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Original Article

The relationship between nodular thyroid disease and metabolic parameters in patients with acromegaly

Akromegali hastalarında nodüler tiroid hastalığı ve metabolik parametreler ile ilişkisi

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ABSTRACT

Aim: The high prevalence of nodular goiter in patients with acromegaly is well known. Insulin-like growth factor-1 (IGF-1) has been claimed to be one of the etiologic factors. The aim of the study was to evaluate the incidence of thyroid lesions in our acromegalic patients and to analyze possible factors influencing thyroid nodule development, especially insulin resistance and hormonal parameters.

Material and Methods: Sixty patients with acromegaly, 32 females, and 28 males, with a mean age of 52.7 ± 10.0 years without known thyroid disease were included. Age and sex matched 100 control subjects also included in the study. Waist and hip circumference, weight, and height, fasting blood glucose, postprandial blood glucose, insulin, thyroid function tests, thyroid autoantibodies, lipid profile, IGF-1, growth hormone, other anterior pituitary hormone levels were measured in all patients. Magnetic Resonance Imaging (MRI) and thyroid ultrasonography (US) was performed in all patients. Thyroid nodule volume and thyroid volume were calculated.

Results: Thirty-five (58.3%) patients with acromegaly had thyroid nodules according to (% 25) in control group ($p<0,0001$). There were significant differences in BMI, thyroid volume, fasting glucose and TSH levels between patients and controls. After regression analysis, thyroid volume was associated with insulin, waist circumference, HOMA-IR, LDL-cholesterol and the size of the pituitary adenoma ($p<0.05$) or diabetes occurrence. During the logistic regression analysis, the presence of nodules was strongly associated with luteinizing hormone (LH) ($p<0.02$) and HDL-cholesterol levels ($p<0.05$). Nodule volume were significantly associated with LH level ($p<0.05$), ACTH (beta = -0.51, $p< 0.01$), plasma cortisol (beta= 0.965, $p <0.05$), free T4 (beta= 0.522, $p<0.05$), the size of adenoma (beta= 0.615, $p<0.05$) in the regression analysis.

Conclusion: The prevalence of nodules in acromegalic patients were found to be higher than usual prevalence. In addition to IGF-1, other hormones and insulin resistance might play an important role in thyroid volume, nodule volume, and nodule formation mechanism in patients with acromegaly.

Key words: Acromegaly, thyroid volume, anterior pituitary hormones

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ÖZ

Amaç: Akromegali hastalarında nodüler guatr sık görüldüğü iyi bilinmektedir. İnsülin benzeri büyüme faktörü-1 (IGF-1)'in etiyolojik faktörlerden biri olduğu iddia edilmiştir. Bu çalışmanın amacı akromegali hastalarında tiroid lezyon insidansının değerlendirilmesi ve insülin direnci ve hormonal paramatreler başta olmak üzere tiroid nodül gelişimini etkileyen olası faktörleri değerlendirmektir.

Gereç ve Yöntem: Bilinen tiroid hastalığı olmayan ortalama yaşları 52.7±10.0 olan 60 akromegali hastası (32 kadın 28 erkek) çalışmaya dahil edildi. Yaş ve cinsiyet uyumlu 100 kontrol hastası çalışmaya alındı. Tüm hastalarda vücut kitle indeksi (VKİ), bel-kalça çevresi, boy, kilo, açlık kan glukozu, tokluk kan glukozu, insülin, tiroid fonksiyon testleri, tiroid otoantikorları, lipid profili, IGF-1, büyüme hormonu ve diğer ön hipofiz hormonlarının ölçümleri yapıldı. Manyetik rezonans görüntüleme ve tiroid ultrasonografi tüm hastalarda uygulandı. Tiroid volümü ve tiroid nodül volümü hesaplandı.

