Original Article

Insulin Resistance in Patients with Benign Thyroid Nodules

Zahra Heidari MD•[1], Mohammad Ali Mashhadi MD[2], Shahin Nosratzehi MD[1]

Abstract

Objective: Recently, it has been questioned whether insulin resistance is associated with thyroid nodules. The aim of this study was to examine insulin resistance prevalence in a case–control study of patients with benign thyroid nodules in an iodine-sufficient area.

Methods: This was a single-center, case–control study on euthyroid patients with benign nodular diseases. Thirty newly diagnosed patients with benign thyroid nodules according to fine needle aspiration cytology were investigated for insulin resistance. As a control group, 30 euthyroid control subjects with normal thyroid sonography without nodule were recruited from the general population. The participants were matched in pairs by age, gender, and body mass index. The diagnosis of insulin resistance was made when the homeostasis model assessment of insulin resistance (HOMA-IR) index was more than 2.5.

Results: The mean of HOMA-IR value was significantly higher in patients compared to controls (1.32 ± 0.65 *vs.* 0.76 ± 0.36, *P*-value < 0.001). Insulin resistance was seen in two subjects with thyroid nodules (6.7%), but none in the control group. There was a positive significant correlation between HOMA-IR and thyroid nodule size (*r*-value: +0.38, $P < 0.03$).

Conclusion: Patients with thyroid nodules have higher HOMA-IR value. There is an association between insulin resistance and benign thyroid nodules. More investigations are required to define the role of this factor in thyroid nodule formation.

Keywords: Benign, insulin resistance, patient, thyroid nodules

Cite this article as: Heidari Z, Mashhadi MA, Nosratzehi S. Insulin resistance in patients with benign thyroid nodules. *Arch Iran Med*. 2015; **18(9):** 572 – 576.

Introduction

Insulin resistance syndrome is a cluster of risk factors of coronary artery disease.[1] This pathological condition is characterized by an inadequate physiological response of peripheral tissues to circulating insulin and results in cardiovascular diseases and type 2 diabetes. Insulin resistance is also a characteristic of impaired glucose tolerance, simple obesity, polycystic ovarian syndrome, essential hypertension, non-alcoholic fatty liver disease and other disorders.[2,3]

In previous studies, increased thyroid volume and nodule prevalence were reported in patients with insulin resistance.[4–8] A thyroid nodule is defined as a discrete lesion within the thyroid gland. A prevalence of thyroid nodules of up to 60% has been described in healthy adults screened with sonography.[9] Thyroid nodules are generally benign nodules. Only 5% to 10% of nodules are carcinomas. There are several known etiological factors for thyroid nodule formation including genetic factors, iodine deficiency and goiterogens.[10] It is well known that insulin acts as a growth factor that stimulates cell proliferation. Increased insulin levels due to insulin resistance decrease the production of insulin-like growth factor-1 (IGF-1) binding proteins and hence increase levels of free IGF-1. The IGFs have many functions including, antiapoptotic, cell-survival, and transforming activities. The IGFs are produced by many tissues and their receptors are expressed in most cells.[11–14]

Epidemiologically, the prevalence of insulin resistance along with obesity has increased in recent years. It is clear that increased prevalence of insulin resistance and compensatory hyperinsulinemia lead to increased clinical syndromes associated with these metabolic changes.[15,16] In a similar trend, the incidence of thyroid nodule is rising. Although this recent rise in thyroid nodules is likely related to improvement of imaging modalities, it should be questioned whether other risk factors such as insulin resistance contribute to this increased risk or not.[17]

There are few reports regarding the effects of hyperinsulinemia on the thyroid gland. Thus, this study aimed to investigate the association between insulin resistance and a benign thyroid nodule in euthyroid patients.

Materials and Methods

Study design and patient population

This was a single-center, case–control study on euthyroid patients with benign nodules. The participants had 1) normal thyroid function (euthyroidism was defined as normal thyroid stimulating hormone [TSH: 0.4 – 4.2 mIU/L] and free thyroxine [FT4: 0.8 – 1.8 ng/dL] levels); 2) thyroid nodules ≥ 1 cm; 3) negative titers of antithyroid peroxidase antibody (TPOAb < 16 IU/mL). Individuals with any of the following characteristics were excluded from the study: those with a history of thyroid disease, previous-thyroid medication therapy at any time, smoking, statin, antihypertensive and oral contraceptive therapy, iodinated contrast material exposure in the previous six months, history of neck irradiation or surgery, overt or subclinical hyperthyroidism, as well as hypothyroidism and malignant features in cytology. Patients were also excluded if they had a family or personal history of diabetes mellitus, endocrine obesity, pregnancy and lactation, hepatic or renal dysfunction, as well as the history of heart failure, significant neurological or psychological illness (depression, epilepsy and schizophrenia) that could have had an impact on thyroid function tests.

