New insight into the pathogenesis of insulin resistance in hyperthyroidism and hypothyroidism

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Background and aim

Thyroid hormones are linked to the different metabolic processes in the body.We evaluated the association of metabolic syndrome and different thyroid diseases.

Patients and methods

Eighty female patients were enrolled in this study; 40 hypothyroid (group I) and 40 hyperthyroid (group II) as well as 40 healthy females as control group. Waist circumference, BMI, fasting blood glucose, fasting insulin, HOMAIR index, adiponectin, free T3, freeT4, TSH, total cholesterol and HDL were measured in all patients.

Results

Adiponectin was lower in hypothyroid group (3.68 ± 0.63 ng/dl) and higher in hyperthyroid group (7.52 ± 0.68 ng/dl) than the control group (5.11 ± 0.67 ng/dl) $P = 0.0001$. The HOMAIR was higher in both hypothyroid (3.56 ± 0.57 ng/dl) and hyperthyroid groups (1.68 ± 0.27) compared to control group (1.33 ± 0.25) $P = 0.0001$. The cholesterol was also higher in both hypothyroid (161.22 ± 12.98 mg/dl) and hyperthyroid (147.02 ± 8.7 mg/dl) compared to control group (134.74 ± 6.34 mg/dl) $P = 0.0001$. The HDL was low in both hypothyroid group (35.86 ± 3.55 mg/dl) and hyperthyroid group (40.34 ± 3.17 mg/dl) compared with the control group (41.64 ± 3.12 mg/dl) $P = 0.04$. The adiponectin was positively correlated to free T3, free T4 and negatively correlated to TSH ($r = 0.8$, $P = 0.0001$; $r = 0.9$, $P = 0.000$; $r = -0.9$, $P = 0.0001$) respectively. HOMAIR was significantly correlated to the thyroid parameters ($r = -0.8$, $P = 0.0001$; $r = -0.9$, $P = 0.0001$; $r = 0.8$, $P = 0.0001$) respectively. The total cholesterol was negatively correlated with the free T3 and T4 ($r = -0.5$, $P = 0.0001$; $r = -0.5$, $P = 0.0001$) and positively correlated with the TSH ($r = 0.5$, $P = 0.0001$), It was also negatively correlated with adiponectin ($r = -0.5$, $P = 0.0001$), and positively correlated with HOMAIR ($r = 0.5$, $P = 0.0001$). The HDL was negatively correlated with TSH ($r = -0.5$, $P = 0.000$) and HOMAIR ($r = -0.5$, $P = 0.0001$), it was positively correlated with free T3, T4 ($r = 0.6$, $P = 0.000$; $r = 0.5$, $P = 0.000$) and adiponectin ($r = 0.5$, $P = 0.0001$).

Conclusion

Both hypo and hyperthyroidism were associated with insulin resistance and disturbances in lipid profiles.

Keywords:
hypothyroidism, hyperthyroidism, adiponectine, HOMAIR, cholesterol and HDL

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Introduction

Thyroid disease, namely, hypothyroidism and hyperthyroidism, constitutes the most common endocrine abnormality in populations aged at least 12 years [1]. Thyroid disease is associated with various metabolic abnormalities because of the effects of thyroid hormones on almost all the major metabolic pathways [2]. Thyroid hormones regulate the basal energy expenditure through their effect on protein, carbohydrate, and lipid metabolism [3]. Whereas thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis, they upregulate the expression of genes such as glucose transporter type 4 and phosphoglycerate kinase, involved in glucose transport and glycolysis, thus acting synergistically with insulin, facilitating glucose disposal and utilization in peripheral tissues [4]. The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population [5]. This indicates a possible interplay between thyroid status and insulin sensitivity.

Patients with thyroid diseases usually show changes in body weight, appetite, and thermogenesis [6]. Hypothyroid patients gain weight, with decreased thermogenesis and decreased metabolic rate, whereas hyperthyroidism is associated with low body weight despite increased appetite because of an increase in the metabolic rate [7]. Thyrotoxicosis is associated with insulin resistance. The mechanism of insulin resistance in thyrotoxicosis has not been completely elucidated. Adipokines that are regulated by thyroid hormones may play a role in insulin resistance [7].

