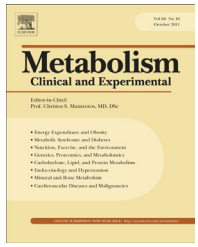
Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com



Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule prevalence in a mild-to-moderate iodine deficient area

Cuneyd Anil[a,*], Aysen Akkurt[b], Semra Ayturk[a], Altug Kut[a], Alptekin Gursoy[a]

[a] Department of Endocrinology and Metabolism, Baskent University Faculty of Medicine, Ankara, Turkey
[b] Department of Internal Medicine, Baskent University Faculty of Medicine, Ankara, Turkey

ARTICLE INFO

Article history:
Received 13 August 2012
Accepted 9 January 2013

Keywords:
Diabetes mellitus
Impaired fasting glucose
Impaired glucose tolerance
Thyroid nodule
Volume

ABSTRACT

Objective. Insulin resistance (IR) is a key factor involved in the pathogenesis of impaired glucose metabolism. IR is associated with increased thyroid volume and nodule prevalence in patients with metabolic syndrome. Data on the association of thyroid morphology and abnormal glucose metabolism are limited. This prospective study was carried out to evaluate thyroid volume and nodule prevalence in patients with pre-diabetes and type 2 diabetes mellitus (DM) in a mild-to-moderate iodine deficient area.

Materials and Methods. Data were gathered on all newly diagnosed patients with pre-diabetes and type 2 diabetes mellitus between May 2008 and February 2010. 156 patients with pre-diabetes and 123 patients with type 2 DM were randomly matched for age, gender, and smoking habits with 114 subjects with normal glucose metabolism. Serum thyroid-stimulating hormone (TSH) and thyroid ultrasonography was performed in all participants.

Results. Mean TSH level in the diabetes group (1.9±0.9 mIU/L) was higher than in the control group (1.4±0.8 mIU/L) and the pre-diabetes group (1.5±0.8 mIU/L) ($P<0.0001$ for both). Mean thyroid volume was higher in the pre-diabetes (18.2±9.2 mL) and diabetes (20.0±8.2 mL) groups than in controls (11.4±3.8 mL) ($P<0.0001$ for both). Percentage of patients with thyroid nodules was also higher in the pre-diabetes (51.3%) and diabetes groups (61.8%) than in controls (23.7%) ($P<0.0001$ for both).

Conclusions. The results suggest that patients with impaired glucose metabolism have significantly increased thyroid volume and nodule prevalence.

1. Introduction

There are multiple well-known etiologic factors for thyroid volume increase and nodule formation including iodine deficiency, smoking, and genetic factors [1]. In two previous reports, for the first time, increased thyroid volume and nodule prevalence were reported in patients with insulin resistance (IR) [2,3]. IR is one of the fundamental defects associated with impaired glucose metabolism and final progression to type 2 diabetes mellitus (DM). Although many studies were conducted in type 1 DM, the reported clinical data about the association of impaired glucose metabolism (pre-diabetes and type 2 DM) with the thyroid gland function and morphology are scarce [4,5]. In these reports, patients with already established diagnosis, poorly controlled disease and/or diabetic complications were included, which preclude

Abbreviations: IR, Insulin resistance; DM, Diabetes Mellitus; BMI, Body mass index; IGF, Insulin-like Growth Factor.

* *Corresponding author.* Department of Endocrinology and Metabolism, Baskent University Faculty of Medicine, 5. Sokak No: 48, 06490 Bahcelievler, Ankara, Turkey. Tel.: +90 312 2122912; fax: +90 312 2154216.
E-mail address: cuneydanil@yahoo.com (C. Anil).

0026-0495/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.metabol.2013.01.009

any definitive conclusion regarding the sole influence of the type 2 DM on thyroid morphology and function. Also, commonly used drugs (especially metformin) and frequently employed procedures such as exposure to iodinated contrast material in this patient group might possibly alter thyroid function and morphology [6–8].

Up to now, no study was performed to evaluate thyroid morphological alterations in patients with newly diagnosed pre-diabetes and type 2 DM in a mild-to-moderate iodine deficient area. The objective of our study was to examine whether diagnosis of pre-diabetes and type 2 DM is associated with thyroid functional and morphological changes.

