METABOLIC SYNDROME AND THYROID DYSFUNCTION IN PATIENTS WITH ACROMEGALY IN SULAIMANI

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ABSTRACT

Background

Acromegaly is a chronic endocrinology disorder caused by the over-production of growth hormone (GH) predominantly by a pituitary adenoma. Acromegaly is associated with metabolic changes and thyroid dysfunction (ThD) in the body. However, the frequency of metabolic syndrome (MtS) in acromegaly patients is unknown, and studies assessing the frequency of different ThD types in acromegaly cases were few.

Objectives

To analyze the frequencies of MtS and ThD in patients with acromegaly in comparison to controls in Sulaimani city, to find the frequencies of MtS and ThDs in active cases compared to inactive cases in acromegaly patients, and to assess the relationship between the cumulative exposure to Insulin-like Growth Factor 1 (IGF-1) with ThD and MtS in acromegaly.

Patients and Methods

In this case-control study, 82 subjects were enrolled, which included 22 patients with acromegaly who visited the Sulaimani endocrinology center from August 2021 to February 2022 and 60 control subjects. The mean age of cases was 47.55 [11.50] years, with 7 (31.8%) male and 15 (68.2%) female. Thyroid function test, clinical, and biochemical parameters of MtS were measured in both groups in addition to IGF1. Chi-square test, Student T-test, and ANOVA were used in data analysis. Correlation between quantitative variables determined by Pearson correlation, with a P-value ≤ 0.05, is significant

Results

Out of 22 patients with acromegaly, 68.2% were euthyroid, 9.1% had primary hypothyroidism, 18.2% had central hypothyroidism, and 4.5% had hyperthyroidism, which is significantly higher than the control group (p-value =0.002). MtS frequency is 68.18% in cases, significantly higher than control, p-value=0.011. Most MtS and ThD parameters were significantly higher in acromegaly patients than in controls, P-value < 0.001. No significant correlation between the last IGF1 and other parameters existed except free T3, which has a significant negative correlation with IGF1, $P < 0.05$.

Conclusion

In acromegaly, the frequency of MtS is high (68.18%), and the frequency of ThD is 31.8%. Both MtS and ThDs are more common in patients compared to controls. No significant relationship exists between disease activity and the presence of MtS or ThD. Because both MtS and ThDs increase the metabolic markers, consequently increasing cardiovascular disease (CVD) morbidity and mortality in cases.

Keywords: *Metabolic syndrome, Acromegaly, Thyroid dysfunction, IGF1, Disease activity, Control.*

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INTRODUCTION

Acromegaly is a chronic progressive disorder of endocrinology caused by the overproduction of growth hormone (GH) predominantly by a pituitary adenoma (macroadenoma and, less commonly, microadenoma). Excess GH stimulates the secretion of Insulin-like Growth Factor 1 (IGF1) from the liver [1]. Although acromegaly is a rare disease, it is more common than gigantism, with a prevalence of 36 to 69 cases per million individuals and an incidence of three to four cases per year [2]. In addition, it is associated with a 1.7-fold increase in mortality rate [3]. The anterior pituitary gland secretes GH in a pulsatile manner, while IGF1 levels are comparatively stable in secretion with minor diurnal changes [4].

Although GH has been reported to be the primary driving force behind the features of acromegaly, GH and IGF-1 act parallel to regulate body composition, including glucose, fat, and protein, and boost basal metabolism. In addition, GH is a lipolytic and anabolic hormone that accelerates fatty tissue breakdown and protein synthesis [5,6]. Metabolic syndrome (MtS) is a collection of biochemical and physical conditions that leads to the development of atherosclerotic cardiovascular disease (CVD), type 2 diabetes mellitus (Type2DM)), and non-alcoholic fatty liver disease [7,8].

In acromegaly, hepatic gluconeogenesis and glycogenolysis increased, peripheral glucose consumption decreased, insulin resistance increased, and dyslipidemia was detected due to over-secretion of GH in patients with acromegaly. Carbohydrate metabolism is impaired in more than 50% of patients with acromegaly [3,9,10] in addition to the elevated glycated hemoglobin (HbA1c), insulin and fibrinogen levels [11,12].

