

Increased Arterial Stiffness and Galectin-3 Expression in Acromegaly: Associations with IGF-1 and Cardiovascular Risk

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Abstract

Secretion of insulin-like growth factor-1 (IGF-1) and growth hormone is heightened in acromegaly, a persistent illness. We aimed to examine the association between carotid femoral pulse wave velocity (CF-PWV) and circulating galectin-3 concentration in subjects with acromegaly. This molecule is hypothesized to be modified in the context of incipient inflammation and atherosclerotic changes. Our work was conceived as a prospective, single-center cross-sectional investigation. The study enrolled 40 healthy controls and 40 patients with recently diagnosed acromegaly, all aged 18-65 years, at Adana City Training and Research Hospital. IGF-1, growth hormone, hemogram, and biochemistry panels were analyzed for the participants. Ready-to-use human galectin-3 assay kits, together with the Enzyme-Linked Immunosorbent Assay technique, were used to quantify galectin-3 concentrations. Subjects were evaluated for CF-PWV by means of Doppler ultrasonography paired with simultaneous electrocardiography. Our data demonstrated that acromegaly cases exhibited elevated values of the fibrotic and inflammatory mediator galectin-3 alongside CF-PWV, the benchmark metric for arterial wall rigidity. In the correlation testing, we detected a relationship between circulating galectin-3 concentration and both IGF-1 levels and CF-PWV readings. Galectin-3 may serve as a novel biomarker to identify and predict the course of cardiovascular disease in acromegaly patients, as well as a molecular target for managing the progression of this pathology.

Keywords: Arterial stiffness, Galectin-3 expression, Acromegaly, Cardiovascular risk

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Introduction

A pituitary adenoma is the near-universal cause of acromegaly, a long-lasting syndrome characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Fatal outcomes from cardiac disorders, cerebrovascular accidents, and pulmonary ailments rise in the absence of suitable acromegaly management [1]. A diagnostic gap exists between the initial manifestation of features and confirmation of acromegaly, given the condition's tendency to evolve

quietly. Delayed identification is tied to greater rates of death and illness [2]. Elevated cardiovascular disease (CVD)-related fatality and sickness are connected to the supraphysiological GH and IGF-1 concentrations characteristic of acromegaly. Curtailing cardiovascular death and disease burden, as well as arresting the advance of cardiac pathology, are both achievable through the treatment of acromegaly and its concurrent health problems [3].

Galectins constitute a family of lectins exhibiting marked preference for β -galactosidases and possessing no fewer

than one carbohydrate-recognition domain. Vessel formation, cell–cell binding, cell–matrix interplay, mitotic activity, cellular expansion, programmed cell death, inflammatory responses, fibrotic remodeling, and neoplastic growth are all modulated by galectin-3, the only mammalian representative of its class [4]. In addition to its participation in inflammation and scarring, galectin-3 serves as a pivotal actor in the initiation and worsening of CVD. Some published evidence suggests that galectin-3 could be applied in CVD cases, might independently forecast death, and could act as an original diagnostic and prognostic indicator [5].

Atherogenic risk factors and advancing age each promote arterial stiffening, signaling widespread atherosclerotic compromise of the vascular tree. Rigid vessels are correlated with an escalated hazard of cardiovascular incidents and all-cause mortality, based on published findings. The ESC and ESH have designated a carotid-femoral pulse wave velocity (CF-PWV) of 10 m/s or greater as the most reliable index of arterial stiffening, capable of anticipating the onset of atherosclerosis and CVD [6, 7].

To the best of our knowledge, no published work has linked CF-PWV to circulating galectin-3 levels in an acromegaly population. The central purpose driving our study was to establish whether, during the initial stages of acromegaly, any interrelationship could be found among serum IGF-1, GH, and galectin-3 – substances presumed to shift alongside inflammation and atherosclerotic activity – and CF-PWV – the reference standard for quantifying arterial rigidity.

