles or antagonists, as observed in the liver. In hyperthyroidism, dysregulation of this balance may end in glucose intolerance, mainly due to hepatic insulin resistance. In hypothyroidism, insulin resistance is present mainly in peripheral tissues [30].

There were some limitations in the study. The small sample size may influence the correlation of insulin resistance components with different thyroid-altered statuses. The number of patients was relatively low due to the exclusionary conditions for the study. In addition, the participants in this study were healthy volunteers and dysthyroid patients in a single diabetology and endocrinology clinic.

Conclusions

Our results suggest that thyroid hormones in excess and hypometabolic state are accompanied by increased total and LDL cholesterol, which leads to IR and may contribute to accelerated oxidative stress. On the other hand, both hyper and hypothyroidism have been associated with IR. We found that in patients with hyperthyroidism, HOMA-IR showed a significant association with FT_4. Whereas serum TSH of hypothyroid subjects is correlated with insulin and HOMA-IR, this shows that TSH plays an important role in regulating women's weight and significantly influences the metabolism of blood glucose and lipids.

Conflict of interest

The authors declare no conflict of interest.

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