The Thyroid Gland is Another Victim of the Insulin Resistance Syndrome

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Abstract

Background: Insulin resistance syndrome is a cluster of risk factors including increased blood pressure, abdominal obesity, lipid abnormalities, and impaired glucose metabolism. Insulin is a thyroid growth factor that stimulates proliferation of thyroid cells in culture. It has been observed that insulin receptors are over expressed in most thyroid tumors as an early step in thyroid carcinogenesis. In order to evaluate the effects of insulin resistance (IR) on the thyroid gland, we developed a cross-sectional study in euthyroid women.

Methods: Eighty women (mean age 36.85 ± 4.71 years) were evaluated by a thyroid ultrasound (US), fasting plasma insulin and HOMA IR. Subjects were divided into four groups as follows: G1 (n: 24), subjects with IR and obesity; G2 (n : 20), subjects with obesity without IR; G3 (n : 16), subjects with IR and normal weight; and G4 (n : 20) control group (without IR and obesity).

Results: The thyroid volume (TV), measured by US, showed the following values: G1, 17.15 ± 1.6mL; G2, 7.4 ± 1.4mL; G3, 16.53 ± 1.9mL; and G4, 6.07 ± 0.95mL. There was no significant difference in TV between G1 and G3, but differences between G1 and G2, and between G3 and G4 were significant at p<0.05. The percentage of nodular thyroid glands observed by US in each group was as follows: G1, 58%; G2, 15%; G3, 50%; G4, 5%. Again, the differences between G1 and G2 and between G3 and G4 were statistically significant (p<0.005 and p<0.001, respectively, for each comparison). Our study also showed that the greater waist circumference, the greater thyroid volume and the higher incidence of thyroid nodules.

Conclusions: It is concluded that the higher circulating levels of insulin cause increased thyroid proliferation. The clinical manifestations are the larger thyroid volume and the formation of nodules. Thus, the thyroid gland appears to be another victim of the insulin resistance syndrome.

Key Words: Thyroid – Insulin resistance syndrome – HOMA IR – Metabolic syndrome.

Introduction

INSULIN resistance (IR) syndrome is a cluster of risk factors for coronary artery disease and it has been recently implicated as an important feature for cell proliferation [1,2]. IR is characterized by an inadequate physiological response of peripheral tissues to circulating insulin and results in metabolic and hemodynamic disturbances [3].

IR has been increasing epidemically in the last years together with the spread of the obesity epidemic. When insulin-resistant individuals cannot maintain the degree of hyperinsulinemia, type 2 diabetes generally develops [4].

It is well known that insulin acts as a growth factor that stimulates cell proliferation. It has been observed that insulin receptors are over expressed in most thyroid tumors as a nearly step in thyroid carcinogenesis [5]. However, the reported data on the effects of hyperinsulinemia data on the effects of hyperinsulinemia on the thyroid gland are scarce [3].

In order to evaluate the effects of IR on the thyroid gland we developed a cross-sectional study in euthyroid females.

Subjects and Methods

80 middle-aged females living in iodine sufficient area were included in this study, selected from Kasr Al-Eini Outpatient Endocrinology Clinic from Nov. 2010 to Oct. 2011.

Age between 25-45 years, inclusion criteria: Negative history of having any thyroid and/or homeopathic medications, Normal thyroid gland
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Palpation, normal thyroid function (TSH, FT3 & FT4).

Subjects were divided into four groups as follows: G1 (n=24) Subjects with insulin resistance and obesity; G2 (n=20) subjects without insulin resistance and with obesity; G3 (n=16) Subjects with insulin resistance and normal weight (16 patients); G4 (n=20) (control group) Subjects without insulin resistance and obesity.

All patients included in this study were subjected to the following: Detailed medical history, Full physical examination, Palpation of thyroid gland.

All patients gave their oral consent to participate in the study.

