

Post-treatment heterogeneity of cardio-metabolic risk in acromegalic patients: The Impacts of GH and IGF-1

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Abstract

Background: Metabolic abnormalities are frequently seen in patients with acromegaly. However, it is not clear to what extent GH /IGF-1 contribute to the development of these abnormalities. This study aimed to explore the impact of GH/IGF-1 on different aspects of metabolic abnormalities in patients with acromegaly.

Methods: This retrospective, registry-based study conducted on 102 patients with acromegaly. Prevalence of diabetes mellitus (DM), hypertension (HTN), and dyslipidemia (DLP) at the time of diagnosis has been explored. Moreover, the impact of GH/IGF-1 on these cardio-metabolic risk factors at 3-12 months after surgery has been investigated using linear and logistic regression models.

Results: At the time of diagnosis, the prevalence of cardio-metabolic risk factors was 79.17 % for DLP, 29.41% for DM, and 15% for HTN. Furthermore, each 1 ng/ml increase in the level of GH was significantly associated with 2 mg/dl increase in the level of FBS, 0.54 mmHg increase in the level of SBP, and 0.88 mmHg increase in the level of DBP. Upon multivariate analysis GH, but not IGF-1, significantly increased the odds of DM (OR; 1.17, 95% CI; 1.02-1.35, $p= 0.025$).

Conclusions: Our findings showed at early postoperative stage, GH is significantly associated with the levels of FBS, SBP, and DBP. Moreover, GH, but not IGF-1, appears as a predictive factor for the presence of DM. However, neither GH nor IGF-1 could predict the presence of HTN, or DLP in this study.

Background

Acromegaly is a disabling disease characterized by an excessive secretion of growth hormone (GH) and an increase in the circulating level of Insulin-like growth factor 1 (IGF-1). Despite being a rare disease, acromegaly is associated with such a broad spectrum of comorbidities that it is considered as a large burden [1]. Cardiovascular disease (CVD) is prevalent in patients with acromegaly contributing to the nearly 60% of deaths [2], although causes of deaths shift from CVD to cancer death in the recent years [3]. Moreover, well-established cardiovascular risk factors, mainly disorders of glucose and lipid metabolism as well as hypertension (HTN), are frequently associated with acromegaly [4]. The same as the general population, ethnic background, age, gender, body mass index (BMI), and family history, all, contribute to the development of these cardio-metabolic risk factors in patients with acromegaly [5, 6]. However, determinants of glucose and lipid abnormalities as well as HTN are more complicated in acromegaly. The reason for this complexity is the fact that metabolic abnormalities in acromegaly are inevitably affected by the GH and IGF-1 levels, alteration in the blood concentration of other hormones, and medications used for treatment of acromegaly [5].

Given the counter-regulatory effects against the insulin, GH has been established to play an important role in the development of glucose and lipid abnormalities in patients with acromegaly [7]. GH exerts its diabetogenic effects by both increasing the insulin resistance and decreasing the insulin secretion [8]. GH-induced insulin resistance, considered as the main responsible factor for glucose and lipid abnormalities in acromegaly, is mainly mediated by overproduction of free fatty acid (FFA) due to lipolytic effects of GH [8]. Furthermore, persistently high FFA in chronic GH excess might cause beta-cell apoptosis and a subsequent

decrease in insulin secretion [9]. However, differently from GH, IGF-1 has been demonstrated to improve glucose hemostasis and insulin sensitivity by interacting with either IGF-I or insulin/IGF-I receptors [10]. In addition, insulin resistance and hyperinsulinemic state in acromegaly have been demonstrated to promote HTN through different mechanisms [11]. Moreover, plasma volume expansion induced by GH [12], and fluid retention due to antinatriotic effect of IGF-1 [13] contribute to the development of HTN in patients with acromegaly.

Considering the well-known pathophysiological mechanisms, mediated by GH/IGF-1, leading to glucose and lipid abnormalities as well as HTN, one would expect full recovery of these cardio-metabolic risk factors after the biochemical control of acromegaly. However, not do all studies make us confident in our expectation of complete normalization of cardio-metabolic abnormalities [5, 14]. Several studies investigating the predictors of diabetes and HTN in patients with acromegaly present controversial results regarding the role of GH/IGF-1 [15, 16]. Yet, a little is known to what extent GH and/or IGF-1 contribute to the development of cardio-metabolic abnormalities in acromegaly. Thus, we designed a registry-based study in a population of Iranian people with acromegaly to determine the impact of GH/IGF-1 on glucose and lipid abnormalities as well as blood pressure (BP) alteration, considering other co-existing risk factors.