2. Methods

2.1. Study subjects

This was a single-center, prospective case–control study in patients with pre-diabetes and type 2 DM. The Baskent University Ethics Committee for Human Studies approved the protocol. All participants provided informed consent. Euthyroidism was defined as TSH (reference range, 0.35–4.0 mIU/L) within the normal reference range. The diagnostic criteria proposed by the American Diabetes Association have been used for the definition of pre-diabetes and type 2 DM [9]. Newly diagnosed 123 patients with type 2 DM and 156 patients with pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) who attended for regular follow-up at the Endocrinology Department of Baskent University Faculty of Medicine in Ankara, Turkey, between May 2008 and February 2010 were consecutively recruited in the study. As a control group, 114 euthyroid control subjects with normal glucose metabolism were recruited from patients admitted to our family practice out-patient clinic for check-up purposes and they did not have any known acute or chronic illness. The inclusion criteria were ages 40 to 65. One control per case was selected after subjects were stratified into 40–49, 50–59, and 60–65 years old age subgroups. The controls were matched according to age, gender, and smoking habits with the cases in that manner.

Subjects with any of the following characteristics were excluded from the study: Those with a history of thyroid disease, overt or subclinical hyperthyroidism and hypothyroidism (as defined by suppressed or elevated TSH levels, respectively), previous-thyroxine suppression therapy at any time, iodinated contrast material exposure in the previous 6 months, high thyroid autoantibody titers or history of neck irradiation or surgery. Patients were also excluded if they exhibited endocrine obesity, pregnancy and lactation, hepatic or renal dysfunction, and history of heart failure or significant neurological or psychological illness (depression, epilepsy, schizophrenia) that will have an impact on thyroid function tests.

2.2. Anthropometric measurements

Measurements of subjects' height, weight, and waist circumference were recorded by the same doctor. Waist circumference was measured with a folding tape at the natural waistline (the level of the umbilicus) in a horizontal plane. Body mass index (BMI) was obtained by dividing the body weight (kg) to the square of height (m).

2.3. Thyroid function and morphology

Turkey was moderately iodine-deficient area before mandatory iodization (average urinary iodine concentration (25.5 μg/L). Further, in 1999, an obligatory model of iodine prophylaxis was initiated with iodization of household salt. The area is mildly iodine deficient (average urinary iodine concentration 92 μg/L) at the moment [10,11].

Thyroid ultrasonography was performed by single physician (A.G), who was unaware of the patients' any clinical conditions, using a 10-MHz linear probe (Logiq 5 Pro, GE Medical Systems, WI, USA). Volumes of thyroid glands and nodules were calculated according to the ellipsoid formula: volume (mL) = depth (cm) × width (cm) × length (cm) × π/6.

2.4. Laboratory analysis

Each venous sample was drawn after a minimum fasting period of 12 h. All samples were collected between 0800 and 0900 h. Thyroid function was evaluated by measuring TSH using immunochemiluminescent assays by an automated analyzer (Immulite 2000; Diagnostic Products, Los Angeles, CA, USA). Thyroid antibodies [antithyroid peroxidase (normal range: < 50 U/mL) and antithyroglobulin (normal range: < 40 U/mL)] were measured by immunochemiluminescent assays employing commercial kits (Diagnostic Products, Los Angeles, CA, USA).

Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics, Mannheim, Germany).

2.5. Statistical analysis

All continuous data were expressed as the mean ± SD. Data were analyzed with SPSS software (Statistical Package for the Social Sciences, version 17.0, SSPS, Chicago). Statistical comparisons were performed by means of independent-samples *t* tests for data with a normal distribution and χ^2 tests for percentages. Continuous variables were analyzed by using one-way ANOVA or Kruskal–Wallis, where appropriate. Pairwise comparisons were made by use of Tukey HSD test or Mann–Whitney-U test with Bonferroni correction. Pearson's correlation test was performed for correlation analysis. Multiple linear regression analysis was used for the assessment of independent predictors of thyroid volume. Predictors of the presence of thyroid nodule were assessed by multivariate binary logistic regression analysis. Because of perfect collinearity between BMI and waist circumference, only waist circumference was included into the final multivariable analysis. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of study population

Study population characteristics are depicted in Table 1. As noted, the study included 156 patients with pre-diabetes, 123 patients with type 2 DM, and 114 subjects with normal glucose

metabolism as a control group. There was no significant difference when gender, age, and smoking habits were considered (Table 1). BMI and waist circumference were significantly higher in the pre-diabetes and diabetes groups than in the control group ($P<0.0001$ for both). There was no significant difference between the pre-diabetes and diabetes groups regarding BMI and waist circumference.