Bulgular: Kontrol grubu (%25) ile kıyaslandığında 35 (%58.3) akromegali hastasında tiroid nodülü mevcuttu (p<0.0001). Hasta ve kontrol grupları arasında VKİ, tiroid volümü, açlık kan şekeri ve TSH düzeyleri açısından anlamlı farklılıklar bulundu (p<0.05). Regresyon analizi sonrasında tiroid volümü ile insülin, bel çevresi, HOMA-IR, LDL-kolesterol ve pituiter adenom boyutu arasında ilişki saptandı (p<0.05). Lojistik regresyon analizinde nodül varlığı ile lüteinizan hormone (LH) (p<0.02) ve HDL-kolesterol (p<0.05) arasında güçlü ilişki bulundu. Regresyon analizinde nodül volümü ile LH düzeyi (p<0.05), ACTH (beta = -0.51, p<0.01), plasma kortizolü (beta= 0.965, p <0.05), serbest T4 (beta= 0.522, p<0.05), adenom boyutu (beta= 0.615, p<0.05) arasında anlamlı ilişki bulundu.

Sonuç: Akromegali hastalarında tiroid nodül prevelansı genel populayona göre daha yüksektir. Bununla birlikte IGF-1, diğer hormonlar ve insülin direnci gibi parametreler akromegali hastalarında tiroid volümü, nodül volümü ve nodül formasyon mekanizmalarında önemli rol oynayabilir.

Anahtar kelimeler: Akromegali, tiroid nodülü, ön hipofiz hormonları

Introductıon

Acromegaly is a chronic disease characterized by the presence of growth hormone (GH) hypersecretion caused by a benign pituitary adenoma and increased levels of insulin-like growth factor 1 (IGF-1). Overproduction of IGF-1 by increased secretion of GH leads to a multisystemic disease characterized by disproportionate skeletal, tissue, and organ growth, multiple comorbidities and premature mortality (1,2). The high prevalence of nodular goiter in patients with acromegaly is well known. Thyroid enlargement in acromegaly may be diffuse or multinodular. Cheung et al reported that 92% of patients with acromegaly had an enlarged thyroid gland determined by ultrasound; mean thyroid size was increased more than five times normal (3). According to a recent meta-analysis, approximately 60% of patients with acromegaly had thyroid nodular disease (4). Acromegalic patients have a high risk for the development of thyroid cancer (5,6). It is well documented that IGF-1 is a thyroid growth factor (7). There is a correlation between IGF-1 levels and thyroid volume (TV) in patients with acromegaly (8). Insulin resistance and hyperinsulinemia are common features of patients with active acromegaly (1). Increased lipolysis and free fatty acids concentrations, deterioration of insulin signal pathway, alterations of adipokines and adipose tissue inflammation are possible underlying mechanisms (9,10). Previous studies have demonstrated that patients with insülin resistance (IR) have larger thyroid volumes and a higher prevalence of thyroid nodules (11,12). The possible mechanisms are the concurrent function of insulin with thyroid-stimulating hormone (TSH) as a growth factor and stimulating thyroid cell proliferation, and insulin/IGF-1 signaling pathway modulating the regulation of thyroid gene expression that leads to thyrocyte proliferation and differentiation (13,14).

The aim of the study was to evaluate the incidence of thyroid lesions in our acromegalic patients and to analyze possible factors influencing thyroid nodule occurrence, especially insulin resistance and hormonal parameters.

Material and Methods

60 acromegaly patients (33 females, 27 males, mean age 47.62 ± 13.27 years), without known thyroid disease, currently managed by the Endocrinology and Metabolism Department of Diskapi Teaching and Research Hospital in Turkey were enrolled to study. Ethics committee approval and written informed consent of participants was obtained prior to the study.

The diagnosis of acromegaly was made on the basis of characteristic clinical features, elevated IGF-1 levels over normal values for age and gender and failure of GH suppression

to <1ng/mL after an oral glucose load (15). All patients had a pituitary adenoma identified clearly by magnetic resonance imaging. All patients were managed according to the recommended guidelines for acromegaly management (15).

