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Research Brief

# Acromegaly: Cardiovascular risk factors, cardiovascular manifestations and early vascular alterations in relation to disease activity

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ABSTRACT

Acromegaly is associated with increased cardiovascular morbidity and mortality. 49 acromegaly patients were evaluated for presence of cardiovascular risk factors and manifestations using 2D-Echocardiography, strain, strain-rate, carotid intima media thickness (CIMT) and flow mediated dilatation (FMD) and correlated with disease activity. 32 patients with growth hormone (GH) level >1 ng/ml were considered active. Patients with active disease have more LV dysfunction as assessed by strain(p-0.031) and strain rate(p-0.001); trend towards lower ejection fraction(p-0.11) with significant correlation to GH(cc −0.252,p-0.05). Patient with active disease have reduced FMD(p- 0.042); with no difference in prevalence of cardiovascular risk factors and CIMT inrelation to disease activity.


## 1. Introduction

Acromegaly is a disorder characterized by growth hormone (GH) hypersecretion, multisystem-associated morbidities, and increased mortality; usually due to GH secreting pituitary adenoma.[1] The prevalence of cardiovascular risk factors in acromegaly patients is increased compared to general population.[2] Acromegaly is associated with increased cardiovascular morbidity and mortality. It is also been observed that acromegaly patients have impaired endothelial function as assessed by flow mediated dilatation (FMD) and carotid intima media thickness (CIMT).[3] Untreated or late diagnosed acromegaly is associated with left ventricular (LV) hypertrophy, impaired systolic and diastolic left ventricular function leading to congestive heart failure.[4]

A significant improvement of CV risk factors and morphological and functional cardiac abnormalities has been reported in acromegalic patients undergoing surgical resection of pituitary adenoma.[5] Berg C et al reported significant decrease in cardiovascular risk factors and Framingham risk score with disease control.[6] FMD was significantly lower in active acromegalic patients compared to controls and to inactive acromegaly patients. However CIMT did not differ between active and cured patients.[3] Several studies have demonstrated that LV hypertrophy can be reversed by suppression of GH and IGF-I levels with octreotide and lanreotide.[6] Toumanidis ST et al showed improvement of left ventricular diastolic function and cardiac hypertrophy in patients with inactive acromegaly and normal systolic cardiac function compared to those with active disease.[7] However the results are conflicting with several trails not observing significant improvement in risk factors and cardiovascular manifestations.[8]

The present study is designed to evaluate cardiovascular risk factors, cardiovascular manifestations and early atherosclerotic markers in acromegaly and its correlation with disease activity.

## 2. Materials and methods

### 2.1. Patient selection and enrolment

49 confirmed acromegaly patients were enrolled in the study. The study was done at tertiary center of north India from June 2015 to May 2018. All subjects underwent detailed clinical examination. Data regarding the presence of cardiovascular risk factors were collected. Blood sample was obtained after an overnight fast.

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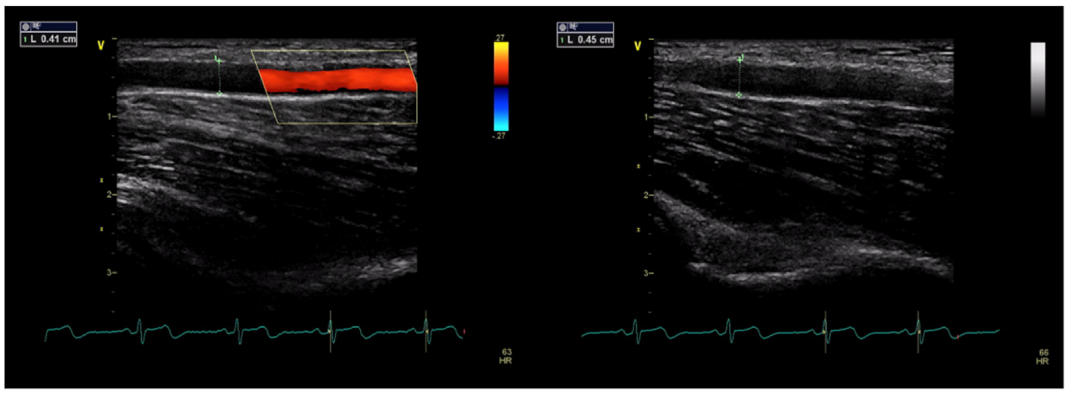


