










Acromegaly and cardiovascular disease: mechanisms, clinical impact, and evolving management

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Abstract

Cardiovascular disease is one of the most common and serious complications of acromegaly and a leading contributor to reduced life expectancy in affected individuals. This review examines the prevalence, mechanisms, diagnosis, and management of cardiovascular complications in patients with acromegaly. Growth hormone and insulin-like growth factor 1 excess promotes a range of cardiovascular disturbances, including structural heart changes, arrhythmias, vascular dysfunction, and an increased burden of traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia. Early recognition and targeted treatment of these complications are critical to reducing cardiovascular morbidity and mortality. While surgery and medical therapies for acromegaly aimed at normalizing hormone levels may lead to partial or full reversal of some cardiovascular alterations, many patients require continued management of comorbid conditions to control their overall cardiometabolic risk. Advances in diagnostic strategies and therapeutic options have contributed to improved survival, yet gaps remain in our understanding of how best to prevent or reverse cardiovascular damage in this population. Multidisciplinary care and individualized risk assessment are essential components of modern acromegaly management.

Keywords acromegaly, growth hormone, cardiovascular disease, cardiovascular risk factors, management, mortality

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers; CT, computed tomography; CV, cardiovascular; ECG, electrocardiogram; ENaC, epithelial sodium channel; GH, growth hormone; HBPM, home blood pressure monitoring; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVM, left ventricular mass; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; SAS, sleep apnea syndrome; SMR, standardized mortality risk.

Essential points

- Cardiovascular complications are the most common and major determinants for the increased morbidity and mortality in acromegaly patients
- An early identification and adequate management of cardiovascular comorbidities is essential to improve patient outcomes and quality of life
- Surgery and medical therapies for acromegaly may lead to partial or full reversal of some cardiovascular alterations,

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but a residual cardiometabolic risk persisted in many patients

- Multidisciplinary care and individualized risk assessment of the cardiometabolic profile of patients with acromegaly is essential for an optimal management of the disease

Acromegaly is a condition caused by chronic growth hormone (GH) hypersecretion, in most cases due to a benign pituitary adenoma (1). GH stimulates the production of insulin-like growth factor-1 (IGF-1) from the liver and systemic tissues. Both IGF-1 and directly GH have somatic and metabolic effects (1, 2).

The epidemiology of acromegaly is difficult to establish, mostly due to the high heterogeneity of study populations, study designs, and diagnostic/inclusion criteria of acromegaly (3). A recent systematic review and meta-analysis showed an annual incidence of 0.38 cases per 100 000 people (95% CI 0.32-0.44) and a pooled global prevalence of 5.9 per 100 000 people (95% CI 4.4-7.9) (3). In the last decades, an increase in both prevalence and incidence has been reported, which may be explained by increased incidental diagnosis and improved physicians' awareness (4). Acromegaly is usually diagnosed in the fifth decade of life, with an estimated delay of 4.5-5 years (5). At the time of diagnosis, most cases are macroadenomas (>2/3 of cases), which may relate to this diagnostic delay (5). An early detection of the disease is crucial to minimize the likelihood of developing systemic comorbidities associated to GH and IGF-1 excess (6).

In patients with acromegaly, chronically elevated serum GH and IGF-1 levels trigger a systemic syndrome characterized by somatic overgrowth, including physical disfigurement, multiple comorbidities, and premature mortality. Cardiovascular (CV) and metabolic complications are among the most prevalent comorbidities and main mortality drivers in patients with acromegaly (6, 7). Therefore, early identification and adequate management are essential to improve patient outcomes, quality of life, and survival (8). The risk of several CV complications including cardiomyopathy, cardiac valve disease, arrhythmias, and sudden cardiac death seemed to be increased in acromegaly compared to the general population (6). In addition, the prevalence of traditional CV risk factors, such as diabetes, hypertension, and dyslipidemia, is also higher, which further negatively impacts the cardiometabolic profile of these patients (9, 10). Given that GH/IGF-1 excess plays a central role in the development of CV complications in acromegaly, achieving biochemical control is the cornerstone of risk reduction. This can partially reverse some of the structural and functional CV alterations observed in these patients (11-17). Subsequently, optimizing the management of classical CV risk factors such as hypertension, diabetes, dyslipidemia, and obesity remains essential to further reduce the overall CV burden (10).

In this review, we provide an updated overview of acromegaly-related CV and metabolic comorbidities, with a focus on their pathophysiology, epidemiology, and specific clinical characteristics. In addition, we offer practical evidence-based recommendations for the diagnosis and management of such comorbidities.

Epidemiological and historical context

Early descriptions of cardiomyopathy in acromegaly

The association between acromegaly and CV complications can be recognized early in medical literature. Pierre Marie's original description of acromegaly in 1886 included cardiac enlargement among a constellation of other features (18). Early 20th-century case series began to document cardiac hypertrophy and heart failure in patients with acromegaly, with autopsy studies revealing significant cardiac enlargement that exceeded what could be attributed to hypertension alone (19). The concept of "acromegalic cardiomyopathy" as a distinct entity emerged later in the 1960s-1970s, when investigators began systematically characterizing the cardiac abnormalities specific to GH excess. Rodrigues et al provided one of the first comprehensive descriptions of the biventricular hypertrophy pattern, distinguishing it from hypertensive heart disease (20). These early observations established that acromegaly could cause intrinsic myocardial disease independent of secondary CV risk factors.

Evolution of cardiovascular mortality over time in acromegaly

Epidemiological studies from the 1970s-1980s estimated a 2- to 4-fold increase in CV mortality among patients with acromegaly compared to the general population, with CV disease accounting for approximately 60% of excess deaths (21, 22) (Table 1 and Fig. 1). Modern epidemiological understanding of CV risk in acromegaly is increasingly based on large registries and population-based cohorts that provide robust data on contemporary outcomes (26, 29). A Danish national cohort study of 405 acromegaly patients and 4050 age and gender-matched general population controls reported a persistently elevated risk for heart failure (Hazard Ratio [HR] 2.5 (95% CI: 1.4-4.5)) (23). More recent large-scale studies have also shown temporal trends toward improved survival. A comprehensive meta-analysis by Dekkers et al, encompassing 16 studies with over 3000 patients, found an overall standardized mortality risk (SMR) of 1.72 (95% CI: 1.62-1.83), representing a notable improvement from earlier estimates (Table 1 and Fig. 1) (22). More recent data from the Finnish registry (24) suggest continued improvement in CV outcomes, though excess risk persists, with a more noticeable impact on women in line with the data from the Spanish study (30). The Finnish researchers also observed a change in the mortality pattern, which shifted from CV to cancer-related deaths (24). Later in 2018, a systematic review of 42 studies including over 9000 patients found that overall mortality has decreased in acromegaly in parallel with improvements in biochemical control, although CV mortality remained elevated with a pooled SMR of 1.42 (95% CI: 1.28-1.58) (26). Similar trends have been observed in other studies (27, 31), suggesting that therapeutic advances (25, 26, 32) and shorter diagnostic delay (33) have a positive impact on overall acromegaly mortality. More recently, the Danish

Table 1 Evolution of cardiovascular mortality in acromegaly

Study	Period	Country	N	SMR and 95% CI	Key observations
Wright et al, 1970 (21)	1937-1967	UK	194	2-4 CV deaths ≈60% of total	Seminal evidence of high CV mortality; basis for clinical concern
Dekkers et al, 2008 (22)	1970-2005	Meta-analysis	4947	1.72 (1.62-1.83)	First quantitative confirmation of mortality trend improvement
Dal et al, 2016 (23)	1991-2010	Denmark	405	SMR Not reported (HR: 1.3 (95% CI: 1.0-1.7))	Mortality risk remains elevated but uninfluenced by mode of treatment.
Ritvonen et al, 2016 (24)	1980-2016	Finland	333	1.9 (1.53-2.34)	Shift from cardiovascular to cancer-related deaths; greater impact in women.
Esposito et al, 2018 (25)	1987-2013	Sweden	1089	Declined from SMR from 3.45 (2.87-4.02) to 1.86 (1.04-2.67)	Decrease in SMR after 1990; improvement linked to better disease control.
Bolfi et al, 2018 (26)	1937-2013 Before and after 2008	Meta-analysis	Before	Before	Reduced total mortality with biochemical control; cancer deaths rising
			5152	1.76 (1.52-2.04)	
Orme et al, 2024 (27)	1970-2016	UK	After	After	Cardiovascular and respiratory diseases were the main causes of death (43% and 19%, respectively).
			5618	1.35 (0.99-1.85)	
Orme et al, 2024 (27)	1970-2016	UK	1845	1.35 (1.24-1.46)	
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Evolution of cardiovascular mortality in acromegaly: overview of selected population-based studies, large multicenter cohorts, and meta-analyses reporting standardized mortality rates over time. Studies were selected based on relevance, methodological robustness, geographical and temporal representativeness. Abbreviations: CI: confidence interval; CV: cardiovascular; SMR: standardized mortality rate.

AcroDEN cohort confirmed a continued decline in CV mortality, with life expectancy in acromegaly now approaching that of the general population (HR: 1.3 [95% CI: 1.0-1.7]) (Table 1 and Fig.1) (34).

The age at acromegaly diagnosis has increased in recent decades, partly due to the overall aging of the population and the broader access to imaging techniques. This has resulted in a growing proportion of newly diagnosed patients being older adults (35-37). As age is a well-established risk factor for CV disease, this shift may impact on the profile and prognosis of acromegaly-related complications. Moreover, delayed diagnosis in elderly individuals may be exacerbated by the nonspecific nature of acromegaly symptoms in this population, which may

overlap with normal aging, further increasing cardiometabolic burden (38). The increase in life expectancy has been associated with more deaths due to cancer (26), leading to the fact that cancer has become a top cause of death in acromegaly in the last decade.