Anthropometric measurements:

Body mass index (BMI) was obtained by dividing the body weight (kg) by the square of height (m). Waist measured at midway point between lowest ribs plane and the iliac crest.

Laboratory investigations:

Each venous sample was drawn after a minimum fasting period of 12h. Thyroid function was evaluated by measuring FT4, FT3, and TSH by ELISA Reader (SLT. Spectra, 2000).

Fasting glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH). The fasting insulin level was assayed by ELISA Reader (SLT. Spectra, 2000).

IR was estimated based on calculation of the homeostasis model assessment (HOMA) index for each patient. This was done using the formula: [fasting plasma insulin (IU/ml) x fasting plasma glucose (mmol/l)] ÷ 22.5 [6].

Cholesterol (HDL, LDL) and TG concentrations were measured by enzymatic assay (Boehringer, Mannheim, Germany).

Thyroid ultrasound:

Thyroid ultrasound scanning was performed in all patients by the same physician by using a 7.5MHz linear transducer. Thyroid volume was calculated by the elliptical shape volume formula \((0.479 \times \text{length} \times \text{width} \times \text{height})\) for each lobe [7]. Normal thyroid gland was evaluated by palpation performed by a senior endocrinologist. We considered thyroid nodules by US lesions >3mm.

Statistical analysis:

Statistical analysis was performed using SPSS statistical software (version 16, SPSS Inc, USA) and Microsoft Excel 2007. Results are expressed as mean ± SD for four groups.

Results are expressed as means ± SD. Between-group comparisons were made using Student t-test for independent samples of cases of normal distribution.

ANOVA is used to compare between groups.

The Wilcoxon ranksum test was used for independent samples of cases of abnormal distribution. The chi-square test was used for nominal variables. The level of significance was set at 0.05.

Results

Clinical characteristics and laboratory data of the 80 women are described in Table (1).

G1 Subjects with insulin resistance (IR) and obesity, G2 subjects with obesity without IR, G3 with IR and normal weight, G4 control group (without IR and obesity).

| Table (1): Clinical characteristics and laboratory data of the study groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Group (I) Mean ± S.D | Group (II) Mean ± S.D | Group (III) Mean ± S.D | Group (IV) Mean ± S.D |
| Number (n)      | 24              | 20              | 16              | 20              |
| Age Years       | 38.25±4.152     | 37.55±4.286     | 35.625±4.924    | 35.95±5.482     |
| Weight kg       | 96.188±7.482    | 94.425±7.858    | 67.032±4.205    | 63.725±3.701    |
| Height cm       | 165.29±5.457    | 166.6 ±4.684    | 159.55±36.499   | 161.55±6.637    |
| BMI Kg/m²       | 35.338±3.089    | 34.055±2.432    | 26.038±1.193    | 23.895±2.07     |
| Waist circum. cm| 91.83±3.406     | 88.4±1.804      | 82.48±5.529     | 75.1±4.367      |
| FBS Mmol/L      | 5.096±0.81      | 4.93±0.612      | 4.93±0.70       | 4.58±0.63       |
| F.insulinmIU/ml | 14.48±2.50      | 9.28±1.75       | 14.28±2.37      | 7.95±1.69       |
| HOMA IR         | 3.23±0.533      | 2.021±0.287     | 3.11±0.403      | 1.59±0.358      |
| Chol mg/dl      | 236.75±39.94    | 198.65±14.550   | 194.38±14.705   | 183.55±8.781    |
| TG mg/dl        | 214.33±49.63    | 150.85±16.45    | 186.063±43.8    | 141.5±4.58      |
Obesity was defined as a BMI >30 & IR was defined as a HOMA-IR >2.5 comparing between GI and GII and reveals that, there is highly significant difference in Waist circumference with ($p$-value = 0.0002), comparing between GIII and GIV and reveals that, there are significant difference in BMI with ($p$-value = 0.0205) comparing between GI and GIII and revealing that, there are highly significant difference in body weight with ($p$-value = 5.21E-18), BMI with ($p$-value = 1.88E-15), Waist circumference with ($p$-value = 3.91E-6) are comparing between GII & GIV and showing that highly significant difference between two groups with ($p$-value = 0.0003), BMI with ($p$-value = 8.34E-18) and Waist circumference with ($p$-value = 3.94E-15).

