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ORIGINAL ARTICLE

Validity of galactin-3 in acromegaly: comparison with traditional markers

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Abstract

Background Acromegaly occurs due to overproduction of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Galectin-3 (Gal-3) has recently emerged as a novel biomarker, related to IGF-1. This study aimed to assess Gal-3 in patients with acromegaly and compare its effectiveness with traditional biomarker tests**.**

Materials and methods A randomized case control study conducted in a single center included 50 acromegaly patients and 40 apparently healthy subjects (HS) serve as control group matched both age and BMI. Laboratory test was measured by routine assay used in center. Gal-3, GH, and IGF-1 were measured by enzyme-linked immunosorbent assay (ELISA).

Result There were 50 patients with an average age of 50.40 ± 12.229 (50% of males). Compared with HS, patients' serum GAL-3 levels have increased significantly. The serum GAL-3 exceeds 14.363 ng/ml, with a sensitivity of 100.0 and a specificity of 100.0. Furthermore, serum Gal-3 levels in combination with traditional tests (GH and IGF-1) by DeLoongs test had a significant difference in discriminating acromegaly more accurately than traditional tests.

Conclusion In a summary, this study recommended clinicians measure serum Gal-3 as biomarkers for patients with acromegaly. In addition, the result above shed light on role of Gal-3 on acromegaly pathogenesis and might provide a therapeutic target of acromegaly patients.

Keywords Acromegaly · Cardiovascular · Galectin-3 · Growth hormone · IGF-1 · Pituitary adenoma

Introduction

Acromegaly is a rare condition (0.2–1.1 cases/100,000 people per year). Mostly, it is caused by pituitary adenoma with excessive production of growth hormone (GH) and subsequent insulin-like growth factor-1 (IGF-1) [1]. Cardiovascular, diabetes mellitus (DM), and hypertension diseases all are public in acromegaly and contribute to increased risk of mortality [2]. The disease can be diagnosed and monitored depending on clinical signs and symptoms, in addition to the biochemical assessments [3]. Important factors such as body mass index (BMI), malnutrition, DM, renal, and liver disease can affect the secretion and action of GH and IGF-1 [4]. The complex diagnostic methods for patients with acromegaly and discrepancies between GH and IGF-1 levels may lead to delay in the diagnosis or difficulty in adjustment of treatment. In addition to the lack of studies to find an accurate diagnostic biomarker for the disease, galectin-3 (Gal-3) was evaluated for patients with acromegaly in this study. Galectin-3 is a part of the galectin family, which are β-galactosids-binding lectins with more than or equal one evolutionary preserved carbohydrate recognition domain. It binds proteins in a carbohydrate dependent. It is included in the regulation of numerous physiological cellular functions, like cellular growth, proliferation, apoptosis, differentiation, cellular adhesion, and tissue repair [5]. Gal-3 play a main role in the pathological remodeling of the myocardium in response to heart injury, chronic stress, or inflammation, which then leads to myocardial fibrosis, atrial fibrillation, and heart failure. In addition, Gal-3 is in the list of validated cardiovascular (CVD) biomarkers [6, 7]. Other studies indicate that there is an interaction between Gal-3 and IGF-1[8, 9]. Recent studies have revealed the high prevalence of CVD in acromegaly patients due to effect of GH and IGf-1 excess on the cardiac

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morphology and function in different mechanisms [10, 11]. Taken all above together, this study aimed to compare Gal-3 levels with two conventional biomarkers used for the diagnosis of acromegaly, GH, and IGF-I.

Materials and methods

Study design

In this single center, a randomized case control study was performed in the National Diabetes Center/Mustansiriyah University between August and October, 2023, 50 patients who were previously diagnosis to have acromegaly more than 5 years based on the endocrine society clinical practice guideline [12], aged between 20 and 55 years were included. Moreover, 43 apparently healthy subjects (HS) matched both age and BMI with no history of pituitary disease or other inflammatory diseases and normal for biochemical tests serve as controls group. Subjects with active malignancies, inflammatory comorbidities, or use of systemic immune-suppressive medication were excluded, all of which were anchored in the systematic questionnaire. All patients had a history of radiologically and biochemically established active acromegaly.