3.2. *Thyroid function and morphology*

As shown in Table 1, mean TSH level in the diabetes (1.9±0.9 mIU/L) group was higher than the control group (1.4±0.8 mIU/L) and the pre-diabetes group (1.5±0.8 mIU/L) ($P<0.0001$ for both). TSH level was similar between the pre-diabetes and control groups. Thyroid autoantibody levels were within normal limits and did not differ significantly between the three groups. As depicted in Fig. 1, mean thyroid volume was higher in the pre-diabetes (18.2±9.2 mL) and diabetes (20.0±8.2 mL) groups than in the controls (11.4±3.8 mL) ($P<0.0001$for both). Mean thyroid volume was not significantly different between the pre-diabetes and diabetes groups. Fig. 1 also shows that the percentage of patients with thyroid nodules was also higher in the pre-diabetes (51.3%) and diabetes groups (61.8%) than in the controls (23.7%) ($P<0.0001$ for both).

In diabetes group, there was a positive correlation between TSH and BMI (rr: +0.43; $p<0.01$), and between TSH and waist circumference (rr: +0.37; $p<0.01$).

Multiple linear regression analysis was used for the assessment of independent predictors of thyroid volume (Table 2). Age, waist circumference, pre-diabetes diagnosis, and diabetes diagnosis remained independently correlated with thyroid volume ($\beta=0.12$; $P=0.004$, $\beta=0.29$; $P<0.0001$, $\beta=0.37$; $P<0.001$, $\beta=0.53$; $P<0.001$, respectively). Predictors of thyroid nodule formation were assessed by multivariate binary logistic regression analysis (Table 3). In the multivariate model, age, pre-diabetes diagnosis, and diabetes diagnosis remained independently correlated with thyroid nodule formation ($\beta=0.03$; $P=0.045$, $\beta=1.11$; $P<0.0001$, $\beta=1.51$; $P<0.0001$, respectively). The odds ratios for the development of thyroid nodule in the presence of pre-diabetes and diabetes were 3.03 and 4.55, respectively. These results provide evidence that abnormal glucose metabolism is an independent risk factor for nodule formation.

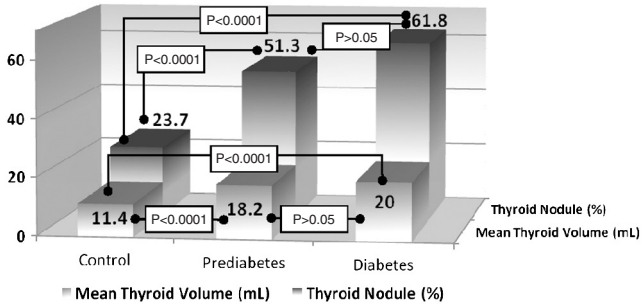


Fig. 1 – Mean thyroid volumes and percentages of thyroid nodules in study subjects.

4. Discussion

Type 2 DM and thyroid disorders are two commonly seen endocrinopathies in the adult population. It is well known that IR and compensatory hyperinsulinemia are the key factors in the pathogenesis of type 2 DM [9]. Recently, an intriguing area of research in thyroidology is the association of IR with thyroid functional and morphological abnormalities. Recent studies have shown consistent association of IR and thyroid morphological changes, raising the question of whether abnormality in glucose metabolism, which is a final consequence of IR, affects thyroid morphology [3,4].

There have been only two studies of thyroid morphological changes among patients with type 2 DM; one from Poland, and the other from Brazil [4,5]. In the Polish study, consecutive 98 type 2 diabetic and 30 type 1 diabetic patients were compared with 50 and 38 controls respectively, in terms of thyroid volumes, gland echogenicity, nodule prevalance, and TSH

Table 1 – Clinical, laboratory, and thyroid ultrasonography characteristics of study subjects.