Forty-three patients with thyroid nodules in our outpatient En-

Authors' affiliations: [1]Department of Endocrinology, Zahedan University of Medical Sciences, Zahedan, Iran, [2]Department of Hematology and Oncology, Zahedan University of Medical Sciences, Zahedan, Iran.
•Corresponding author and reprints: Zahra Heidari MD, Department of Endocrinology, Zahedan University of Medical Sciences, Zahedan, I. R. of Iran. Tel: +98-5433430230, Fax: +98-5433425607, E-mail: z.heidari10@yahoo.com.
Accepted for publication: 15 July 2015

docrinology Clinic in Zahedan city, Iran, were chosen as the potential study population between June 2012 and September 2013. Among them, eight patients were excluded due to positive thyroid antibodies. Also, three patients due to subclinical hypothyroidism and two because of pregnancy were excluded. Finally, 30 newly diagnosed patients with benign thyroid nodules according to fine needle aspiration cytology (Bethesda system classification), who lived in an iodine-sufficient area[18] were consecutively recruited as the patient group of this study.

Thirty-six euthyroid healthy individuals were chosen as the control group from the hospital staff. Three participants with positive thyroid antibodies and three with detected small thyroid nodules in ultrasonography were excluded. Thus, 30 control participants were chosen with normal thyroid sonography after considering the inclusion and exclusion criteria. They did not have any known acute or chronic illness. For each of the 30 participants of the case group, a pair was selected. The control group was matched according to age, gender, and Body Mass Index (BMI) with the case group. The age difference was not more than one year and body mass index was not more than one between the pair participants of each group. The Ethics Committee for Human Studies of Zahedan University of Medical Sciences approved the study protocol. All participants provided informed consent before their participation.

Anthropometric measurements

Weight was measured while participants were minimally clothed without shoes, using digital scales, and recorded to the nearest 100 g. Height was measured in a standing position without shoes, using a tape meter, while the shoulders were in a normal state. Body mass index was calculated as weight in kilograms, divided by height in square meters.

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 –70ºC until assay. Serum glucose was measured by the glucose oxidase technique. The serum insulin level was assayed with a solid-phase competitive chemiluminescent enzyme immunoassay (Diagnostic Product LIAISON, Italy).

Insulin resistance was estimated based on calculation of the homeostasis model assessment (HOMA) index for each patient. This was done, using the formula: (fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5.[19] A HOMA-IR index equal or higher than 2.5 denotes insulin resistance.

Thyroid function was evaluated by measuring free T4 and TSH using immunochemiluminescent assays by an automated analyzer (Diagnostic Products LIAISON, 2011, Italy). Antithyroid peroxidase was measured by immunochemiluminescent assays employing commercial kits (Diagnostic Products LIAISON).

Thyroid ultrasound

Thyroid ultrasonography was done for all participants by the same physician using a 7.5 MHz linear probe (Aloka Co. Ltd., Tokyo, Japan). All participants with thyroid nodules ≥ 1 cm were offered to undergo fine needle aspiration biopsy.

Cytology

All fine needle aspiration biopsies were performed and analyzed by the same thyroid expert pathologist. According to Bethesda system, the cytology was diagnostic and consistent with benign nodules in all cases. There was no diagnosis of thyroid cancer or follicular neoplasm.

Statistical analysis

By studying 30 cases and 30 controls, the study had a 90 % power to detect a mean difference in HOMA-IR value of 2.6 between case and control groups at the 5 % significance level, assuming the standard deviations of HOMA-IR value to be 1.7 and 0.3 in case and control groups, respectively.[20] Continuous variables were presented as the mean ± standard deviation and categorical variables as absolute numbers and percentages. An independent sample *t*-test or a Mann–Whitney U-test was used to assess significance of differences for continuous variables and $\chi 2$ tests for percentages. Pearson's correlation test was performed for correlation analysis. Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 18.0, Chicago). *P*-values less than 0.05 were considered significant.

Results

Study population characteristics are depicted in Table 1. As noted, the study included a total of 60 subjects (30 in the patient group and 30 in the control group). Among the 30 patients with thyroid nodules in the study, 26 (86.7%) were female and 4 (13.3%) were male.

