

# Thyroid Nodules of Iraqi Patients with Acromegaly

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## Abstract

Acromegaly is a chronic endocrine disorder caused by excessive secretion of growth hormone. The incidence of malignancy like colorectal carcinoma is well documented to increase in patients with acromegaly. While the real incidence of thyroid neoplasm in these patients are not well known.

**Aims:** Find out the rate of structural thyroid disorders in a sample of Iraqi patients with acromegaly; Identify the rate of thyroid malignant transformation in patients with acromegaly.

**Settings and Design:** A case control study

**Methods and Material:** seventy patients with acromegaly were enrolled compared with 70 controls from 2 endocrinology centers from Jan. -Dec. 2017. Their mean age 46+/-11years ;41(58.5%) males. Thyroid ultrasound was conducted for all participants while fine needle aspirate conducted for those with nodule diameter  $\geq 1$ cm.

**Results:** . Goiter was founded more in patients with acromegaly versus control group (81.4% vs 18.5% respectively ; $P < 0.0001$ ). The overall nodular thyroid disease were found in (61.4%) acromegalic patients (of those : (11.4%) had single thyroid nodule and (50%) had multiple thyroid nodules. The ultrasonic feature of thyroid nodule were suspicious in (13.9%) of acromegaly group and none in control;  $P < 0.0001$ ). The fine needle aspirate results were suspicious in (9.3%) acromegaly group versus none in control group,  $P < 0.05$ ). One patient (2.3%) with acromegaly had papillary thyroid carcinoma and none in control;  $P = 0.31$ ).

**Conclusions:** Nodular thyroid disease were more prevalent in Iraqi patients with acromegaly but the risk of malignancy is not significantly different from normal population.

**Keywords:** thyroid nodule, acromegaly, goiter, multinodular goiter, ultrasonography

## Introduction

Acromegaly is a chronic endocrine disorder caused by excessive secretion of growth hormone (GH) [1] and subsequently Insulin-like Growth Factor 1 (IGF-1) [2]. IGF1 is considered as a potent mitogen for different cells [3]. Some reports appear that these patients are at a high risk of developing neoplastic disease [4]. The incidence of some types of malignancy like colorectal, breast & prostatic carcinoma are well documented in patients with acromegaly [5]. While the real incidence & prevalence of thyroid neoplasm in patients with acromegaly are not well known [6]. However, this study

designed to identify the prevalence of thyroid tumors in Iraqi patients with acromegaly.

## Subjects and Method

This is a case control study in which 70 patients with acromegaly were enrolled from January - December 2017 from 2 endocrinology specialized centers compared with 70 (age and sex matched) healthy control.

This study has been accepted by research ethics committee of Iraqi Board of Medical Specialization before starting a study. An informed consent has been obtained from all patients, signed and dated before participation in

this study. The enrolled subjects were already diagnosed as acromegaly clinically, biochemically & radiologically before their enrolment in the study. The diagnosis of acromegaly was based on unsuppressed GH level after OGTT ( $>1.2$  mUI/L) and increased IGF-1 value for age and sex; fortified by detection of pituitary adenoma by MRI either macroadenoma ( $>10$ mm) or microadenoma ( $<10$ mm).

The collection of data in regard of age per years, sex, duration of acromegaly, size of tumor (micro or macroadenoma), history of hypophysectomy, radiotherapy, medical therapy (total dose for each patient) GH level in 1st and last visits (by chemiluminescent immunoassay), IGF1 in 1st and last visits (according to sex and age matched limits measured by immunochemiluminometric assay), disease activity (assessed as described in the 2009 international consensus statement [7]), history of smoking, family history of thyroid disease, family history of malignant disease.

The thyroid ultrasonography conducted to all patients and control subjects by to assess the morphology of thyroid gland (size of thyroid gland and thyroid nodule(s) -if any- its/their characteristics). According to American thyroid association guidelines 2015[8] suspicious thyroid nodule(s) sent for Fine Needle Aspirate (FNA). Furthermore according to the cytology report patients with suspicious nodules sent to thyroid surgeon for thyroidectomy; followed by histopathological examination of the removed specimen.