Materials and Methods

Study population

Our project was structured as a prospective, single-center cross-sectional investigation. Spanning the interval from July 01, 2021, to July 01, 2023, a total of 40 individuals at the University of Health Sciences, Adana City Training and Research Hospital, whose ages fell between 18 and 65 years, were prospectively included. Forty of these individuals had recently received a primary diagnosis of acromegaly and were neither in biochemical remission nor undergoing hormone substitution. An additional forty participants forming the comparator arm were in good health. The diagnostic reference method, the oral glucose tolerance test, was used to verify the diagnosis of acromegaly. GH output was suppressed, and the lowest GH values were recorded following the glucose load. Persons excluded from eligibility due to coexisting factors that might confound the results included those with: cardiac muscle, valvular, or coronary artery pathology, cardiac pump failure, COPD, renal or hepatic dysfunction, systemic inflammatory conditions, hematologic disorders,

malignancy, rheumatologic illness, cerebrovascular episodes, thyroid gland irregularities, gestation, and any background of tobacco use.

Official authorization for our trial was provided by the Clinical Research Ethics Committee of Cukurova University's Faculty of Medicine. Every individual involved, including both cases and healthy volunteers, was made fully aware of the study details before enrollment. The research dataset was sourced from the electronic data processing archives of Adana City Training and Research Hospital and from the daily outpatient records of patients. Written informed consent documentation was obligatory for anyone wishing to take part. Thorough physical assessments and detailed health background interviews were conducted for both the research cohort and the healthy comparison set. In-clinic blood pressure readings were utilized to establish a diagnosis of hypertension. Age, gender, personal medical background, physical findings, and laboratory parameters were systematically logged for all participants. Measurements of stature, body weight, and body mass index were taken from the subjects. All procedures were performed in alignment with the ethical standards outlined in the Declaration of Helsinki.

Laboratory measurements

The biochemical assays required for this study were performed in the University of Health Sciences' institutional laboratory at Adana City Hospital. Determinations of IGF-1 and GH, in addition to other parameters, were performed on an automated chemistry platform (Abbott Aeroset, Plymouth, MN) utilizing commercially procured Abbott reagent kits. Each patient's IGF-1 result was benchmarked against normative ranges tailored to age and sex, with all IGF-1 values corrected for these variables.

Galectin-3 measurements

In addition to standard hematological and biochemical sampling, a single extra tube containing gel with a yellow closure was drawn from each study participant and each control subject to procure blood specifically earmarked for the research. These specimens were transported without delay to the laboratory, centrifuged at 4000 rpm for 10 minutes to separate the serum, then aliquoted into Eppendorf tubes and maintained frozen at -80 °C until assayed. After the enrollment phase concluded, the frozen samples were shipped to the Medical Microbiology Laboratory at Istanbul Bezmialem Vakif University, which ensured the proper analytical environment. Circulating galectin-3 concentrations were quantified using the Enzyme-Linked Immunosorbent Assay technique with human galectin-3 kits from eBioscience (Europe/International, Austria).

Carotid femoral pulse wave velocity measurements

Carotid femoral pulse wave velocity was captured using a high-resolution Doppler ultrasound unit (Philips EPIQ 7) fitted with a 12 MHz linear broadband transducer (Philips Health Care, Bothell, WA). Every subject was monitored concurrently with a 12-lead electrocardiogram (ECG). Owing to the impracticality of simultaneously interrogating both common carotid arteries together with the common femoral artery, flow waveforms from the right common carotid, left common carotid, and common femoral artery were acquired in sequence under ECG-gated conditions.

Subjects remained recumbent and at rest for a full 10 minutes before recordings commenced. To optimize the acoustic window, the head was rotated roughly 45 degrees away from the side undergoing insonation. Doppler flow tracings were sampled at a site 10 mm upstream from the bifurcation of each common carotid artery while the ECG trace ran simultaneously. Femoral artery waveforms were likewise obtained 10 mm proximal to the common femoral artery bifurcation. The flow transit time (flowTT) was measured as the time interval between the foot of the Doppler velocity envelope and the peak of the R wave on the QRS complex at both the carotid and femoral sites. Six individual flowTT measurements—comprising 3 cardiac cycles from two distinct carotid and two distinct femoral windows—were averaged to produce the mean flowTT. From these, the average carotid-femoral flow transit time differential (Δ CF-flow TT, s) was computed.

The surface distance between the skin marks placed at the carotid and femoral sampling positions was next recorded. Using the sternal jugular notch as the anatomic reference point, the carotid-notch and notch-femoral segments were measured, thereby approximating the true vascular path traveled by the pulse wave from the aortic arch outward to the peripheral arteries. CF-PWV (m/s) was ultimately

calculated from the Δ CF-distance (m) divided by the Δ CF-flow TT (s). All sonographic acquisitions and distance measurements were performed by a single radiologist with a decade of clinical experience.