Serum concentrations of free T4 and anti-thyroid peroxidase levels were within normal limits and did not differ significantly between both groups. Mean TSH level in the control group was higher than patient group. The mean of HOMA-IR value was significantly higher in patients than in controls (1.32 ± 0.65 *vs*. 0.76 ± 0.36, *P*-value < 0.001). Fasting plasma glucose and fasting insulin levels were also higher in the patient group. Insulin resistance was found in two participants with thyroid nodules (6.7%) and none in the control group.

There was a positive significant correlation between HOMA-IR and thyroid nodule size in patients (*r*-value: +0.38, $P < 0.03$). However, there was no correlation between TSH and thyroid nodule size. Also, there was a positive correlation between body mass index and HOMA-IR (Table 2).

Discussion

This study shows that patients with thyroid nodules have a higher HOMA-IR value and there is an association between HOMA-IR and benign thyroid nodules. Thyroid nodules are characterized by excessive growth of one or several areas within the normal thyroid gland. Their etiology involves interactions between environmental and genetic factors. The environmental predisposing factors might be the low iodine intake, natural goitrogens and certain drugs. These factors interact with gender and genetic background.[21]

In recent years, the epidemiological prevalence of insulin resistance has increased along with the increasing prevalence of obesity.[22] On the other side, the prevalence of thyroid nodules is also increasing.[23] This is probably due to higher use of neck ultrasonography in the general population, which can increase the diagnosis of thyroid nodules. However, it is also possible that this higher incidence rate of thyroid nodules is related to increased prevalence of obesity and insulin resistance.

There is a limited data about the effect of insulin resistance

Table 1. Clinical and laboratory characteristics of study participants

	Patient group	Control group	*P*-value
Female (%)	26 (86.7)	26 (86.7)	1
Age (year)			1
Mean ± SD	37.80 ± 10.00	37.80 ± 10.00	
Median	36.50	36.50	
Range	22.00–59.00	22.00–59.00	
BMI			0.69
Mean ± SD	26.60 ± 4.50	26.20 ± 4.40	
Median	26.10	25.50	
Range	20.20–35.40	20.00–35.00	
Fasting plasma glucose (mg/dL)			< 0.001
Mean ± SD	95.33 ± 10.04	78.23 ± 12.61	
Median	97.50	81.50	
Range	60.00–112.00	56.00–104.00	
Fasting insulin (µu/mL)			0.006
Mean ± SD	5.67 ± 2.83	3.88 ± 1.51	
Median	5.35	3.50	
Range	1.80–13.80	1.80–7.60	
HOMA-IR (score)			< 0.001
Mean ± SD	1.32 ± 0.65	0.76 ± 0.36	
Median	1.22	0.70	
Range	0.44–3.03	0.25–1.71	
IR (%)	2 (6.66%)	0	0.49
TSH (mIU/L)			0.004
Mean±SD	1.92 1.17±	2.76 ± 1.31	
Median	1.30	2.78	
Range	0.60–4.70	0.88–4.90	
Ft4 (ng/mL)			0.69
Mean ± SD	0.99 ± 0.13	1.06 ± 0.40	
Median	0.99	0.96	
Range	0.87–1.23	0.81–1.80	
Anti TPO (IU/mL)			0.30
Mean ± SD	4.65 ± 4.42	6.07 ± 10.10	
Median	5.42	8.51	
Range	0.00–15.80	0.00–16.00	

BMI: body mass index; HOMA: homeostasis model assessment of insulin resistance; IR: insulin resistance; TSH: thyroid stimulating hormone; FT4: free T4; Anti TPO: antithyroid peroxidase.

Table 2. Correlation of thyroid nodule size and HOMA-IR with BMI and laboratory parameters.

Variable	Thyroid nodule size		HOMA-IR	
	Correlation (*r*-value)	*P*-value	Correlation (*r*-value)	*P*-value
BMI	0.13	0.48	0.29	0.02
Anti TPO (IU/mL)	-0.09	0.62	0.15	0.24
FT4 (ng/ml)	-0.28	0.12	-0.08	0.54
TSH (mIU/l)	0.10	0.57	-0.10	0.43
HOMA-IR	0.38	0.03	- - -	- - -

BMI: body mass index; HOMA: homeostasis model assessment of insulin resistance; TSH: thyroid stimulating hormone; FT4: free T4; Anti TPO: antithyroid peroxidase.