**Fig. 1.** Flow mediated dilatation.

Fasting lipid profile, fasting blood sugar, glycosylated hemoglobin, serum creatinine, hemoglobin along with basal GH, 60 min GH after 75 g of oral glucose, Insulin like growth factor-1 were measured. Those with growth hormone levels of >1 ng/ml at 60 min of glucose loading were considered active.

A detailed 2-dimensional echocardiography was done in all patients as per recommendations from American Society of Cardiology.[9] TDI was applied at medial and lateral mitral annulus and E/E' was assessed. Left ventricular longitudinal strain and strain rate were measured using tissue doppler imaging. CIMT was measured at far wall of common carotid artery using 1 cm length proximal to carotid sinus, measured on 3 views on both side and the average was taken. FMD of brachial artery was imaged above antecubital fossa using proximal compression with sphygmomanometer cuff inflated to atleast 50 mm Hg above systolic pressure for 5 min.[10] ECG gated brachial artery diameter is obtained from 2D-imaging at baseline and upon 60 s of cuff release. A linear array transducer of 7 MHz in longitudinal plane was kept inplace throughout the study, position reaffirmed by nearby anatomical landmarks (Fig. 1).

### 2.2. Statistical analysis

Data were entered using the statistical package SPSS version 20. Data were summarized using descriptive statistics: mean, standard deviation, number and percentage for qualitative values. Statistical differences between groups were tested using the Chi Square test for qualitative variables, independent sample t test for quantitative normally distributed variables while the Nonparametric Mann Whitney test will be used for quantitative variables which are not

**Table 1**
Baseline characteristics and cardiovascular risk factors in relation to disease activity.

| | TOTAL (n = 49) | GH < 1 (n = 17) | GH >1 (n = 32) | P value |
|---|---|---|---|---|
| Age | 37.63 (11.19) | 39.47 (11.14) | 36.65 (11.30) | 0.4076 |
| Male | 28 | 8 | 20 | 0.299 |
| Female | 21 | 9 | 12 | |
| Hypertention | 15 | 6 | 9 | 0.604 |
| Diabetes Mellitus | 10 | 1 | 9 | 0.117 |
| IGT | 5 | 3 | 2 | |
| HbA1C | 6.19 (1.63) | 5.77 (1.00) | 6.41 (1.85) | 0.192 |
| Dyslipidemia | | | | |
| Low density lipoprotein LDL (mg/dl) | 100.35 (30.76) | 106.52 (33.62) | 96.96 (29.10) | 0.308 |
| LDL 130–160 | 6 | 3 | 3 | 0.332 |
| LDL >160 | 3 | 2 | 1 | |
| Triglycerides-TG (mg/dl) | 151.32 (77.40) | 144.23 (67.47) | 155.09 (82.98) | 0.645 |
| TG150-199 | 9 | 4 | 5 | 0.501 |
| TG>199 | 10 | 2 | 8 | |
| High Density Lipoprotein-HDL (mg/dl) | 40.07 (10.7) | 38.70 (11.39) | 41.73 (9.32) | 0.321 |
| HDL>40Male, >50 Female | 29 | 10 | 19 | 0.361 |
| HDL>40Male, >50 Female | 20 | 7 | 13 | |
| Total Cholesterol | 171.57 (34.89) | 174. 05 (42.02) | 170.21 (31.12) | 0.720 |
| Tobacco | 5 | 2 | 3 | |
| Systolic BP (mmHg) | 125.61 (16.04) | 120 (12.24) | 129.89 (16.17) | 0.034 |
| Diastolic BP (mmHg) | 77.55 (9.19) | 77.65 (7.52) | 77.50 (10.08) | 0.958 |
| Body Mass Index (BMI) | 28.91 (4.96) | 30.09 (5.09) | 28.28 (4.85) | 0.228 |
| BMI < 22.9 | 6 | 2 | 4 | 0.153 |
| BMI 23–24.9 | 6 | 0 | 6 | |
| BMI >25 | 37 | 15 | 22 | |
| Creatinine | 0.89 (0.22) | 0.87 (0.14) | 0.91 (0.25) | 0.533 |
| Disease Duration | 9.00 (6.64) | 13.7 (7.96) | 6.5 (4.12) | <0.001 |
| GH-0 | 12.32 (16.45) | 0.44 (0.42) | 18.63 (17.33) | <0.001 |
| GH-60 | 11.81 (15.91) | 0.28 (0.17) | 17.94 (16.74) | <0.001 |
| IGF | 561.02 (386.14) | 186.95 (262.13) | 773 (264.76) | <0.001 |