Acromegaly is considerably associated with the impairment of glucose and lipid metabolism. Insulin resistance is the primary pathogenetic mechanism for glucose intolerance, diabetes mellitus (DM), and dyslipidemia. These are common presentations of acromegaly, clinically and biochemically, and appear to be risk factors for cardiovascular disease and death [13,14].

The disorders associated with glucose metabolism in acromegaly include impaired glucose tolerance test (IGT), impaired fasting glucose (IFG), and DM; these conditions more commonly occur in cases with acromegaly than in non-acromegalic people [11,13,15].

The lipid metabolism disorders that occur with acromegaly include hyper-triglyceridemia and lowering high-density lipoprotein (HDL) cholesterol levels. In contrast, the frequency of hyper-cholesterolemia in cases with acromegaly is identical to that of the general population [13]. Although all these biochemical parameters were investigated in previous studies, as long as we know, no known published study exists to determine the frequency of MtS in acromegaly cases.

Thyroid-stimulating hormone (TSH) secretion from the anterior pituitary gland is affected by several different factors. The synthesis and secretion of TSH are inhibited by the action of liothyronine (T3) and Thyroxine (T4) and stimulated by the effect of Thyrotropin-releasing hormone (TRH) and, to a lesser extent, the impact of other factors like leptin, dopamine, GH, IGF1, and somatostatin [16–18]. The autonomic nervous system can also modulate the thyroid gland's sensitivity to TSH [19]. Octreotide and bromocriptine cause suppression of the secretion of TSH, but chronic use of those drugs does not change thyroid function in most patients [20–23]. This inhibition may be a secondary effect of reducing GH levels caused by octreotide as GH activates peripheral de-iodination of T4 [20,24–26]. Other studies exhibit that somatostatin can directly inhibit the release of T4 and T3 from thyroid tissue[20,27].

Studies also demonstrate that GH and IGF-1 directly or indirectly adjust TSH secretion by thyrotrophin cells [28]. In thyrotrophic cells, by activating two somatostatin receptor subtypes, SST2 and SST5, somatostatin causes inhibition of TSH secretion [29]. In physiological states, GH has a feedback mechanism on somatostatin secretion from the hypothalamus. Stimulating its secretion and inhibiting the growth hormone-releasing hormone (GHRH) secretion [30]. This increase in somatostatin secretion affects thyrotrophic cells, which causes inhibition of the TSH secretion. Furthermore, the GHRH has synergistic effectiveness on the TRH and TSH secretion in healthy people and acromegaly patients [31].

Elevating the intra-pituitary conversion of T3 to T4 in thyrotrophic cells due to GH rise can inhibit TSH synthesis and excretion [32]. Moreover, due to the feedback mechanism, the increase of GH with somatostatin contribution has an inhibitory effect on TSH release [16]. Therefore, the TSH secretion can also be inhibited by the existence of a pituitary tumour [28]. In addition, acromegaly can cause panhypopituitarism and compressive effect of the pituitary tumour on

the surrounding structures; for that purpose, there may be secondary thyroid or adrenal dysfunction hypogonadism or amenorrhea [33,34]. Although thyroid function tests were assessed in acromegaly cases throughout the literature, only a few studies investigated the frequency of all different ThDs, including primary hypothyroidism, central hypothyroidism, and hyperthyroidism in acromegaly cases.

This study aims to assess the frequencies of MtS and ThD in patients with acromegaly and their relation with the disease activity.

PATIENTS AND METHODS

This case-control study enrolled 22 patients with acromegaly who visited the Sulaimani endocrinology center from Aug 15 2021, to Feb 15 2022, with 60 age-matched non-acromegalic subjects. Written informed consent was taken from all participants before participation in this study, and the study's aims and methods were explained to them. The study received approval from the Ethical Committee of the Kurdistan Higher Council of Medical Specialties, College of Medicine, University of Sulaimani, and Shar Teaching Hospital Administration.

The enrolled cases were already clinically, biochemically, and radiologically diagnosed as acromegaly. They fulfil the criteria for diagnosis of acromegaly as their IGF1 exceeds the cutoff value for their age and gender, GH level above the reference range, and GH fails to drop below 1ng/ml after the glucose tolerance test. The detection of pituitary adenoma was confirmed by MRI, either microadenoma (<10mm in diameter) or macroadenoma (>10mm in diameter).