	Controls (n=114)	Pre-diabetes (n=156)	Diabetes (n=123)	P_{0-1} value	P_{0-2} value	P_{1-2} value
Male/Female	31/83	51/105	43/80	> 0.05	> 0.05	> 0.05
Age (year)	52.5±7.2	53.1±7.3	54.6±6.85	> 0.05	> 0.05	> 0.05
Smoking (%)	57	51	43	> 0.05	> 0.05	> 0.05
BMI (kg/m^2)	27.4±5.2	31.0±5.3	31.9±4.9	< 0.0001	< 0.0001	> 0.05
WC (cm)	91.0±12.5	99.2±12.6	101.4±11.8	< 0.0001	< 0.0001	> 0.05
TSH (mIU/L)	1.4±0.8	1.5±0.8	1.9±0.9	> 0.05	< 0.0001	< 0.0001
Anti-TPO (N: <50 U/mL)	24.4±4.6	27.5±4.9	20.1±4.1	> 0.05	> 0.05	> 0.05
Anti-Tg (N: <50 U/mL)	18.2±3.8	16.5±2.9	23.7±4.2	> 0.05	> 0.05	> 0.05
Thyroid volume (mL)	11.4±3.8	18.2±9.2	20.0±8.2	< 0.0001	< 0.0001	> 0.05
Nodule (%)	23.7	51.3	61.8	< 0.0001	< 0.0001	> 0.05

(Data are given as mean±SD as appropriate).
BMI; Body Mass Index, WC; Waist Circumference, TSH; Thyroid Stimulating Hormone, anti-TPO; N, normal values; anti-thyroid peroxidase antibody, anti-Tg; anti-thyroglobulin antibody.
P_{0-1}; Comparisons between controls and patients with prediabetes.
P_{0-2}; Comparisons between controls and patients with type 2 diabetes mellitus.
P_{1-2}; Comparisons between patients with prediabetes and patients with type 2 diabetes mellitus.

Table 2 – Multiple linear regression analysis for the assessment of independent predictors of thyroid volume.

	Thyroid volume			
	Beta	standard error	t	*P* value
Age	0.12	0.003	2.9	0.004
WC	0.29	0.001	6.9	< 0.0001
Pre-diabetes *vs.* control	0.37	0.05	7.6	< 0.0001
Diabetes *vs.* control	0.53	0.05	10.4	< 0.0001

WC; Waist circumference.

levels. Significant increases in median thyroid volume were observed in both subjects with type 1 and type 2 DM in comparison to their control groups. Moreover, thyroid nodules appeared more frequently in patients with type 2 DM than in their control group (48% *vs.*28%, $P<0.02$). Thyroid nodule prevalence was similar in patients with type 1 DM and control group. TSH levels did not differ between type 2 DM and control cases; it was significantly lower than controls in type 1 DM patients, albeit witihin the normal range [4]. A direct comparison of these findings and our results is not possible because these investigators performed this study in an iodine replete area and in patients with poorly controlled diabetes and/or diabetic complications. Nonetheless, the results of our study, except TSH evaluations, are consistent with their findings, lending support to the notion that thyroid morphology is altered in patients with type 2 DM. In the Brazilian study, 256 diabetic patients were compared with 75 non-diabetic controls, and they were subjected to thyroid ultrasonography, and TSH, T4, and thyroid autoantibody measurements. The cases in each group were sorted and compared with respect to their thyroid functional states (i.e. existence of hyperthyroidism, hypothyroidism, and euthyroidism), and morphological states (i.e. existence of nodular goiter, Hashimoto's thyroiditis). Thyroid volumes, nodule prevalance, and nodule diameters were not reported. Although not aimed to compare thyroid volume and nodule prevalence, thyroid disorders were more commonly found in patients with type 2 DM. The only reported significant difference was the more frequent observation of Plummer disease in diabetic group [5].

There are multiple potential explanations for our findings. In this study, we determined the relation between abnormal glucose metabolism (final consequence of IR) and thyroid morphology, as assessed by thyroid US. We found that serum TSH level was higher in patients with type 2 DM than in patients with pre-diabetes and in controls. Also, TSH level was significantly positively correlated with BMI and waist circumference. Some humoral or hormonal mediators from adipose tissue stimulate the hypothalamus–pituitary–thyroid axis to increase TSH secretion [12]. There is evidence in the literature indicating that there is a possible relationship between leptin and the thyroid hormones via an influence of leptin on the negative feedback regulation of thyroid hormones and TRH expression. Leptin may also act directly on TRH neurons through leptin receptors on these cells [13]. Serum leptin levels were found to be increased in type 2 DM [14]. Leptin secretion increases exponentially with increasing fat mass and insulin also increases total leptin levels [15]. Thus, increased fat mass along with IR in patients with type 2 DM may contribute to increased serum TSH levels via effects on serum leptin concentrations [16].

Table 3 – Multivariate binary logistic regression analysis for the assessment of independent predictors of thyroid nodule formation.