IGT-Impaired Glucose tolerance, IGF- Insulin like growth factor-I, GH- Growth Hormone.

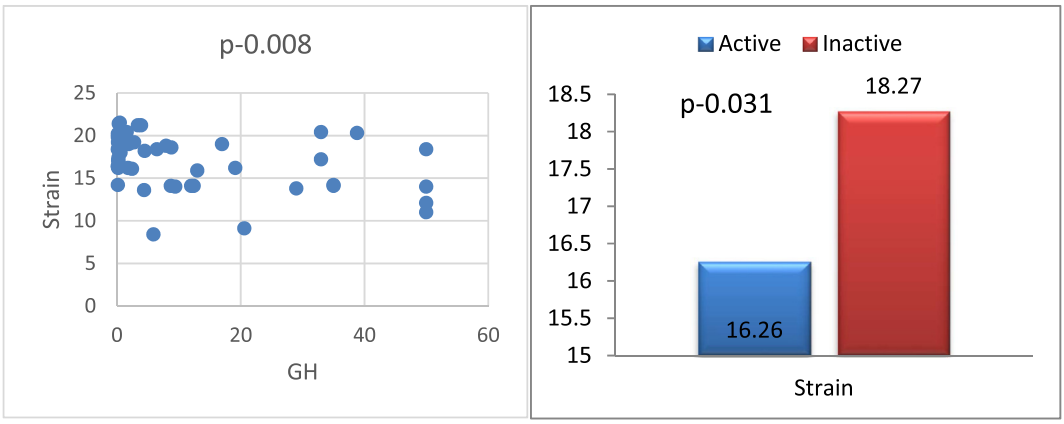


**Fig. 2.** Strain in relation to acromegaly disease activity.

normally distributed. Correlation coefficient was calculated with regard to growth hormone levels. P-values less than or equal to 0.05 will be considered statistically significant.

## 3. Results

Detail Baseline characteristics and cardiovascular risk factors in relation to disease activity are shown in Table 1. Diabetes mellitus and Hypertension was seen in 20.4% and 30.6% respectively. Majority of the patients were obese (BMI ≥25). There was no difference in lipid parameters in relation to disease activity.

LV mass (224.8 ± 61.9 gm) and LV mass index (120.8 ± 31.7 gm/m) were significantly higher in acromegaly patients compared to reference range for general population.[12] LV mass and LV mass index showed trend towards higher value in disease active group than in controlled disease. Significant correlation was seen between LV mass and growth hormone levels (p-0.015). Inter ventricular septal thickness was higher in disease active group than control group. E/E' was non-significantly higher in active disease group (9.1 ± 3.4 vs 8.3 ± 1.8; p-0.378). Patients with active disease had significantly lower strain (16.26 ± 3.41 vs 18.27 ± 1.99; p-0.031) (Fig. 2) and longitudinal strain rate (1.03 ± 0.16 vs 1.20 ± 0.14 vs; p<0.001). LV ejection fraction showed trend towards lower value in active group (57.76 ± 4.48 vs 54.59 ± 8.54; p-0.11) with significant correlation to growth hormone levels (coefficient −0.252, p-0.05). 2 patients had severe LV systolic dysfunction in active group (Table 2). Hypertension was not a confounding factor for LVEF (p-0.761) and Strain (p-0.709) between groups.