and hyperinsulinemia on the development of thyroid nodules or goiter.[4,5,8,24] Regarding the association of insulin resistance with thyroid morphological abnormalities, our findings are in agreement with these studies. In a study by Rezzonico, et al.[5] subjects with thyroid nodules were found to have an increased prevalence of insulin resistance and hyperinsulinemia. Consistent with these findings, euthyroid patients with nodular disease were found to have higher HOMA-IR values in our study compared with the individuals with normal thyroid gland. A correlation was found between the nodule size and HOMA-IR levels, which is consistent with Rezzonico and colleagues. In another study, ayturk and colleagues showed that due to metabolic syndrome, patients with insulin resistance have significantly an increased thyroid volume and nodule prevalence.[4] A similar study in Argentina showed that patients with a skin tag as a marker of insulin resistance have a higher prevalence of US-detected thyroid nodules and larger thyroid glands.[24] Yasar, et al. investigated insulin resistance in patients with euthyroid nodular goiter. In their study, HOMA-IR was found to be significantly higher and thyroid volume was significantly greater in the patient group.[8]

It is clear that TSH is a major growth factor for thyroid gland. TSH is involved in the control of expression of growth factors and their receptors[25–27] and IGF-1-dependent signaling.[28] In addition to TSH, insulin is also a thyroid growth factor that stimulates proliferation of thyroid cells in culture.[29] Evidence suggests that IGF-I-dependent, and TSH-independent signaling may play a major role in growth regulation of the human thyroid gland. This hypothesis is supported by conditions not associated with increased TSH secretion, like acromegaly, in which high levels of intra-thyroid IGF-1 may contribute to thyroid enlargement.[30]

Insulin like growth factor-1 is a major growth and differentiation factor for a number of cell types. The IGF system consists of a network of ligands (IGF-1 and IGF-2) and their receptors (IGF-1 receptor) which are highly homologous to insulin and its receptor.[31] Insulin/IGF-1 signaling pathway modulates regulation of thyroid gene expression and is an additional important factors in proliferation and differentiation of thyroid cells.[13] It has been demonstrated that IGF-1, IGF-2, IGF-1 receptor and insulin receptor isoforms, are expressed at high levels in thyroid follicular cell precursors. Thus, one explanation for our findings may be the activation of the IGF system and insulin pathway. Insulin resistance and abnormal glucose metabolism cause higher serum insulin levels, which in turn will increase thyroid proliferation and nodule formation.

The present study has several limitations. First was the relative small number of participants. Second, since this was a cross-sectional observation study, a causal relationship between insulin resistance and benign thyroid nodule cannot be made. Third, the lack of gold standard measures of insulin resistance, the glucose clamp method. This method is invasive and costly, so HOMA-IR was used as a surrogate measure of insulin resistance. In this regard, there is a good correlation between results of insulin resistance based on HOMA and the glucose clamp method.[32,33] Thus, HOMA-IR equation has been widely used in clinical and epidemiological studies.

Having a control group with no thyroid nodules, complete information about some morphological characteristics of thyroid nodules such as nodule diameters and uni-/multi-nodularity in each group, assessment of cytological and/ or histopathological outcome of each thyroid nodule as well as anti-thyroid peroxidase measurement were potential advantages of this study. In conclusion, patients with thyroid nodules have a higher HOMA-IR value. There is an association between insulin resistance and benign thyroid nodules. Including larger sample size in a prospective design may improve the strength of future studies. More investigations are required to define the role of this factor in thyroid nodule formation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgement

The authors would like to thank the patients who participated in the study. This study was supported by Zahedan University of Medical Sciences.