	Thyroid nodule			
	Beta	Standard error	*P* value	OR (%95 CI)
Age	0.03	0.015	0.045	1.03 (1.00–1.06)
Pre-diabetes *vs.* control	1.11	0.28	< 0.0001	3.03 (1.74–5.27)
Diabetes *vs.* control	1.51	0.31	< 0.0001	4.55 (2.48–8.34)

OR; Odds Ratio, CI; Confidence Interval for Beta.

We found that patients with pre-diabetes and type 2 DM had larger thyroid volumes and higher risk for formation of thyroid nodules. TSH is a major regulator of the growth and differentiation of thyroid cells [17]. Insulin-like Growth Factor-1 (IGF-1) is an important hypertrophic and cell cycle progression factor for a number of cell types. It was previously shown that TSH in cooperation with insulin or IGF-1 stimulate cell cycle progression and proliferation in various thyrocyte culture systems [18]. The IGF system comprises a network of ligands (IGF-1 and IGF-2), which are highly homologous to insulin; IGF-1 receptor, which shares structural homology with the insulin receptor [19]. Insulin/IGF-1 signaling pathway has long been known to modulate regulation of thyroid gene expression and might be considered as additional important factors in thyrocyte proliferation and differentiation [18–21]. Very recently, an elegant cell culture work by Malaguarnera et al. demonstrated that insulin receptor isoforms, IGF-1 receptor, IGF-1 and IGF-2, were expressed at high levels in thyroid follicular cell precursors and markedly decreased in differentiating cells. Insulin and IGFs stimulated the growth of thyroid cancer precursors [22]. Thus, activation of the insulin pathway might be plausible explanation for our findings. The higher circulating levels of insulin in case of abnormal glucose metabolism may cause increased thyroid proliferation and thyroid nodules.

The role of adiponectin in thyroid carcinomas has been comprehensively investigated in a tissue and in vitro study by Mitsiades et al. They found that patients with thyroid carcinomas have decreased plasma adiponectin levels compared with controls. They also showed the existence of both types of adiponectin receptors in human thyroid cancer specimens immunohistochemically. The authors confirmed this in thyroid cancer cell lines (BHP7 and SW579) and in human papillary thyroid cancer tissue using RT-qPCR. Despite the expression of adiponectin receptors in thyroid cancer tissue, the authors observed that treatment with recombinant adiponectin at low and high physiological concentrations did not have any significant effect on cell proliferation or cell death of thyroid carcinoma cell lines *in vitro*. They concluded that inverse relation between circulating adiponectin levels and risk of thyroid cancer in humans could be due to the indirect effects of adiponectin, potentially through regulation of other metabolic pathways and insulin resistance [23]. Considering that plasma

adiponectin levels have been shown to be decreased in obesity, insulin resistance states and type 2 DM [24], it is conceivable that adiponectin may be another important contributor to the effects we observed on thyroid morphology in addition to the aforementioned factors. Although not precisely shown as leptin yet, adiponectin also has possible various interactions with thyroid hormones [25,26].

A limitation of the present study may be the lack of further information and comparison about some morphological characteristics of thyroid nodules such as nodule diameters and uni-/multinodularity in each group. The cytological and/or histopathological outcome of each thyroid nodule in the study groups has not been assessed according to the study design which is another important limitation. Including this assessment in such a prospective design may improve the strength of future studies. Inclusion of a control group with no impaired glucose metabolism, including only newly diagnosed, naive type 2 diabetic and prediabetic patients, thus sidelining the possible effects of any antidiabetic medication, may be potential advantages of the study.

5. Conclusion

In this case–control study, we explored the associations between abnormal glucose metabolism and the occurrence of thyroid morphological abnormalities on US. The risk of increased thyroid volume and nodule prevalence was found to be significantly elevated with increasing BMI and abnormal glucose metabolism. This association may be owing to possible interactions with insulin signalling pathway. Working on screening programs for thyroid morphology from the initial diagnosis of diabetics may provide early diagnosis, prevention, and timely treatment of nodular thyroid disease and thyroid cancer in patients with abnormal glucose metabolism.

Author contributions

Each author contributed equally to design and conduct of the study, data collection and analysis, data interpretation and manuscript writing.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgments

None.