Thyroid hormones influence all aspects of lipid metabolism including synthesis, mobilization, and degradation. It affects lipoprotein lipase activity and, thus, the hydrolysis

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of triglycerides into very low-density lipoprotein and chylomicrons into fatty acids and glycerol [3].

In hypothyroidism, lipoprotein lipase activity in the adipose tissues has been found to be normal or decreased, in addition to decreased hepatic lipase activity, resulting in normal or high levels of triglycerides. In hyperthyroidism, although lipoprotein lipase activity is usually normal, an increased liver fatty acid synthesis and oxidation is observed because of enhanced acetyl coenzyme A carboxyl I and carnitine palmitoyltransferase Ia expression, leading to increased very low-density lipoprotein biosynthesis [3].

Adipocytokines play crucial roles in the regulation of energy homeostasis, insulin sensitivity lipid, and carbohydrate metabolism, and even inflammatory and atherogenic reactions. Among the adipocytokines, only adiponectin has anti-inflammatory and antiatherogenic properties. It is paradoxically decreased in an insulin resistance state [7].

Homeostatic model assessment (HOMA) is a method used for assessment of β cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C peptide concentrations. The HOMA-IR derives estimates of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations [4]. We aimed to evaluate the correlation between insulin resistance, lipid profile, and altered thyroid state clinically and to assess β cell function and insulin resistance by HOMA-IR.

Patients and methods

Patients

The study was carried out in the teaching hospital of Benisweif University, Egypt. Eighty female patients visiting the outpatient internal medicine clinic were screened and only new cases with thyroid problems were included in our study. They were divided into two groups: 40 women with hypothyroidism and 40 women with hyperthyroidism. Both groups of patients were not on treatment for the thyroid disease yet. The study also included 40 normal women as a control group. All the participants included signed a written consent.

Exclusion criteria

Patients with diabetes mellitus, previous history of thyroid disease, or those taking medications that alter thyroid functions or lipid profile were excluded from the study. Pregnant and lactating women were also not included.

Laboratory methods

Blood samples were drawn in the morning hours after a 12-h overnight fast. The samples were left at room temperature for 30 min, centrifuged for 15 min at 2500 rpm to separate the serum, and then stored at -70°C. Fasting serum glucose, total cholesterol, and high-density lipoprotein (HDL)-cholesterol were determined using an autoanalyzer (Hitachi 747 auto-analyzer; Hitachi, Tokyo, Japan). Free T3, free T4, thyroid-stimulating hormone (TSH), and insulin levels were measured with a chemiluminescence immunometric assay using a UniCell DXI 800 analyzer (Beckman Coulter Inc., Fullerton, California, USA). Serum adiponectin was measured using the enzyme-linked immunosorbent assay kit (Quantikine; R&D Systems, Minneapolis, Minnesota, USA).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 15.0 (IBM New York, USA) was used for analysis of data. Data were summarized as mean and SD. The *t*-test was used for analysis of two quantitative data and the one-way analysis of variance test was used for analysis of more than two quantitative data, followed by a post-hoc test for detection of significance. Pearson's correlation was also performed. *r*-value was considered weak if <0.25, mild if >0.25 – <0.5, moderate if >0.5 – <0.75, and strong if >0.75. *P*-value was considered significant when less than 0.05.

Results

The waist circumference was not significantly higher in the hypothyroid group (90.52 ± 9.78 cm) compared with the control group, but it was significantly lower in the hyperthyroid group (72.50 ± 4.59 cm) than in the control group (88.19 ± 7.82 cm). The BMI was not significantly high in the hypothyroid group (29.24 ± 2.68 kg/m^2), but it was significantly lower in the hyperthyroid group (22.92 ± 2.36 kg/m^2) compared with the control group (28.81 ± 1.31 kg/m^2). The free T3 was not lower in the hypothyroid patients (3.43 ± 0.53 ng/dl) than the control group (3.43 ± 0.53 ng/dl), but it was high in the hyperthyroid group (17.72 ± 5.0 ng/dl). The free T4 was lower in the hypothyroid group (0.59 ± 0.24 ng/dl) than in the control group (1.36 ± 0.26 ng/dl) and was higher in the hyperthyroid group (5.12 ± 0.78 ng/dl). The TSH was significantly higher in the hypothyroid group (59.3 ± 13.21 μl/ml) and significantly lower in the hyperthyroid group (0.01 ± 0.1 μl/ml) than in the control group (2.17 ± 0.67 μl/ml). The adiponectin was lower in the hypothyroid group (3.68 ± 0.63 ng/dl) and higher in the hyperthyroid group (7.52 ± 0.68 ng/dl) than the control group (5.11 ± 0.67 ng/dl). The fasting blood glucose was