Continuous variables were expressed by mean  $\pm$  SD while categorical variables as percentage, all these collected data & variables analyzed by using Chi square test or Student's unpaired t-test. The value of  $<0.05$  considered as statistically significant.

## Results

Seventy cases of acromegaly were enrolled in this study with a mean age  $46 \pm 11$  years. forty one (58.5%) males and 29(41.5%) females. Duration of disease ranged from 1 year -30 years (average  $8 \pm 6$ ). A growth hormone producing macroadenoma was the cause of acromegaly in 62 patients (88.5%) and in the remaining 8(11.5%) had microadenoma. Thirty six (51.4%) underwent hypophysectomy. Six patients (8.5%) were exposed to gamma knife & another one to conventional radiotherapy. All of our patients received monthly Octreotide (Sandostatin (LAR)). Twelve (17.2%) had

inactive disease while the remainder 58(82.8%) had active disease.

Hypophysectomy, radiotherapy and/or medical therapy for acromegaly induced a significant reduction of mean GH and IGF-1 levels ( $27.83 \pm 25.69$  vs.  $4.73 \pm 6.72$  ng/ml,  $p < 0.001$  and  $772.15 \pm 521.9$  vs.  $404.2 \pm 278.6$  ng/ml,  $p < 0.001$  respectively).

Thirteen patients (18.5%) were smoker.

Family history revealed thyroid disease or goiter in 17(24.2%). While 12(17.1%) had family history of malignancy [of those : 2 of them had family history of thyroid malignancy].

The control group was composed of 70 healthy subjects 47 (67%) female and 23(33%) with the mean age  $42.9 \pm 14.3$ .

### *Ultrasound characteristics*

Goiter discovered in 57(81.4%); of these 14(20%) had diffuse and 43(61.4%) had nodular goiter (both single 8(11.4%) and multinodular goiter (MNG) 35(50%)).

### *Cytological & histopathological diagnosis*

Out of 43 patient with nodular goiter; FNA performed in 23(53.4%) patients while none of nodules in control group required FNA because all of their ultrasound characteristics were either benign looking or purely cystic.

The FNA results were benign follicular cells without any metaplasia or dysplasia in 19 patients with acromegaly (44.2% out of all nodular disease and 82.6% out of all cytological examined sample);  $P$  value  $< 0.05$ . While 4 of patients with acromegaly (9.3% out of all nodular disease and 17.4% out of all cytological examined sample) had suspicious for dysplasia, metaplasia or malignancy, ( $P$  value  $< 0.05$ ).

Seven patients sent to thyroid surgeon for thyroidectomy (all 4 patients of suspicious FNA cytology & 3 had large multinodular goiter with obstructive symptoms). One patient had malignant histopathology in form of papillary thyroid carcinoma (2.3% out of patients with thyroid nodules and 1.4% out of the entire group of patients with acromegaly) that was statistically non-significant compared with control group ( $P$  value = 0.3), while the others had benign histopathological results.

### Correlation study

In table (1) the patients subdivided according to thyroid ultrasound findings.

There is a significant differences in gender with male predominance in diffuse goiter group and female predominance in MNG group (13(97%) male vs 1(3%)female, (19(54%) female versus 16(46%) male ; respectively  $P < 0.05$  in both). There is significant predominance of MNG among patients with macroadenoma versus microadenoma (34(97%) vs 1(3%) ;  $P < 0.05$ ) . There is also a significant development of MNG in patient who had active disease versus inactive disease (32(91.4%) vs 3(8.6%) ;  $P < 0.05$ ) . While there is a significant difference in development of both diffuse goiter and MNG in non-smoker patient versus smokers((8(57%) vs 6 (43%), and 10 (91.5%) versus 3(8.5%)respectively;  $P < 0.05$ .)

We could not found statistically significant differences disease duration, mean last GH , mean last IGF1, history of hypophysectomy or family history of thyroid disease between patient with diffuse goiter ,single thyroid nodule or MNG( table 2).

In table (3) the patients who had thyroid nodule (whether single or multiple) are subdivided according to ultrasonic feature and cytological examination .There is a significant female predominance in patients with benign ultrasonic feature group (20(54%) female versus 17(46%) male,  $< 0.05$ ).