Laboratory values in each group show that women with hyperinsulinemia had significantly higher levels of HOMA IR than other groups.

Normal thyroid hormones in all groups shown in Table (2).

Table (2): Thyroid function.

<table>
<thead>
<tr>
<th>Group (I)</th>
<th>Group (II)</th>
<th>Group (III)</th>
<th>Group (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT3 mIU/ml</td>
<td>Mean ± S.D</td>
<td>2.65±0.52</td>
<td>2.74±0.62</td>
</tr>
<tr>
<td>FT4 mIU/ml</td>
<td>Mean ± S.D</td>
<td>1.28±0.21</td>
<td>1.31±0.28</td>
</tr>
<tr>
<td>TSH mIU/ml</td>
<td>Mean ± S.D</td>
<td>2.39±0.69</td>
<td>2.56±0.69</td>
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Thyroid abnormalities:

Biological and morphological thyroid evaluation was performed in all 80 patients shown in (Table 3). The thyroid volume (TV), measured by US, showed the following values: G1, 17.15 ± 1.6mL; G2, 7.4±1.4mL; G3, 16.53 ± 1.9mL; and G4, 6.07±0.95mL shown in (Chart 1). There was no significant difference in TV between G1 and G3, but differences between G1 and G2 and between G3 and G4 were significant at $p<0.05$.

Table (3): Thyroid morphology in the 80 subjects included in the study.

<table>
<thead>
<tr>
<th>Group (I)</th>
<th>Group (II)</th>
<th>Group (III)</th>
<th>Group (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± S.D</td>
<td>Thyroid volume cm$^3$</td>
<td>17.15±1.607</td>
<td>7.4±1.427</td>
</tr>
<tr>
<td>Mean ± S.D</td>
<td>Thyroid nodule</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Percentage of nodules</td>
<td>58%</td>
<td>15%</td>
<td>50%</td>
</tr>
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The percentage of nodular thyroid gland observed by US in each group was G1 (58%), G2 (15%), G3 (50%), G4 (5%) shown in Chart (2).

These indicate that, the higher the insulin resistance, the higher the thyroid volume and the greater incidence of thyroid nodules.

Correlation between HOMA-IR and thyroid volume in all subjects, represents that there is a positive correlation with correlation coefficient $r=0.518$ shown in Chart (4). This means that the higher HOMA-IR, the higher the incidence of thyroid nodule.

Chart (5,6) showed the correlation between waist circumference & thyroid nodules and thyroid volume in all subjects, represents that there is a strongly positive correlation with correlation coefficient $r=0.613$ & $r=0.51$ respectively.

This indicates that the greater waist circumference, the greater thyroid volume and the higher incidence of thyroid nodules. This means that insulin resistance and not only simple obesity that causes thyroid hyperplasia and increases the incidence of thyroid nodule development.
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Chart (1): Thyroid volume mean and standard deviations for all groups.

Chart (2): Represents the number of cases have thyroid nodules and their percentage in the group.

Chart (3): Correlation between HOMA-IR & thyroid volume in all subjects.

Chart (4): Correlation between HOMA-IR & incidence of thyroid nodules in all subjects.

Chart (5): Correlation between waist circumference & incidence of thyroid nodule.

Chart (6): Correlation between waist circumference & thyroid volume in all subjects.
Discussion

Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population, because patients with one organ-specific autoimmune disease are at risk of developing other autoimmune disorders, and thyroid disorders are more common in females, it is not surprising that up to 30% of female type 1 diabetic patients have thyroid disease. The rate of postpartum thyroiditis in diabetic patients is three times that in normal women. A number of reports have also indicated a higher than normal prevalence of thyroid disorders in type 2 diabetic patients, with hypothyroidism being the most common disorder [11].