**Table 3**
Correlation coefficient in relation to growth hormone.

| GH | Correlation Coefficient | P value |
|---|---|---|
| LV Mass | 0.346 | 0.015 |
| E/E′ Septal | 0.132 | 0.364 |
| LVEF | −0.252 | 0.05 |
| Strain | −0.376 | 0.008 |
| Strain Rate | −0.422 | 0.002 |
| FMD | −0.300 | 0.036 |
| CIMT | 0.149 | 0.307 |

Endothelial Dysfunction: Mean CIMT was 6.97 ± 1.65 mm with no significant difference between patients of active and inactive disease group (6.61 ± 1.25 vs 7.17 ± 1.81; p-0.268). Brachial artery FMD was significantly less in patients with active disease (9.96 ± 2.86 vs 7.78 ± 3.75; p-0.042). Brachial artery FMD showed significant correlation with growth hormone levels with correlation coefficient of −0.300 (p-0.036). CIMT showed non-significant trend with growth hormone (0.149; p-0.307) (Table 3 and Fig. 3).

## 4. Discussion

This study shows the prevalence of cardiovascular risk factors in acromegaly patients. Diabetes was seen in 20.4% and impaired glucose tolerance in 10.2%, which is similar to Colao et al.[11] Hypertension is seen in 30% of patients with no significant difference in prevalence in relation to disease activity, though systolic blood pressure was higher in patients with active disease (p-0.034). The

**Table 2**
Echocardiographic parameters in relation to disease activity.

| | TOTAL | GH < 1 | GH > 1 | P VALUE |
|---|---|---|---|---|
| Interventricular Septum | 12.85 (1.69) | 12.29 (1.57) | 13.15 (1.70) | <0.001 |
| Posterior Wall | 11.82 (1.77) | 11.35 (1.80) | 12.07 (1.83) | 0.175 |
| LV Diastolic Diameter | 47.08 (5.04) | 46.23 (5.41) | 47.53 (4.86) | 0.398 |
| LV Systolic Diameter | 26.24 (4.70) | 25.41 (4.00) | 26.68 (5.04) | 0.372 |
| LV Mass | 224.8 (61.9) | 208.6 (77.1) | 233.4(51.4) | 0.184 |
| LV Mass Index | 120.8 (31.7) | 112.8(40.0) | 125.0(26.1) | 0.203 |
| E/E′ Septal | 0.088 (0.029) | 0.083 (0.018) | 0.091 (0.034) | 0.378 |
| Ejection Fraction % | 55.69 (7.54) | 57.76 (4.48) | 54.59 (8.54) | 0.112 |
| Strain | 16.96 (3.13) | 18.27 (1.99) | 16.26 (3.41) | 0.031 |
| Strain Rate | 1.09 (0.18) | 1.20 (0.14) | 1.03 (0.16) | 0.001 |
| Brachial artery pre | 38.94 (9.57) | 39.17 (5.84) | 38.81 (11.14) | 0.903 |
| Brachial artery post | 42.26 (10.10) | 43.00 (5.92) | 41.86 (11.81) | 0.713 |
| FMD | 8.54 (3.59) | 9.96 (2.86) | 7.78 (3.75) | 0.042 |
| CIMT | 6.97 (1.65) | 6.61 (1.25) | 7.17 (1.81) | 0.268 |

LV- Left Ventricle, FMD- Flow mediated dilatation, CIMT-Carotid Intima Media Thickness.