Pathophysiology of cardiovascular comorbidities in acromegaly

Chronic GH and IGF-1 excess in acromegaly promotes a wide spectrum of CV phenotypes, including cardiac hypertrophy,

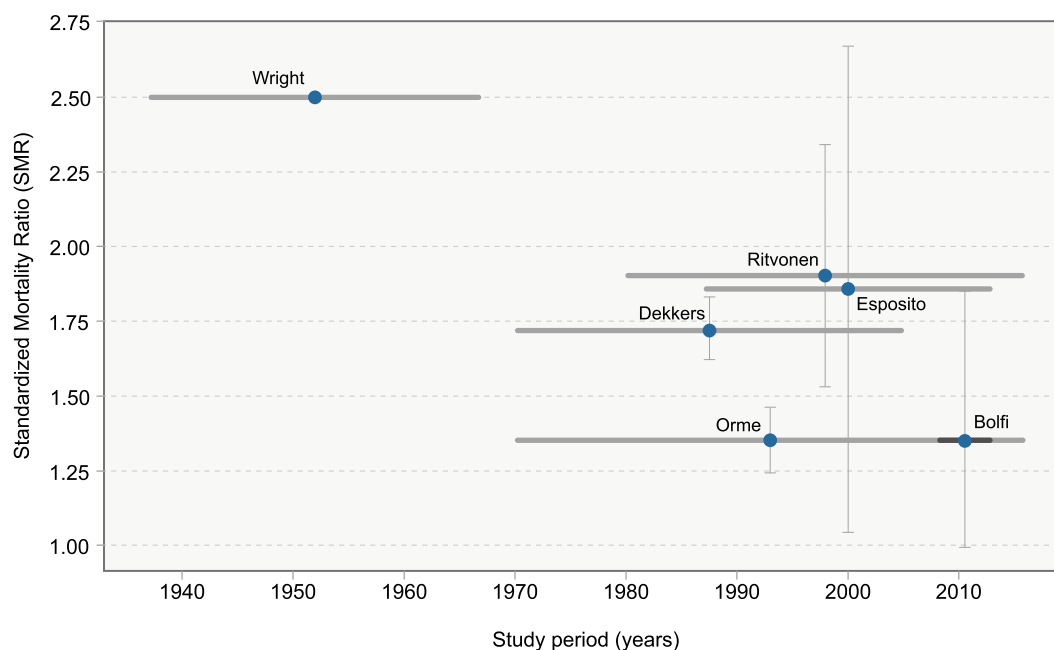


Figure 1 Trend in cardiovascular mortality in patients with acromegaly over time. Standardized mortality ratio (SMR) in acromegaly across historical cohorts according to study period. Each horizontal gray bar represents the time span during which mortality was assessed in each study. Black dots indicate the mid-point of the study period and correspond to the SMR values, with vertical lines representing the 95% CIs, where available. CIs were not reported for the Wright 1970 study. Included studies: Wright (1970) (21), Dekkers (2008; meta-analysis) (22), Ritvonen (2016) (24), Esposito (2018) (25), Bolfi (2018; meta-analysis) (26), Orme (2024) (27). The Dal et al (2016) (23) and L Alexander et al (1980) (28) studies were not included due to the absence of SMR data.

diastolic and systolic dysfunction, hypertension, arrhythmias, and valvular disease. Although these complications are often viewed as a unified consequence of somatotrophic hypersecretion, experimental and clinical data suggest that GH and IGF-1 act through distinct yet overlapping pathways affecting myocardial growth, fibrosis, and vascular tone. Their specific contributions to each CV phenotype remain difficult to separate in vivo. To facilitate interpretation across phenotypes, we propose an integrative framework organized into four partially overlapping domains: anatomical/structural, hemodynamic, molecular/cellular, and systemic abnormalities. These domains interact dynamically over time, and the relative contribution of each may vary according to disease duration, biochemical control, comorbidities, and age. More detailed information on the pathophysiology of cardiovascular comorbidities in acromegaly is available in Supplementary material.

Hypertension

The proposed mechanisms in acromegaly-related hypertension include direct effects of GH and IGF-1 in the heart, plasma volume expansion, vascular and insulin resistance, which also impairs endothelial function (39, 40) (Fig. 2). GH and IGF-1 receptors, as well as IGF-1, are expressed in the heart and vasculature, regulating cardiac growth, myocardial contractility, and vascular tone (8, 41). The expansion of plasma volume is a key mechanism leading to hypertension in acromegaly, which results from the sodium and water retention in the distal convoluted tubule induced by excessive levels of GH and IGF-1 (39, 40). Notably, GH stimulates the epithelial sodium channel (ENaC), further enhancing sodium reabsorption

and extracellular fluid expansion (42). Another key factor is the stimulation of the renin-angiotensin-aldosterone system by GH (43, 44), which causes adrenergic activation, aldosterone secretion, and increased peripheral vascular resistance (43, 45). It has been proposed that direct activation of the adrenergic system by GH and IGF-1 also contribute to the development of hypertension in acromegaly (Fig. 2) (10, 41, 42, 46-48).

Acromegaly-related cardiomyopathy

Acromegaly-related cardiomyopathy is defined by the presence of morphological and functional cardiac changes. It typically comprises concentric biventricular hypertrophy, mainly involving the left ventricle, with concomitant diastolic dysfunction occurring in half of cases (8, 49).

The primary mechanism involves the trophic effects of GH and IGF-1 on cardiac myocytes, which have direct anabolic effects on the myocardium, given the expression of GH and IGF-1 receptors in cardiac myocytes (50). In acromegaly-related cardiomyopathy, ventricular walls become concentrically thickened due to an increase in myocyte size, but there are rarely enlarged heart chambers. Additionally, there is increased interstitial fibrosis, which appears to be the main histological feature impairing heart structure and function, increase in interstitial fibroblasts, myofibrillar derangement, and also lympho-mononuclear cell infiltration resembling multifocal myocarditis, which in turn leads to myocyte apoptosis and necrosis (8, 49, 51). The increase in left ventricular mass (LVM) occurs because of a homogeneous increase in both intracellular myocardial mass as well as extracellular myocardial matrix (52).

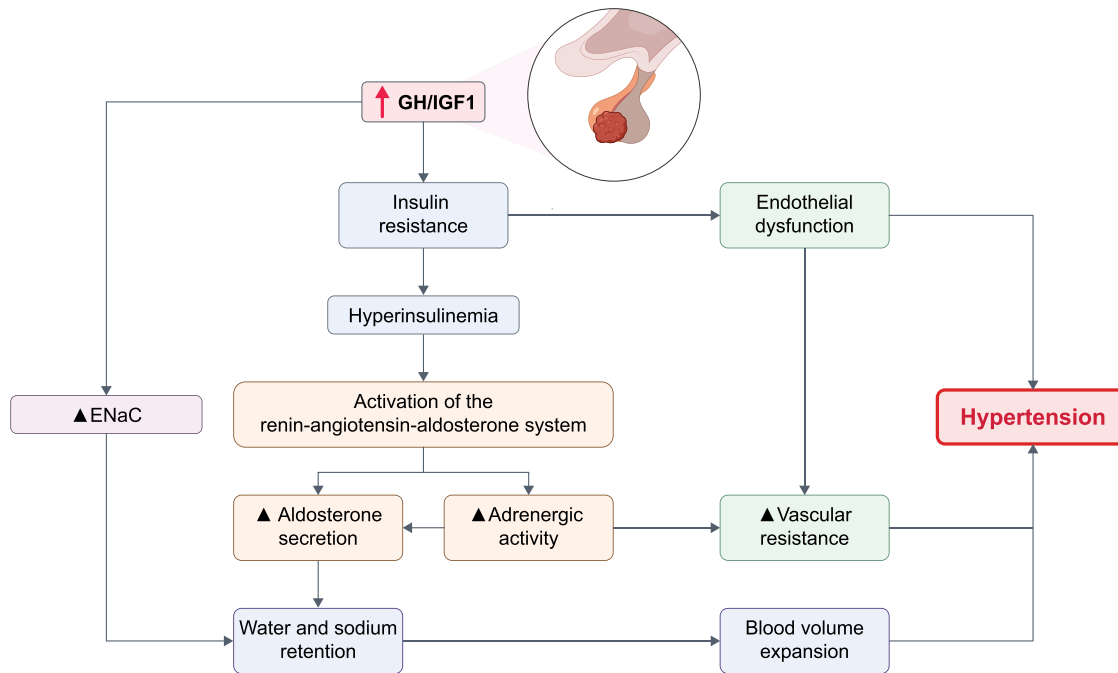


Figure 2 Pathophysiology of hypertension in acromegaly.

Although it is known that lipid deposition in cardiomyocytes and GH-specific effects on lipid metabolism and beta-oxidation may aggravate cardiac hypertrophy (50, 53), some authors suggest that there is no evidence of ectopic lipid accumulation in the pathophysiology of the acromegalic cardiomyopathy as they found that after the control of GH excess, myocardial and hepatic lipid content remained unchanged, while pericardial fat was increased in the patients in whom GH excess was controlled (54, 55). In accordance with these findings, it is reported that patients with GH deficiency have an increase of ectopic lipids such as intramyocellular lipids (56).

The evolution of cardiomyopathy in acromegaly follows three stages: (1) the first stage is reversible and is characterized by a bi-ventricular concentric hypertrophy, with increased myocardial contractility and systolic output, and increased heart rate, determining a hyperkinetic syndrome (increased cardiac index); (2) the second stage is characterized by a more pronounced ventricular hypertrophy, associated with a decreased diastolic filling and prolongation of the pre-ejection period at rest, and a systolic dysfunction on effort; and (3) end-stage irreversible cardiomyopathy typically occurs in patients with late diagnosis, uncontrolled or untreated acromegaly, and comprises resting diastolic and systolic dysfunction, low cardiac output, and heart failure (10, 57) (Fig. S1) (58).

Acromegaly-related cardiomyopathy can appear independently of hypertension (10, 49), as supported by reports of about 20% of normotensive young patients with acromegaly developing cardiac hypertrophy (59), and by the demonstration of structural cardiac changes after short-term exposure to GH (60). In this regard, cardiomyopathy can be found in acromegaly patients who do not have hypertension or other CV risk factors (10, 49, 61, 62). Nevertheless, hypertension remains a key factor exacerbating left ventricular hypertrophy (LVH) due to mechanical stress of pressure overload (52, 63). The coexistence of additional CV risk factors, such as dyslipidemia or diabetes, may further accelerate the onset and progression of cardiac complications and outcomes (64).

Heart valve disease and arrhythmias

Prolonged exposure to high GH and IGF-1 levels leads to increased synthesis of extracellular matrix components and deposition of mucopolysaccharides and collagen in valvular leaflets, resulting in diffuse interstitial fibrosis and myxomatous degeneration of the cardiac valves. This process causes leaflet thickening, redundancy, and impaired coaptation, predisposing to valvular dysfunction, most commonly regurgitation, particularly of the mitral and aortic valves (65-71). Aortic ectasia is also more frequent in patients with acromegaly than in controls (72, 73) (Fig. 3).

Cardiac dysrhythmia in acromegaly may occur because of interstitial fibrosis, myofibrillar derangement and cardiac hypertrophy promoted by IGF-1 and GH excess. These structural alterations, together with pressure overload particularly in hypertensive patients, lead to abnormalities in heart conduction and arrhythmias (70, 74). The pathogenesis is usually multifactorial, including the effects of IGF-1 (75), cardiac structural changes (76), and electrophysiological alterations (increased QT interval variability) (Fig. 3).