Statistical analysis

All statistical computations were executed with SPSS version 24.0 (Chicago, IL). The Kolmogorov–Smirnov procedure was applied to check whether each continuously distributed variable adhered to a Gaussian pattern. Categorical data are summarized as frequencies and corresponding percentages. Continuous measures are reported as the arithmetic mean \pm one standard deviation. Intergroup contrasts for continuous parameters used either the independent-samples Student t test or the Mann–Whitney U test, depending on the data distribution. Categorical factors were compared by means of the chi-square (χ^2) statistic. Receiver operating characteristic curve methodology was employed to discriminate subjects with a CF-PWV of 10 m/s or greater. Univariate associations with galectin-3 concentration were explored through Pearson and Spearman correlation analyses. Linear regression modeling was then performed to identify independent predictors of galectin-3 levels.

Results and Discussion

The enrolled cohort consisted of 40 individuals with a confirmed diagnosis of acromegaly, plus an equal number of healthy volunteers in the control arm. As delineated in **Table 1**, concentrations of galectin-3, along with CF-PWV readings, were considerably higher among the acromegaly group relative to their healthy counterparts. Blood pressure profiles did not differ significantly between the two study arms.

Table 1. Demographic, clinical, laboratory findings, and carotid femoral pulse wave velocity (CF-PWV) measurements of a patient with acromegaly and a healthy control group.

Variable	P-value	Healthy control group (n = 40)	Acromegaly patient group (n = 40)
Age (years)	.537	41.5 \pm 10.2	43.2 \pm 14.3
Gender (M/F, n)	.119	18/22	25/15
Body mass index (kg/m ²)	.164	27.3 \pm 4.08	28.4 \pm 3.18
Systolic blood pressure (mm Hg)	.294	146.9 \pm 18.2	151.3 \pm 19.4
Diastolic blood pressure (mm Hg)	.170	99.3 \pm 11.0	103.4 \pm 14.9
Basal heart rate (beats/min)	.071	78.0 \pm 12.1	82.8 \pm 11.6
Hemoglobin (g/dL)	.391	12.9 \pm 0.90	13.2 \pm 1.85
White blood cell (10 ³ / μ L)	.468	7.11 \pm 2.14	7.42 \pm 1.66
Platelet (10 ³ / μ L)	.355	287.8 \pm 33.2	304.0 \pm 104.0
Creatinine (mg/dL)	.236	0.61 \pm 0.15	0.65 \pm 0.15
Sodium (mmol/L)	.979	139.8 \pm 3.54	139.8 \pm 2.05
Potassium (mmol/L)	.436	4.30 \pm 0.34	4.37 \pm 0.42
Calcium (mg/dL)	.063	9.14 \pm 0.65	9.48 \pm 0.89

Aspartate aminotransferase (μ/L)	.243	19.2 ± 3.58	20.6 ± 6.51
Alanine aminotransferase (μ/L)	.482	15.9 ± 4.86	16.9 ± 7.69
Thyroid-stimulating hormone (μIU/mL)	.102	1.65 ± 0.54	1.48 ± 0.35
Insulin-like growth factor 1 (ng/mL)	<.001	73.9 ± 7.8	330.8 ± 194.8
CRP (mg/L)	<.001	2.01 ± 3.55	7.88 ± 7.61
Galectin-3 (ng/mL)	<.001	8.65 ± 1.71	17.9 ± 7.17
Carotid–femoral PWV (m/s)	<.001	8.39 ± 1.13	9.48 ± 1.25
CF-PWV ≥ 10 m/s, n (%)	.018	5 (12.5%)	14 (35%)

Values reaching statistical significance were printed in bold type. Abbreviation: CF-PWV = carotid femoral pulse wave velocity.

Based on their CF-PWV measurements, the acromegaly cases were stratified into two groups: those with CF-PWV > 10 m/s and those with CF-PWV < 10 m/s. Among patients with CF-PWV < 10 m/s, those with CF-PWV >

10 m/s were characterized by significantly greater age and more pronounced elevations in IGF-1 and galectin-3 concentrations (**Table 2**).

Table 2. Demographic, clinical, laboratory findings, and CF-PWV measurements of the patient group with acromegaly with CF-PWV ≥ 10 m/s and CF-PWV < 10 m/s.