higher in the hypothyroid group (6.28 ± 0.61 mmol/l) and the hyperthyroid group (3.65 ± 0.49 mmol/l) compared with the control group (3.34 ± 0.44 mmol/l). The fasting insulin was significantly higher in the hypothyroid group (12.95 ± 1.12 μIU/ml) and the hyperthyroid group (10.23 ± 0.72 μIU/ml) compared with the control group (9.07 ± 0.87 μIU/ml). The HOMA-IR was higher in both the hypothyroid group (3.56 ± 0.57) and the hyperthyroid group (1.68 ± 0.27) compared with the control group (1.33 ± 0.25). The cholesterol was also higher in both the hypothyroid (161.22 ± 12.98 mg/dl) and the hyperthyroid (147.02 ± 8.7 mg/dl) group compared with the control group (134.74 ± 6.34 mg/dl). The HDL was low in both the hypothyroid (35.86 ± 3.55 mg/dl) and the hyperthyroid group (40.34 ± 3.17 mg/dl) compared with the control group (41.64 ± 3.12 mg/dl) as shown in Table 1.

The study showed that the adiponectin was correlated positively to free T3, free T4 and correlated negatively to TSH (r = 0.8, P = 0.0001; r = 0.9, P = 0.000; r = –0.9, P = 0.0001), respectively, as shown in Tables 2 and 3. The HOMA-IR was correlated significantly to the thyroid parameters (r = –0.8, P = 0.0001; r = –0.9, P = 0.0001; r = 0.8, P = 0.0001), respectively. The BMI was also correlated significantly with the thyroid functions (r = –0.7, P = 0.0001; r = –0.8, P = 0.0001; r = 0.733, P = 0.000), respectively, as shown in Table 2. The waist circumference was correlated negatively to free T3 and free T4 and correlated positively to TSH (r = –0.7, P = 0.0001; r = –0.7, P = 0.0001; r = 0.7, P = 0.0001). The fasting blood glucose was correlated negatively to free T3 and free T4 and correlated positively to TSH (r = –0.8, 0.0001; r = –0.9, 0.0001; r = 0.9, P = 0.0001) as shown in Table 2. The fasting insulin was also correlated positively to TSH (r = 0.8, P = 0.0001) and correlated negatively to both free T3 and free T4 (r = –0.7, P = 0.0001; r = –0.8, 0.0001), respectively. The total cholesterol was correlated negatively with the free T3 and free T4 (r = –0.5, P = 0.0001; r = –0.5, P = 0.0001) and correlated positively with the TSH (r = 0.5, P = 0.0001) as shown in Table 2. It was also correlated negatively with adiponectin (r = –0.5, P = 0.0001) and correlated positively with HOMA-IR (r = 0.5, P = 0.0001) as shown in Table 3. Although the HDL was correlated negatively with TSH (r = –0.5, P = 0.000) and HOMA-IR (r = –0.5, P = 0.0001), it was correlated positively with free T3, free T4 (r = 0.6, P = 0.000; r = 0.5, P = 0.000) and adiponectin (r = 0.5, P = 0.0001) as shown in Tables 2 and 3.

Discussion

Thyroid diseases are accompanied by changes in the metabolism including alterations in body weight, insulin resistance, and lipid profile [8].

In the present study, waist circumference and BMI were higher in the hypothyroid group but the result was not significant. Meanwhile, it was significantly lower in the hyperthyroid group. The waist circumference and BMI were correlated positively with the TSH and correlated negatively with free T3 and free T4. Our findings are in agreement with the results reported by Kota *et al.* [9] and Erdogan *et al.* [10].