Vascular disease

Chronic GH and IGF-1 excess promotes vascular injury through direct and indirect mechanisms, including endothelial dysfunction, smooth muscle proliferation, oxidative stress, inflammation, and extracellular matrix remodeling (42, 77, 78). These alterations lead to early vascular stiffening, accelerated atherosclerosis, and a prothrombotic state, contributing to both coronary artery disease (CAD) and cerebrovascular disease in acromegaly (Fig. 3 and Fig. 4).

In acromegaly, GH and IGF-1 excess lead to endothelial dysfunction and atherosclerosis through various mechanisms: (1) increased oxidative stress; (2) increase in pro-inflammatory cytokines; (3) impairment of endothelial repair processes; (4)

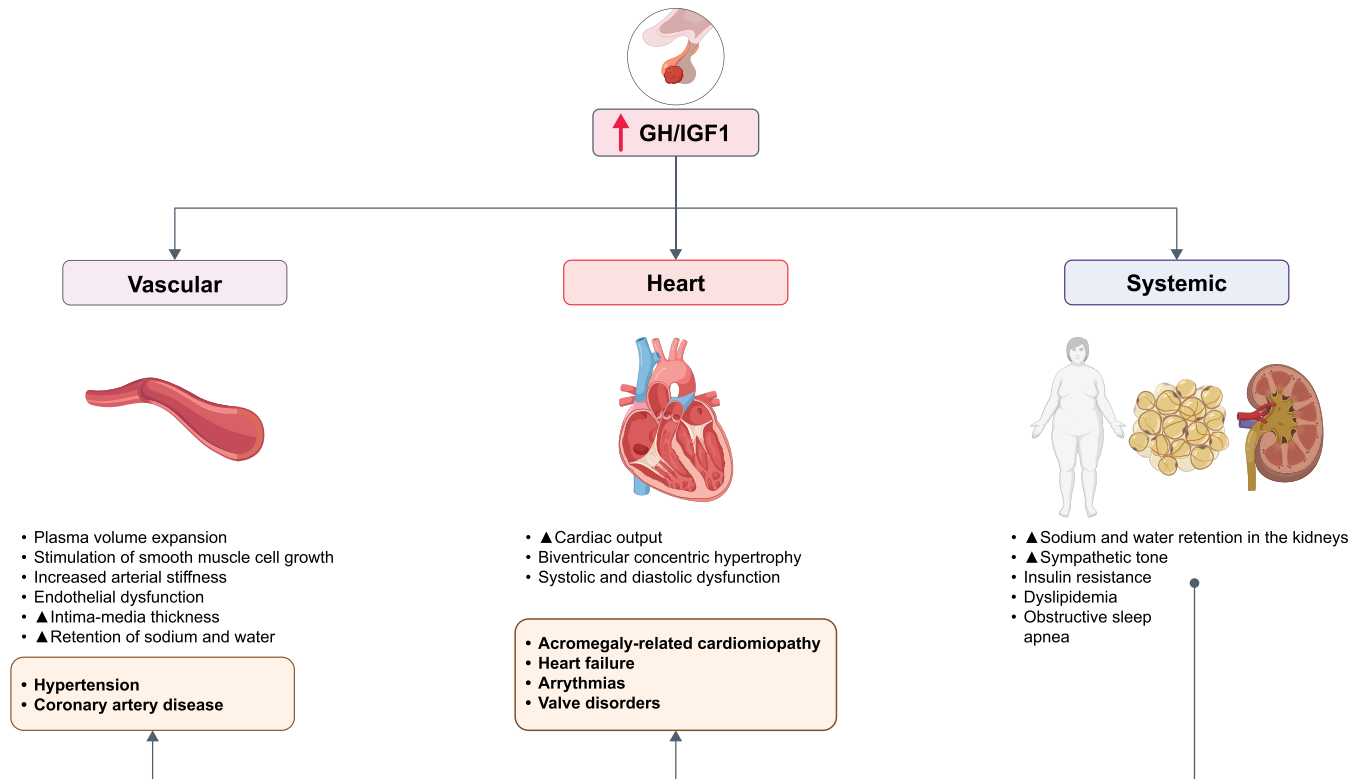


Figure 3 Cardiovascular effects of acromegaly.

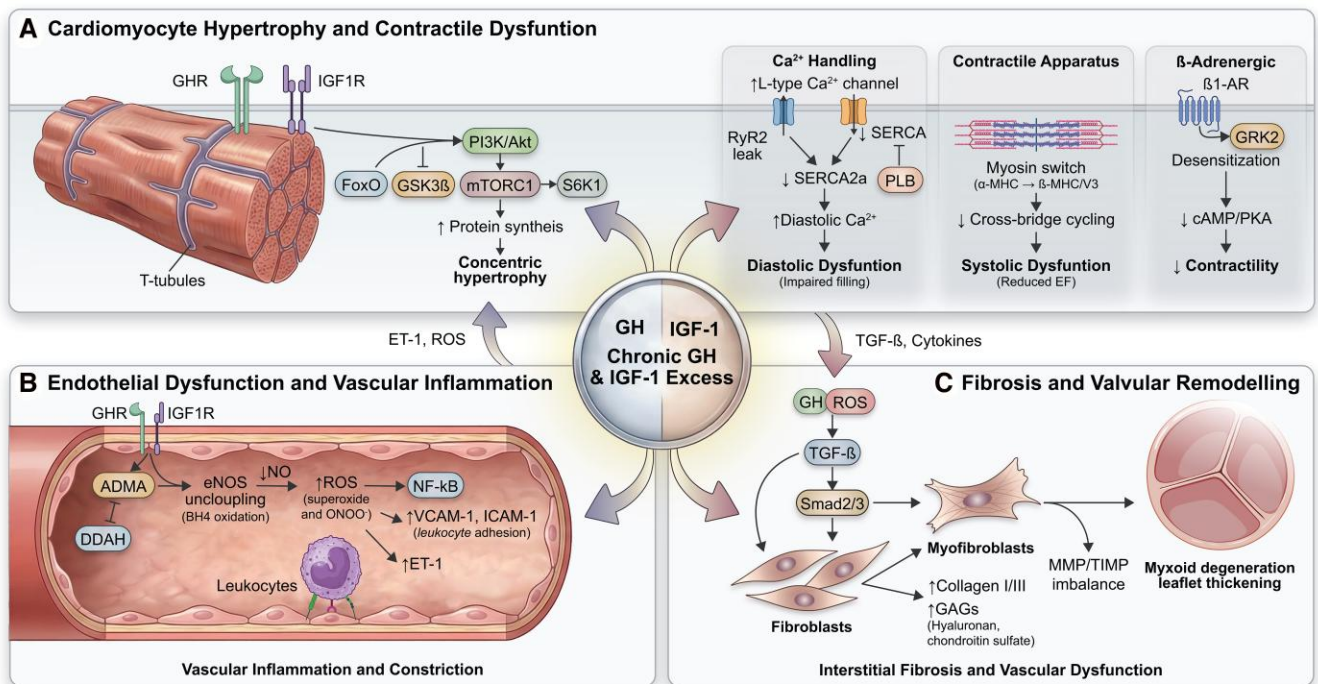


Figure 4 Molecular/cellular mechanisms of cardiovascular complications in acromegaly.

modification of hemodynamic forces; (5) alteration of vascular morphological through the proliferation of vascular smooth muscle cells; (6) inducing expression of adhesion molecules; and (7) coexistence of CV comorbidities such as hypertension, insulin resistance, diabetes, SAS, dyslipidemia, and metabolic

syndrome (79, 80). Despite these GH/IGF-1-related vascular effects and the increased burden of cardiometabolic risk factors, the prevalence of overt CAD and myocardial infarction appears to be lower than anticipated (23, 81-83) potentially due to the vasodilatory and anti-atherogenic properties of physiological

IGF-1 (79), and suggesting that the excess of GH *per se* may not be associated with an additional risk for CAD (79, 83). In experimental models, IGF-1 infusion reduced plaque size and oxidative stress, and enhanced endothelial NO bioavailability and anti-inflammatory pathways (84). However, chronic supraphysiological exposure may override these protective effects, leading to subclinical atherosclerosis and vascular dysfunction (79, 85).

Patients with acromegaly show early cerebrovascular involvement, including impaired flow-mediated dilation, increased carotid-femoral pulse wave velocity, and reduced microvascular reactivity, even in the absence of clinical disease (84, 86). Endothelial biomarkers such as von Willebrand factor, VCAM-1, and intercellular adhesion molecule 1 are elevated, reflecting vascular inflammation and damage (87, 88). Additionally, a prothrombotic milieu is frequent, with increased fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and platelet hyperreactivity (Fig. 4 and Table S1) (58, 89). The risk of cerebrovascular events increases with age, disease duration, poor biochemical control, and prior radiotherapy exposure, which is associated with delayed vascular injury, carotid stenosis, and white matter hyperintensities on MRI (8, 90).

Thrombosis and hypercoagulability

Studies consistently show elevated levels of fibrinogen in acromegaly (77, 89, 91-97). Campello et al (92), described an increase in factor VIII, and significantly enhanced thrombin generation, with this last parameter surprisingly showing a significant inverse correlation with GH and IGF-1 levels, being higher in treated patients, which overall suggests a complex relationship between the disease activity and coagulation dynamics. Alterations of natural anticoagulant agents, such as decreased protein C (89, 95) and its cofactor protein S (89, 94, 95), decreased tissue factor pathway inhibitor (89), as well as increased antithrombin III (89, 95) and fibrinogen have also been described (77, 91, 92). Fibrinolysis may be impaired, due to increased levels of tissue plasminogen activator (89), PAI-1 (89), and thrombin-activatable fibrinolysis inhibitor antigen (22), further contributing to a hypercoagulability and hypofibrinolytic state. However, some studies did not replicate these findings (89, 91, 92, 94, 96), and hemostasis data remains inconsistent (92, 95) and insufficient to draw firm conclusions (Table 2).

Diabetes Mellitus and dyslipidemia

Excessive GH secretion in patients with acromegaly promotes insulin resistance in the liver and muscle, which can eventually lead to the development of diabetes when the β -cell exhausts its capacity to enhance insulin secretion. The pathogenesis of glucose abnormalities in acromegaly is complex (98-100). In acromegaly-induced diabetes mellitus, insulin resistance seems to be driven mostly by direct and indirect effects of GH. GH is the primary factor, promoting lipolysis and raising free fatty acid levels, while IGF-1 has a minor role in its pathophysiology and conversely, has some insulin-sensitizing effects (101).

An older age, longer disease duration, active disease (high GH/IGF-1 levels), family history of diabetes, increased body mass index (BMI), hypertension and dyslipidemia are well-recognized risk factors for diabetes mellitus in patients with acromegaly. Notably, many cases of acromegaly-associated diabetes mellitus

are reversible or may significantly ameliorate after achieving acromegaly biochemical control, but persistent metabolic risk remains elevated (102, 103). Body composition changes, such as increased lean mass, decreased subcutaneous adipose tissue, and increased intermuscular adiposity, as well as the coexistence of several CV risk factors, may further contribute to the adverse pro-diabetogenic metabolic milieu in acromegaly (104).