In practice, there are several implications for patients with both diabetes and hyperthyroidism. First, in hyperthyroid patients, the diagnosis of glucose intolerance needs to be considered cautiously, since the hyperglycemia may improve with treatment of thyrotoxicosis. Second, underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia. Third, in diabetic patients with hyperthyroidism, physicians need to anticipate possible deterioration in glycemic control and adjust treatment accordingly. Restoration of euthyroidism will lower blood glucose level [11].

Insulin resistance syndrome, as described by Reaven [4] is a cluster of risk factors for coronary artery disease. This pathological condition is characterized by an inadequate physiological response of peripheral tissues to circulating insulin and results in metabolic and hemodynamic disturbances [3].

Hyperinsulinemia has also characteristically been found in subjects with type 2 diabetes as a result of insulin resistance, which is considered to be of primary importance in the pathogenesis of diabetes. There is scarce information on the effect of hyperinsulinemia in the development of thyroid nodules or thyroid cancer. Thus, hyperinsulinemia might act by increasing thyroid proliferation, independently of the patient BMI.

Recently, an intriguing area of research in thyroidology is the association of IRS (or its related components) with thyroid functional/morphological abnormalities [8,9].

In almost all of these studies, consistent relationship between obesity and thyroid functional changes was reported, thus supporting the hypothesis that the axis involving the hypothalamus, the pituitary, the thyroid, and the adipose tissue was somehow disrupted [10].

In our study subjects with IR have a larger thyroid gland volume by ultrasound and have a significantly increased thyroid nodule prevalence a significant correlation between the degree of insulin resistance measured by HOMA-IR and the thyroid volume and the incidence of thyroid nodules in euthyroid insulin resistant females. Our results were comparable with a previous report by Rezzonico 2008, Ayturk S, Rezzonico 2011 [8,11,12].

We could not find an association between serum-free thyroid hormones (FT4 and FT3) & TSH and the presence of IRS.

Although previous studies evaluating thyroid functional changes in obese patients reported discrepant findings, the most consistently reported finding is that the serum levels of TSH are higher in obese patients than in healthy controls [13,14,15]. Contradictory findings of these reports might be related to the study design, in which the investigators included patients with different severity of obesity and iodine intake.

In patients with insulin resistance humoral or hormonal mediators from adipose tissue stimulate the hypothalamus-pituitary-thyroid axis in order to increase TSH secretion [16,17]. The main suspected mechanism is a possible relationship between leptin and the thyroid hormones. There is possibly a relationship between leptin and the thyroid hormones via an influence of leptin on the negative feedback regulation of thyroid hormones. Leptin regulates TRH expression [18]. Recent evidence has suggested that the relationship between
leptin levels and fat mass is curvilinear, so that leptin secretion increases exponentially with increasing fat mass. Insulin also increases total leptin levels.

Thyroid nodules, due to multinodular goiter, are enlargements of the thyroid gland characterized by excessive growth and structural transformation of one or several areas within the normal thyroid tissue. Their etiology seems to involve complex interactions between environmental, genetic, and endogenous factors. The exogenous predisposing factors might be iodine intake, smoking, certain drugs, and natural goitrogens. All of these factors are supposed to interact with gender and genetic aspects [19].

At first glance, it seems clear that TSH is the major growth factor of the thyroid gland. However, this straightforward interpretation neglects some findings that point to an intricate complexity of TSH-dependent and-independent mechanisms within a network of interacting positive and negative signals [20]. TSH is not only involved in the control of differentiated functions, it also regulates the expression of growth factors and their receptors [21].