All patients underwent an evaluation of thyroid volume (TV) by ultrasound and determination for IGF-1, free T4, TSH, antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (AntiTg). None had a history of thyroid disease, and all were euthyroid on biochemical testing. Growth hormone and IGF-1 levels were analyzed with chemiluminescence method in IMMULITE 2000 Xpi (Siemens Healthcare Diagnostics Inc.). The normal range for GH is 0–0.8 ng/mL. Serum IGF-1 levels were compared with age-gender adjusted normal range. Thyroid stimulating hormone (TSH), free thyroxine (fT4), anti-thyroglobulin (anti-Tg) and thyroid peroxidase antibody (anti-TPO) were measured with specific electrochemiluminescence immunoassays method with a commercially available kit (Immulite 2000, Bio DPC, Los Angeles, CA, USA). The normal range for fT4 as 0.74-1.52 ng/dL. TSH levels ranging between 0.55-4.78 mIU/L was considered normal and normal ranges for anti-Tg and anti-TPO are 0–40 IU/mL and 0–35 IU/mL, respectively. Homeostasis model assessment (HOMA-IR) was used for calculation of IR (16). Serum levels of glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol (in women), total testosterone (in men) were also measured. FSH, LH, and estradiol (in women) were measured in pre-ovulatory period if they still menstruate. Blood samples were obtained at 08.00 h to evaluate the basal plasma ACTH and serum cortisol concentration.

Demographic data and medical history of all subjects were recorded; physical examination and anthropometric measurements were performed. Weight, height, waist circumference (WC), hip circumference (HC) and systolic and diastolic blood pressure (BP) were measured. The body mass index (BMI) was measured by dividing the weight by the square of the height (kg/m2). WC was determined by measuring the narrowest point between the costal margin and iliac crest at the end of a normal expiration. The blood pressure (BP) at rest was measured on the right arm using a standard mercury sphygmomanometer, with the patient in the sitting posture for 10 min before the test, and the average of two measurements was recorded.

Thyroid ultrasound

Thyroid ultrasonography (US) was performed using High-resolution B-mode ultrasound images (EUB 7000 HV; Hitachi, Tokyo, Japan) with a 13-MHz linear array transducer. The volume of each thyroid lobe was calculated by the ellipsoid model formula (length x thickness x width x 0.52) (17). Total TV >18 mL in men and >13 mL in women was considered as goiter. TV was considered as the sum of the volumes of each lobe. Nodule volume was calculated with the same formula. Nodule and thyroid volumes were evaluated at the time of Acromegaly diagnosis.

Statistical Analyses

All statistical analysis was performed using SPSS (The Statistical Package for Social Sciences) Version 17.0 (SPSS, Inc, Chicago, IL, USA). Whether the distributions of continuous variables were normality or not was determined by using Kolmogorov-Smirnov test. The data obtained by the measurement is given by the arithmetic mean ± standard deviation. Qualitative analysis of the data was performed using. Differences in the groups of patients with and without nodules were analyzed by using Mann-Whitney U test. The relationship between continuous variables in patients' group was determined by using Spearman Correlation analysis; correlation coefficients and p values were calculated. The effects of variables that could be considered as significant on thyroid volume and nodule volume were examined by using multiple linear regression analysis. Multistep regression analysis was performed. Independent variables that may affect the presence of nodules were determined by using Multivariate logistic regression analysis. Adjusted R-squared and statistically significant p-values are presented. A p-value <0.05 was considered statistically significant.