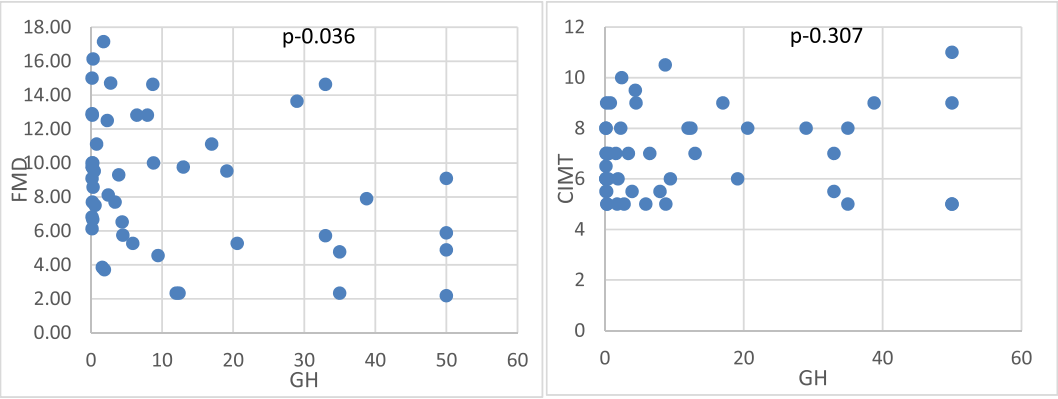


**Fig. 3.** Correlation between growth hormone with flow mediated dilatation and CIMT.

reported prevalence of hypertension in acromegalic patients ranges from 18 to 60%, with a mean prevalence of about 35%.[12] There was no difference in lipid profile and BMI in either group. Berg C et al has observed similar findings.[2]

LV mass and LV mass index was significantly higher in acromegaly patients compared to reference range for general population as observed in earlier studies.[9,11] We observed a trend towards higher LV mass in active disease group, though not statistically significant. A significant regression of LV mass with disease control has been noted by others.[6,7] LV function as assessed by strain and strain rate was significantly less in patients with active disease compared to controlled disease. LV ejection fraction has significant correlation with growth hormone levels with trend towards lower value in active patients. Colao A et al also observed similar improvement in LV ejection fraction with disease control; whereas no significant difference was observed by Bruch C et al.[8,13] This is the largest study evaluating strain in acromegaly to the best of our knowledge. Di Bello V et al have reported impaired strain and strain rate in acromegaly patients which improved with treatment.[14] Occurrence of LV systolic dysfunction in acromegaly is observed with long standing active disease.[4] Systolic dysfunction observed in our trial is likely because of long disease duration in active group before consulting tertiary centre. LV diastolic dysfunction as assessed by E/E' showed a trend towards improvement in inactive disease group, a significant improvement was reported by Bruch C et al.[8]

Flow mediated dilatation of brachial artery was significantly less in disease active patients as observed by Brevetti G et al.[3] The precise mechanism of endothelial dysfunction in acromegaly is not well understood. Morphological and functional alterations of vascular smooth muscle cells may lead to impaired vaso-reactivity of the brachial artery. Growth hormone excess may play a role in generating endothelial dysfunction. Baykan et al has observed impairment of brachial artery FMD compared to healthy controls.[15] CIMT was not different in either group as also observed by Brevetti G et al.[3]

There was significant correlation of LV mass, LV ejection fraction, strain, strain rate and FMD (all $p<0.05$). This suggests even partially controlled acromegaly may have lesser cardiovascular manifestations, with those who are in good control or cured benefitting the most.

The study has some limitations. Patients are enrolled in either group unlike Colao A et al, where only disease active patients were enrolled and followed after successful treatment. Also we did not consider duration of remission in controlled disease group and its implications. This may be the reason for not observing significant difference in cardiovascular risk factors and LV mass, although trend was observed.

In conclusion, acromegaly patients with active disease have significant left ventricular systolic dysfunction and impaired flow mediated dilatation compared to patients with controlled disease. There was no significant difference in prevalence of cardiovascular risk factors and CIMT in relation to disease activity.

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