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► **To cite this version:**

Peter Wolf, Luigi Maione, Peter Kamenický, Philippe Chanson. Acromegalic Cardiomyopathy: An Entity on its own? The Effects of GH and IGF-I Excess and Treatment on Cardiovascular Risk Factors. Archives of Medical Research, 2023, 54, 10.1016/j.arcmed.2023.102921 . hal-04503406

HAL Id: hal-04503406

<https://hal.science/hal-04503406>

Submitted on 13 Mar 2024

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REVIEW ARTICLE

Acromegalic Cardiomyopathy: An Entity on its own? The Effects of GH and IGF-I Excess and Treatment on Cardiovascular Risk Factors

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Received for publication August 10, 2023; accepted November 15, 2023 (ARCMED-D-23-00657).

Acromegaly is a chronic disease resulting from constantly elevated concentrations of growth hormone (GH) and insulin-like growth factor I (IGF-I). If not adequately treated, GH and IGF-I excess is associated with various cardiovascular risk factors. These symptoms mainly include hypertension and impaired glucose metabolism, which can be observed in approximately one-third of patients. Other comorbidities are dyslipidemia and the presence of obstructive sleep apnea syndrome.

However, even in the absence of conventional cardiovascular risk factors, myocardial hypertrophy can occur, which reflects the impact of GH and IGF-I excess itself on the myocardium and is defined as acromegalic cardiomyopathy. Whereas previous echocardiography-based studies reported a high prevalence of cardiomyopathy, this prevalence is much lower in cardiac magnetic resonance imaging-based studies. Myocardial hypertrophy in acromegaly is due to a homogeneous increase in the intracellular myocardial mass and extracellular myocardial matrix and improves following successful treatment through intracellular changes. Intramyocardial water retention or ectopic lipid accumulation might not be of relevant concern.

Successful treatment significantly improves myocardial morphology, as well as cardiovascular risk factors. In addition to GH/IGF-I-lowering therapy, the diagnosis and treatment of cardiovascular complications is crucial for the successful management of acromegaly. © 2023 Instituto Mexicano del Seguro Social (IMSS). Published by Elsevier Inc. All rights reserved.

Keywords: Acromegaly, Growth hormone, Insulin-like growth factor I, IGF-I, Myocardial hypertrophy, Cardiomyopathy, Pituitary.

Introduction

Acromegaly results from constantly elevated concentrations of growth hormone (GH) and insulin-like growth factor I (IGF-I) due to a somatotroph pituitary adenoma in almost all cases (1). If not adequately treated, GH and IGF-I excess is associated with increased morbidity and mortality. Systemic complications in acromegaly include cardiovascular disease, metabolic complications, res-

piratory complications, osteoarthropathy, perhaps an increased risk of colon neoplasia, and decreased quality of life (2,3). Cardiovascular complications have long been considered the main cause of death (4). However, recent advances in acromegaly treatment and in the management of cardiovascular risk factors, such as arterial hypertension or diabetes, have largely decreased the severity of cardiovascular involvement in acromegaly patients.

In this review, we will provide an overview of the current knowledge on cardiovascular comorbidities in patients with acromegaly, focusing on cardiomyopathy. We will summarize the effects of increased GH and IGF-I

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concentrations on conventional cardiovascular risk factors and discuss the impact of treatment.

Materials and Methods

Original studies, reviews and case reports on acromegaly and cardiovascular diseases have been searched in PUBMED databases. The most relevant articles were chosen for the narrative literature review. A rigorous review of the publications was performed to summarize the main information on cardiovascular outcomes as a consequence of acromegaly.

Results

Cardiovascular Risk Factors in Acromegaly

Chronically elevated concentrations of GH and IGF-I in individuals with untreated acromegaly are associated with arterial hypertension, dyslipidemia, insulin resistance or diabetes mellitus (5–7), which are well-known risk factors for the development of cardiovascular disease. However, despite significantly higher Framingham risk scores in patients with acromegaly (8), the risk of overt coronary artery disease or cerebrovascular disease seems similar to that in the general population. Recent studies systematically performing coronary CT scans in patients with acromegaly showed only a low prevalence of coronary heart disease, as well as no evidence of major cardiovascular events during follow-up (9–11). This is in line with results from the German acromegaly registry, which reported comparable incidences of myocardial infarction and stroke in patients with acromegaly and in the general population (12).