Ethical approval

The study was performed in accordance with the Declaration of Helsinki (2013) and approved by our local ethical committee in Mustansirayh University/National Diabetes Center. All participants informed written agreement to enroll in this study.

Collection of blood sample and laboratory analysis

Blood samples were collected from all subjects who full filled the inclusion criteria between 8 and 10 am after at least 8 h overnight fasting. Samples were centrifuged at 3000 rpm for 10 min, and serum was divided into aliquots and stored at – 70 °C until analysis. IGF-1 and GH levels were measured with commercial ELISA tests kits (DRG-USA) according to the manufacturer's instruction. Furthermore, a sandwich enzyme immunoassay kit (ELISA) was used to quantify human Gal-3 in vitro at my BioSource, USA, by ELISA plate reader (Human Reader, Germany). Other biochemical test (FBG, lipid profile) was determined using an automated chemical analyzer standard of the relevant Diabetic National Center.

Statistical analysis

Normality assumption of the variables were examined by Shapiro–Wilk and the Kolmogrorov-Smirnov tests. All variables are presented using mean and standard division (SD). For comparisons between different groups were analyses by parametric independent *t*-test. The predictive value of serum Gal-3 was evaluated by measuring the area under the receiving operating characteristic curve (AUC). Also using DeLong et al. test for correlated ROC curve [13, 14]. The optimal threshold value was obtained by calculating the Youden index [15]. SSPS (version 24), GraphPad Prism (version 8), and Medcalc (version 20.027) performed all analysis.

Result

Subject characteristic

There are 50 patients ((50.40 ± 12.229), 50% of male), and 43 HS with similar ages and gender distribution. As shown in Table 1, the BMI of patients with acromegaly is higher than HS ($P = 0.001$).

Biochemical and traditional biomarkers tests

Fasting blood glucose (FBG) and lipid profile were remarkably higher in acromegaly patients compared to HS ($P = 0.001$ for each). The traditional biomarkers GH and IGF-1 were remarkably higher in the acromegaly patients than HS ($P = 0.001$). Table 1 shows the comparative results for laboratory tests belonging to the groups.

Serum galectin-3 in study groups

The levels of Gal-3 were significantly elevated in acromegaly patients when compared to age-matched HS [41.87 ± 9.074, 11.90 ± 1.324 ng/ml], respectively, at $P = 0.0001$, as shown in Fig. 1.

Receiving operating characteristic curve (ROC)

To assess the ability of Gal-3 levels to discriminate between acromegaly patients and HS, ROC curve was plotted (Fig. 2A). Gal-3 serum levels revealed AUC of 1.00 (95% CI 92.9–100.0 $P = 0.001$) and cut off value (Youdens index) of less than 14.363 ng/ml with sensitivity 100.0 and specificity 100.0, as shown in Table 2.

Table 3 and Fig. 2B show the combined prediction of Gal-3 with traditional tests (GH and IGF-1) using DeLoongs test for correlated ROC curves. As there was significant difference

Table 1 Demographics feature and laboratory test of study groups

Parameters	Acromegaly ($n=50$)	HS ($n=43$)	*P*-value
Subject characteristic			
Age (year)	50.40 ± 12.229	50.03 ± 6.154	0.621
Sex	25 (50%)	18 (41.86%)	
Female, *n* (%)	25 (50%)	25 (58.14%)	
Male, *n* (%)			
BMI (kg/m2)	33.60 ± 3.494	24.28 ± 1.005	0.001
Duration (year)	9.14 ± 2.392	——	
Biochemical and traditional biomarkers test			
FBG (mg/dl)	134.18 ± 28.977	92.20 ± 10.613	0.001
VLDL (mg/dl)	26.80 ± 4.390	16.85 ± 2.732	0.002
LDL (mg/dl)	89.94 ± 7.555	75.95 ± 19.826	0.001
HDL (mg/dl)	40.46 ± 11.214	47.15 ± 1.902	0.001
Triglycerides (mg/dl)	132.04 ± 7 0.984	84.05 ± 13.548	0.001
Cholesterol (mg/dl)	162.80 ± 37.027	139.93 ± 20.414	0.002
IGF-1 (ng/ml)	489.14 ± 83.845	309.20 ± 37.230	0.001
GH(mg/m^2)	5.05 ± 0.3	1.35 ± 0.02	0.001

All data represents by mean ± SD or no. (percentage)

$P \leq 0.05$ is significant

between Gal-3 and GH, IGF at $P=0.0001$ for each, differences between areas are 0.209 and 0.248, respectivly.