The lipid disorders in acromegaly mainly include hypertriglyceridemia (approximately 3 times higher than in the general population) and low high-density lipoprotein (HDL) cholesterol levels (11, 105, 106). Acromegaly is also associated with derangements in the lipoprotein metabolism, mainly consisting of increase in circulating lipoprotein(a), Apo A-I, and Apo E (involved in the transport of cholesterol and triglycerides), as well as small dense low-density lipoprotein (LDL) particles (107). The development of dyslipidemia in acromegaly is multifactorial, driven by the direct effects of GH and IGF-1 excess and indirect effects mediated by the underlying metabolic disturbances, especially insulin resistance (78, 108, 109).

Sleep apnea syndrome

Respiratory complications in acromegaly originate due to structural and functional changes in the entire respiratory system, resulting in sleep apnea syndrome (SAS) and/or respiratory insufficiency (8). Excessive levels of GH and IGF-1 in acromegaly lead to marked anatomical changes mainly concerning the craniofacial bones and soft tissues, including the swelling of the tongue, alterations in the respiratory mucosa and cartilages, lung volume, as well as changes in muscle structure, reduction of lung elasticity and increase in lung distensibility (70). For obstructive SAS, modifications of the facial skeleton, pharynx, and tongue have a key role for its occurrence in patients with acromegaly (110, 111). Small and upper airway narrowing has been described in 35% and 26% of acromegaly patients, respectively (112-114), and overall, SAS may be found in 20-80% of patients with acromegaly (115, 116).

In central SAS, that represents one-third of the cases of SAS in acromegaly, excess GH and IGF-1 impair brain control of respiration (117). Higher IGF-1 levels, male gender, older age, increased BMI, and longer disease duration have been associated with a higher risk of SAS (118). However, other studies identified smoking, female gender, and presence of lung disease as risk factors of more severe SAS, while no correlation was found between SAS and disease duration, serum GH and IGF-1, SRLs treatment, BMI, and associated comorbidities (119). In addition, acromegaly treatment complications, such as hypopituitarism, could be related to obstructive SAS prevalence (120).

Cardiovascular comorbidities in acromegaly and its distinctive features

Hypertension

Epidemiology

Early studies reported very discrepant prevalences of hypertension in patients with acromegaly, ranging from 18% to 60%

Table 2 Studies focusing on coagulation and fibrinolysis alterations in acromegaly

Study (year)	Design	N	Comparison	Fibrinogen (mg/dL)	Factor VIII (%)	AT III	Protein C (%)	Protein S (%)	PAI-1 (ng/mL)
Landin-Wilhelmsen et al (1997) (77)	Comparative	20 ACR 20 controls	20 ACR with active disease vs 20 healthy controls	↑ 400 (310–610) vs 240 (130–300) **	n/a	n/a	n/a	n/a	n/a
Sartorio et al (2000) (96)	Case-control	10 ACR 64 controls	All acromegalic patients vs healthy controls	↑ 398 ± 111 vs 291 ± 71 **	n/a	n/a	n/a	n/a	NS
Vilar et al (2007) (94)	Case-control	62 ACR 36 controls	Active disease vs healthy controls	↑ 434.8 ± 117.6 vs 314.3 ± 65.8 **	n/a	NS	NS	↓ 71.9 ± 24.7 vs 99.6 ± 12.9 *	n/a
Erem et al (2008) (89)	Case-control	22 ACR 22 controls	Active disease vs healthy controls	↑ 370.3 ± 81.2 vs 249.3 ± 14.4 **	NS	↑ 31.9 ± 7.0 vs 24.2 ± 2.2 mg/dL *	NS	↓ 103.1 ± 20.3 vs 119.3 ± 26.7 *	↑ 72.3 ± 39.7 vs 30.3 ± 8.3 **
Colak et al (2016) (95)	Case-control	39 ACR 35 controls	Active disease vs healthy controls	↑ 436.9 ± 143.7 vs 362 ± 44.9 **	n/a	↓ 94.5 ± 27.7 vs 113.9 ± 8.3 % **	↓ 97.3 ± 18.2 vs 123.4 ± 23.1 **	↓ 81.5 ± 13.2 vs 100.5 ± 14.7 **	n/a
Amado et al (2018) (97)	Case-control	23 ACR 11 controls	Active disease vs NF pituitary adenomas	↑ 427.1 ± 61.93 vs 356.91 ± 86.03 *	NS	↑ 1.13 ± 0.09 vs 0.95 ± 0.16 U/mL **	NS	NS	NS
Campello et al (2020) (92)	Case-control	40 ACR 40 controls	All acromegalic patients vs healthy controls	↑ 342 (308.8–386.3) vs 314 (256–349) **	↑ 138 (124–170) vs 132 (104–158) *	NS	NS	NS	NS

(continued)

Table 2 Continued

Study (year)	Design	N	Comparison	Fibrinogen (mg/dL)	Factor VIII (%)	AT III	Protein C (%)	Protein S (%)	PAI-1 (ng/mL)
Kyriakakis et al (2020) (91)	Case-control	40 ACR 40 controls	Active disease vs healthy controls	↑ 38 ± 2 vs 26 ± 2 **	n/a	n/a	n/a	n/a	NS

Values are expressed as means ± standard deviation or as median (interquartile range). Some studies like Vilar et al (94), Amado et al (97), Campello et al (92), and Kyriakakis et al (91) run multiple comparisons between active disease, controlled disease, and controls, in which case only the comparisons between active disease and controls are shown in this table to allow results comparability. Abbreviations: ↑/↓, significantly increased or decreased; ACR, patients with acromegaly; AT III, antithrombin III; NF, non-functioning; PAI-1, plasminogen activator inhibitor 1; n/a, not assessed; NS, non-significant difference; * $P < .05$; ** $P < .01$.

(25, 45, 121-130). This wide range may be explained by the different criteria to diagnose hypertension, as well as by the heterogeneous populations across the studies, often not accounting for possible confounding factors, such as age, sex, or ethnicity (25, 121, 123-130). Also, data from studies relying only on a single BP determination to establish the diagnosis of hypertension seem to vastly overestimate the prevalence of hypertension in comparison with 24-hour ambulatory blood pressure monitoring (ABPM) (131, 132).

A recent systematic review showed that CV comorbidities such as myocardial/LVH, diastolic dysfunction, and hypertension are among the most frequent comorbidities, with a reported mean prevalence of 38% (7). A compilation of data from 19 national acromegaly registries encompassing more than 16 000 patients reported hypertension as the most prevalent comorbidity, with a weighted mean prevalence of 35.7%, varying across the registries from 11% to 54% (29). Considering only data from large national registries, summarized in Table 3, the reported prevalence of hypertension in acromegaly ranges from 27% up to 48%. In the Mexican acromegaly registry, the prevalence of hypertension was 27%, but this cohort with more than 2000 patients displayed a relatively young age at diagnosis (mean of 41.1 years) (128). In contrast, the Austrian and French registries reported higher prevalence rates of 47.8% and 47.5%, respectively (129, 130). The Italian (123), the Canadian (124), and the German (125) registries reported intermediate prevalences of 33%, 37%, and 45%, respectively. Recent data from the Iberian (Spain and Portugal) acromegaly registry encompassing 434 acromegaly patients found that 209 (48.2%) had hypertension at the time of acromegaly diagnosis (122) (Table 3). Overall, the data from these large registries suggest that nearly one-third to one-half of acromegaly patients may have hypertension at the diagnosis of acromegaly or during the disease course (25, 121, 123-130).

Screening and diagnosis

Acromegaly patients with hypertension typically show a pattern characterized by higher diastolic and lower systolic BP and a higher prevalence of non-dippers when compared to patients without acromegaly (133-135). Hypertension tends to occur at early ages and appears to be unrelated to gender or family history (133). In addition, the morning BP surge was reported to be higher (ie, 29 mmHg) when compared with patients without acromegaly (ie, 19 mmHg), and this correlated with higher IGF-1 levels (136).

Hypertension is one of the most relevant negative prognostic factors for CV mortality (137-140). In the ACROSTUDY, the presence of hypertension was associated with a higher BMI, diabetes, hyperlipidemia, CV disease, and increased mortality, when compared with acromegaly patients without hypertension (13). Therefore, early detection and appropriate management of hypertension are crucial in acromegaly to reduce CV morbidity and mortality (141).

Given the often insidious onset of hypertension in acromegaly and its high frequency, active screening for hypertension is recommended at diagnosis and then periodically (eg, every 6 months); for patients under anti-hypertensive treatment, monitoring is also advised every 6 months or after titration of antihypertensive drugs (Table S2 and Fig. 5) (58, 141). A more comprehensive assessment of hypertension-related end-organ

Table 3 Hypertension prevalence in large (>500 cases) national acromegaly registries

Registry: country and year	Study population Size (n)	Prevalence of hypertension (%)	Age at diagnosis (years)	Sex Ratio (F/M)	Mean or median IGF-1 levels
Italy (2012) (123)	1512	33.0	45.0	1.42	744 ± 318 ng/mL
Canada (2013) (124)	649	37.0	45.0	0.97	311.8 (148.3) % ULN
Germany (2013) (125)	1344	45.0	44.5	1.36	NA
South Korea (2013) (126)	1350	NA	44.1	1.15	985.4 ± 504.7 µg/L
UK (2013) (127)	2572	NA	47.4	0.99	NA
Mexico (2016) (128)	2057	27.0	41.1	1.47	678 ng/mL (IQR 533.4-887)
Austria (2016) (129)	607	47.8	40.0-45.0	1.18	NA
France (2017) (130)	980	47.5	46.0	1.13	NA
Sweden (2018) (25)	1089	NA	51.6	1.14	NA
Spain and Portugal (2025) (122)	434	48.2	50.4	1.40	3.0 ± 3.11 above the ULN

This table summarizes the prevalence of hypertension and clinical features in national acromegaly registries and large multicenter studies including over 500 patients. The data shown depicts the variability of hypertension prevalence and demographic features across the different registries. Hypertension diagnosis was based on office blood pressure measurements. "NA" indicates data not available in the source registry. Abbreviations: F/M, female/male; IGF-1, insulin-like growth factor 1; IQR, interquartile range; ULN, upper limit of normality.

damage may also be necessary in acromegaly, particularly if specific CV complications are present or suspected (Table S2) (58).