References

1. Reaven GM . Role of insulin resistance in human disease. *Diabetes*. 1988; **37:** 1595 – 607.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005; **365:** 1415 – 1428.
3. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am*. 2004; **33:** 283 – 303.
4. Ayturk S, Gursoy A, Kut A, Anil C, Nar A, Tutuncu NB. 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.
5. Rezzonico J, Rezzonico M, Pusiol E, Pitoia F, Niepomniszcze H. Introducing the thyroid gland as another victim of the insulin resistance syndrome. *Thyroid*. 2008; **18:** 461 – 464.
6. Gursoy A. Rising thyroid cancer incidence in the world might be related to insulin resistance. *Med Hypotheses*. 2010; **74:** 35 – 36.
7. Anil C, Akkurt A, Ayturk S, Kut A, Gursoy A. Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule prevalence in a mild-to-moderate iodine deficient area. *Metabolism*. 2013; **62:** 970 – 975.
8. Yasar HY, Ertuğrul O, Ertuğrul B, Ertuğrul D, Sahin M. Insulin resistance in nodular thyroid disease. *Endocr Res*. 2011; **36:** 167 – 174.
9. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med*. 1997; **126:** 226 – 231.
10. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. *Endocrinol Metab Clin North Am*. 2007; **36:** 707 – 735.
11. Pothiwala P, Jain SK, Yaturu S. Metabolic syndrome and cancer. *Metab Syndr Relat Disord*. 2009; **7:** 279 – 288.
12. Vella V, Sciacca L, Pandini G, Mineo R, Squatrito S, Vigneri R, et al . The IGF system in thyroid cancer: new concepts. *Mol Pathol*. 2001; **54:** 121 – 124.
13. Kimura T, Van Keymeulen A, Golstein J, Fusco A, Dumont JE, Roger PP. Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. *Endocr Rev*. 2001; **22:** 631 – 656.
14. Kimura T, Dumont JE, Fusco A, Golstein J. Insulin and TSH promote growth in size of PC Cl3 rat thyroid cells, possibly via a pathway different from DNA synthesis: Comparison with FRTL-5 cells. *Endocr Rev*. 2001; **22:** 631 – 656.
15. Ford ES, Mokdad AH, Giles WH. Trends in waist circumference among U.S. adults. *Obes Res*. 2003; **11:** 1223 – 1231.
16. Bessesen DH. Update on obesity. *J Clin Endocrinol Metab*. 2008; **93:** 2027 – 2034.
17. Enewold L, Zhu K, Ron E, Marroqi AJ, Stojadinovic A, Peoples GE, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Bio-*

markers Prev. 2009; **18:** 784 – 791.
18. Delshad H, Mehran L, Azizi F. Appropriate Iodine Nutrition in Iran: 20 Years of Success. *Acta Medica Iranica*. 2010; **48:** 361 – 366.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; **28:** 412 – 419.
20. Rezzónico J, Rezzónico M, Pusiol E , Pitoia F, Niepomniszcze H. Increased Prevalence of Insulin Resistance in Patients With Differentiated Thyroid Carcinoma. *Metabolic Syndrome and Related Disorders*. 2009; **7:** 375 – 380.
21. Hegedus L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. *Endocr Rev*. 2003; **24:** 102 – 132.
22. Li C, Ford ES, McGuire LC, Mokdad AH, Little RR, Reaven GM. Trends in hyperinsulinemia among nondiabetic adults in the U.S. *Diabetes Care*. 2006; **29:** 2396 – 2402.
23. Mitchell I, Livingston EH, Chang AY, Holt S, Snyder WH, Lingvay I, et al. Trends in thyroid cancer demographics and surgical therapy in the United States. *Surgery*. 2007; **142:** 823 – 828.
24. Rezzónico J, Rezzónico M, Pusiol E, Pitoia F, Niepomniszcze H. High prevalence of thyroid nodules in patients with achrocordons (skin tags). Possible role of insulin-resistance. *Medicina (B Aires)*. 2009; **69(3):** 302 – 304.
25. Derwahl M, Studer H. *Pathogenesis and treatment of multinodular goiter*. In: Fagin JA (ed). Thyroid Cancer. Boston/Dordrecht/London: Kluwer; 1998: 155 – 186.
26. Studer H, Derwahl M. Mechanisms of nonneoplastic endocrine hyperplasia— a changing concept: A review focused on the thyroid gland. *Endocr Rev*. 1995; **16:** 411 – 426.
27. Westermark K, Karlsson FA, Westermark B. Thyrotropin modulates EGF receptor function in porcine thyroid follicle cells. *Mol Cel Endocrinol*. 1985; **40:** 17 – 23.
28. Eggo MC, King WJ, Black EG, Sheppard MC. Functional human thyroid cells and their insulin-like growth factor-binding proteins: Regulation by thyrotropin cyclic 3',5' adenosine monophosphate, and growth factors. *J Clin Endocrinol Metab*. 1996; **81:** 3056 – 3062.
29. Burikhanov R, Coulonval K, Pirson I, Lamy F, Dumont JE, Roger PP. Thyrotropin via cyclic AMP induces insulin receptor expression and insulin co-stimulation of growth and amplifies insulin and insulin-like growth factor signaling pathways in dog thyroid epithelial cells. *J Biol Chem*. 1996; **271:** 29400 – 29406.
30. Cheung NW, Boyages SC. The thyroid gland in acromegaly: An ultrasonographic study. *Clin Endocrinol (Oxf).* 1997; **46:** 545 – 549.
31. Riedemann J, Macaulay VM. IGF1R signalling and its inhibition. *Endocr Relat Cancer*. 2006; **13(Suppl 1):** S33 – S43.
32. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004; **27:** 1487 – 1495.
33. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998; **21:** 2191 – 2192.