In our study, adiponectin was significantly higher in the hyperthyroid group and lower in the hypothyroid group. It was correlated positively to free T4 and correlated negatively to TSH. This means that adiponectin may not be involved in mediating insulin resistance in hyperthyroidism. Iglasias *et al.* [11] reported that adiponectin was not different between control, hyperthyroid, and hypothyroid groups and found that there was no correlation between adiponectin and insulin glucose and the HOMA-IR index. They also suggested that thyroid hormones play a minor role in modulating adiponectin levels. The use of different immunoassay techniques may explain their findings. In addition, Chu *et al.* [7] showed that insulin, glucose,

Table 1 Comparison of laboratory data of hypothyroid patients, hyperthyroid patients, and controls

Variables	Hypothyroid patients		Hyperthyroid patients		Controls		*P*-value
	Mean	SD	Mean	SD	Mean	SD	
Waist (cm)	90.52 (NS)	9.78	72.50*	4.59	88.19	7.82	0.0001*
BMI (kg/m^2)	29.2 (NS)	2.68	22.92*	2.36	28.81	1.31	0.0001*
FT3 (ng/dl)	3.43 (NS)	0.53	17.72*	5.0	3.43	0.53	0.0001*
FT4 (ng/dl)	0.59*	0.24	5.12*	0.78	1.36	0.26	0.0001*
TSH (μl/ml)	59.30*	13.21	0.01*	0.1	2.17	0.67	0.0001*
Adiponectin (ng/dl)	3.68*	0.63	7.52*	0.68	5.11	0.67	0.0001*
Fasting blood glucose (mmol/l)	6.28*	0.61	3.65*	0.49	3.34	0.44	0.001*
Fasting insulin (μIU/ml)	12.95*	1.12	10.23*	0.72	9.07	0.87	0.0001*
HOMA-IR	3.56*	0.57	1.68*	0.27	1.33	0.25	0.0001*
Cholesterol (mg/dl)	161.22*	12.98	147.02*	8.70	134.74	6.34	0.0001*
HDL (mg/dl)	35.86*	3.55	40.34*	3.17	41.64	3.12	0.04*

HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; TSH, thyroid-stimulating hormone; *Significant.

Table 2 Correlation between thyroid profile and other laboratory data of patients included in the study

Variables	Correlation	FT3	FT4	TSH
Adiponectin (ng/dl)	*r*-value	0.8	0.9	−0.9
	P-value	0.0001*	0.000*	0.0001*
HOMA-IR	*r*-value	−0.8	−0.9	0.8
	P-value	0.0001*	0.0001*	0.0001*
BMI (kg/m^2)	*r*-value	−0.7	−0.8	0.733
	P-value	0.0001*	0.0001*	0.000
Waist (cm)	*r*-value	−0.7	−0.7	0.7
	P-value	0.0001*	0.0001*	0.0001*
Fasting blood glucose (mmol/l)	*r*-value	−0.8	−0.9	0.9
	P-value	0.0001*	0.0001*	0.0001*
Fasting insulin (μIU/ml)	*r*-value	−0.7	−0.8	0.8
	P-value	0.0001*	0.0001*	0.0001*
Cholesterol (mg/dl)	*r*-value	−0.5	−0.5	0.5
	P-value	0.0001	0.0001*	0.0001*
HDL-c (mg/dl)	*r*-value	0.6	0.5	−0.5
	P-value	0.000	0.000	0.000

HDL-c, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; TSH, thyroid-stimulating hormone; *Significant.

Table 3 Correlation between adiponectin and HOMA-IR and other laboratory data of patients included in the study

Variables	Correlation	Adiponectin	HOMA-IR
FT3 (ng/dl)	*r*-value	0.8	−0.8
	P-value	0.0001*	0.0001
FT4 (ng/dl)	*r*-value	0.911	−0.9
	P-value	0.0001*	0.0001*
TSH (μl/ml)	*r*-value	−0.913	0.8
	P-value	0.0001*	0.0001*
Adiponectin (ng/dl)	*r*-value	—	−0.9
	P-value	—	0.0001*
HOMA-IR	*r*-value	−0.9	1.0
	P-value	0.0001*	—
BMI (kg/m^2)	*r*-value	−0.7	0.7
	P-value	0.0001*	0.0001*
Waist (cm)	*r*-value	−0.7	0.7
	P-value	0.0001*	0.0001*
Fasting blood glucose (mmol/l)	*r*-value	−0.8	0.8
	P-value	0.0001*	0.0001*
Fasting insulin (μIU/ml)	*r*-value	−0.8	0.8
	P-value	0.0001*	0.0001*
Cholesterol (mg/dl)	*r*-value	−0.5	0.5
	P-value	0.0001*	0.0001*
HDL-c (mg/dl)	*r*-value	0.5	−0.5
	P-value	0.0001*	0.0001*