In the absence of specific studies, the current diagnosis criteria of hypertension are the same as for the general population, which means an office BP ≥ 140/90 mmHg or home blood pressure monitoring (HBPM) ≥ 135/85 mmHg (Fig. 5) (141, 142). BP can be measured in the office and in ambulatory settings (ie, HBPM and ABPM). While the opportunistic screening of hypertension is typically performed using office BP measurement, the diagnosis of hypertension in most cases should be confirmed with either HBPM or ABPM (142). A recent meta-analysis showed a higher specificity for the diagnosis of hypertension with ABPM in comparison to office BP measurements (143). Both HBPM and ABPM identify white-coat and masked hypertension, but ABPM offers a more comprehensive assessment as it also evaluates nocturnal hypertension and the nocturnal dipping status. However, ABPM is more expensive and less practical than HBPM and office measurements, and may also be less available (144). The frequency of hypertension was reported to be higher in patients with acromegaly assessed by ABPM than office BP measurements, with 31% of the non-hypertensive cases by office BP measurement being identified by ABPM (145).

Cardiomyopathy

Epidemiology

In acromegaly patients younger than 40 years with active disease for 3-7 years, 54% had evidence of LVH on echocardiography, with this rate rising to 72% in patients aged 41-60 years and with an estimated disease duration of 5-15 years (49, 146). Progression to systolic dysfunction occurs in <3% of acromegaly patients, and the presence of overt congestive heart failure is rare, ranging between 1% and 4% in patients with active disease (41). A recent systematic review reported a myocardial hypertrophy mean prevalence of 59% in acromegaly, while congestive heart failure was estimated at 11% (7). Hong et al (147) reported that congestive heart

failure in acromegaly patients was approximately 2-fold higher than in the controls, and remained significantly higher by 1.5-fold after adjusting for diabetes, hypertension, and dyslipidemia. However, recent studies employing cardiac MRI reported a lower prevalence of myocardial hypertrophy in acromegaly, ranging from 5% to 24%. These prevalence rates contrast with the high hypertrophy prevalence described in older echocardiography-based studies (as high as 80%) (52, 62, 148). This prevalence rate discrepancy may be related to the distinct accuracy of the different methods and due to the several limitations of the 2D-echocardiography in comparison to cardiac MRI (50).

Screening and diagnosis

Although several consensus and position statements have addressed the management of acromegaly and its complications, a universal approach for screening of cardiomyopathy and CV disease has not yet been established. In particular, there is no general agreement on the preferred diagnostic methods or how often to test (10).

Echocardiography is widely available and has been traditionally considered the standard technique to evaluate cardiac hypertrophy. However, recent studies tend to document by MRI in order to provide accurate measurement of LVM and myocardial fibrosis in the general population (52, 149, 150). Cardiac MRI provides accurate measurements of ventricular wall thickness, myocardial mass, atrial and cardiac geometry, and it can inform about dense myocardial fibrosis. On the other hand, cardiac MRI is less susceptible to operator-related factors, errors related with calculations of ventricle mass, or artifacts related with patient's body weight and thoracic kyphosis (50, 52). Thus, cardiac MRI may be superior to echocardiography to characterize cardiomorphological alterations, which can explain the methodological shift in recent studies. However, in routine clinical practice, echocardiography is more commonly used because of the lower costs and wider availability than cardiac MRI. Thus, in general, cardiac MRI should be reserved for selected cases, only when clinically indicated.

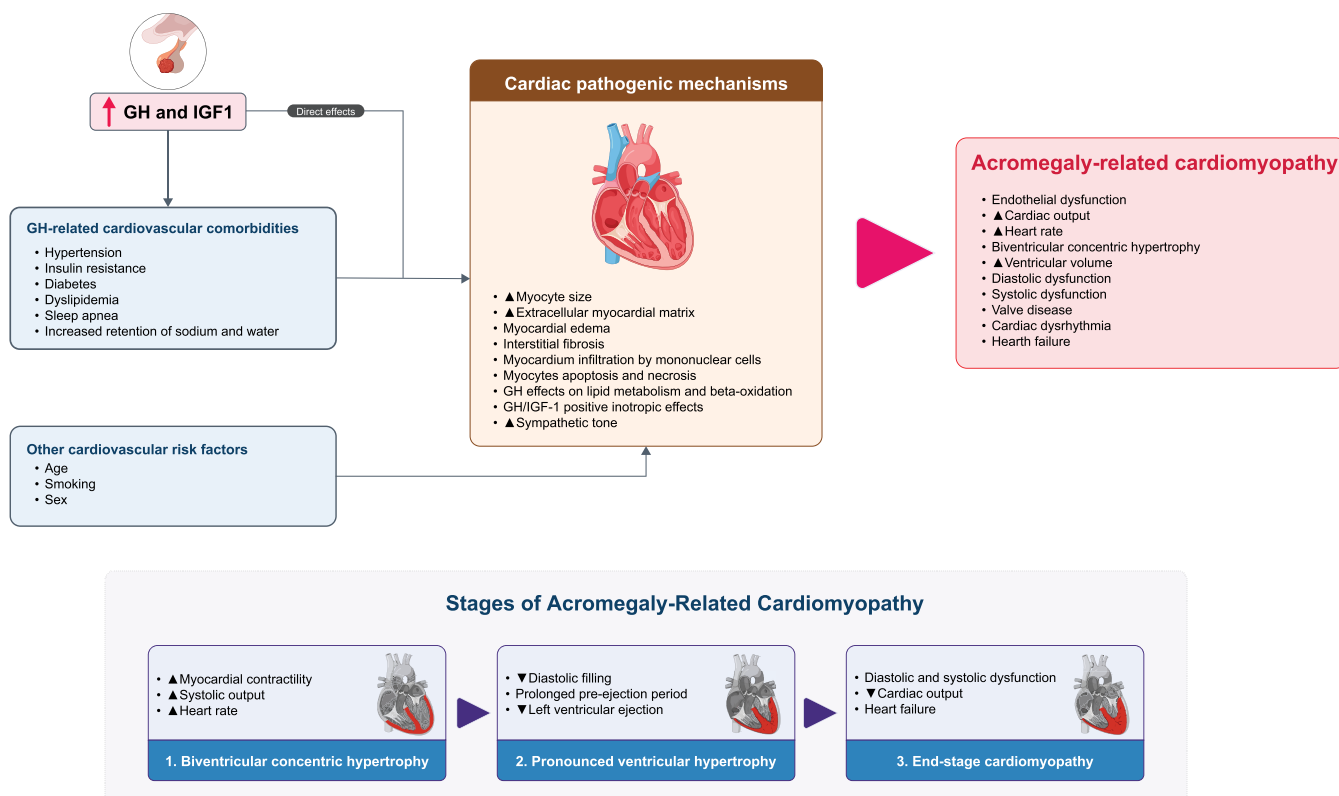


Figure 5 Suggested approach for screening and diagnosing hypertension in acromegaly. ABPM, ambulatory blood pressure monitoring; ACR, albumin to creatinine ratio; BP, blood pressure; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HBPM, home blood pressure monitoring; LVH, left ventricular hypertrophy. These recommendations are in accordance with the guidelines from the general population (142).

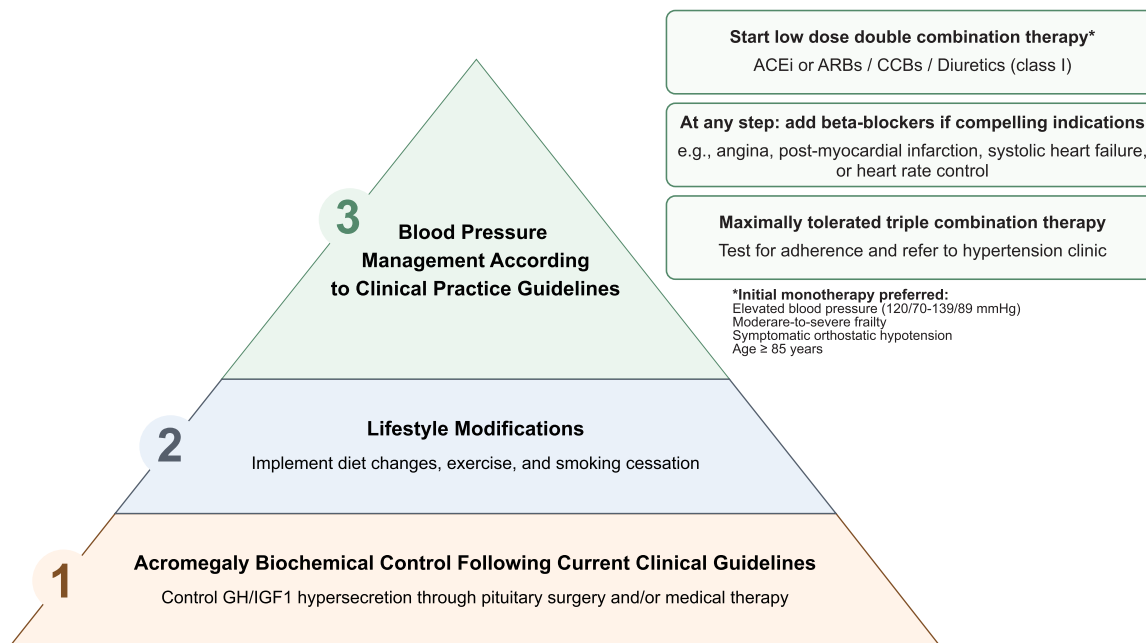


Figure 6 Treatment algorithm for hypertension in acromegaly. This flowchart outlines a stepwise approach to managing hypertension in acromegaly, integrating biochemical control, lifestyle modifications, and blood pressure (BP) management. The algorithm emphasizes the importance of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) normalization through surgery or medical therapy, followed by lifestyle modification. Hypertension treatment follows current clinical guidelines, starting with low-dose combination therapy and escalating as needed. Beta-blockers are added for specific indications. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; GH, growth hormone; IGF-1, insulin-like growth factor 1. Recommendations are based on guidelines from the general population as there is no specific data in acromegaly (142).