The discrepancy between the theoretically increased cardiovascular risk according to well-established scores validated in the general population (13) and the comparable incidence of overt cardiovascular diseases in patients and control cohorts might best be explained by the disease-specific pathophysiologic background.

According to several national or international multicenter registries, arterial hypertension can be observed in about one third of acromegalic patients (14) and might play an important role in aggravating the cardiovascular risk (15).

Arterial hypertension is mainly due to the increase in plasma volume (16,17). We have previously shown that GH and IGF-I both exert a direct antinatriuretic action in the distal nephron by stimulating epithelial sodium channel (ENaC)-dependent sodium reabsorption (18–20). An indirect action of GH/IGF-I *via* the stimulation of the renin-angiotensin-aldosterone system, which is in control of the hormonal fine regulation of sodium homeostasis in the distal tubule, does not seem plausible (20). In addition to the water retaining effects, other systemic complications of acromegaly such as insulin resistance and obstructive sleep apnea syndrome (OSAS) participate in the pathogenesis of high blood pressure (5).

With regards to other metabolic *sequelae* of GH and IGF-I excess, patients with acromegaly exhibit a unique, disease-specific profile of severe insulin resistance and dyslipidemia despite reduced visceral and ectopic fat mass (21–24). The metabolic effects of GH include anabolic actions on muscle and bone and catabolic actions on adipose tissue (25–27). GH counteracts the suppressive effects of insulin on gluconeogenesis and stimulates endogenous glucose production (24,25). Furthermore, GH strongly stimulates lipolysis in adipose tissue, which results in increased concentrations of circulating nonesterified fatty acids and is followed by lipid-induced peripheral insulin resistance and impaired glucose disposal in skeletal muscle (28). In addition, beta cell dysfunction is frequently observed in a state of GH and IGF-I excess, resulting in a failure to cope with the increased needs for insulin secretion due to severe insulin resistance (29). Therefore, impaired glucose tolerance and diabetes are highly prevalent in patients with acromegaly. At the time of acromegaly diagnosis, 20–40% of patients have an increase in fasting glucose values and between 12 and 35% are diagnosed with diabetes mellitus (30).

Lipid abnormalities in patients with acromegaly include mainly hypertriglyceridemia and reduced HDL cholesterol concentrations (31). Furthermore, a pro-inflammatory state in adipose tissue has recently been described, characterized by the increased expression of adipokines and cytokines (32,33).

Finally, OSAS is highly prevalent in active acromegaly (34–36) and may contribute to increased cardiovascular risk. Morphological changes following long-term GH and IGF-I excess, i.e., skeletal deformities of the mandibular bone, pharyngeal and tongue modifications, as well as soft-tissue thickening due to increased glycosaminoglycan deposition and tissue edema, are the two major determinants of OSAS in acromegaly (37). Intermittent episodes of hypoxemia in OSAS promote sympathetic activation, inflammation, hypercoagulability and endothelial dysfunction, increasing the risk for hypertension and atherosclerosis (38). Successful treatment of acromegaly improves the results of polysomnography in some but not all patients (39,40).

Acromegalic Cardiomyopathy

Acromegalic cardiomyopathy is defined as the presence of morphological and functional changes in the absence of other risk factors. Myocardial hypertrophy can occur in the absence of hypertension and even in young patients, which reflects the impact of GH and IGF-I excess itself on the myocardium (41,42).

With regard to epidemiologic evidence, previous echocardiography-based studies reported a high prevalence of hypertrophy ranging from 11% to up to 80% of patients with acromegaly (43). This wide range might best