Conflict of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

REFERENCES

[1] Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007;36:707–35.
[2] Ayturk S, Gursoy A, Kut A, et al. Metabolic syndrome and its components are associated with increased thyroid volume and nodule prevalence in a mild-to-moderate iodine-deficient area. Eur J Endocrinol 2009;161:599–605.
[3] Rezzonico J, Rezzonico M, Pusiol E, et al. Introducing the thyroid gland as another victim of the insulin resistance syndrome. Thyroid 2008;18:461–4.
[4] Junik R, Kozinski M, Debska-Kozinska K. Thyroid ultrasound in diabetic patients without overt thyroid disease. Acta Radiol 2006;47:687–91.
[5] Pimenta WP, Mazeto GM, Callegaro CF, et al. Thyroid disorders in diabetic patients. Arq Bras Endocrinol Metabol 2005;49:234–40.
[6] Cappelli C, Rotondi M, Pirola I, et al. Thyreotropin levels in diabetic patients on metformin treatment. Eur J Endocrinol 2012;167(2):261–5 [Epub 2012].
[7] Rezzónico J, Rezzónico M, Pusiol E, et al. Metformin treatment for small benign thyroid nodules in patients with insulin resistance. Metab Syndr Relat Disord 2011;9(1):69–75.
[8] Rhee CM, Bhan I, Alexander EK, et al. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med 2012;172(2):153–9.
[9] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008;1(Suppl 1):S55–60.
[10] Erdoğan G, Erdogan MF, Emral R, et al. Iodine status and goiter prevalence in Turkey before mandatory iodization. J Endocrinol Invest 2002;25:224–8.
[11] Erdoğan MF, Demir O, Emral R, et al. More than a decade of iodine prophylaxis is needed to eradicate goiter among school age children in a moderately iodine-deficient region. Thyroid 2009;19:265–8.
[12] Rosenbaum M, Hirsch J, Murphy E, et al. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. Am J Clin Nutr 2000;71:1421–32.
[13] Zimmermann-Belsing T, Brabant G, Holst JJ, et al. Circulating leptin and thyroid dysfunction. Eur J Endocrinol 2003;149:257–71.
[14] Schmidt MI, Duncan BB, Vigo A, et al, ARIC Investigators. Leptin and incident type 2 diabetes: risk or protection? Diabetologia 2006;49:2086–96.
[15] Lewandowski K, Randeva HS, O'Callaghan CJ, et al. Effects of insulin and glucocorticoids on the leptin system are mediated through free leptin. Clin Endocrinol 2001;54:533–9.
[16] Menendez C, Baldelli R, Camiña JP, et al. TSH stimulates leptin secretion by a direct effect on adipocytes. J Endocrinol 2003;176:7–12.
[17] Rapoport B, Chazenbalk GD, Jaume JC, et al. The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. Endocr Rev 1998;19:673–716.
[18] Kimura T, Van Keymeulen A, Golstein J, et al. Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. Endocr Rev 2001;22:631–56.
[19] Riedemann J, Macaulay VM. IGF1R signalling and its inhibition. Endocr Relat Cancer 2006;13(Suppl 1):S33–43.
[20] Mohan S, Baylink DJ, Pettis JL. Insulin-like growth factor (IGF)-binding proteins in serum–do they have additional roles besides modulating the endocrine IGF actions? J Clin Endocrinol Metab 1996;81:3817–20.
[21] Santisteban P, Acebrón A, Polycarpou-Schwarz M, et al. Insulin and insulin-like growth factor I regulate a thyroid-

specific nuclear protein that binds to the thyroglobulin promoter. Mol Endocrinol 1992;6:1310–7.
[22] Malaguarnera R, Frasca F, Garozzo A, et al. Insulin receptor isoforms and insulin-like growth factor receptor in human follicular cell precursors from papillary thyroid cancer and normal thyroid. J Clin Endocrinol Metab 2011;96: 766–74.
[23] Mitsiades N, Pazaitou-Panayiotou K, Aronis KN, et al. Circulating adiponectin is inversely associated with risk of thyroid cancer: in vivo and in vitro studies. J Clin Endocrinol Metab 2011;96(12):E2023–8.
[24] Barb D, Williams CJ, Neuwirth AK, et al. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 2007;86:s858–66.
[25] Kokkinos A, Mourouzis I, Kyriaki D, et al. Possible implications of leptin, adiponectin and ghrelin in the regulation of energy homeostasis by thyroid hormone. Endocrine 2007;32(1):30–2.
[26] Lin SY, Huang SC, Sheu WH. Circulating adiponectin concentrations were related to free thyroxine levels in thyroid cancer patients after thyroid hormone withdrawal. Metabolism 2010;59(2):195–9.