Indeed, TSH promotes the insulin IGF-I signaling. Moreover, exposure to TSH- or cyclic adenosine monophosphate (cAMP)-elevating agents increased the responsiveness of thyroid cells to stimulation with insulin, IGF-I, and IGF-II.

However, IGF 1 is actively involved in the TSH-mediated proliferation of thyrocytes. Contribute to increased serum TSH levels via effects on serum leptin concentrations. The relationship between increased TSH levels and BMI can also be expressed in the reverse manner. Animal and human studies have yielded convincing evidence that adipocytes and preadipocytes express TSH receptors [22].

The action of TSH on its receptors in fat tissue induces differentiation of preadipocytes into adipocytes, causing stimulation of adipogenesis [23]. All of these reciprocal mechanisms suggest that leptin and the thyroid axis maintain a complex and dual relationship and it might be proposed that a hypothalamic-pituitary-thyroid axis.

Accumulated evidence indicates that IGF-I-dependent, TSH-independent signaling may be of major importance for growth regulation of the human thyroid gland. This assumption is supported by findings in conditions not accompanied by increased TSH secretion, such as in acromegaly, in which high intrathyroidal IGF-I levels may contribute to goiter development [20]. Thus, on one hand, TSH induces the expression of growth factors and their receptors and may contribute to an increased responsiveness to growth factor.

Previous studies support the concept that insulin concurrently functions with TSH as a growth factor and stimulates thyroid cell proliferation. This effect is partially mediated via insulin-like growth factor 1 (IGF 1)-dependent mechanisms; therefore, IGF 1 might be involved in the pathogenesis of thyroid morphological abnormalities [8].

Sustained exposure to high serum IGF-1 levels is likely to play a role in the development of thyroid proliferation in this disease. An additive role for the autocrine-paracrine action of locally produced IGF-1 is also possible. This situation could be similar to that observed in subjects with insulin resistance syndrome [12].

Metabolic syndrome has been associated with high risks of several common adult cancers. Although exact molecular mechanisms and the pathophysiology responsible for increased risk are not fully understood, the most likely mechanism seems to be insulin resistance [24].

In a recent analysis, Gursoy in 2010, has proposed a relationship between insulin resistance and thyroid cancer [26]. This hypothesis is in part supported by the demonstration of the significant association between insulin resistance and differentiated thyroid cancer [24,25]. As it is well known with some other nonthyroid carcinomas [27].

Treatment of patients with insulin resistance decreases thyroid volume and nodules in study done by Rezzonico [12] showed that correction of IR with Metformin would decrease thyroid nodule size. Following this rationale, not surprisingly, patients with IR who were treated only with L-T4, there was no decrease in thyroid nodule volume. However, in patients with IR who received only Metformin, 74% of their nodules decreased, which was also enhanced when the combination treatment with Metformin and L-T4 was administered (95.2%). L-T4 alone only prevented the nodular growth, but it was not effective in reducing the nodular volume in the subjects with IR. Because TSH and insulin are thyroid growth factors, the combined treatment, which decreased the serum levels of both hormones, appears to be a very good therapeutic tool in these patients. More studies will be necessary to reproduce these results.
Conclusion:

Our data suggest that higher circulating levels of insulin might be causing increased thyroid proliferation. The clinical manifestations are the larger thyroid volume and the formation of nodules. This goitrogenic action of insulin would be another risk factor for those patients with IR. Then, the thyroid gland appears to be another victim of the insulin resistance syndrome that should be carefully examined and properly investigated in patients having insulin resistance syndrome.

Recommendation:

Follow-up thyroid nodule size and thyroid volume by sonar in insulin resistance patients.

Fine needle aspiration for nodules >1cm in insulin resistance patients for high risk for malignant transformation reaching up to (2.7%) in nodular goiter.

References
20- MENENDEZ C., BALDELLI R., CAMINNA J.P., ESCUDERO B., PEINO R., DIEGUEZ C. and CASANUEVA