The mean last IGF1 has significant relationship with development of both suspicious ultrasonic feature group and suspicious FNA cytology group( $P$  value  $< 0.05$  respectively).

In patients with suspicious FNA group there is a significant occurrences in patients with past history of hypophysectomy versus those without surgery ( $P$  value  $< 0.05$ ).

While there is no significant relationship between any nodular thyroid characteristics from one side and duration of disease of acromegaly ,size of pituitary adenoma, activity of the disease and mean last GH level on the other side .

### Discussion

In our study of 70 patients with acromegaly we searched for structural thyroid abnormalities, we found an increase prevalence of goiter(81.4%) both diffuse and nodular types ,thyroid nodules were(61.4%), MNG were(50%). These result of nodular disease are similar to newer studies that shows prevalence 62% in Gullu et al [9] ,63% in Baldys-Waligórska et al [10] , 57.6% in Tita et al [11] and 74.1% in Anagnostis et al. [12].

In our study we found that diffuse goiter was in 20% which was slightly higher than what is founded in Turkish study; Dugan S. et al.[13] which shows approximate results of 14.1%& in Brasil study [14] were 10.4% however the differences can be accepted because of individual and environmental factors. While in comparison with these studies we found that MNG were 50 % in our patients ;which is similar to Turkish study [13] that shows 48.6% ,while on the other side our results was lower than other study in Brasil [14] that shows (32.5%) this could be explained by similarity of geographical ,environmental factors that had an effect on our patients &Turkish patients

The suspicious FNA cytology was detected in 9% of the FNAs specimens in our study which were lower than the finding in other studies that was 13% [14]. However the differences between our study and the other study can be accepted.

We found a significant relationship between MNG and activity of acromegaly which is similar to what is found in other study like Uchoa et al. [14]. We also found a significant relationship between MNG and the size of pituitary macroadenoma.

We fail to found a relationship between goiter development ,thyroid nodule and the last GH,IGF1 ,and disease duration that are similar to other studies[13,15]. The prevalence of thyroid cancer was (2.3%)in our study which is like other studies 0.8% [16] and 2.9% [10] ,but these results are much less than other studies which found thyroid cancer in 11.8 % [17] and 7.2% [11].

Table.(1)shows the positive relationship between structural thyroid disease and different variables:

variable	all	normal	diffuse goiter	single thyroid nodule	MNG
patients No.	70 (100%)	13(18.6%)	14(20%)	8(11.4%)	35(50%)
Age	46.2±10.9	44.6+/-10	46.5+/-8.4	45.8+/-9.6	46.7+/-12.5
Female	29(41.5%)	4(31%)	1(7%)	5(62%)	19(54%)
Male	41(58.5%)	9(69%)	13(93%)	3(38%)	16(46%)
<i>P value</i> *		0.38	<b>0.003</b>	0.19	<b>0.028</b>
Macroadenoma	62(88.5%)	10(77%)	12(85.7%)	6(75%)	34(97%)
Microadenoma	8(11.5%)	3(23%)	2(24.3%)	2(25%)	1(3%)
<i>P value</i> *		0.14	0.7	0.19	<b>0.02</b>
Active disease	58(82.8%)	9(70%)	11(78.5%)	7(87.5%)	32(91.4%)
Inactive disease	12(17.2%)	4(30%)	3(21.5%)	1(12.5%)	3(8.6%)
<i>P value</i> *		0.14	0.63	0.7	<b>0.05</b>
smokers	13	2(15%)	6(43%)	2(25%)	3(8.5%)
Non smokers	57	11(85%)	8(57%)	6(75%)	32(91.5%)
<i>P value</i> *		0.74	<b>0.008</b>	0.61	<b>0.03</b>
<b>*Done by Chi square test</b>					