Results

Thirty-five (58.3%) patients with acromegaly had thyroid nodules when compared to control group (%25) (p<0,0001). Mean thyroid volume was 32.09 ± 33.45 and mean nodule volume was 0.74 ± 0.97 in acromegaly group. BMI was higher in in acromegaly group when compared to controls (29.74 ± 4.58 to 26.06 ± 4.68, p=0.009). There were also significant differences in thyroid volume, fasting glucose and TSH levels between patients and controls (p<0.05). Mean GH and IGF-1 levels were 17.83 ± 13.23 ng/mL and 924.71 ± 446.71 ng/mL, respectively (Table-1). IGF-1 levels were correlated with thyroid volume (r2:0.471, p=0.026) but not with nodule volume (p>0.05). After regression analysis, thyroid volume was associated with insulin, waist circumference, HOMA-IR, LDL-cholesterol and the size of the pituitary adenoma (beta= 0.615, p<0.05). The presence of nodules was strongly associated with LH (p<0.02) and HDL-cholesterol levels (p<0.05) according to the logistic regression analysis. Nodule volume were significantly associated with luteinizing hormone (LH) level (p<0.05), ACTH (beta =-0.51, p<0.01), plasma cortisol (beta= 0.965, p <0.05) and free T4 (beta= 0.522, p<0.05) (Figure 1-2).

Table 1. Basic demographics and laboratory values of patients and control group

	Acromegaly Group		Control Group		
	Mean	SD	Mean	SD	P
Age (years)	47.62	13.27	42.18	10.62	0,066
Weight (kg)	83.92	16.42	69.55	13.90	0.005
Height (cm)	167.53	8.90	163.21	7.13	0.091
BMI (kg/m2)	29.74	4.58	26.06	4.68	0.009
SBP (mmHg)	131.42	7.51	124.36	5.43	0.007
DBP (mmHg)	81.12	6.32	77.82	5.21	0.012
Glucose (mg/dl)	107.78	27.10	84.92	7.98	<0.0001
Insulin (mU/L)	11.15	8.19	11.67	6.49	0.777
HOMA-IR	1.52	1.09			
Total Cholesterol (mg/dL)	185.46	42.78			
Triglyceride (mg/dL)	142.15	77.71			
HDL-C (mg/dL)	47.05	15.86			
LDL-C (mg/dL)	112.78	35.22			
Free T4 (ng/dL)	3.45	14.04	1.02	0.14	0.210
TSH (mIU/L)	1.79	1.34	2.08	0.95	0.319
FSH (IU/L)	22.05	33.27	-	-	-
LH (IU/L)	8.43	8.64	-	-	-
Prolactin (ng/mL)	78.96	212.07	-	-	-
Estradiol (pg/mL)	53.66	80.17	-	-	-
Total testosterone (ng/dL)	54.91	103.95	-	-	-
Cortisol (mg/dL)	11.97	7.91	-	-	-
ACTH (pg/mL)	30.49	24.89	-	-	-
GH (ng/mL)	17.83	13.23	-	-	-
IGF-1 (ng/mL)	924.71	446.71	-	-	-

Abbreviations: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostasis model assessment, TSH: Thyroid stimulating hormone, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein FSH: Follicle-stimulating hormone, LH: luteinizing hormone, ACTH: Adrenocorticotroph hormone, GH: Growth hormone, IGF-1: Insulin-like growth factor-1.