Variable	P-value	CF-PWV < 10 m/s (n = 26)	CF-PWV ≥ 10 m/s (n = 14)
Age (years)	<.001	37.4 ± 13.5	54.0 ± 8.44
Gender (M/F, n)	.868	16/10	9/5
Diabetes mellitus, n (%)	.711	6 (23.1%)	4 (28.6%)
Hyperlipidemia, n (%)	.465	4 (15.4%)	1 (7.1%)
Hypertension, n (%)	.227	18 (69.2%)	12 (85.7%)
Body mass index (kg/m ²)	.475	28.2 ± 3.39	28.9 ± 2.78
Systolic blood pressure (mm Hg)	.483	152.7 ± 22.5	148.8 ± 12.0
Diastolic blood pressure (mm Hg)	.542	102.3 ± 15.4	105.4 ± 14.4
Basal heart rate (beats/min)	.526	82.0 ± 11.7	84.5 ± 11.8
Hemoglobin (g/dL)	.400	13.4 ± 2.12	12.8 ± 1.19
White blood cell (10 ³ /μL)	.469	7.56 ± 1.40	7.15 ± 2.09
Platelet (10 ³ /μL)	.059	276.6 ± 72.8	354.8 ± 134.2
Creatinine (mg/dL)	.708	0.66 ± 0.14	0.64 ± 0.18
Sodium (mmol/L)	.465	139.7 ± 2.00	140.2 ± 2.18
Potassium (mmol/L)	.108	4.29 ± 0.38	4.52 ± 0.47
Calcium (mg/dL)	.261	9.36 ± 0.78	9.70 ± 1.07
Aspartate aminotransferase (μ/L)	.318	19.8 ± 5.03	22.0 ± 8.67
Alanine aminotransferase (μ/L)	.526	16.4 ± 5.35	18.0 ± 10.9
Thyroid-stimulating hormone (μIU/mL)	.479	1.45 ± 0.24	1.54 ± 0.49
CRP (mg/L)	.332	8.75 ± 8.87	6.27 ± 4.28
Insulin-like growth factor 1 (ng/mL)	.003	265.2 ± 182.7	452.5 ± 158.2
Growth hormone (ng/mL)	.112	4.34 ± 6.78	13.5 ± 19.6
Galectin-3 (ng/mL)	<.001	15.3 ± 5.77	22.8 ± 7.16

Values reaching statistical significance were printed in bold type. Abbreviation: CF-PWV = carotid femoral pulse wave velocity.

To autonomously distinguish which subjects with acromegaly would register a CF-PWV value exceeding 10 m/s, we applied a multivariate logistic regression framework incorporating variables that had yielded P-values < .05 and were adjudged statistically meaningful during the univariate stage. Within this model, individuals whose CF-PWV reached or exceeded 10 m/s were

assessed specifically regarding galectin-3 levels as an explanatory factor. The output indicated that, among the acromegaly population studied, a single-unit (1 ng/mL) increase in serum galectin-3 was associated with a 18% higher probability of manifesting a CF-PWV greater than 10 m/s (**Table 3**).

Table 3. Multivariate logistic regression analysis for detection of CF-PWV ≥ 10 m/s in patients with acromegaly.

Variable	P value	95% confidence interval	Odds ratio
Galectin-3 (ng/mL)	.007	1.048–1.348	1.189

Using the predictors that remained significant in the multivariate logistic regression, a receiver operating characteristic curve was generated. The corresponding predictive performance metrics are presented in **Table 4**, and the curve is shown in **Figure 1**. A galectin-3 threshold of 17.5, when applied to the acromegaly cohort, flagged patients with a CF-PWV above 10 m/s, with a sensitivity of 85.7% and a specificity of 84.6%. We subsequently explored potential ties between circulating galectin-3 concentrations and an extensive panel of demographic descriptors, clinical indices, and laboratory results,

performing correlation analyses on the pooled dataset of 80 participants—both acromegaly patients and healthy volunteers. As enumerated in **Table 5**, body mass index, IGF-1, GH, CRP, and CF-PWV each emerged as factors associated with galectin-3 levels. Variables demonstrating a robust association with galectin-3 were subsequently entered into a linear regression model. The regression output, presented in **Table 5** and shown in **Figure 2**, indicates that galectin-3 level is independently associated with IGF-1 concentration.

Table 4. ROC analysis of galectin-3 level identifying patients with CF-PWV ≥ 10 m/s in patients with acromegaly.