Methods

Patients and methods

This retrospective cohort study analyzed data from 102 patients with acromegaly registered at the Iran Pituitary Tumor Registry (IPTR) between 2015 and 2018 [17]. Patient data were categorized in two different visits. Initial visit included data at the time of diagnosis “before surgery”. Follow-up visit included the first postoperative data obtained within 3–12 months after surgery. For each patient the following data have been considered for the final analysis: age, sex, BP, body mass index (BMI), waist circumference (WC), symptoms at the time of diagnosis, basal GH, IGF-1 levels (absolute, and times the upper limit of normal range), prolactin levels, maximum pituitary tumor diameter measured by magnetic resonance imaging (MRI), presence of hormonal pituitary deficiency, and biochemical data including fasting blood sugar (FBS), glycated hemoglobin (HbA1C), triglyceride (TG), total cholesterol (chol), low density lipoprotein (LDL), and high density lipoprotein (HDL). The main objective of this study was to evaluate the impact of GH/IGF-1 on the cardio-metabolic risk factors at early postoperative stage in acromegaly. Cardio-metabolic risk factors as the primary outcomes were considered both as the continuous variables (i.e. systolic blood pressure (SBP), diastolic blood pressure (DBP), FBS, TG, total cholesterol, LDL, HDL) and as the binary measures i.e. HTN, DM, and DLP. Informed consent has been obtained from the patients. The protocol was approved by the ethics committee of Iran University of Medical Sciences (approval number: IR.IUMS.FMD.REC.1397.252).

Definitions

Acromegaly was diagnosed based on a glucose-suppressed GH ≥ 1 ng/ml and IGF-1 more than the upper limit of normal reference range (ULN) specific for age and sex in a patient with the classical symptoms and signs of GH excess. Panhypopituitarism was defined as the presence of at least two pituitary hormone deficiencies. Diabetes mellitus was defined as the presence of FBS of ≥ 126 mg/dl, HbA1C ≥ 6.5 . HTN was

considered to be present if the systolic or diastolic blood pressures were ≥ 140 or 90 mmHg, respectively, or the patient consumed antihypertensive medication. Dyslipidemia (DLP) was defined as TG ≥ 150 mg/dl or HDL < 40 mg/dl in men and < 50 mg/dl in women or consumption of hypolipidemic agents. Based on basal GH and IGF-1 times ULN obtained at the first visit after surgery, patients were classified into 4 groups as follows:

1- Cured/controlled group: patients with basal GH < 1 ng/ml and IGF-1 less than ULN.

2- Active group: patients with basal GH ≥ 1 ng/ml and IGF-1 more than ULN.

3- GH discordance: patients with basal GH ≥ 1 ng/ml and IGF-1 less than ULN.

4- IGF-1 discordance: patients with IGF-1 more than ULN and basal GH < 1 ng/ml.

Statistical analysis

Descriptive statistics are presented as mean \pm standard deviation (SD) for continuous variables and number (percentage) for categorical ones. Comparisons between continuous variables were performed using non-parametric tests such as Mann-Whitney and Kruskal-Wallis, and Chi-squared test was used for assessing the association between categorical variables. In addition, the linear regression model was applied to assess the determinants of the continuous outcomes, and logistic regression model was fitted in the case of binary responses. Moreover, for diabetes as the binary outcome, ROC curve was drawn for significant determinants and the related sensitivity/specificity were calculated. All analyses were performed using Stata ver. 9, and significant level was set at P- value < 0.05 .