HDL-c, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; TSH, thyroid-stimulating hormone; *Significant.

and HOMA-IR were significantly decreased after treatment of hyperthyroidism. However, adiponectin levels did not change after the treatment; thus, they concluded that the insulin resistance in hyperthyroidism is not adiponectin mediated. Sieminska *et al.* [12] also showed that adiponectin level was high in patients with Graves' disease, but they found that HOMA-IR was not correlated to adiponectin. This means that the cause for insulin resistance in this group is not mediated by adiponectin but may be because of other metabolic causes. Meanwhile, the study carried out by Yaturu *et al.* [6] showed that adiponectin was correlated positively to free T4 and they related the adiponectin level to the degree of adiposity in their patients.

Recent studies carried out by Seifi *et al.* [13,14] showed that adipose adiponectin gene expression and adiponectin receptor gene expression are mediated by thyroid hormones at the translation level. In addition, the lipid and carbohydrate disturbances in patients with thyroid dysfunction may be because of gene expression.

Thyrotoxic patients frequently show impaired glucose tolerance. This is a result of increased glucose absorption through the gastrointestinal tract and elevated hepatic glucose output, as well as decreased hepatic insulin sensitivity [15]. An alternative explanation could be peripheral insulin resistance because of increased secretion of bioactive mediators (adipokines) such as interleukin-6 and tumor necrosis factor-α from the adipose tissue in hyperthyroidism [16]. These adipokines, which exert both proinflammatory and insulin resistance effects, have been found to be elevated in hyperthyroid women [16]. These possible factors were not evaluated in the present study.

HOMA is a method of assessing β cell function and insulin resistance from fasting glucose and fasting insulin concentrations [17]. Many studies have confirmed that hypothyroidism is associated with insulin resistance [9,18,19]. Tuzcu *et al.* [20] reported that even in subclinical hypothyroidism, there is a state of hyperinsulinemia. In hypothyroidism, the mechanism of insulin resistance was attributed by Brenta [15] to a decrease in insulin-mediated glucose disposal and decreased ability of insulin to increase the blood flow to the hyperthyroid tissues, which leads to lower glucose disposal. In our study, fasting blood glucose, fasting insulin, and HOMA-IR were significantly higher in both the hypothyroid and the hyperthyroid groups and they were correlated positively to TSH and correlated negatively to free T3 and free T4. However, Chu *et al.* [7] showed that there is a state of insulin resistance in hyperthyroid patients; they suggested that the mechanism of insulin resistance associated with hyperthyroidism is because of unmeasured factors other than adiponectin. In addition, Kapadia *et al.* [4] and Purohit [21] confirmed that both hypothyroid and hyperthyroid groups had a state of insulin resistance.

In our study, total cholesterol was significantly high in both the hypothyroid and hyperthyroid groups. It was correlated positively to TSH and HOMA-IR

and correlated negatively to adiponectin and free T3 and free T4. This was in agreement with the results of Kapadia *et al.* [4]. In addition, Singh *et al.* [18] reported that the triglycerides and low-density lipoprotein were significantly higher in hypothyroidism, whereas the HDL was significantly lower. Purohit [21] concluded that the estimation of traditional lipid profile along with serum insulin, insulin resistance, C peptide, apo A1, and apo B would not only aid assessment of the thyroid status but also enable early evaluation of a possible risk of cardiovascular disease.

In our study, HDL was significantly low in both the hypothyroid and the hyperthyroid group, and it was correlated positively to free T3, free T4, and adiponectin and correlated negatively to TSH and HOMA-IR; this was in agreement with the results of Kapadia *et al.* [4].

Purohit showed that the total cholesterol/HDL ratio was correlated positively to HOMA-IR in both the hypothyroid and hyperthyroid groups and it had a direct correlation with a risk of cardiovascular disease [21].

Conclusion

Both hypothyroidism and hyperthyroidism are associated with insulin resistance and lipid abnormalities. However, as the pathogenesis is multifactorial, the insulin resistance associated with hyperthyroidism might be mediated by factors that are not dependent on adiponectin. We suggest more studies to confirm the pathogenesis theories with higher numbers to confirm the mechanism of metabolic syndrome in these diseases and the effect of treatment on insulin resistance.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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