Inclusion criteria

All patients diagnosed with acromegaly and registered at the Endocrinology department-Shar teaching hospital. Healthy volunteering participants who do not have acromegaly were enrolled as control participants.

Exclusion criteria

Pregnancy, postpartum, and cases with a history of thyroid disease.

A detailed questionnaire was filled out for each participant. The questionnaire contained sociodemographic status (age, gender, height, weight, waist circumference (W.cir), and lifestyle), history of systemic diseases, thyroid disease, drug, and surgical history. It also includes clinical features of acromegaly, history of hypophysectomy, radiotherapy or gamma knife therapy, medical therapy (the types and doses of somatostatin analogue Long-Acting Repeatable (LAR), number of injections), IGF1 in 1st and last visits, disease activity (according to last IGF1 age and sex-matched and clinical assessment). Moreover, the acromegaly cases are further subdivided into active and inactive diseases according to the disease activity.

All participants were assessed for the anthropometric data. Height and weight, and waist circumferences (Wcir) were measured and recorded. Blood pressure and pulse rate were measured for all participants during rest.

The subjects were assessed for goiter by WHO classification [35], Zulewski clinical score used by the author, which included 14 symptoms and signs of hypothyroidism [36]; the patient was clinically considered hypothyroid if the score was ≥5, euthyroid if the score was <3, and intermediate if the score was between 3 and 5. Wayne's Index used to assess hyperthyroidism consists of nine symptoms, and ten signs are listed, each with differential weightage in scoring. The score ranges from + 45 to -25. A score greater than 19 indicates toxic hyperthyroidism, less than 11 implies euthyroidism, and a score between 11 and 19 is equivocal [37]. The diagnosis of MtS was made according to 2005 revised guidelines by the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA)[38], and it will require at least three of the following five conditions; fasting plasma glucose ≥100 mg/dL (or on treatment for hyperglycemia, blood pressure ≥130/85 mm Hg (or drug therapy for hypertension), Triglycerides ≥150 mg/dL (or receiving treatment for hypertriglyceridemia), HDL-C < 40 mg/dL in male or < 50 mg/dL in female (or receiving treatment for low HDL-C), W.cir ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.

Primary hypothyroidism is defined as an elevated serum TSH as a TSH concentration above the upper limit of the normal TSH reference range of 4 to 5 mU/L [39]. Central (secondary) hypothyroidism is caused by a hypothalamus or pituitary gland disease. TSH secretion does not rise appropriately when T4 secretion decreases. For that reason, the symptoms and the serum-free T4 value should be used to make the diagnosis[40].

Laboratory measurement and reference ranges

A fasting blood sample was withdrawn from 08:30-to 10:00 am, and all the required biochemical parameters were measured; Fasting blood glucose (FBG), haemoglobin A1c (HbA1C), lipid profile, TSH, free T4, and free T3, and age and sex-matched IGF1.

Reference ranges blood glucose 70-100mg/dl, s. Cholestrole 110-200mg/dl, s.TG 50-150mg/dl, HDL 40-80mg/dl, LDL 0-130 mg/dl, TSH 0.5-4.2mg/dl, free T4 12-22 pmol/l, free T3 3.1-6.8 pmol/l.

FBG, HbA1c measured in a centralized accredited laboratory with standard method, thyroid function test measured by electrochemiluminescence immunoassay, IGF1 level (according to sex and age-matched limits) also from the old registered data at first and last visit (measured by immuno-chemiluminometric assay (ICMA).

Statistical Analysis

Data analysis was performed by statistical package for social sciences (SPSS) program version 22. Frequency and percentages with the mean and standard deviation were used for qualitative and quantitative data, respectively. The Chi-square test was used to detect the association between categorical data. The student T-test and ANOVA were used to determine the quantitative and categorical data association. Correlation between quantitative variables was determined by Pearson correlation. P-Value equal to or less than 0.05 was regarded as statistically significant.

RESULTS

In this study, 22 (26.8%) acromegaly and 60 (73.2%) control subjects were enrolled, which account for 82 overall subjects. There were no significant differences in the mean age of acromegaly cases compared to controls (47.55 [±11.50] vs 39.63 [±6.12].

Among the Acromegaly group, 7 (31.8%) were male & 15 (68.2%) were female. Among the controls, 29 (48.3%) were male, and 31 (51.7%) were female. Mean BMI (kg/m2) in cases vs control were 32.43[±7.15] vs. 27.33[±2.65]. The sociodemographic characteristics of the studied participants are demonstrated in Table 1.