Results

Initial data

The studied population consisted of 102 patients of whom 50.98% (n = 52) were men. The mean age of the participants was 40.80 (± 12.23) years. The mean WC and BMI were 96 cm (± 9.49) and 28.67 kg/m² (± 5.46), respectively. Table 1 depicts the clinical and biochemical characteristics of the patients, as well as tumor size, and the prevalence of cardio-metabolic risk factors at the time of diagnosis. Acral enlargement was the most common clinical presentation (84.16%) followed by headache (59.41%), arthralgia (57.43%), and diaphoresis (40.59%). MRI revealed macroadenoma in 75% (n = 57) of the patients, with the mean tumor size of 18.88 (± 11.25) mm. The mean levels of basal GH and IGF-1 were 18.18 ng/ml (± 19.73) and 750.10 ng/ml (± 318.91), respectively. The mean IGF-1 level was shown to be 3 (± 1.28) times ULN. The concomitant prolactin elevation was observed in 32.76% of the patients. The mean SBP was 122.75 (± 16.74) mmHg and the mean DBP was 78.25 (± 14.80) mmHg. The mean FBS and HbA1C were 124.12 mg/dl (± 48.80) and 6.73% (± 1.52), respectively. The mean TG, total cholesterol, LDL, and HDL were 167.58 (± 135.11), 206.75 (± 80.65), 115.2 (± 39.81), and 42.43 (± 9.89) mg/dl, respectively. At the time of diagnosis, the most frequent cardio-metabolic risk factors were DLP (79.17%), DM (29.41%), and HTN (15%).

Table 1
Baseline characteristics of the participants at the time of diagnosis.

Variables	
Age (yr)	40.80 (12.23)
Sex (Male %)	52(50.98%)
Waist circumference (cm)	96.00 (9.49)
BMI(kg/m ²)	28.67(5.46)
Symptoms at presentation	59.41%
Headache	57.43%
Arthralgia	40.59%
Diaphoresis	84.16%
Acral enlargement	
Mean tumor size (mm)	18.88(11.25)
Macroadenoma (%)	57(75%)
Basal GH(ng/ml)	18.18 (19.73)
IGF1(ng/ml)	750.10(318.91)
IGF1*ULN	3.00(1.28)
PRL elevation (%)	19(32.76%)
SBP(mmHg)	122.75(16.74)
DBP (mm Hg)	78.25(14.80)
FBS (mg/dl)	124.12(48.80)
HbA1C (%)	6.73(1.52)
TG (mg/dl)	167.58(135.11)
Chol (mg/dl)	206.75(80.65)
LDL(mg/dl)	115.2(39.81)
HDL (mg/dl)	42.43(9.89)
DM (%)	15(29.41%)
HTN (%)	3(15%)

Percentages were relative to the patients for whom these alterations were evaluated.

Data are presented as mean (SD) or number (percentage).

Variables	
DLP (%)	19(79.17%)
Percentages were relative to the patients for whom these alterations were evaluated.	
Data are presented as mean (SD) or number (percentage).	

Follow-up data

We also analyzed data stratifying by the disease status at early postoperative stage (Table 2). All 102 patients underwent transsphenoidal surgery (TSS) of whom 45 patients received medical therapy with the second generation of somatostatin analogues (SSA), and 9 patients received radiotherapy as an adjuvant therapy. According to the disease status, 44 (43.14%) patients have been classified as active group, while 37 (36.27%) patients were considered as cured/controlled group. The others were stratified as GH discordance group (n = 12, 11.76%) or IGF-1 discordance group (n = 9, 8.82%). There was no significant difference in demographic characteristics, tumor size, GH/IGF-1 levels, and percentage of SSA users, as well as metabolic status of the patients in each group with those from the cured/controlled group.

Table 2
Postoperative characteristics of patients stratified by the disease status