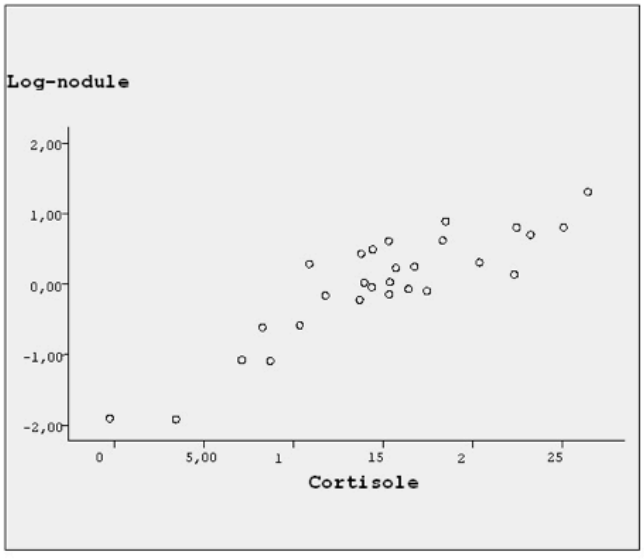

Figure 1. Correlation of thyroid nodule volume with Cortisol levels

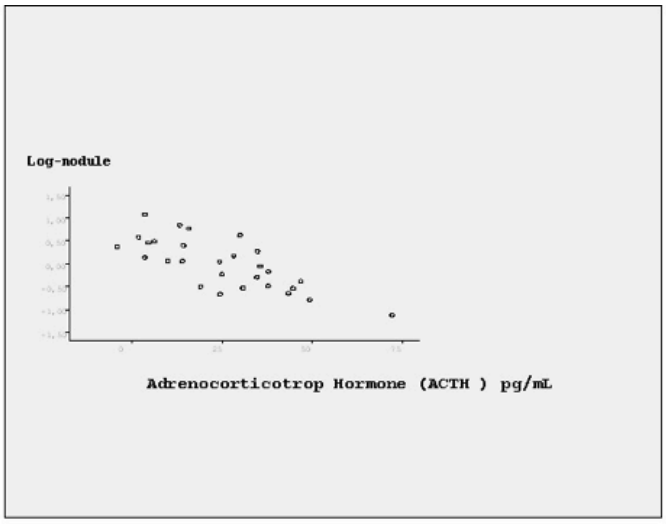

Figure 2. Correlation of thyroid nodule volume with ACTH levels

Discussion

Nodule prevalence in our acromegaly patients (58%) was demonstrated to be significantly higher. Insulin resistance, IGF-1, GH was not associated with nodule prevalence. We found an association between nodule volume and, LH and FSH concentrations.

Insulin resistance is commonly seen in patients with acromegaly. The increased lipolysis induced increased FFAs by GH stimulation may have an impact on insulin sensitivity by competition with glucose for substrate oxidation, deterioration in insulin signal pathway and b-cell function, or triggering adipose tissue inflammation (9,18,19). Mori et al observed that serum IGF-1 levels were associated with insulin resistance in patients with acromegaly and improvement glucose tolerance in was demonstrated after a postoperative decrease in serum IGF-1 levels (20). It may be possible that IGF-insulin hybrid receptors and post receptor pathways cross-talk play role in development of IR in acromegaly patients (21). However, O'Connell et al demonstrated that IGF-1 administration induced by a GH-receptor antagonist decreased blood glucose and insulin resistance in patients with controlled acromegaly (22). Low IGF-1 levels in patients with Laron syndrome are related to insulin resistance that is reversed after IGF-1 treatment (23). These two studies might indicate a GH-independent mechanism may have a role IR in acromegaly patients.

A thyroid nodule is a discrete lesion within the thyroid gland, which can be distinguished from the thyroid parenchyma as (24) increased epithelial hyperplasia and excessive distention of some follicles that have undergone involution are considered to cause of nodule development (25). Genetic factors, iodine deficiency, age, gender, smoking, and goitrogens are well-known etiological factors

for thyroid nodule formation (26,27). IGF-1 stimulates synthesis of protein and DNA in thyrocytes and stimulates the proliferation and differentiation of these cells (13,28). Ongoing exposure to high serum IGF-1 levels may play a role in the development of thyroid nodules in acromegaly patients (29). Völzhe et al reported that high serum IGF-1 levels were associated with thyroid nodules (30). In our study, thyroid volume was associated with IGF-1 levels which are consistent with the literature.