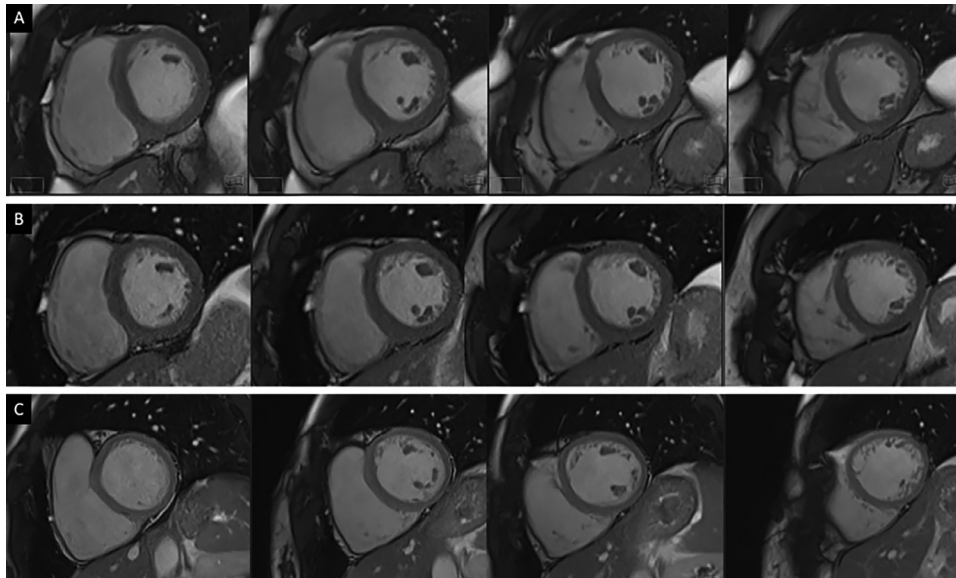


Figure 1. Example of cardiac MRI in short axis SSFP cine views from base to apex in a 50 years old patient with acromegaly at baseline (row A: LV mass index 100g/m²) and follow-up after treatment (row B: LV mass index = 81g/m²) compared to a healthy control (row C: LV mass index = 40g/m²).

be explained by methodological limitations of transthoracic ultrasound, since the measurement of volumes and mass by 2D echocardiography requires assumptions to be made concerning ventricular geometry, which introduces a source of inaccuracy (44). In addition, central obesity and thoracic kyphosis result in suboptimal image quality and off-axis images, limiting the precision of echo-based calculations of ventricular mass and volumes. In contrast, cardiac magnetic resonance imaging (MRI) provides a highly accurate and reproducible assessment of cardiac geometry and function (Figure 1). Studies using cardiac MRI have recently reported a much lower frequency of hypertrophy of only 5–24% (45,46).

The main feature of cardiomyopathy in acromegaly is myocardial hypertrophy. This concentric hypertrophy of the interventricular septum and the posterior wall of the left ventricle is due to an increase in the size of cardiac myocytes through the apposition of new sarcomeres (47,48). The receptors for GH and IGF-I are both expressed in cardiomyocytes, supporting direct anabolic effects on the myocardium (2). Stimulation of neonatal rat cardiomyocytes with IGF-I, but not with GH, induced hypertrophy and the generation of sarcomeres and myofibrils (49). Furthermore, a positive inotropic action of IGF-I by increased Ca²⁺ sensitivity was reported (50). Increased pre- and afterload and arterial hypertension due to sodium and water retention additionally contribute to the ventricular volume extension and its hypertrophic remodeling in acromegaly (20,51).

Of note, we recently showed that the increase in left ventricular mass in patients with acromegaly is due to a homogeneous increase in the intracellular myocardial mass and extracellular myocardial matrix and improves following successful treatment through intracellular changes;

these latter changes are mainly related to a decrease in systolic blood pressure (46). This disease-specific distribution is different from observations in patients with essential hypertension and highlights the direct impact of GH and IGF-I on the heart. GH strongly correlates with left ventricular mass, and the presence of acromegaly is a strong and independent predictor of myocardial hypertrophy (46).

With regard to myocardial edema, which might be due to the abovementioned anti-natriuretic effects of GH and IGF-I, we did not observe differences in T2-weighted sequences as a surrogate of tissue water content (46), in contrast to a single previous study (52). This suggests against myocardial water retention in active acromegaly as an explanation for increased extracellular mass. Another possible explanation for myocardial hypertrophy might be excessive ectopic lipid deposition in the cardiomyocytes, since at least in the general population, insulin resistance and type 2 diabetes, both frequently present in acromegaly patients, are closely linked to cardiac steatosis (53). However, the ectopic fat and epicardial fat content are even lower in acromegaly patients than in controls, which might be explained by direct tissue specific effects of GH on lipolysis, lipid synthesis or beta oxidation (54).

Systolic function is normal in the majority of patients. In early stages, systolic performance can even be increased, related to the positive inotropic effects of GH and/or IGF-I (55). Overt systolic dysfunction with congestive heart failure is currently rare, encountered in less than 3% of patients (56,57). It may develop in patients with severe uncontrolled GH hypersecretion with other concomitant and insufficiently treated risk factors, such as diabetes, arterial hypertension, and sleep apnea. Functional signs first appear on effort before becoming permanent.