	Active n = 44	IGF1 discordance n = 9	GH discordance n = 12	Cured/controlled n = 37
Age (yr)	*37.75 (11.12)	40.67 (11.48)	41.50 (14.99)	44.24 (12.26)
Sex (% male)	20 (45.45%)	8 (88.89%)	3 (25.0%)	21 (56.76%)
Waist circumference (cm)	*94.43 (10.39)	106.88 (9.93)	98.33 (13.62)	99.88 (9.03)
BMI(kg/m ²)	28.25 (4.62)	29.92 (5.54)	30.16 (6.70)	28.81 (4.09)
Mean tumor size (mm)	*9.27 (7.11)	2.60 (4.34)	7.83 (14.84)	1.13 (2.51)
Macroadenoma (%)	16 (43.24%)	2 (25.0%)	2 (22.2%)	2 (7.41%)
Basal GH(ng/ml)	*7.59 (11.29)	*0.64 (0.26)	*2.46 (1.40)	0.31 (0.29)
IGF1*ULN	*2.18 (0.77)	*1.47 (0.40)	0.59 (0.26)	0.56 (0.26)
SSA(%)	33 (75.0%)	7 (77.78%)	4 (33.33%)	4 (10.81%)
SBP(mmHg)	120.39(17.53)	127.22 (21.67)	120.00 (14.14)	124.63(15.12)
DBP(mmHg)	80.66 (13.86)	82.22 (8.33)	78.33 (6.12)	78.30(16.68)
FBS (mg/dl)	107.70 (23.55)	101.33 (10.10)	120.5 (44.94)	102.26(26.62)
HbA1C	6.29 (1.45)	5.57 (0.47)	7.5 (2.95)	6.66%(1.03)
TG (mg/dl)	159.28 (83.84)	151.14 (101.89)	130.6 (68.13)	141.26(101.28)
Cholesterol (mg/dl)	190.38 (38.62)	176.43 (35.75)	153.4 (26.68)	170.55(45.58)
LDL (mg/dl)	114.77 (32.56)	95.33 (18.56)	82.2 (12.36)	96.94(31.83)
HDL(mg/dl)	46.58 (12.33)	43.43 (6.90)	46.6 (14.03)	43.22(10.26)
DM (%)	5 (14.29%)	0 (0%)	2 (25.00%)	7 (20.00%)
HTN (%)	10 (26.32%)	3 (33.33%)	3 (33.33%)	8 (29.63%)
DLP (%)	18 (62.07%)	4 (57.17%)	4 (80.00%)	11 (55.00%)
Percentages were relative to the patients for whom these alterations were evaluated.				
Data are presented as mean (SD) or number (percentage).				
*P-value < 0.05 vs. "Cured/controlled group".				

GH/IGF-1 and cardio-metabolic risk factors presented as continuous outcomes

Simple and multiple linear regression models were used to predict the impact of GH/IGF-1 times ULN on the cardio-metabolic risk factors (Table 3). The results showed each 1 ng/ml increase in the level of GH is significantly associated with 2.92 mg/dl increase in the level of FBS, and 0.47 mmHg increase in the level of DBP. Moreover, each one time ULN of IGF-1 is significantly associated with 10.98 mg/dl increase in the level of total cholesterol, and 11.20 mg/dl increase in the level of LDL. Upon adjusting with other potential cardio-metabolic risk factors, including age, sex, wc, panhypopituitarism, and SSA, 1 ng/ml increase in the level of GH was still significantly associated with 2 mg/dl increase in the level of FBS, 0.54 mmHg increase in the level of SBP, and 0.88 mmHg increase in the level of DBP. Interestingly, each one time ULN of IGF-1 was significantly associated with 4.58 mmHg reduction in the level of DBP. However, the significant impact of IGF-1 times ULN on total cholesterol and LDL has been eliminated after adjustment with GH and other potential risk factors.

Table 3

Linear regression analyses predicting the impact of GH/IGF-1 on the cardio-metabolic risk factors

Outcome of interest	Simple linear regression model				Multiple linear regression model†			
	IGF1*ULN		GH		IGF1*ULN		GH	
	Regression Coefficient (95% CI)	P-value	Regression Coefficient (95% CI)	P-value	Regression Coefficient (95% CI)	P-value	Regression Coefficient (95% CI)	P-value
FBS	12.17 (-0.98-25.32)	0.069	2.92 (1.57-4.27)	0.000	5.36 (-12.73-23.44)	0.556	2.00 (0.13-3.88)	0.037
SBP	-1.16 (-5.08-2.75)	0.556	0.18 (-0.30-0.66)	0.465	-2.36 (-7.01-2.28)	0.314	0.54 (0.04-1.03)	0.035
DBP	-1.13 (-4.22-1.96)	0.470	0.47 (0.09-0.85)	0.015	-4.58 (-8.41/-0.76)	0.019	0.88 (0.47-1.29)	0.000
TG	12.29 (-12.49-37.06)	0.325	2.24 (-0.65-5.14)	0.126	6.01 (-30.14-42.17)	0.739	2.69 (-0.89-6.27)	0.137
Chol	10.98 (0.11-21.85)	0.048	1.28 (-0.007-2.57)	0.051	13.29 (-3.73-30.32)	0.123	0.91 (-0.77-2.60)	0.281
HDL	0.16 (-3.22-3.55)	0.922	-0.05 (-0.42-0.33)	0.808	2.48 (-2.07-7.02)	0.278	-0.28 (-0.72-0.16)	0.212
LDL	11.20 (2.59-19.82)	0.012	0.90 (-0.10-1.89)	0.077	2.48 (-4.88-21.55)	0.209	0.11 (-1.15-1.39)	0.855