Serum TSH level has been recognized as the main growth factor for thyroid cells. Insulin is a thyroid growth factor act as a co mitogenic factor and it might partly enhance responsiveness to IGFs in response to TSH. This increases the probability of potential role of TSH-insulin interactions in the regulation of thyroid growth and function in vivo (31). Regulation of thyroid gene expression is modulated by insulin/IGF-1 signaling pathway that is an additional important factor in proliferation and differentiation of thyroid cells (13). It is well known that insulin acts as a growth factor that stimulates cell proliferation. IR-induced increased insulin levels decrease Insulin-like growth factor-1 (IGF-1) binding proteins production and consequently increase IGF-1 levels. Antiapoptotic, cell survival and transforming activities are well-known functions of IGFs. Many tissues produce IGFs and most cells express IGFs receptors (13,32,33,34). Heidari et al demonstrated that patients with thyroid nodules had increased HOMA-IR values and there was a relation between HOMA-IR and benign thyroid nodules (35). Rezzonico et al reported that patients with higher circulating levels of insulin due to IR had larger thyroid volumes and a higher risk for the thyroid nodule formation (11). In another study, increased thyroid volume and nodule prevalence were observed in patients with IR due to metabolic syndrome (12). Yasar et al reported that IR may lead to increased thyroid proliferation and nodule formation (36). IR increases visceral fat accumulation via effects on serum leptin concentrations and this visceral fat increases TSH secretion that increase thyroid proliferation (37).

Rezzonico et al demonstrated that patients with differentiated thyroid carcinoma (DTC) had a higher frequency of IR (38). Karimifar et al reported that metformin decreased the size of small solid thyroid nodules via decreasing serum TSH levels and also prevented the thyroid volume increase in patients with prediabetes (39). In another study, metformin therapy was demonstrated to decrease thyroid volume and nodule size in patients with insulin resistance (40). In our study, thyroid volume was associated with insulin and HOMA-IR that may indicate IR may play a role in thyroid nodule formation in patients with acromegaly.

Luteinizing hormone (LH) is a glycoprotein hormone-like TSH and has similar alpha subunit. LH was shown to increase thyroid adenylate cyclase activity 65 times more robustly than human chorionic gonadotropin (hCG) (41). Yoshimura et al also demonstrated that human LH bound to the TSH receptor and stimulated adenylate cyclase more potently than hCG (42). hCG and LH have a proliferative effect on rat and human thyroid cells. Knudsen et al reported that oral contraceptive users had a lower thyroid volume and risk of goiter (43). Oral contraceptive induced LH decrease might have an effect on the decrease in thyroid volume. In our study, thyroid volume was associated with LH that may indicate LH may play a role in thyroid nodule formation in patients with acromegaly.

Glucocorticoids (GCs) are generally considered to increase renal iodide clearance and decrease thyroid iodine uptake hence decrease intrathyroidal iodine availability (44). It was shown that hydrocortisone directly stimulated the function of porcine thyroid cells via glucocorticoid receptor and cAMP pathways (45). GCs, inhibit TSH secretion via acting on both specific receptors located on hypothalamic TRH neurons (46) and pituitary (47). Finally, GCs treatment decrease plasma levels of thyroxine-binding globulin (48) and peripheral conversion of T4 to T3 (49) in vivo. Cushing's disease (CD) and GCs administration in healthy volunteers impair thyrotropin-releasing hormone (TRH) secretion (50,51). Both thyrotropin (TSH) pulses and the nocturnal serum TSH release are disturbed in patients with CD (50) and after GCs infusion (51,52). Invitti et al demonstrated that patients with Cushing's disease had a higher prevalence of nodular thyroid disease (53). In our study, thyroid volume was positively associated with cortisol and negatively associated with ACTH levels that may indicate they may play a role in thyroid nodule formation in patients with acromegaly.

Conclusion

The prevalence of nodules in acromegalic patients were found to be higher than usual prevalence. In addition to IGF-1, other hormones and insulin resistance might play an important role in thyroid volume, nodule volume, and nodule formation mechanism in patients with acromegaly.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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