Table 4 Prevalence and characteristics of cardiac valve disease in acromegaly

Study (Year)	Design/N	Cardiac valve disease prevalence	Valve(s) involved	Key observations
Colao et al (2003) (65)	Case-control, 42 active, 22 cured, 64 controls	86% (active), 73% (cured), 24% (controls)	Mitral and aortic; abnormalities persisted post-cure	Valve disease persists after biochemical cure; not always associated with LVH
Pereira et al (2004) (67)	Prospective, 40 acromegaly, 120 controls	22% (acromegaly) vs 6.7% (controls) significant valve disease	Aortic regurgitation (30% vs 7%), mitral regurgitation (5% vs 0%)	Risk increases with disease duration (OR 1.19/year)
van der Klaauw et al (2006) (158)	Prospective, 37 acromegaly	Baseline: 46%; Follow-up: 67%	Mitral regurgitation increased (32%→60%); aortic unchanged	Progression seen only in active disease, not controlled
Ságová et al (2023) (68)	Case-control, 129 acromegaly, 80 controls	43% (acromegaly)	Predominantly mitral regurgitation (31%)	IGF-1, BMI, lean mass correlated with LVM
Hinojosa-Amaya et al (2021) (66)	Retrospective, 110 acromegaly	87.3% any valve defect; 14.6% significant	Not specified	Concentric LV remodeling common; early diagnosis recommended
Abreu-Lomba et al (2025) (159)	Retrospective, 193 acromegaly	6.6% isolated cardiac valve disease; 6.6% LVH + cardiac valve disease	Not specified	AHD defined as structural/functional abnormality; carpal tunnel syndrome associated

Abbreviations: AHD: acromegalic heart disease; BMI: body mass index; GH: growth hormone; IGF-1: insulin-like growth factor 1; LV: left ventricle; LVH: left ventricular hypertrophy. LVM: left ventricular mass; OR: odds ratio.

Due to the high prevalence of cardiomyopathy, hypertension and other structural abnormalities, such as valvular heart disease in individuals with acromegaly, a baseline echocardiogram, as well as an electrocardiogram (ECG), are indicated, even if cardiac symptoms or known heart disease are absent (Table S2) (58, 151, 152). Echocardiogram and ECG can be repeated annually or biannually, depending on the presence of underlying cardiac symptoms, hypertension control, and other CV complications, as well as based on acromegaly activity and on the severity of GH excess. Cardiac exams may be performed comprehensively and more frequently in patients with severe cardiomyopathy, progressing cardiac-related symptoms, and poorly controlled disease (10). Other useful resources to diagnose and monitor cardiomyopathy besides cardiac MRI, include 24-hour Holter ECG monitoring and stress tolerance test, particularly in cases of abnormal ECG and/or echocardiogram, as well as for assessment completeness in cases with suspected heart disease or dysrhythmias (Table S2) (10, 58, 151, 152). Additional diagnostic tests may be used to identify specific CV complications and should be requested based on individual clinical indication, following the same indications as for the general population (Table S2) (58, 153, 154). Serum NT-pro-BNP may be useful for the prediction of CV events in patients with acromegaly (155). A recent study measured serum NT-pro-BNP levels in 76 patients with acromegaly and compared with other predictors of CV events, and they found that mean NT-pro-BNP concentration was higher in patients who had CV events than in those who did not, and in patients who died due to CV events than in those deceased due to other causes. They observed that the risk of developing a CV event was 19 times greater in patients with serum NT-pro-BNP levels above 91.55 pg/mL. In another study where the

relationship between serum IGF-1 levels and NT-pro-BNP concentrations was investigated in the general population, it was found that higher IGF-1 levels and IGF-1/IGFBP-3 ratio were associated with higher NT-pro-BNP values in women, while a U-shaped relation of baseline IGF-1, IGFBP-3, and IGF-1/IGFBP-3 ratio with increased NT-pro-BNP levels was observed in men (156).

Cardiac valve disease

Epidemiology

The prevalence of heart valve disease at the time of acromegaly diagnosis varies across studies, depending on the definition and severity of cardiac valve disease and on the population studied. Several echocardiographic studies suggested a high burden of valvular abnormalities in acromegaly, and its severity seems to correlate with duration and activity of acromegaly (Table 4) (8, 10, 39, 57, 65-68, 157-159).

In a case-control study of 42 patients with active acromegaly, the prevalence of any cardiac valve abnormality (including mild lesions) was 86% at diagnosis compared to 24% in matched controls; this prevalence remained elevated at 73% even in patients with cured acromegaly, compared to 9% in matched controls (65). A large study found valve defects in 87.3% of patients at baseline echocardiogram, with 14.6% having significant valvular heart disease (66). Another prospective study reported significant heart valve disease in 22% of acromegaly patients at diagnosis, with aortic valve regurgitation in 30% and moderate or greater mitral regurgitation in 5% of patients (67). Additional data from a multicenter study identified valvulopathies in 6.6% of patients with acromegaly, but this low rate

likely reflects only clinically significant cases (159). In a recent case-control study valvulopathy was reported in 43% of acromegaly patients, with mitral regurgitation being the most common lesion (31%) (68). In summary, the prevalence of any echocardiographically detectable heart valve abnormality in newly diagnosed acromegaly is up to 87%, while the prevalence of moderate or severe valvular heart disease is lower at 14-22%. The most frequently affected valves are the mitral and aortic valves, with regurgitation being the predominant abnormality (Table 4) (67, 68).

The risk of valvular disease increases with longer disease duration, advancing age, and in patients with poorly controlled GH excess. The odds of valvular disease increase by 19% per year of exposure to elevated GH levels (66, 67, 159). Moreover, valvular disease is only partially reversible with control of acromegaly, as valve fibrosis may persist after normalization of GH/IGF-1 levels (65, 67).

Screening and diagnosis

Valvular heart disease, particularly mitral and aortic regurgitation, is often subclinical and becomes more prevalent with longer disease duration and inadequate biochemical control, contributing to heart failure and increased CV morbidity (1, 65-68, 159). Therefore, screening for cardiac valve disease with transthoracic echocardiography is recommended at the diagnosis of acromegaly and may be needed periodically during the follow-up (Table S2) (58). However, clinical examinations should precede the conduction of serial cardiac ultrasound examinations.

Echocardiographic studies demonstrated that up to 86% of patients with active acromegaly and 73% of those with controlled disease have some form of mitral or aortic valve abnormality, with significant regurgitation present in a minority of patients (68). Advanced echocardiographic techniques, such as speckle tracking echocardiography, may detect subclinical myocardial and valvular dysfunction before overt changes in ejection fraction or clinical symptoms, supporting their use in selected cases for early risk stratification (160). Additional CV risk factors should be aggressively managed, as they accelerate the progression of cardiac complications (159, 161).

Cardiac arrhythmias and conduction defects

Epidemiology

Acromegaly is associated with an increased prevalence and incidence of cardiac arrhythmias, particularly atrial fibrillation and complex ventricular arrhythmias (9). Dysrhythmias may be detected in up to 48% of patients with acromegaly, and as high as 90% of patients with active disease (70, 162, 163). However, data from a recent systematic review reported a lower mean prevalence of 13% (7). Several studies showed that patients with acromegaly have a higher prevalence of ECG changes compared to controls that increase the risk for ventricular arrhythmia, such as prolongation of the QT interval, QT dispersion, or changes in Tp-e/QT ratios (164, 165).

Kahaly et al (74) found that 48% of individuals with acromegaly exhibited complex ventricular arrhythmias, compared to only 12% in controls. In that study, the frequency of premature ventricular complexes increased with the duration of acromegaly,

and the severity of arrhythmia correlated with LVM but not with GH levels (74). Similarly, in a large matched cohort study comprising 1874 acromegaly patients and 9370 controls, the risk of atrial fibrillation was higher in the acromegaly group (HR 1.59; 95% CI 1.09-2.31), even after adjustment for major cardiometabolic risk factors (147). Overall, atrial fibrillation seems to be more common than ventricular arrhythmias. For example, in the French study with 3551 patients included, the prevalence of atrial fibrillation was 7.7%, while ventricular tachycardia/fibrillation was present in only 0.8% of patients (37). In addition, late potentials (recognized predictors of malignant ventricular arrhythmias and sudden cardiac death) are commonly detected in this population (6). This is clinically relevant, as arrhythmias are closely linked to increased mortality, mainly through its association with sudden cardiac death. In the Dutta study, 6 out of 150 acromegaly patients had overt congestive heart failure (4.0%), and 3 of these 6 patients died due to refractory ventricular arrhythmias (166). However, it should be taking into account that the 6 patients had advanced CV disease as 4 patients had New York Heart Association Functional Classification (NYHA) class IV dyspnea and 2 had class III and left ventricular ejection fraction was 30% or less with echocardiographic features suggestive of global biventricular hypokinesia in all patients. Table 5 summarizes the cardiac arrhythmias described in patients with acromegaly and their prevalence.

Screening and diagnosis

Considering the high prevalence of conduction abnormalities and arrhythmias in patients with acromegaly, at least one ECG should be performed at the time of the diagnosis of acromegaly (10, 58) (Table S2). The 24-h Holter ECG monitoring is advised if there is an abnormal baseline ECG and clinical suspicion of cardiac dysrhythmia (170). Nevertheless, the last Acroconsensus on the management of acromegaly-associated comorbidities only recommends ECG, as arrhythmias are relatively uncommon in acromegaly, and when present, these are likely related to structural heart disease, particularly cardiomyopathy (141).

Coronary artery disease

Epidemiology

The prevalence CAD in acromegaly has been a matter of controversy and seems to be lower than expected. A recent review reported a lower mean prevalence of CAD in acromegaly at 6% (7). Paisley et al (171). did not report an increased prevalence of CAD, nor carotid atherosclerosis, or increased carotid intima media thickness in acromegaly patients when compared to control subjects. Data from Italy, Belgium, France, and Mexico suggest that CAD rates are similar to those of the general population (10, 31, 172, 173). Moreover, the incidence of myocardial infarction or other CV events in adequately treated acromegaly patients does not differ from the general population (81, 147), nor from patients with non-functioning pituitary tumors (174). Concomitant presence of additional CV risk factors such as smoking, SAS, hyperglycemia, dyslipidemia, and obesity, seems to have a greater impact on the development of CAD and atherosclerosis, rather than the long-term GH and IGF-1 excess (10, 175). Other studies showed an increased CAD risk in patients

Table 5 Prevalence of cardiac arrhythmias in patients with acromegaly

Study, year	Study population (N)	Overall prevalence	Type of arrhythmias
Hayward et al 1987 (163) (ECG diagnosis)	256	3.5%	Repolarization disorders or intraventricular conduction defects
Rodriguez EA (20), 1989 (ECG diagnosis)	34	41%	Conduction disorders
Kahaly G (74), 1992 (ECG diagnosis)	32	48%	Complex ventricular arrhythmias (Lown III-IV) in 48% and repetitive ventricular arrhythmias (Lown IV a/b) in 31%
Hermann (167), 2001 (ECG diagnosis)	48	56%	Late potentials in ECG
Lombardi (168), 2002 (24-hour dynamic ECG diagnosis)	19	40%	16.6% had supraventricular premature beats, and 35% ventricular premature beats
Warszawski et al (162) 2016 (Diagnosis with 24h-Holter)	36	89%	Isolated and paired ventricular ectopy in 71% and 21%, isolated and paired supraventricular ectopy in 89% and 39%, non-sustained ventricular tachycardia in 11% and non-sustained supraventricular tachycardia in 46%
Melkozerov (169), 2020 (ECG diagnosis)	461	42%	Most frequent: bradycardia 19.1% and conduction disorders of bundle branch blocks 14.5%.
Hong S (147), 2022 (ECG diagnosis)	1874	2.24% (incidence)	Atrial fibrillation in 2.24% (vs 1.25% in controls)

Abbreviation: ECG: electrocardiogram

with acromegaly (27, 172, 176), and elevated IGF-1 has been associated with an increased risk of mortality, diabetes, major adverse cardiovascular events and cancer (176).