Table 2 demonstrates the clinical features among cases (acromegaly subjects), with some features of adenoma and types of management. The most common clinical presentation was tongue and acral enlargement in 21 out of 22 cases (95.5%), followed by skin changes (sweating and oily skin) in 20 cases (90.9%), while the least clinical presentation was bleeding per rectum in one case (4.5%).

The mean disease duration from the time of diagnosis of acromegaly was 7.86 [±6.46] years. The range is between 2 and 23 years. Macroadenoma was the cause of GH hypersecretion in 15 cases (68.2%) & microadenoma in seven cases (31.8%). Seventeen patients (77.3%) underwent an operation (hypophysectomy), either trans-sphenoidal (15) or transcranial (2) and two patients were treated by radiotherapy. One patient received conventional radiotherapy, the other one gamma knife. Sixteen acromegaly cases (72.7%) immediately received medical therapy in the form of monthly Octreotide (Sandostatin long-acting release; LAR) injection & Octreotide (Sandostatin LAR) plus cabergoline combination. The treatment was given even to those with a history of hypophysectomy/gamma knife; if they did not achieve remission.

Regarding sexual dysfunction & infertility in males,5 cases (13.9%) had decreased libido & sexual dysfunction, and one case (2.8%) had infertility. Only one patient (2.8%) had infertility in female participants with acromegaly. Among both genders, no history of galactorrhea was mentioned. In Figure 1, the comparison between 1st IGF1 and last IGF1 in acromegaly patients was shown. Hypophysectomy, medical therapy, and/or radiotherapy for acromegaly, induced a significant reduction of mean IGF1; mean 1st IGF1 vs. the last IGF1, 928.314 vs 289.986; P-value <0.001). Table 3 compares acromegaly cases and controls in biochemical and some clinical parameters. Mean BMI and Wcir were significantly higher in cases than controls (BMI: 32.43 vs 27.33; P-value <0.001, waist circumference: 100.86 vs 95.62 cm, P-value= 0.002). Figure 2 represents the frequency of MtS between cases and control groups. In acromegaly cases, 68.,18% have MtS in comparison to the 36.67% in the controls with a significant P-value of 0.011. Figure 3 (A) outlines the frequency of ThD in acromegaly cases and a control group; 31.82% and 5%, respectively, with a P-value of 0.003. There was no ThD in 68.18% of cases & 95% of controls. Figure 3(B) shows the frequency of different thyroid statuses (different ThD) in patients with acromegaly compared to the control subject. Table 4, depicts the association between acromegaly activity with each thyroid status and MtS. The disease activity was assessed by the last IGF1 for the age-matched normal range. 61.5% of the cases

with euthyroid have active disease at the time of data collection; in the patients with primary hypothyroidism, 7.7% of them have active disease, 23.1% of patients with central hypothyroidism have active disease & 7.7% of acromegaly cases with hyperthyroidism have an active disease with P-value 0.709. Regarding MtS association with activity of acromegaly, 23.1% of those with no MtS have active disease, and 76.9% of its patients have an active disease with a P-value of 0.276. A significant inverse correlation between mean the last IGF1 and mean free T3 exists, P-value= 0.020 (Figure 4). There was no significant correlation between IGF1 and other biochemical parameters.

Table 1. Sociodemographic characteristics of the studied participants.

Sociodemographic characteristics		Total N (%) Mean [SD]	Acromegaly N (%) Mean [SD]	Control N (%) Mean [SD]
Total numbers (percentages)		82 (100)	22(26.8)	60(73.2)
Age (year)		41.7[8.58]	47.55 [11.50]	39.63[6.12]
Gender	Male	36 (43.9)	7 (31.8)	29 (48.3)
	female	46 (56.1)	15 (68.2)	31 (51.7)
BMI (kg/m2)		28.70 [4.85]	32.43[7.15]	27.33 [2.65]
Residency	Inside City	72 (87.8)	14(63.6)	58(96.7)
	Outside City	10 (12.2)	8(36.4)	2(3.3)
Ethnic group	Kurdish	76 (92.7)	18(81.8)	58(96.7)
	Arabic	6 (7.3)	4(18.2)	2(3.3)
Smoking	No	70 (85.4)	21(95.5)	49(81.7)
	Yes	12 (14.6)	1(4.5)	11(18.3)
Alcohol	No	79 (96.3)	22(100)	57(95)
	Yes	3 (3.7)	0	3(5)
Marital status	Single	16(19.5)	5(22.7)	11(18.3)
	Married	66(80.5)	17(70.3)	49(81.7)

Note: The numerical parameters are expressed as frequency (percentage), and the continuous parameters are expressed as mean [SD].