Discussion

Acromegaly is a multi-organ disease caused by excessive production of GH. As mentioned above GH and IGF-1 have numerous immunological, metabolic, and CDV effects [10]. The high prevalence of CDV disturbances in acromegaly patients [16, 17], and Gal-3 is listed as biomarker of CDV. Patients with conflicting biochemical data from GH and IGF-I have provided special diagnostic and monitoring challenges for acromegaly.

Serum levels of GH and IGF-I are used as biomarkers in the diagnosis of acromegaly, but they have not yet undergone systematic validation [3, 18]. Therefore, reevaluation of the novel biomarker Gal-3 is a substitute for reliable biochemicals in the diagnosis of acromegaly. To date there are limited reports of biomarker assays in this disease; therefore, our study aimed to estimate the role of GAL-3 in the diagnosis and monitoring of the disease in patients with acromegaly and compare with traditional tests. In this

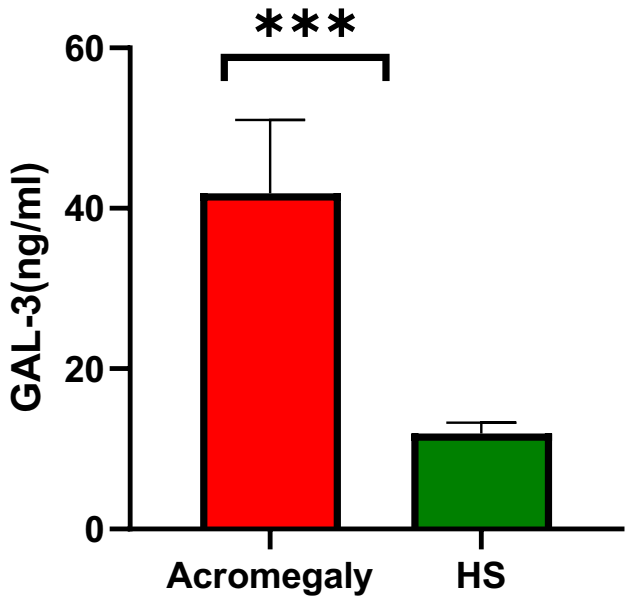

Fig. 1 Comparison of Gal-3 in acromegaly patients and HS groups

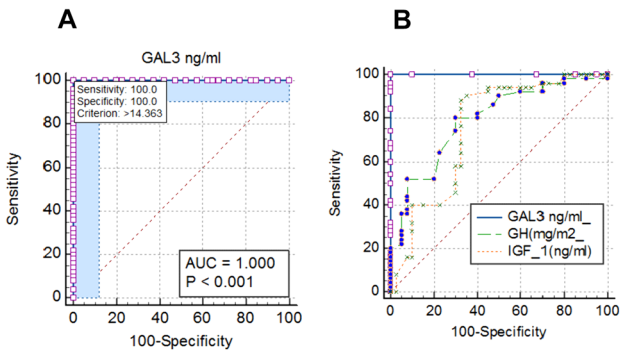

Fig. 2 **A** ROC curves for serum Gal-3 discriminating the acromegaly from HS. **B** The comparison predicted of Gal-3 serum levels and traditional tests

Table 2 AUC and the validity of Gal-3 to discriminants between acromegaly and HS groups

Cut-off	Sensitivity	Specificity	+ LR	− LR	+ PV	− PV	*P*-value
> 14.363	100.00	100.00	-	0.00	100.0	100.0	0.0001

LR likelihood ratio, + *PV* positive predictive value, − *PV* negative predictive value

Table 3 Comparison between Gal-3 and traditional tests to determine the discrimination power of each biomarkers using DeLong et al. test for correlated ROC curve