Studies using non-invasive imaging techniques (eg, coronary computed tomography [CT] or calcium scoring) have yielded conflicting results, with some showing increased coronary artery calcium (177), while others reporting preserved coronary flow reserve (178), suggesting that other mechanisms beyond atherosclerotic disease may drive CV morbidity in these patients.

Screening and diagnosis

Given the inconsistent and relatively uncommon association between acromegaly and CAD, the routine screening for CAD in asymptomatic acromegaly patients is not recommended by current guidelines. Nevertheless, traditional CV risk factors, such as age, hypertension, dyslipidemia, insulin resistance, smoking, and SAS, remain highly prevalent in acromegaly and should be systematically evaluated, and baseline CV screening should be performed (Table S2) (58, 141).

Specific investigation for CAD in acromegaly patients should follow the general population recommendations and should be guided by the CAD risk stratification and clinical manifestations (179). If ischemic heart disease is suspected, different investigations can be requested based on local resources and experience (eg, stress tolerance test, exercise treadmill, CT calcium score) (Table S2) (58).

Cerebrovascular disease

Epidemiology

Several cohort and registry studies demonstrated a 2-fold to 3-fold increased risk of cerebrovascular disease in acromegaly

than in the general population (22, 33). However, recent series suggested that the incidence of stroke in acromegaly patients with controlled disease does not differ from the general population (81), nor from patients with non-functioning pituitary tumors (81). Specifically, the German Acromegaly Registry (81) reported an incidence of stroke similar to matched controls (standardized incidence ratio 1.17), similar to the Danish nationwide acromegaly cohort (23). However, the risk for stroke is notably higher in the presence of additional CV risk factors (13), as well as in irradiated patients (180, 181), however, studies applying newer stereotactic techniques reported low stroke risk, with the highest quality nationwide study identifying no significant difference in ischemic stroke (182).

Cerebrovascular disease accounts for approximately 5-10% of mortality in older series, although its incidence has declined over the recent decades, likely due to earlier diagnosis, improved disease control, and reduced use of radiotherapy (7, 23, 183). A meta-analysis confirmed this decrease in mortality rates, including 26 observational studies (26), which showed that cerebrovascular mortality was higher in studies published before 2008 (SMR of 3.4) but declined to near-normal levels after 2008 (SMR 1.3). The risk of cerebrovascular death is greatest in patients with prolonged diagnostic delay or persistent active disease (184-186).

A special risk factor for hemorrhagic cerebrovascular events are the cerebral aneurysms, which appear to be more prevalent in patients with acromegaly than in the general population. In a large Japanese cohort (187), cerebral aneurysms were found in 4.3% of the 208 patients with acromegaly, compared to 1.8% of the 7390 control subjects. In contrast, Manara et al (90) reported a considerably higher prevalence of 17.3% among 152 acromegaly patients evaluated with MR angiography. Given the 3.2% prevalence rate reported in the general population (188), acromegaly appears to confer an increased risk of cerebral

aneurysm formation. However, no systematic data is available on aneurysm-specific mortality in acromegaly.

In relation to ischemic stroke, one recognized risk factor in patients with acromegaly is diabetes mellitus (37). In the French cohort study of 3551 acromegaly cases, it was found that those patients with diabetes were at higher risk for most comorbidities: myocardial infarction (odds ratio [OR] 3.14 [1.92-5.13]), ischemic stroke (OR 1.64 [1.18-2.28]), and cancer of any type (OR 1.53 [1.27-1.84]) (37). Moreover, other cardiometabolic disorders like hypertension and dyslipidemia are higher in acromegaly patients than in general. These predisposing factors are concerned with the induction of acute ischemic stroke. High circulating GH levels in acromegaly may predispose to the development of acute ischemic stroke (189).

Screening and diagnosis

Since the current evidence does not suggest an increased risk of cerebrovascular disease in acromegaly, no specific screening program is recommended (Tables S3 and S4) (58, 190). Hence, screening tools and timing should be performed based on the patient's CV risk profile (Framingham score (191)), as for the general population. Brain imaging studies should be performed as clinically indicated, including in the acute setting if a stroke is suspected. An overview of the different diagnostic tools and their indication is provided in Table S3 and S4 (58).

Thrombosis and hypercoagulability

Epidemiology

Isolated cases of venous thromboembolism (192), massive pulmonary embolism (192, 193), and intracardiac thrombus (194) have been reported in patients with acromegaly without other risk factors. Nevertheless, acromegaly is not among the classically high-risk comorbidities associated with this condition. Most of the available nationwide cohorts do not mention thrombotic events in acromegaly, either at diagnosis or during the follow-up (123, 128, 130, 173, 195). Only the Danish national registry reported an increase in venous thromboembolism, with an adjusted HR of 2.3 (95% CI: 1.1-5.0) and 9.3 (95% CI: 5.4-16.0) at diagnosis and during the 30-year period after, respectively (23). However, it has been hypothesized that a hypercoagulable state may be fostered in acromegaly, which could be a relevant factor for atherothrombotic complications (26).

Screening and diagnosis

Routine screening for thrombosis or laboratory markers of hypercoagulability is not currently recommended in patients with acromegaly, either at diagnosis or during follow-up. Although acromegaly may be associated with a hypercoagulable state, current evidence is insufficient to justify routine screening for thrombophilia or subclinical thrombosis in asymptomatic patients, or, for instance, to recommend thromboprophylaxis in acromegaly. Targeted coagulation tests may be appropriate in selected cases, particularly in individuals with a personal or family history of thrombosis, unexplained vascular events, or additional predisposing risk factors, as for the general population recommendations (196).

Table 6 Prevalence of diabetes mellitus in the main registry series of patients with acromegaly

Author, year [reference]	Country	Study population Size (n)	Prevalence of diabetes (%)
Gatto et al 2018 (199)	Italy	74	14.6%
Arosio M. 2012 (200)	Italy	1512	16%
Vallette S, 2013 (124)	Canada	649	27%
Schöfl C, 2013 (125)	Germany	1344	45.0%
Kwon O, 2013 (126)	South Korea	1350	28.6%
Howlett TA 2013 (127)	UK	2572	28%
Portocarrero-Ortiz LA, 2016 (128)	Mexico	2057	18.4%
Vila G, 2016 (129)	Austria	607	29%
Fieffe S, 2011 (201)	France	519	47.5%
Maione L, 2017 (130)	France	980	27%
Esposito D, 2018 (25)	Sweden	1089	27%
Mestron A, 2004 (195)	Spain	1219	37%
Araujo-Castro M, 2024 (121)	Spain	604	26%

Diabetes Mellitus and impaired glucose metabolism

Epidemiology

Diabetes mellitus and glucose metabolism disorders are prominent comorbidities in acromegaly, affecting up to two-thirds of newly diagnosed acromegaly patients (7). The prevalence of diabetes mellitus increases with duration of acromegaly (33) and, notably, diabetes frequently persists despite biochemical remission of acromegaly (48). A systematic review (3) revealed a pooled diabetes prevalence of 28-33% across continents, but single-center and regional cohorts reported higher glucose abnormality rates as high as 52% (197) and over 60% (198). In a Spanish study performed in 2004, including 1219 cases, diabetes mellitus was reported in 37% (195), while in a more recent series, including more than 600 patients, the diabetes prevalence was 26% in GH-secreting pituitary adenomas and 13% in GH&PRL co-secreting tumors (121). In two distinct Italian series, the prevalence of diabetes mellitus was lower at 14% and 16% (199, 200), whereas the French acromegaly registry reported a prevalence rate of 47% and 27% (Table 6).

Screening and diagnosis

The current acromegaly guidelines strongly recommend systematic screening for diabetes and glucose intolerance at diagnosis and during follow-up (1, 141, 202). Initial screening should include measurement of FPG, HbA1c, and OGTT. After the diagnosis of acromegaly, FPG, and HbA1c should be performed every 6 months, especially those with CV risk factors, and following changes in the medication or disease activity. The most-accepted diagnostic criteria for diabetes and glucose intolerance in acromegaly align with the American Diabetes Association and the World Health Organization guidelines: FPG ≥ 126 mg/dL, 2-hour OGTT glucose ≥ 200 mg/dL, or HbA1c $\geq 6.5\%$ (203).

Table 7 Prevalence of dyslipidemia in the main registry series of patients with acromegaly

Author, year [reference]	Country	Study population Size (n)	Prevalence of dyslipidemia (%)
Gatto F, 2018 (199)	Italy	74	NR
Arosio M, 2012 (200)	Italy	1512	NR
Vallette S, 2013 (124)	Canada	649	NR
Schöfl C, 2013 (125)	Germany	1344	NR
Kwon O, 2013 (126)	South Korea	1350	NR
Howlett TA 2013 (127)	UK	2572	NR
Portocarrero-Ortiz LA, 2016 (128)	Mexico	2057	24%
Vila G, 2016 (129)	Austria	607	NR
Fieffe S, 2011 (201)	France	519	NR
Maione L, 2017 (130)	France	980	NR
Esposito D, 2018 (25)	Sweden	1089	NR
Mestron A, 2004 (195)	Spain	1219	NR
Pascual-Corrales E, 2024 (103)	Spain	604	29.2%

In some specific situations, it is recommended to re-screen the patients for glucose metabolism abnormalities, particularly after initiation of SRLs (especially pasireotide), dose escalation, or therapy switching. Pasireotide, in particular, necessitates close glycemic monitoring in the short term due to the high risk of early therapy-induced hyperglycemia, which may appear in approximately 50% of patients treated with pasireotide (204, 205).

Dyslipidemia

Epidemiology

Dyslipidemia is highly prevalent in acromegaly, with up to 61% of patients exhibiting lipid abnormalities regardless of their GH and IGF-1 levels (9, 108, 157, 206) (Table 7). Typical lipid profile changes in acromegaly include elevated total cholesterol, LDL, VLDL, triglycerides, and Lp(a), along with decreased HDL cholesterol (9, 108, 157, 206) (107).

Hypertriglyceridemia affects 33-40% of acromegaly patients, roughly 3 times higher than in the general population, while low HDL levels are observed in 39-47% of patients (108). Furthermore, an increased proportion of small, dense LDL particles, which are more atherogenic, is commonly observed in patients with acromegaly (207). Other apolipoproteins, such as Apo A-I and Apo E, involved in lipid transport, are also found elevated in these patients (108).

