THYROID
Volume 18, Number 4, 2008

DOI: 10.1018/thy.2007.0223

Introducing the Thyroid Gland as Another Victim of the Insulin Resistance Syndrome

Jorge Rezzonico,[1] Mariana Rezzonico,[1] Eduardo Pusiol,[1] Fabián Pitoia,[2] and Hugo Niepomniszcze[2]

Background: Insulin is a thyroid growth factor that stimulates proliferation of thyroid cells in culture. In order to evaluate the effects of insulin resistance (IR) on the thyroid gland, we developed a prospective study in euthyroid women.
Methods: One hundred eleven women (mean age 32.2 ± 7 years) were evaluated by a thyroid ultrasound (US) and basal and postprandial serum insulin. Subjects were divided into four groups as follows: G1 ($n = 42$), subjects with IR and obesity; G2 ($n = 21$), subjects with obesity without IR; G3 ($n = 17$), subjects with IR and normal weight; and G4 ($n = 31$) control group (without IR and obesity).
Results: The thyroid volume (TV), measured by US, showed the following values: G1, 17 ± 3 mL; G2, 13.8 ± 2.8 mL; G3, 16.2 ± 2.1 mL; and G4,12.1 ± 2.4 mL. 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, 50%; G2, 23.8%; G3, 61%; G4, 16.1%. 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).
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.

Introduction

Insulin resistance (IR) is a characteristic feature of most patients with type 2 diabetes mellitus, simple obesity, polycystic ovarian syndrome, and impaired glucose tolerance, as well as other disorders (1). Decreased insulin sensitivity is the central feature of this syndrome. In recent years, the general concept has emerged that chronic activation of the pro-inflammatory pathway can be a mechanism for insulin resistance (2). Various studies have implicated chronic activation of the NF-κB pro-inflammatory pathway and/or JNK1 as underlying mechanisms, and most of these studies have focused on activation of this pathway within insulin target tissues (adipose, liver, and muscle) as an etiologic mechanism (2). It is well known that insulin acts as a growth factor that stimulates cell proliferation. It has been observed that insulin receptors are overexpressed in most thyroid tumors as an early step in thyroid carcinogenesis (3). However, the reported data on the effects of hyperinsulinemia on the thyroid gland are scarce (3,4).

In order to evaluate the effects of IR on the thyroid gland we developed a prospective study in euthyroid women.

Subjects and Methods

Subjects

One hundred eleven women (mean age 32.2 ± 7 years) living in an iodine-sufficient area (5) were included in this study. To be included in this protocol, subjects had to have 1) normal thyroid function (euthyroidism was defined as normal thyrotropin [TSH], triiodothyronine [T_3], and thyroxine [T_4] levels); 2) normal thyroid gland palpation; 3) negative titers of antithyroid antibodies (TPOAb); 4) no past history of having received any thyroid and/or homeopathic medications.

Subjects were divided into four groups as follows: G1 ($n = 42$), subjects with IR and obesity; G2 ($n = 21$), subjects with obesity without IR; G3 ($n = 17$), subjects with IR and normal weight; and G4 ($n = 31$), control group (without IR and obesity).

[1]Centro Privado de Endocrinología, Mendoza, Argentina.
[2] Division of Endocrinology, Hospital de Clínicas – University of Buenos Aires, Buenos Aires, Argentina.

Table 1. Clinical Characteristics in the 111 Women Included in the Study[a]

	G1	G2	G3	G4
n	42	21	17	31
Age (years)	31.2 ± 9	34.2 ± 8	32.2 ± 7	31.2 ± 5
Weight (kg)	89.8 ± 13	92.3 ± 12	65.9 ± 5.9	62.2 ± 5
Height (m)	1.602 ± 0.05	1.598 ± 0.04	1.606 ± 0.04	1.602 ± 0.04
BMI (kg/m^2)	35 ± 3	36 ± 5	25 ± 6	25 ± 2

[a]G1, subjects with insulin resistance (IR) and obesity; G2, subjects with obesity without IR; G3, subjects with IR and normal weight; G4, control group (without IR and obesity); BMI, body mass index.

All subjects gave written voluntary consent to participate in the study. Procedures were applied in agreement with the ethical guidelines of our institution.

Anthropometric measurements

Body weights (kg) and heights (cm) were measured without shoes and/or cap. Body mass index (BMI) was expressed as weight per height squared (kg/m^2). Obesity was defined as a BMI > 30.

Biochemical evaluations

All blood samples were taken between 8:00 and 9:00 AM after 12 hours of fasting. After collection, serum samples were stored at -20°C until assayed.