Difference between areas	SE	95% CI	*z* statistic	Significance level
Gal-3 (ng/ml)–GH (mg/m^2)				
0.209	0.0478	0.116 to 0.303	4.380	$P < 0.0001$
Gal-3 (ng/ml)–IGF-1 (ng/ml)				
0.248	0.0556	0.139 to 0.357	4.460	$P < 0.0001$
GH (mg/m^2)–IGF-1 (ng/ml)_				
0.0388	0.0656	− 0.0898 to 0.167	0.591	$P = 0.5547$

SE standard error, *95% CI* 95% confidence interval

study, we found serum Gal-3 concentration is remarkably increased in patients with acromegaly. This is consistent with the only recent study that dealt with measuring the biomarker and comparing it with the pulse wave velocity in acromegaly patients [19–21]. The Gal-3 is involved in inflammation and fibrosis in different diseases impacting vital organs such as the heart, liver, kidney, lungs, and the brain [22]. The main cell types implicated in Gal-3-driven disease processes are myofibroblasts, epithelial cells, endothelial cells, and macrophages. Gal-3 is a potential biomarker for the early stages of several of diseases, even though it is not a disease-specific marker per se [23].

The traditional biomarkers of acromegaly show significant increase in acromegaly patients compared to HS. Similar results were reported by Farhan LO et al. [24], and Hepşen S [1]. The FBG and lipid profile show significant increase in acromegaly patients and this agreed with previous study [21, 25].

In this study the validity of Gal-3 was evaluated by ROC curve which revealed that serum Gal-3 have AUC 1.00 with sensitivity 100.0 and specificity 100.0 specific for diagnosis acromegaly. Moreover, when compare Gal-3 serum levels with traditional tests (GH and IGF-1) by DeLoongs test for correlated ROC curves show significant difference to discriminate acromegaly more accurate than traditional tests. In addition, this conclude that GAL-3 is a biomarker particularly sensitive to excess growth hormone.

There are certain limitations as the study was conducted at a single center. The number of patients, particularly serve ones, were relatively small to draw clear conclusion. In addition, given the rarity of acromegaly, the small sample size of the patients might be acceptable.

In order to prevent bias, we also used strict exclusion criteria and eliminated all patients who had renal failure, heart disease, or any inflammatory condition.

Conclusion and future directions

This study revealed that the Gal-3 is a new and effective prediction biomarker for patients with acromegaly compared with traditional tests. It may play a role in monitoring acromegaly. Gal-3 is a promising biomarker to diagnose acromegaly with high sensitivity and specificity. Its close association with GH secretory status and status make it a helpful tool, particularly in cases where measurements of GH and IGF-I provide discrepant information.

However, a larger study is needed to confirm these findings particularly in newly diagnosed acromegaly particularly those with CVD. Prospective studies should look into whether this can be used to enhance long-term outcome prediction.

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Author contribution All authors contributed equally in the design and conception of the study. Maryam Thaer Saadi and Baydaa Ahmed Abed carried out the experiment. Noor Ulhuda G. Mohammed wrote the manuscript. Layla Othman Farhan and Isam Noori Salman helped supervise the project. All authors reviewed the manuscript and approved the final manuscript.

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Data availability The datasets generated and analyzed during the study are available per request from the corresponding author.

Declarations

Consent for publication It has been taken informed consent from volunteers for this study.

Competing interests The authors declare no competing interests.