Variable	Area under the ROC curve	Specificity	Sensitivity	Cutoff	P-value
Galectin-3 (ng/mL)	0.835 (0.693–0.977)	84.6%	85.7%	17.5	.001

Abbreviations: CF-PWV = carotid femoral pulse wave velocity, ROC = receiver operating characteristic.

Table 5. Parameters related to galectin-3 level and linear regression analysis (n = 80).

Variable	Multivariate analysis (P)	β	Univariate analysis (P)	r
Body mass index (kg/m ²)	.611	0.045	.020	0.230
Insulin-like growth factor 1 (ng/mL)	<.001	0.579	<.001	0.694
Growth hormone (ng/mL)	.299	0.096	.001	0.354
CRP (mg/L)	.926	-0.009	.006	0.278
CF-PWV (m/s)	.228	0.131	<.001	0.501

Statistically significant values were given in bold. Abbreviation: CF-PWV = carotid femoral pulse wave velocity.

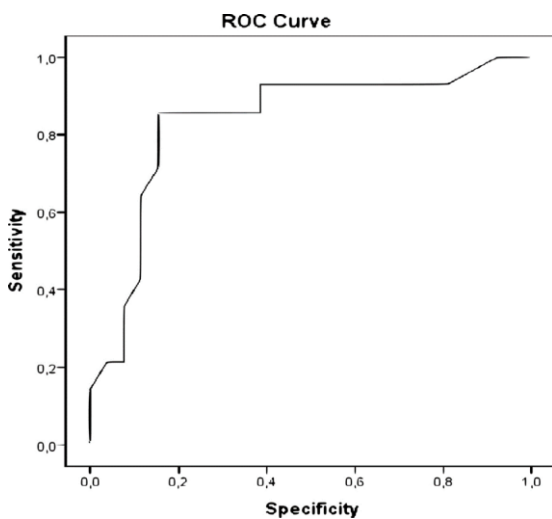


Figure 1. ROC curve of galectin-3 level identifying patients with CF-PWV ≥ 10 m/s in patients with acromegaly. Abbreviations: CF-PWV = carotid femoral pulse wave velocity, and ROC = receiver operating characteristic.

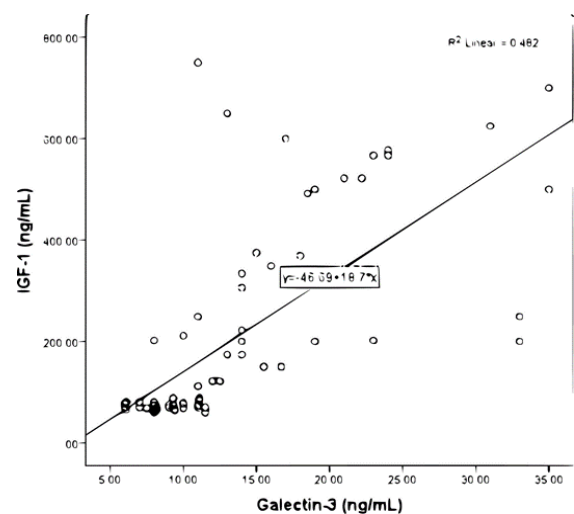


Figure 2. Scatter plot diagram between galectin-3 and IGF-1 level. Abbreviation: IGF-1 = insulin-like growth factor-1.

According to published reports, endothelial dysfunction and architectural changes in the vessel wall occur during the initial phases of acromegaly, and established cardiovascular risk factors are more frequently encountered in this population. Galectin-3 has been suggested to participate in the cascade that progresses from inflammation and tissue fibrosis through to atherosclerosis, and it may constitute a novel diagnostic and prognostic biomarker for CVD as well as a potentially viable molecular target for intervention [5]. Our data

revealed that individuals with acromegaly had elevated galectin-3 levels and increased CF-PWV. Having conducted a thorough review of the available literature, we were unable to identify any prior work establishing a link between CF-PWV and IGF-1 or galectin-3 levels in acromegaly.

The body of evidence on galectin-3 in acromegaly remains limited, and the studies that do exist are largely oriented toward malignancy. Keskin *et al.* [8], using immunohistochemical assessment, found that acromegaly patients diagnosed with papillary thyroid carcinoma expressed galectin-3 and IGF-1 at substantially higher levels than those with the same thyroid malignancy but without acromegaly. The authors proposed that galectin-3 may be useful for pinpointing malignant nodules in this patient group. Similarly, Marova *et al.* [9] applied immunohistochemical techniques to adenoma specimens obtained from 39 acromegaly cases treated via transsphenoidal surgery, reporting that preoperative GH concentrations were notably higher in those whose tumors stained positively for galectin-3, a putative marker of malignant potential.