Basal and 2-hour postprandial glycemia and insulinemia were monitored. The postprandial samples were obtained 2 hours after a standard mixed meal intake (6,7). Breakfast included proteins, carbohydrates, and fats.

Insulin determination techniques. Insulin was determined by a two-site chemiluminescent immunometric assay with solid phase anti-insulin murine monoclonal antibodies and sheep polyclonal anti-insulin antibodies, and mouse monoclonal anti-insulin antibodies conjugated with calf intestine alkaline phosphatase in buffer solution (IMMULITE® INSULIN, Diagnostic Products Corporations, Los Angeles, CA), with 2 μIU/mL sensitivity. Intra-assay precision of the equipment used was 6.4% and 5.3% for 7.39 and 300 μIU/mL values, respectively. Total precision was 8% and 7% for 7.39 and 300 μIU/mL values, respectively.

Hyperinsulinemia was considered when basal levels were > 20 μIU/mL or > 60 μIU/mL in the postprandial state.

Glycemia determination techniques. Glycemia was determined using the GOD/PAP automated method (SEA-PAK® Plus, Bayer Corporation, manufactured in Sées, Industrial Area, France). Spectrophotometer sensitivity at 505 nm is 0.70 mg/dL.

TSH, T_3, T_4, and TPOAb assessment. The thyroid hormones, TSH and TPOAb were measured by electrochemiluminescent technology with an automatic analyzer (Roche Diagnostics Elecsys 2010 Immunoassay System, Mannheim, Germany).

Evaluation of the thyroid gland morphology

Thyroid ultrasound scanning (US) was performed in all patients by using a 7.5 MHz linear transducer. Thyroid volume (TV) was calculated by the elliptical shape volume formula (0.479 × length × width × height) for each lobe (8). Normal thyroid gland was evaluated by palpation performed by a senior endocrinologist. We considered as thyroid nodules all the US nodular lesions > 3 mm.

Statistical analysis

Results are expressed as means ± SD. Between-group comparisons were made using Student *t* test for independent samples of cases of normal distribution. The Wilcoxon rank-sum 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 of the 111 women are described in Table 1. There were no significant differences when age was

Table 2. Laboratory Values in the 111 Subjects Included in the Study[a]

	G1	G2	G3	G4
n	42	21	17	31
B glucose (mg/dL)	91.1 ± 7.4	87.4 ± 13.1	85.4 ± 11.7	84.1 ± 7.3
PP glucose (mg/dL)	112.7 ± 20.2	97.7 ± 10.4	97.2 ± 14.5	91.6 ± 10
B insulinemia (μU/mL)	23.2 ± 11.1	12.7 ± 7.2	21.4 ± 12.7	7.0 ± 4.1
PP insulinemia (μU/mL)	119.2 ± 55.3	35.5 ± 13	79.5 ± 22	20.5 ± 10.2
T_3 (ng/dL)	114.3 ± 17.8	131.2 ± 26.4	117.8 ± 15	120.7 ± 17
T_4 (μg/dL)	8.2 ± 1	7.8 ± 0.52	7.9 ± 1.27	7.8 ± 1.1
TSH (μU/mL)	2.26 ± 0.9	2.3 ± 0.89	2.27 ± 1	2.21 ± 0.72

[a]G1, subjects with insulin resistance (IR) and obesity; G2, subjects with obesity without IR; G3, subjects with IR and normal weight; G4, control group (without IR and obesity); B, basal; PP, postprandial; T_3, triiodothyronine; T_4, thyroxine; TSH, thyrotropin.

considered among groups, and when weight and BMI were considered between G1 and G2 ($p = $ ns) and between G3 and G4 ($p = $ ns). However, as expected, there was a statistically significant difference when weight and BMI were considered between G1 and G3 ($p < 0.01$) and between G2 and G4 ($p < 0.02$).

Laboratory values in each group are described in Table 2. It can be observed that women with hyperinsulinemia had significantly higher levels of postprandial insulinemia than women without IR. Serum thyroid hormones and TSH were not significantly different among groups.

Thyroid abnormalities

Biological and morphological thyroid evaluation was performed in all 111 subjects. The TV, measured by US, showed the following values: G1, 17 ± 3 mL; G2, 13.8 ± 2.8 mL; G3, 16.2 ± 2.1 mL; and G4:12.1 ± 2.4 mL. There was no significant difference when TV was considered between G1 and G3 (both groups with IR), while comparison between G1 and G2 (both obese but with or without IR, disclosed a p value < 0.05). Equally, comparison between G3 and G4 (both with normal weight but with or without IR, disclosed a p value < 0.05) (Table 3).