Table 2. Clinical features and management among Acromegaly patients.

Clinical Parameters		Frequency	Percent
Headache		17	77.3
Visual defect		13	59.1
Acral enlargement		21	95.5
Arthralgia		17	77.3
Abdominal pain		11	50.0
Bleeding per rectum		1	4.5
Sleep disturbance		19	86.4
Skin (sweating,oily skin)		20	90.9
Apnea		6	27.3
Enlarged Tongue		21	95.5
Size of Adenoma	Micro Adenoma	7	31.8
	Macro Adenoma	15	68.2
Surgery	Yes	17	77.3
Type of Surgery (N=17)	Transsphenoidal	15	88.2
	Transcranial	2	11.8
Radiotherapy	Yes	2	9.1
Medical Therapy	Yes	16	72.7
Types of Medical Treatment (N= 16)	Octreotide	10	62.5
	Octreotide & cabergoline	6	37.5
Disease Activity	Inactive	9	40.9
	Active	13	59.1
Total		**22**	**100.0**

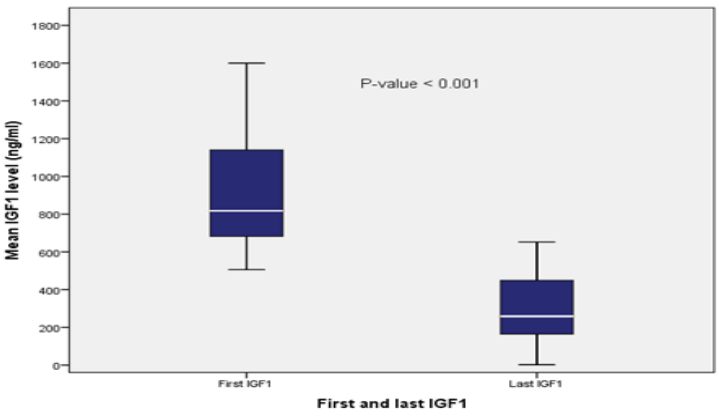

Figure 1. Comparison between first IGF1 and last IGF1 in Acromegaly patients.

Table 3. Comparison of metabolic syndrome and thyroid function parameters between Acromegaly cases and controls.

Parameters	Case (N= 22) Mean [SD]	Control (N=60) Mean [SD]	P-value
BMI	32.43[7.15]	27.33[2.65]	< 0.001
W. cir. cm	100.86[9.16]	95.62[5.57]	0.002
SBP mmHg	124.55[18.70]	117.75[9.67]	0.035
DBP mmHg	78.18[8.24]	73.25[7.75]	0.014
FBG mg/dl	151.86[92.32]	96.10[7.59]	< 0.001
HBA1C %	6.51[1.34]	5.54[0.37]	< 0.001
TG mg/dl	191.23[90.98]	145.00[43.08]	0.003
LDL mg/dl	123.07[39.72]	98.55[15.76]	< 0.001
HDLmg/dl	45.91[8.37]	45.82[7.52]	0.962
HR b/min	88.05[6.73]	83.08[8.08]	0.012
TSH Uiu/ml	2.38[2.36]	3.87[2.93]	0.035
FT4 pmol/ml	14.91[3.45]	14.77[1.62]	0.796
FT3 pmol/ml	3.69[1.13]	3.96[0.31]	0.101
Zulewiski score	4.64[1.866]	1.88[1.027]	< 0.001
Waynes's score	4.82[2.442]	4.00[1.605]	0.081

Represents the frequency of MtS between cases and control groups. In acromegaly cases, 68.,18% have MtS in comparison to the 36.67% in the controls with a significant P-value of 0.011.