References

1. Hepşen S, Akhanli P, Düğer H et al (2021) Fatty acid-binding protein-4 as a biomarker predicting acromegaly-associated diabetesmellitus. Turkish J Med Sci 51:2592–2599
2. Mercado M, Ramírez-Rentería C (2018) Metabolic complications of acromegaly. Metab Syndr Consequent to Endocr Disord 49:20–28
3. Peixe C, Sánchez-García M, Grossman AB et al (2022) Biochemical discrepancies in the evaluation of the somatotroph axis: elevated GH or IGF-1 levels do not always diagnose acromegaly. Growth Horm IGF Res 64:101467
4. Witkowska-Sędek E, Pyrżak B (2020) Chronic inflammation and the growth hormone/insulin-like growth factor-1 axis. Cent Eur J Immunol 45:469–475
5. Hara A, Niwa M, Noguchi K et al (2020) Galectin-3 as a next-generation biomarker for detecting early stage of various diseases. Biomolecules 10:389
6. de Boer RA, Daniels LB, Maisel AS, Januzzi JL Jr (2015) State of the art: newer biomarkers in heart failure. Eur J Heart Fail 17:559–569
7. Bouffette S, Botez I, De Ceuninck F (2023) Targeting galectin-3 in inflammatory and fibrotic diseases. Trends Pharmacol Sci 44:519–531. https://doi.org/10.1016/j.tips.2023.06.001
8. Zhou Z, Feng Z, Sun X et al (2023) The role of galectin-3 in retinal degeneration and other ocular diseases: a potential novel biomarker and therapeutic target. Int J Mol Sci 24:15516
9. Lalancette-Hébert M, Swarup V, Beaulieu JM et al (2012) Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. J Neurosci 32:10383–10395
10. Wolters TLC, van der Heijden C, Pinzariu O et al (2021) The association between treatment and systemic inflammation in acromegaly. Growth Horm IGF Res 57:101391
11. Rivera FB, Taliño MK, Ansay MF et al (2023) Cardiovascular effects of excess growth hormone: how real is the threat? 24:95. https://doi.org/10.31083/j.rcm2404095
12. Katznelson L, Laws ER Jr, Melmed S et al (2014) Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 99:3933–3951
13. Liang H, Li X, Lin X et al (2021) The correlation between nutrition and frailty and the receiver operating characteristic curve of different nutritional indexes for frailty. BMC Geriatr 21:1–7
14. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845
15. Mohammed NUG, Khaleel FM, Gorial FI (2022) The role of serum chitinase-3-like 1 protein (YKL-40) level and its correlation with proinflammatory cytokine in patients with rheumatoid arthritis. Baghdad Sci J 19:1014. https://doi.org/10.21123/bsj.2022.6293
16. Colao A, Pivonello C, Grasso LFS, Pirchio R (2022) Acromegaly BT - Endocrine Pathology. In: La Rosa S, Uccella S (eds) Springer International Publishing, Cham, pp 9–11. https://doi.org/10.1007/978-3-030-62345-6_5098
17. Rolla M, Jawiarczyk-Przybyłowska A, Halupczok-Żyła J et al (2021) Complications and comorbidities of acromegaly—retrospective study in Polish center. Front Endocrinol (Lausanne) 12:642131
18. Kashtl GJ, Abed BA, Farhan LO et al (2023) A comparative study to determine LDH enzyme levels in serum samples of women with breast cancer and women with breast cancer and type 2 diabetes mellitus. J Med Chem Sci 6:883–890. https://doi.org/10.26655/JMCHEMSCI.2023.4.20
19. Abed BA, Hamid GS (2022) Evaluation of lipocalin-2 and vaspin levels in in Iraqi women with type 2 diabetes mellitus. Iraqi J Sci 63(11):4650–4658. https://doi.org/10.24996/ijs.2022.63.11.3
20. Ozturk HA, Sumbul HE (2023) The relationship between serum galectin-3 level and carotid femoral pulse wave velocity in patients with acromegaly. J Hypertens 41:e98
21. Mehde AA, Yusof F, Mezal SA et al (2015) Study the effect of increased levels of lead on sera alpha amylase activity, and some biochemical parameters from a large private electrical generators workers. Adv Environ Biol 9:163–168
22. Farhan LO, Abed BA, Dawood A (2023) Comparison study between adipsin levels in sera of Iraqi patients with diabetes and neuropathy. Baghdad Sci J 20:726
23. Szczepanek-Parulska E, Sokolowski J, Dmowska D et al (2022) Lipid profile abnormalities associated with endocrine disorders. Endokrynol Pol 73:863–871
24. Farhan LO, Abed BA, Salman IN (2023) Insulin like growth factor binding protein 7 as a novel diagnostic marker in sera of Iraqi patients with acromegaly. Baghdad Sci J 20:979
25. Newman CB (2023) Effects of endocrine disorders on lipids and lipoproteins. Best Pract Res Clin Endocrinol Metab 37:101667