The percentage of nodular thyroid glands observed by US in each group was as follows: G1, 50%; G2, 23.8%; G3, 61%; and G4, 16.1%. 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) (Table 3 and Fig. 1). The mean number of thyroid nodules in both IR groups (G1 and G3) was near three, while in the groups without IR (G2 and G4), the average was 1.5. When we considered the percentage of nodules greater than 10 mm, they were observed in 30% of G1, 35% of G3, and in 5% and 7% of G2 and G4, respectively.

Discussion

Insulin resistance syndrome, as described by Reaven (9), 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 (10). 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 (11,12).

Table 3. Thyroid Morphology in the 111 Subjects Included in the Study[a]

	G1	*G2*	*G3*	*G4*
n	42	21	17	31
TV (mL)[b]	17 ± 3	13.8 ± 2.8	16.2 ± 2.1	12.1 ± 2.4
Thyroid nodules (%)[c]	50	23.8	61	16.1

[a]G1, subjects with insulin resistance (IR) and obesity; G2, subjects with obesity without IR; G3, subjects with IR and normal weight; G4, control group (without IR and obesity); TV, thyroid volume.

[b]Statistical comparison for TV: G1 vs. G3, $p = $ ns; G1 vs. G2, $p < 0.05$; G3 vs. G4, $p < 0.05$; G2 vs. G4, $p = $ ns.

[c]Statistical comparison for thyroid nodules: G1 vs. G3, $p = $ ns; G1 vs. G2, $p < 0.005$; G3 vs. G4, $p < 0.001$; G2 vs. G4, $p = $ ns.

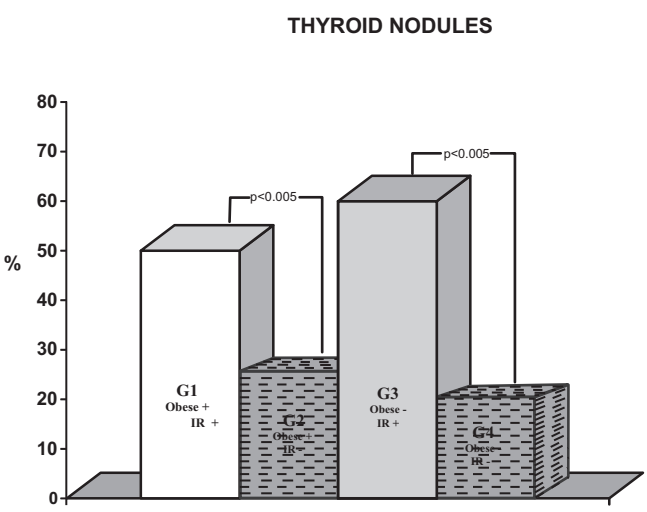

FIG. 1. Frequency of thyroid nodules diagnosed by ultrasonography in the 111 subjects included in the study. G1, subjects with insulin resistance (IR) and obesity; G2, subjects with obesity without IR; G3, subjects with IR and normal weight; G4, control group (without IR and obesity).

On the other side, insulin resistance is a characteristic feature of most patients with simple obesity, polycystic ovarian syndrome, and impaired glucose tolerance, as well as other disorders (1). In recent years, the general concept has emerged that chronic activation of the pro-inflammatory pathway can be a mechanism for insulin resistance (13). There is scarce information on the effect of hyperinsulinemia in the development of thyroid nodules or thyroid cancer. However, it has been shown that insulin receptors are overexpressed in most thyroid tumors as an early step in thyroid carcinogenesis (3). The role of overexpressed insulin receptors is not clear, because insulin is not locally produced in these tumors. One possibility is that these receptors may contribute to transmit the mitogenic signals of insulin homolog IGF-1 and IGF-2, produced locally in thyroid cancers (14). IGFs are potent mitogenic and anti-apoptotic factors that play a major role in a variety of human malignancies (15). Both IGFs are believed to signal through the IGF-2 receptor, because they have a low affinity for insulin receptors (16,17). However, paracrine mechanisms were recently identified for the interaction of IGFs with the mentioned receptor (18,19).

On the other hand, it is well known that the frequency of thyroid disorders in acromegalic patients is higher than that observed in normal subjects (20,21). 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 (14). This situation could be similar to that observed in subjects with insulin resistance syndrome. Thus, hyperinsulinemia might act by increasing thyroid proliferation, independently of the patient BMI.