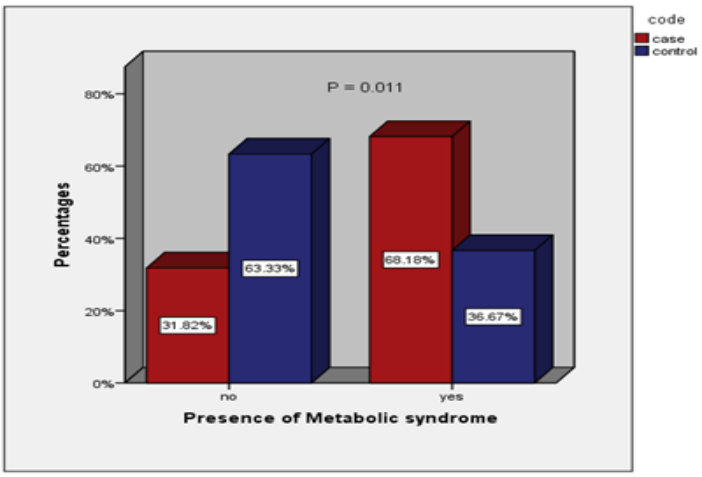

Figure 2. Frequency of Metabolic Syndrome in acromegaly cases versus control.

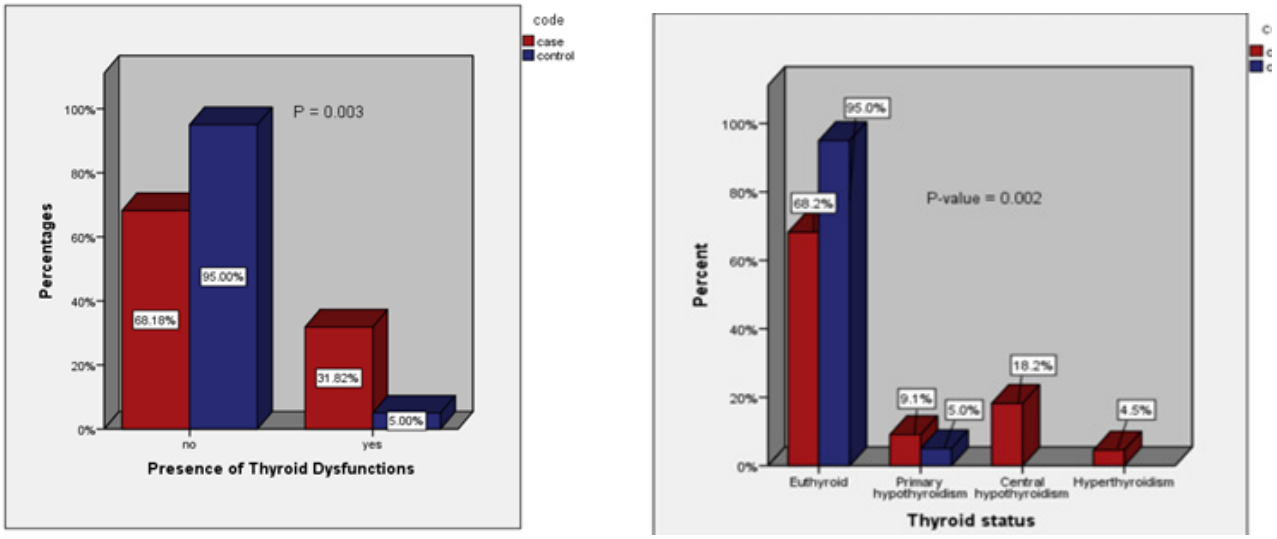

Figure 3. Frequency of presence or absence of thyroid dysfunction (A), and different thyroid status in acromegaly cases versus controls(B)

Table 4. Association between Thyroid status and Metabolic Syndrome with the disease activity.

			Activity			
			Inactive% N=9	Active% N=13	Total % N=22	P-Value
Thyroid Status	Euthyroid	Count	7	8	15	0.709
		%	77.8	61.5	68.2	
	Primary Hypothyroid	Count	1	1	2	
		%	11.1	7.7	9.1	
	Central Hypothyroid	Count	1	3	4	
		%	11.1	23.1	18.2	
	Hyperthyroid	Count	0	1	1	
		%	0.0	7.7	4.5	
Metabolic Syndrome	No	Count	4	3	7	0.276
		%	44.4	23.1	31.8	
	Yes	Count	5	10	15	
		%	55.6	76.9	68.2	