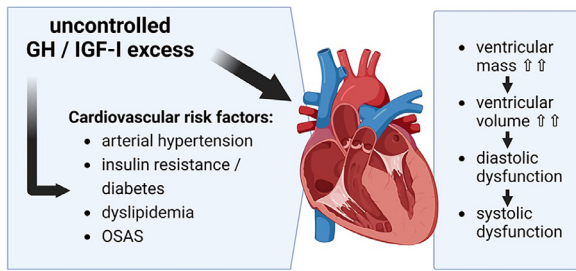


Figure 2. Illustration of the effects of uncontrolled GH and IGF-I excess directly on the heart, as well as on cardiovascular risk factors, which contribute to the development of cardiomyopathy in patients with acromegaly.

Diastolic dysfunction can be observed in the absence of left ventricular hypertrophy and seems to be related to acromegalic disease activity (58). Impaired diastolic function occurs on the background of impaired relaxation and wall rigidity of the left and right ventricles (59,60). The direct effects of excess GH and IGF-I on the heart, as well as indirect effects via cardiovascular risk factors, are illustrated in Figure 2.

In addition to these morphological and functional changes, cardiac valve disorders are common in patients with active acromegaly and mainly include aortic or mitral regurgitation (61). The risk of valve disease increases with disease duration (62). Cardiac valve abnormalities may be related to fibrotic changes but may also be secondary to ventricular hypertrophy and volume overload and seem to persist after effective treatment of acromegaly (63). Similar to patients treated with cabergoline for prolactinoma (64,65), no cabergoline-induced cardiac valve remodeling was observed in acromegaly patients (66).

A recent South Korean nationwide cohort study reported an increased risk of arterial fibrillation in patients with acromegaly compared to matched controls (67). However, consistent with the low frequency of structural changes in the myocardium reported by recent studies, no clinically significant arrhythmias were reported in patients with active acromegaly using 24 h Holter-EKG monitoring in prospectively performed trials (40,68–70). Due to the small sample size of these prospective trials, further investigations might be warranted to clarify whether cardiac arrhythmias are a relevant clinical problem.

The Effects of Acromegaly Treatment on Cardiovascular Comorbidities

Successful treatment of acromegaly significantly improves myocardial morphology. In our cohort, a significant reduction in left and right ventricular mass and volume, assessed by cardiac MRI, could be observed following biochemical disease control (45,46). These improvements following the normalization of GH/IGF-I can be observed independently of the type of treatment. Improvements in ventricular mass can be observed in patients treated by pituitary surgery

alone in short- and long-term follow-up (71,72) but also in patients whose acromegaly is medically controlled by somatostatin-receptor ligand therapy (73) or the GH receptor antagonist pegvisomant (74,75).

Younger patients and patients with a shorter history of acromegaly show better “recovery” from diastolic disorders, myocardial hypertrophy or subclinical systolic dysfunction (74,76). In contrast, when clinically symptomatic, dilatative congestive heart failure is present, systolic function might show a short-term improvement (77), but the longer-term prognosis is worse than that of patients with heart failure due to other causes (56,57). However, currently, the presence of symptomatic heart failure with reduced left ventricular ejection fraction is rare and restricted to case reports (78,79) likely due to advancements in medical treatments in past decades for disease control per se but also due to the improved treatment of concomitant comorbidities. Therefore, the prognostic validity of estimations of long-term survival based on older studies is rather limited.

In addition to the direct effects of biochemical disease control on the heart, cardiovascular risk factors also improve following successful treatment of acromegaly (80).

A substantial improvement in or even a remission of arterial hypertension can be observed in some patients (81). However, a large longitudinal retrospective cohort study in patients with acromegaly did not find differences in the prevalence of hypertension at the time of diagnosis compared to follow-up (82). This lack of significant differences could be explained by the effects of aging or by changes in concomitant antihypertensive medication, which are difficult to control for in retrospective studies. Patients with uncontrolled acromegaly have a sixfold higher risk of arterial hypertension than patients cured after pituitary surgery (15). Patients achieving remission after surgery show a significant decrease in systolic blood pressure (83) and a significant improvement in 24 h ambulatory blood pressure monitoring (84). With regard to the effects of medical treatment, studies investigating changes in blood pressure following biochemical disease control with first-generation somatostatin receptor ligands (SRLs) show conflicting results. Significant improvements in a longitudinal follow-up of five years were reported by some authors (85,86), whereas a large meta-analysis did not find any changes (73). Similarly, in patients treated with the GH receptor antagonist pegvisomant, some studies have reported a significant improvement in systolic and diastolic blood pressure, especially in those with a normalization of IGF-I (8), whereas other studies have not found any differences during follow-up (87). To date, there are no data on the effects of cabergoline or the second-generation SRL pasireotide on blood pressure.