†Model including "age, sex, waist circumference, panhypopituitarism, SSA "as covariates".

GH/IGF-1 and cardio-metabolic risk factors presented as binary outcomes

We further examined the impact of GH/ IGF-1 times ULN on cardio-metabolic risk factors applying logistic regression models. As shown in Table 4, each 1 ng/ml increase in the level of GH significantly increased the odds of DM (OR; 1.06, 95% CI; 1.00-1.12, p = 0.030). Moreover, the impact of GH on DM remained significant even after adjustment for other potential cardio-metabolic risk factors including age, sex, wc,

panhypopituitarism, and SSA (OR; 1.17, 95% CI; 1.02–1.35, p = 0.025). However, GH or IGF-1 times ULN did not significantly increase the odds of HTN, and DLP.

Table 4
Logistic regression analyses predicting the impact of IGF1/GH on the cardio-metabolic complications

Outcome of interest	Simple logistic regression model				Multiple logistic regression model†			
	IGF1*ULN		GH		IGF1*ULN		GH	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
DM	0.98 (0.55–1.75)	0.953	1.06 (1.00–1.12)	0.030	1.03 (0.23–4.65)	0.966	1.17 (1.02–1.35)	0.025
HTN	0.75 (0.47–1.20)	0.228	1.01 (0.95–1.07)	0.808	0.57 (0.28–1.18)	0.131	1.08 (0.97–1.20)	0.145
DLP	1.22 (0.68–2.19)	0.493	1.12 (0.94–1.34)	0.193	1.70 (0.47–6.11)	0.417	1.24 (0.88–1.74)	0.218
†Model including “age, sex, waist circumference, panhypopituitarism, SSA “as covariates								

Receiver Operating Characteristic (ROC) curve analysis

We also evaluated the diagnostic performance of basal postoperative GH level for prediction of DM using ROC curve analysis (Fig. 1). Analysis of ROC curve revealed an area under the curve of 0.95. The optimal GH cut-off point for prediction of DM was 14.31 ng/ml, which provided a sensitivity of 80%, specificity of 98.4%, positive predictive value of 88.9%, and negative predictive value of 96.9%.

Discussion

This registry-based study investigating the cardio-metabolic risk factors in a cohort of Iranian people with acromegaly demonstrated DLP is the most prevalent metabolic abnormality in this population followed by DM, and HTN. Moreover, analysis of postoperative data showed GH acts as a determinant of FBS, SBP, and DBP levels. It appears also as a predictive factor for DM after adjusting for the other co-existing risk factors.

With regard to the impact of GH/IGF-1 on all aspects of metabolism, association of acromegaly with a wide spectrum of metabolic abnormalities is not far from the expectation. However, clinical manifestations of these metabolic abnormalities vary among patients with different ethnic background. DM has been reported to be present in 16–56% of patients with acromegaly [18, 19]. Hypertriglyceridemia and low HDL-cholesterol

are the most common lipid abnormalities associated with acromegaly reported in 33–47% of the patients [18, 20, 21]. HTN is another common comorbidity of acromegaly with an average prevalence of 35%, ranging from 18–60% [22]. The prevalence of metabolic abnormalities obtained from this registry-based study, including DM (29.4%), HTN (15%), and DLP (79.17%), is comparable with those from the previous studies in most but not all cases. This variability is explained by heterogeneity in the study populations and differences in the criteria used for the diagnosis of metabolic abnormalities. Moreover, the status of disease activity and different therapeutic intervention could affect the frequency and severity of these cardio-metabolic risk factors.