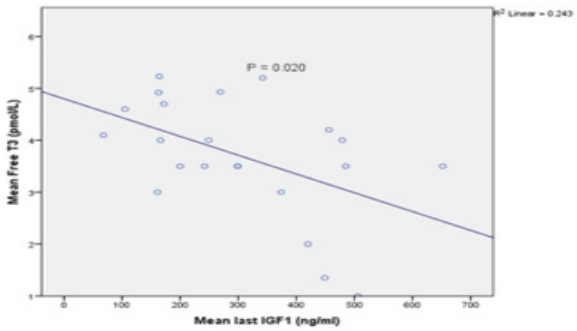

Figure 4. Scatterplot of correlation between mean of the last IGF1 with FT3 level in acromegaly cases.

DISCUSSION

Our study found that BMI, W.cir, FBG, HbA1C, and TG levels were significantly higher in acromegaly cases compared to the control group. These elevated parameters are probably because of the metabolic changes that will occur after hypophysectomy due to deficiency of GH in most hypophysectomized patients. Moreover, consequently, abnormality in the body composition (increased fat mass, decreased lean body mass) and thus raised cardiovascular risk for mortality and morbidity [41]. On the other hand, because of prolonged exposure to excessive GH, acromegaly cases increase cardiovascular mortality and atherosclerosis via an increase in glucose production, reduced peripheral glucose use, and enhanced hepatic and peripheral insulin resistance dyslipidemia and hypertension [1,42].

In the current study, 68.18% of cases have MtS, and 36.67% of the controls have MtS. In the literature, no known research was found analyzing MtS in acromegaly patients; only a study by Altuntaś SÇ et al.; assessed the markers of MtS in patients with pituitary adenoma in whom 54 had acromegaly [43]. In comparison to our study, the mean BMI, Wcir, SBP, and DBP were higher in Altuntaś SÇ et al.. In contrast, the mean FBG and HbA1c in our study were approximate to the result of Altuntaś SÇ et al., TG is higher in our study than the result of Altuntaś SÇ et al., and Mean LDL cholesterol in our data is lower than Altuntaś SÇ et al. these differences in outcomes may be due to the differences in the number of cases and type of the samples in both studies. In the Altuntaś SÇ et al. study, most of the acromegaly cases were in remission compared to 76.9% of active cases in our study.

Regarding thyroid function tests in acromegaly patients, most cases were euthyroid 68.18%. In comparison, 31.82% have ThD (9.1 % primary hypothyroidism, 18.2 central hypothyroidism, and 4.5% had hyperthyroidism), consistent with the results of Canova et al. that 67 % were euthyroid and 25% had hypothyroidism. Still, the types of hypothyroidism were not assessed in their study[44]. While inconsistent with Nihad A et al. study, which displayed a higher frequency of ThD (50%) in acromegaly cases, 20% primary hypothyroidism, 15.7 % central hypothyroidism, and 12.8% hyperthyroidism. The differences in the prevalence of ThD in these two studies could be due to the difference in ethnicity, and the number of cases, in which higher than triple of the patients were taken in Selman et al. study in comparison to the current research because two centers of endocrinology contributed during data collection [45]. Hyperthyroidism was the least common presentation in cases with ThD, about 4.5%; the approximate results were found in other studies (3.5–26% of patients with acromegaly) [46].

In the present study, we did not find a correlation between disease activity with ThD, in line with the study by Nihad A et al. [45].

The strength of this study is that this is the first study on acromegaly in Sulaimani City and, to our knowledge, the first study in the literature assessing the frequency of the MtS in cases with acromegaly. The limitation of this study is the small number of acromegaly cases because it is a rare disease, and we could not involve patients from multicenter. Acromegaly cases are not treated by endocrinologists in other cities but rather followed up at oncology centers and regarded as cancer cases. In addition, different follow-up protocols make the situation even worse in assessing other centers. However, we decreased the study bias of small sample size by comparing acromegaly patients with control groups.

In conclusion, the frequency of metabolic syndrome in acromegaly patients is very high, and about one-third of acromegaly cases also have ThD. We also concluded that MtS and ThD are more common in acromegaly cases than in the control group. Because both MtS and ThD were raising metabolic markers, consequently increasing CVD and cerebrovascular morbidity and mortality. Our study did not find associations between disease activity with MtS and ThD.

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