In patients with acromegaly and increased blood pressure, antihypertensive drugs should therefore be used as in essential hypertension. There is not enough evidence to support the use of a particular type of antihypertensive

drug for the treatment of arterial hypertension in patients with acromegaly. However, given the high prevalence of ventricular hypertrophy and impaired glucose metabolism, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be the first-line treatment (5). The sodium overload contributing to arterial hypertension in acromegaly might, in theory, be efficiently prevented by the administration of the ENaC blocker amiloride (51).

With regard to diabetes, impaired glucose tolerance is strongly related to disease activity (88) and substantially improves following successful treatment of GH and IGF-I excess (27). Interestingly, despite the detrimental role of lipid-induced insulin resistance in the pathogenesis of impaired glucose tolerance in acromegaly, the preservation of beta cell function might be crucial for recovery following GH- and IGF-I-lowering therapy (89). Changes in metabolic parameters vary according to the type of acromegaly treatment. Whereas pituitary surgery (89,90), treatment with the GH receptor antagonist pegvisomant (91–93) and dopamine agonist treatment (94,95) all improve insulin sensitivity, glucose metabolism may improve or worsen when patients are treated with first-generation somatostatin receptor ligands (SRLs), octreotide and lanreotide (96–99). Pasireotide treatment is frequently associated with impairments of glucose metabolism due to the antagonistic effects on beta cells resulting in impaired insulin secretion, despite its effectiveness in disease control of acromegaly (100).

Similar to hypertension, there is insufficient evidence to recommend a particular treatment strategy, given the lack of randomized controlled prospective studies. However, antidiabetic drugs with proven cardiovascular benefit, which target insulin resistance, i.e., metformin or GLP-1 receptor agonists, appear to be a logical first choice and should be used in a stepwise approach similar to the treatment of conventional type 2 diabetes mellitus (101). Given their natriuretic/diuretic effects, sodium-glucose cotransport-2 (SGLT-2) inhibitors might also be of special interest in acromegalic patients (102). Additionally, the concomitant increase in ketone bodies and decrease in insulin levels associated with SGLT-2 inhibitor treatment (103) might lead to a downregulation of hepatic GH receptor expression and thereby reduce IGF-I levels (104). Of note, given the strong lipolytic effects of GH, the risk of (euglycemic) diabetic ketoacidosis might be increased in patients with uncontrolled acromegaly (105), although the risk has been reported to be very low in recent case series (106). The use of glitazones should be restricted to selected patients because of its side effects on water retention and worsening of heart failure (107). Insulin is the treatment of choice in severe cases (108).

Dyslipidemia in acromegaly does not routinely require a specific medical treatment, but disease control following pituitary surgery results in an improved lipid profile characterized by decreased levels of LDL cholesterol and

triglyceride and increased levels of HDL cholesterol (109). Similarly, medical treatment by first generation SRL increased HDL cholesterol and decreased triglyceride levels in retrospective studies (110). Finally, when OSAS persists after biochemical disease control, a specific therapy such as continuous positive airway pressure is recommended (37,111).

Conclusions

GH and IGF-I excess are associated with numerous cardiovascular risk factors, but also exert direct effects on the heart. Whereas cardiovascular complications have long been considered the main cause of death, recent advances in GH/IGF-I lowering treatment combined with the increased awareness for optimized management of cardiovascular risk factors have largely improved the severity of cardiovascular involvement in acromegaly patients. Accordingly, recent studies using state of the art cardiac magnetic resonance imaging techniques observed much lower frequencies of myocardial hypertrophy and cardiomyopathy compared to previous reports. Disease specific, but most often “subclinical”, changes in myocardial tissue characteristics in follow up after successful acromegaly treatment highlight the direct effects of GH/IGF-I on the myocardium.

Acknowledgments

We thank Khaoula Bouazizi, Nadija Kachenoura and Alban Redheuil for their help in creating [Figure 1](#). [Figure 2](#) was designed by using [biorender.com](#). Peter Wolf was supported by a grant (KLI 1015-B) from the [Austrian Science Fund](#) (FWF).

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