Of note, a history of cancer rendered subjects ineligible for our trial. The literature contains investigations into the conceivable roles of galectin-3 across both oncologic and non-oncologic disorders. It is well recognized that acromegaly confers an elevated predisposition to neoplasia, and the inflammatory milieu associated with cancer may trigger a rise in galectin-3 expression.

Our findings established a relationship between galectin-3 and IGF-1 levels that proved statistically independent. Based on the extent of our literature search, no earlier report has identified a correlation between galectin-3 and IGF-1 specifically within an acromegaly cohort. This independent association may hold clinical utility for risk-stratifying acromegaly patients, facilitating earlier CVD detection, and guiding management strategies.

In a study led by Can *et al.* [10], which included 25 active, 26 well-controlled, and 9 newly diagnosed acromegaly subjects, pulse wave velocity (PWV) was elevated in the acromegaly arm compared with healthy volunteers. PWV was higher among acromegaly patients who carried CVD risk factors relative to controls, while those devoid of such factors displayed PWV values comparable to those of the control group. Within their acromegaly sample, PWV demonstrated a statistically significant relationship with both age and blood pressure.

Our work did not employ stratification based on CVD risk factors. The CF-PWV readings were significantly elevated in the acromegaly arm compared with healthy controls. Additionally, we observed a substantially greater proportion of patients with CF-PWV reaching or exceeding 10 m/s in the disease group than in the control arm. Whereas Can *et al.* recruited treated patients with

either active or controlled disease, our study was restricted to cases not yet in remission. Given that treatment of acromegaly can reverse cardiac pathology, this disparity in study design may explain the absence of a meaningful PWV difference between controls and those without CVD risk factors in their analysis.

Cansu *et al.* [11] similarly documented a higher PWV among acromegaly subjects compared with healthy individuals. No significant divergence in PWV measurements was detected when controlled and uncontrolled disease subgroups were juxtaposed. Paisley *et al.* [12] demonstrated that 56 patients with either active or remitted acromegaly had markedly higher blood pressure and CF-PWV than 46 healthy control subjects. In the acromegaly group, CF-PWV was correlated with age, blood pressure, and body mass index. Since our cohort consisted solely of patients who had not achieved remission, we could not compare those in remission with those with active disease. Further exploration of this topic is necessary.

Among 33 acromegaly patients who underwent transsphenoidal surgery and were subsequently classified by the degree of disease control, no statistically meaningful difference in CF-PWV emerged across the subgroups [13]. That investigation examined surgically managed acromegaly and did not incorporate a healthy reference group. Such a design may have obscured any genuine variation in CF-PWV measurements. In our study, we divided the acromegaly group into two subsets anchored on CF-PWV. Those with CF-PWV ≥ 10 m/s exhibited significantly elevated IGF-1 levels compared to their counterparts with CF-PWV below this threshold. Elevated IGF-1 in the acromegaly setting escalates cardiovascular risk, thereby increasing both morbidity and mortality.

Published work investigating the interplay between galectin-3 levels and CF-PWV in different clinical scenarios also exists. Oikonomou *et al.* [14] reported a statistically significant association between circulating galectin-3 and CF-PWV in a cohort of 40 patients with heart failure, concluding that galectin-3 may be useful for predicting CVD outcomes. The connection between galectin-3 and CF-PWV may be relevant to the timely recognition of cardiovascular disease.

This study carries original value, representing a first-of-its-kind exploration. At the same time, several constraints must be acknowledged. The inclusion criteria were restricted to patients whose acromegaly was not in remission; however, the precise duration of exposure to the disease state remains uncertain. We could not compare a subset with active acromegaly against one in which the disease was medically controlled. Additional research is needed to assess the effectiveness of therapy in newly diagnosed acromegaly by longitudinally reassessing

galectin-3 levels and CF-PWV in both treated and untreated groups.

Conclusion

Timely identification and therapy of acromegaly and its associated comorbidities can halt the advance of cardiac dysfunction and lower cardiovascular-associated mortality and morbidity. In this framework, galectin-3 could serve as both a novel therapeutic target and a biomarker for CVD detection and prognostication. Quantifying galectin-3 in acromegaly patients may help identify early atherosclerotic changes and estimate impending cardiovascular risk.

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