The results of our study provide support for an association between hyperinsulinemia, in the females with insulin resistance, and the thyroid volume and the thyroid nodularity among these patients. Undoubtedly, those subjects with thyroid nodules had increased prevalence of significantly higher baseline and postprandial serum insulin levels.

In conclusion, 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.

References

1. Eckel RH, Grundy SM, Zimmet PZ 2005 The metabolic syndrome. Lancet **365:**1415–1428.
2. Wellen KE, Hotamisligil GS 2005 Inflammation, stress, and diabetes. J Clin Invest **115:**1111–1119.
3. Vella V, Sciacca L, Pandini G, Mineo R, Squatrito S, Vigneri R, Belfiore A 2001 The IGF system in thyroid cancer: new concepts. Mol Pathol **54:**121–124.
4. Grozovsky R, Morales MM, Carvalho DP 2003 Modulaçao do sustrato do receptor de insulina (IRS1) durante a bociogenese. Arq Bras Endocrinol Metabol **45(Suppl 1):**S99.
5. Saborido L, Latres de Rauek B, Rezzonico JN, Guntsche Z, Cabut V, Leiva R, Munoz P, Bidot L, Vitoria C, Rosso A 1996 Iodine in schoolchildren. Relationship with incidence of goiter, socioeconomic group and salt intake. Medicina (B Aires) **56:**448–454.
6. Wolever TM, Chiasson JL, Csima A, Hunt JA, Palmason C, Ross SA, Ryan EA 1998 Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care **21:**336–340.
7. Liljeberg Elmståhl H, Björck I 2001 Milk as a supplement to mixed meals may elevate postprandial insulinaemia. Eur J Clin Nutr **55:**994–999.
8. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC 1981 Volumetric analysis of thyroid lobes by real-time ultrasound. Dtsch Med Wochenschr **106:**1338–1340.
9. Reaven GM 1988 Role of insulin resistance in human disease. Diabetes **37:**1595–1607.
10. Ascaso JF,Pardo S, Real JT, Lorente RI, Priego A, Carmena R 2003 Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care **26:**3320–3325.
11. Rojo-Martinez G, Esteva I, de Adana SR, Catala M, Merelo MJ, Tinahones F, Gomez-Zumaquero JM, Cuesta AL, Cardona F, Soriguer F 2004 Patterns of insulin resistance in the general population of southeast Spain. Diabetes Res Clin Pract **65:**247–256.
12. Kahn SE 2000 The importance of the beta-cell in the pathogenesis of type 2 diabetes mellitus. Am J Med **108:**2S–8S.
13. Bloomgarden ZT 2007 Insulin resistance concepts. Diabetes Care **30:**1320–1326.
14. Tode B, Serio M, Rotella CM, Galli G, Franceschelli F, Tanini A, Toccafondi R 1989 Insulin-like growth factor-I: autocrine secretion by human thyroid follicular cells in primary culture. J Clin Endocrinol Metab **69:**639–647.
15. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS, Obin MS 2005 Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res **46:**2347–2355.
16. Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumié A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clément K 2005 Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes **54:**2277–2286.
17. Fukumura D, Ushiyama A, Duda DG, Xu L, Tam J, Krishna V, Chatterjee K, Garkavtsev I, Jain RK 2003 Paracrine regulation of angiogenesis and adipocyte differentiation during *in vivo* adipogenesis. Circ Res **93:**E88–E97.
18. Bråkenhielm E, Cao R, Gao B, Angelin B, Cannon B, Parini P, Cao Y 2004 Angiogenesis inhibitor, TNP-470, prevents diet-induced and genetic obesity in mice. Circ Res **94:**1579–1588.
19. Hausman GJ, Richardson R 2004 Adipose tissue angiogenesis. J Anim Sci **82:**925–934.
20. Kasagi K, Shimatsu A, Miyamoto S, Misaki T, Sakahara H, Konishi J 1999 Goiter associated with acromegaly: sonographic and scintigraphic findings of the thyroid gland. Thyroid **9:**791–796.
21. Tita P, Ambrosio MR, Scollo C, Carta A, Gangemi P, Bondanelli M, Vigneri R, degli Uberti EC, Pezzino V 2005 High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol (Oxf) **63:**161–167.

Address reprint requests to:
Hugo Niepomniszcze, M.D., Ph.D.
Division of Endocrinology, Hospital de Clínicas
University of Buenos Aires
Avenida Córdoba 2351, 5to piso
Buenos Aires
Argentina

E-mail: hniepom@elsitio.net