**Table (2): The negative relationship between thyroid disease and different variables:**

variable	all	normal	diffuse goiter	single thyroid nodule	MNG	
Patients No.	70 (100%)	13(18.6%)	14(20%)	8(11.4%)	35(50%)	
Last GH		4.7+/-7.7	5.1+/-9	4.7+/-5.4	4.5+/-5.7	
<b>P value†</b>		0.489	0.42	0.49	0.818	
Last IGF1		343+/-235	412.4+/-308.4	403.9+/-329	423+/-278	
<b>P value†</b>		0.166	0.45	0.49	0.563	
<b>Duration of disease</b>						
≤10years	52(74%)	11(85%)	8(57%)	6(75%)	27(77%)	
>10years	18(36%)	3(15%)	6(43%)	2(25%)	8(23%)	
<b>P value*</b>		0.34	0.1	0.96	0.58	
history of hypophysectomy		4(30%)	6(43%)	6(75%)	20(57%)	
<b>P value*</b>		0.09	0.47	0.15	0.33	
Family history of thyroid disease	present	17(24%)	0(0%)	3(21.4%)	3(37.5%)	11(31.4%)
	absent	53 (76%)	13 (100%)	11(78.6%)	5(62.5%)	24 (68.6%)
<b>P value*</b>		0.14	0.7	0.35	0.16	
*Done by Chi square test						
†Done by Student's unpaired t-test						

**Table(3): The relationship between nodular thyroid disease characteristics and different variables:**

variable		benign nodule by US*	suspicious nodule by US	benign nodule by FNA †	Suspicious nodule by FNA	malignant after surgery
<b>No. of patients (%out of all nodular thyroid disease)</b>		37(86%)	6(14%)	19(44.2%)	4(9.3%)	1(2.3%)
<b>Age</b>		46.5+/-11.5	47.1+/-15.5	49.4+10.7	46.7	46
<b>Female</b>		20(54%)	4(66.7%)	10(52%)	2(50%)	1
<b>Male</b>		17(46%)	2(33.3%)	9(48%)	2(50%)	0
<b>P value ‡</b>		<b>0.023</b>	0.18	0.24	0.72	
<b>family history of thyroid disease</b>	present	13(35%)	1(17%)	6(31%)	1(25%)	0
	absent	24(65%)	5(83%)	13(69%)	3(75%)	1(100%)
<b>P value‡</b>		<b>0.02</b>	0.64	0.38	0.9	
<b>family history of malignancy</b>	present	6(16%)	1(17%)	4(21%)	0	0
	absent	31(84%)	5(83%)	15(79%)	4(100%)	1(100%)
<b>P value ‡</b>		0.82	<b>0.01</b>	0.59		
<b>Last IGF1</b>		454.1+/-289	209+/-113	483.9+/-341	208/+143	137
<b>P value §</b>		0.11	<b>0.003</b>	0.28	<b>0.03</b>	
<b>history of hypophysectomy</b>		21(56.7%)	5(83%)	10(52%)	4(100%)	1(100%)
<b>P value‡</b>		0.34	0.1	0.9	<b>0.04</b>	0.32
<b>Microadenoma</b>		3(8%)	1(17%)	1(5%)	1(25%)	0(0%)
<b>macroadenoma</b>		34(92%)	5(83%)	18(95%)	3(75%)	1(100%)
<b>P value ‡</b>		0.35	0.67	0.32	0.37	0.71
<b>Active disease</b>		33(89%)	5(83%)	16(84%)	3(75%)	0
<b>Inactive disease</b>		4(11%)	1(17%)	3(16%)	1(25%)	1
<b>P value ‡</b>		0.13	0.97	0.85	0.66	<b>0.07</b>
<b>Last GH</b>		4.5+5.6	4.8+/-5.9	3.89+/-5.1	6+/-7	0.2
<b>P value §</b>		0.796	0.94	0.59	0.82	
* US :ultrasound ‡ done by Chi square test † FNA:Fine Needle Aspirate § Done by Student's unpaired t-test						

### Conclusion

The prevalence of structural thyroid disease are increased in Iraqi patients with acromegaly compared to the general population in form of goiter[ both diffuse & nodular types ]mainly MNG, increased thyroid nodules

of suspicious ultrasound & cytological characteristics. While the rate of thyroid cancer is not significantly different from that in general population .

**Ethical Clearance:** The Research Ethical Committee at scientific research by ethical approval of

both environmental and health and higher education and scientific research ministries in Iraq

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Funding:** Self-funding

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