Analysis of postoperative data, stratified by disease activity, revealed no significant difference in the frequency and severity of cardio-metabolic risk factors between active/ discordant groups compared to the cured/controlled one. Moreover, a proportion of patients in the cured/controlled group continued to show metabolic abnormalities. Similarly, previous studies demonstrated some residue of metabolic disturbances even after successful treatment of acromegaly [14, 18]. Nevertheless, it is not well-known whether this reflects the ethnogenetic background of the people or is the result of some irreversible derangements secondary to the chronic GH excess [23].

Many studies investigating the predictors of diabetes in acromegaly demonstrated age, gender, BMI, and family history of diabetes are the well-established risk factors of diabetes in acromegaly [5]. However, the association between diabetes and the main indicators of disease activity in acromegaly (i.e., GH and IGF-1 levels) is somewhat controversial. One study, based on the French Acromegaly Registry data, claimed that “the GH and IGF-1 levels did not appear as predictive factors for the presence of diabetes” [15], while others suggested high IGF-1 rather than high GH is a predictor of diabetes in acromegaly [14, 16]. The present study showed GH is significantly associated with the level of FBS. Moreover, it acts as a main determinant of DM upon adjusting for the potential risk factors. This controversy is partly explained by the fact that GH directly acts as a diabetogenic hormone by increasing lipolysis and inducing insulin resistance [24] while indirectly, via increasing IGF-1, may facilitate insulin action and result in hypoglycemia [25]. As shown in this study, the predictive role of GH, but not IGF-1, in developing DM is pathophysiologically compatible with the impact of GH and IGF-1 on glucose metabolism. However, at the early stage of the disease, patients with acromegaly maintain normal glycemic status at the expense of increasing insulin production by the pancreatic beta cells [24, 26]. Chronic GH excess, leading to insulin resistance, overcomes the beneficial effects of IGF-1 excess on insulin sensitivity, increases fasting glucose, and eventually leads to overt hyperglycemia [26].

A few studies investigated the hypertension-related factors in patients with acromegaly leading to inconclusive results. One study showed in patients with active acromegaly IGF-1 was a predictor of SBP level, mediating by albuminuria, while in patients with controlled disease; other cardiovascular risk factors such as abdominal obesity and TG were associated with BP levels [6]. A more recent study demonstrated the risk of having HTN was only significantly associated with the IGF-1 > 2 ULN at diagnosis and the coexistence of diabetes (14). However, in some study, HTN in acromegaly was not related to IGF-1 levels [27]. The current study showed GH is significantly associated with both SBP and DBP levels; However, GH could not predict the presence of HTN defined as BP \geq 140/90 mmHg in this population of patients with acromegaly. Moreover, IGF-1 times ULN was inversely associated with DBP level, but there was no predictive role for IGF-1

times ULN in predicting HTN. Although the vasodilatory effect of IGF-1, mediated by nitric oxide, and the role of GH in Na and water retention [12, 13, 28] clearly explain the protective role of IGF-1 on diastolic blood pressure and the effect of GH in increasing systolic and diastolic blood pressure, as shown in this study, the level of BP might be determined by the interaction between various influencing factors at different stages of acromegaly. Moreover, the inconclusive results regarding the impact of GH/IGF-1 on HTN, coming from different studies, might be explained by different studied population, duration of follow-up, and disease activity status at which the studies have been done. Moreover, a recent study showed different treatments used to control acromegaly are associated with different changes in metabolic parameters and cardiovascular risk factors [29].

Lipid abnormalities, including hypertriglyceridemia and low HDL, are frequently seen in patients with acromegaly. DLP was found to be the most prevalent metabolic abnormality in this study. Regarding the determinants of DLP in patients with acromegaly we found no predictive role for neither GH nor IGF-1 times ULN. Similarly, another study suggested hypertriglyceridemia of acromegaly does not correlate with basal GH or IGF-1 concentration but is associated with insulin resistance [30]. However, a most recent study showed a correlation between low HDL and basal IGF-1 [20]. Although a significant improvement in lipid profile after successful treatment of acromegaly supports the role of GH and /or IGF-1 in the development of these abnormalities, no predictive role of GH/IGF-1 for DLP has been well-established. This is likely due to the influence and interaction of other co-existing risk factors.

Strengths And Limitations

To the best of our knowledge this is the first study evaluated the role of GH/ IGF-1 in predicting various aspects of metabolic abnormalities in a population of patients with acromegaly. The study population was relatively large and the impact of GH/IGF-1 on metabolic abnormalities was assessed considering other potential risk factors. However, data on the main measurements were not available for a proportion of patients. Moreover, due to the lack of postoperative GH suppression test for all patients, disease status was classified according to the basal GH rather than nadir GH level during glucose tolerance test.

Conclusion

This study gives us more insights on the prevalence of various aspects of cardio-metabolic risk factors in acromegaly. In this population, DLP was the most prevalent metabolic disturbance, followed by DM, and HTN. GH was significantly associated with the FBS, SBP, and DBP level while IGF-1 times ULN was inversely associated with DBP. Moreover, GH, but not IGF-1, appears as a predictive factor for the presence of diabetes. Our findings highlight the importance of a comprehensive approach for management of these patients with great emphasis on the control of both GH and IGF-1 levels to cover all aspects of cardio- metabolic abnormalities.

Abbreviations

CVD: Cardiovascular disease; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; BMI: Body mass index; HTN: hypertension; IPTR: Iran Pituitary Tumor Registry; WC: Waist circumference; MRI: Magnetic resonance imaging; FBS: Fasting blood sugar; HbA1C: Glycated hemoglobin; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Declarations

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Authors' Contributions

MK and MM contributed to study concept and design. NHM drafted the manuscript. MH, MG and ZE acquired data. MK and NHM contributed to the analysis and interpretation of data. MK critically revised the manuscript. AK contributed to statistical analysis. All authors have approved the final submission.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and consent to participate

The ethics committee of Iran University of Medical Sciences approved the study protocol (approval number: IR.IUMS.FMD.REC.1397.252).

Consent for publication

Not applicable.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interest.

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Figures

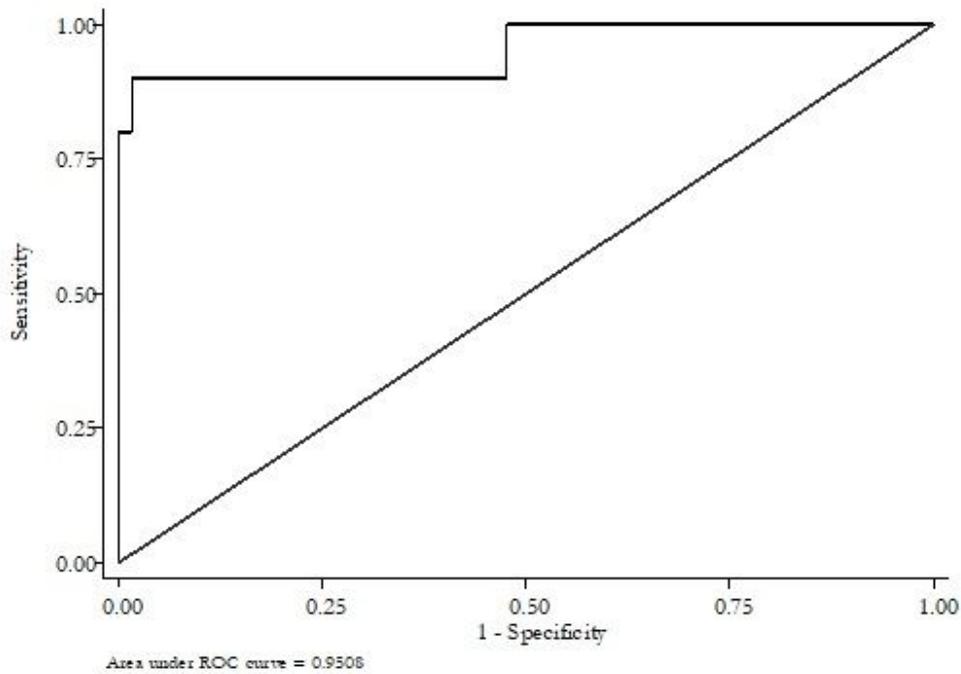


Figure 1

Roc curve analysis presenting prediction of DM applying basal GH level Cut-off= 14.31 ng/ml, sensitivity= 80%, specificity= 98.4%, positive predictive value= 88.9%, negative predictive value= 96.9%. ROC; receiving operative curve, DM; diabetes mellitus, GH; growth hormone