Screening and diagnosis

Given the absence of acromegaly-specific recommendations for lipid screening and the heterogeneity of reported findings, current practice is to follow the guidelines for the general population (208). Nonetheless, in patients with additional risk factors (eg, diabetes, obesity, or previous radiotherapy), a more proactive approach to lipid assessment and CV risk stratification may be warranted. Future studies are needed to define lipid-related risk in this population better and to determine

whether tailored screening or treatment algorithms would provide incremental benefit (209).

Sleep apnea syndrome

Epidemiology

In patients with acromegaly, respiratory complications frequently present as respiratory failure and obstructive SAS (70). Obstructive SAS is defined by an apnea-hypopnea index greater than 5 events per hour. This condition is associated with sleepiness, fatigue, poor concentration, and increased mortality and morbidity linked to CV disease (49). In this regard, it should be noted that respiratory disorders constitute a relevant cause of illness and impaired physical performance in patients with acromegaly. In relation to respiratory mortality, a recent retrospective analysis from the UK Acromegaly Register reported an excess mortality due to vascular and respiratory disease in patients with acromegaly and the risk was highest in the first 5 years following diagnosis, but was mitigated by normalizing GH levels (27).

It is estimated that 20% to 80% of patients with acromegaly are affected by sleep apnea, mainly due to the obstructive form (two-thirds of cases) (70, 210, 211). Although it may be expected a higher prevalence in patients with active disease, a meta-analysis of 21 articles for a total of 24 studies with 734 patients included that compared obstructive SAS prevalence in patients with active and controlled acromegaly found a similar prevalence of obstructive SAS between groups (ES = -0.16; 95% CI, -0.47 to 0.15; $P = .32$) (212). On the other hand, the prevalence of acromegaly in patients with obstructive SAS ranges between 0.14% and 0.35%, being higher than the reported the general population (0.003%–0.014%) (213-215). The Danish national registry reported an HR of obstructive SAS of 11.7 (95% CI, 7.0 to 19.4) in acromegaly compared with the general population (23). However, guidelines on SAS management do not propose systematic screening for the presence of acromegaly (216).

Screening and diagnosis

Guidelines for diagnosis and treatment of acromegaly suggest a screening test and IGF-1 measurement when there are multiple associated comorbidities, including SAS (217). In those patients with a newly diagnosed acromegaly, clinical guidelines recommend that every patient should have a careful symptomatic assessment (eg, by Epworth score), and if necessary laboratory assessment, for sleep apnea at the time of diagnosis, in collaboration with a respiratory physician (152). The gold standard for the diagnosis of SAS is polysomnography. Furthermore, it should be taking into account that sleep apnea does not consistently resolve after effective treatment of acromegaly, so post-treatment evaluation is recommended (218).

Recommendations for the diagnosis and screening of cardiovascular comorbidities in acromegaly

Currently, there are no guidelines specifically focused on the diagnosis and screening of CV comorbidities in acromegaly;

Table 8 Evidence robustness assessment for cardiovascular complications in acromegaly

CV complication	Level of evidence	Number of studies	Total patients studied	Key study types	Evidence quality	Main limitations
Hypertension	High	>50 studies	>20 000	Large registries, meta-analyses, prospective cohorts	★★★★★	Variability in diagnosis methods (office vs ABPM); heterogeneous definitions across studies
Cardiomyopathy/LVH	High	>40 studies	>5000	Echocardiography studies, cardiac MRI studies, prospective cohorts	★★★★★	Different imaging modalities yield different prevalence; older echo-based studies overestimate compared to MRI
Valvular Heart disease	Moderate-High	~15 studies	~1500	Case-control studies, prospective echocardiography series	★★★★★	Most cases are mild; clinical significance unclear; limited long-term outcome data
Cardiac arrhythmias	Moderate	~10-15 studies	~1000	ECG studies, Holter monitoring, registry data	★★★★★	Small cohorts; heterogeneous definitions; limited data on clinical outcomes and sudden death
Diabetes Mellitus	High	>30 studies	>15 000	Large registries (n = 10), meta-analyses, prospective cohorts	★★★★★	Variability in diagnostic criteria (FPG vs OGTT vs HbA1c); different study designs
Coronary artery disease	Moderate	~15-20 studies	~2000	Imaging studies (CT, angiography), registry data	★★★★★	Conflicting results; unclear if prevalence truly elevated; heterogeneous patient populations; limited prospective data
Cerebrovascular Disease	Moderate	~10 studies	~5000	Registry data, national cohorts	★★★★★	Most data from registries; limited mechanistic studies; confounding by radiotherapy in older cohorts
Hypercoagulability	Low	~8-10 studies	<300	Small case-control studies	★★★★★	Very small cohorts; inconsistent findings; most studies <50 patients; lack of prospective data
Thrombotic events	Low	5-7 studies	~2000	Registry data, case reports	★★★★★	Mostly registry mentions; very few dedicated studies; incidence unclear; limited mechanistic understanding
Dyslipidemia	Moderate	~15 studies	~1500	Cross-sectional studies, small cohorts	★★★★★	Prevalence varies widely (33-61%); limited data on clinical impact; unclear relationship with atherosclerosis in acromegaly

(continued)

Table 8 Continued

CV complication	Level of evidence	Number of studies	Total patients studied	Key study types	Evidence quality	Main limitations
Sleep apnea syndrome	Moderate-High	~20-25 studies	~2500	Polysomnography studies, meta-analyses	★★★★★	Variable diagnostic criteria; unclear reversibility with treatment; limited prospective data
Overall mortality	High	>40 studies	>25 000	Meta-analyses, national registries, long-term cohorts	★★★★★	Temporal trends complicate interpretation; changing treatment paradigms; residual confounding

Evidence Quality Rating Scale:

- ★★★★★ **Very high:** Multiple large studies (>1000 patients), consistent findings, meta-analyses available, prospective data
- ★★★★ **High:** Several studies (>500 patients), mostly consistent findings, some prospective data
- ★★★ **Moderate:** Multiple small-moderate studies (100-500 patients), some inconsistency, mostly retrospective
- ★★ **Low:** Few small studies (<100 patients), significant inconsistency, case series predominate
- ★ **Very low:** Very few studies, case reports/small series only, highly inconsistent or absent data

Summary of Evidence Gaps:**Well-established (high confidence):**

- Hypertension: ~35-45% prevalence, clear pathophysiology, treatment benefits established
- Cardiomyopathy: ~15-60% prevalence (method-dependent), reversible with treatment, clear mechanisms
- Diabetes: ~20-45% prevalence, well-defined risk factors, treatment effects known
- Mortality: Clear historical excess, improvement with modern treatment, robust registry data

Moderately established (moderate confidence):

- Valvular disease: Prevalence clear but clinical significance uncertain
- Arrhythmias: Present but relationship to disease activity unclear
- CAD: Paradoxically lower than expected; mechanisms unclear
- Cerebrovascular disease: Risk elevated but magnitude uncertain
- Sleep apnea: Common but reversibility uncertain

Poorly established (low confidence):

- Hypercoagulability: Laboratory abnormalities inconsistent
- Thrombotic events: Clinical significance unclear despite laboratory changes
- Precise mechanisms linking GH/IGF-1 excess to specific complications remain incomplete

Abbreviations: ABPM, ambulatory blood pressure monitoring; CAD, coronary artery disease; CT, computed tomography; ECG, electrocardiography; FPG, fasting plasma glucose; GH, growth hormone; HbA1c, glycated hemoglobin; IGF-1, insulin-like growth factor 1; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test.

however, a few consensus recommendations have been generated (219, 220). The management of diabetes and dyslipidemia should follow general population guidelines (Table 8).

There are many exams available to diagnose these comorbidities (Tables S2 and S3) (58). The method of choice and its frequency is not established; thus, it may be decided on an individual basis considering the underlying CV risk factors, cardiometabolic comorbidities, and duration and severity of the disease (10, 57).

Given the high prevalence of CV disease in acromegaly, which may be further aggravated in hypertensive patients, a general cardiac status assessment at diagnosis and during follow-up should be performed. The minimal baseline assessment should include BP measurement (at least every 6 months), an ECG (annually), and an echocardiogram (annually, particularly in case of hypertension, cardiac abnormality, active disease, or moderate-high CV risk) (152). The use of echocardiograms at diagnosis and during follow-up for all patients is recommended, especially for patients with hypertension and/or diabetes mellitus (151). In the presence of clinical disease or suspicion of it, or before pituitary surgery, a detailed cardiac evaluation is advisable.

Regarding CAD and atherosclerosis, due to the heterogeneity in prevalence across different studies, establishing an optimal screening approach is complex. The current evidence does not seem to suggest an increased risk of CAD in acromegaly. Hence, screening tools and timing should be performed based on the patient's CV risk profile (Framingham score), as for the general population. In case of suspected ischemic heart disease, the assessment includes an ECG or a stress and/or exercise tolerance test to evaluate cardiac performance, while other exams, such as CT angiography, CT calcium score, coronary catheterization, positron-emitted tomography, and carotid ultrasonography, allow a better evaluation of arterial damage and provide further information when needed (10, 57, 151).

Despite the diagnostic approach followed to identify CV comorbidities, it is important to maintain a longitudinal monitoring of the cardiometabolic status of these patients, and a rigorous management of their individual complications during the long-term follow-up (10, 57). In addition, for those patients with symptomatic CV disease we recommend referring these patients to the dedicated specialist who will decide about the optimal management.

Impact of acromegaly treatments on cardiovascular and metabolic comorbidities

Effects on hypertension

There is an inverse relationship between serum IGF-1 and BP in conditions associated with low IGF-1 concentrations, and a positive correlation between IGF-1 and BP in high IGF-1 conditions (208). Addressing GH hypersecretion in acromegaly is crucial, as reducing or normalizing GH/IGF-1 levels leads to BP reduction. Surgery is the preferred first-line treatment for acromegaly, as it offers the potential for cure (1, 221, 222). Following successful surgery, most patients have BP improvements, with greater benefits in those with pre-existing hypertension (122, 223). In a

recent large Iberian acromegaly cohort study, it was observed a significant BP improvement just 3 months after the pituitary surgery with a marked reduction of systolic and diastolic BP. Hypertension remission was achieved in around 15% of hypertensive acromegaly patients after pituitary surgery, and it was more likely in patients who had a greater decrease in GH and IGF-1 levels after the operation (122).

Several other studies have demonstrated that GH/IGF-1 normalization, regardless of the treatment modality, positively impacts BP reduction, particularly in hypertensive patients (11-13). Treatment with first-generation SRLs (fgSRLs) (16) and pegvisomant (17) reduces the progression of LVH and improves structural cardiac dysfunction, including left ventricular ejection fraction. The effects of pasireotide in BP and hypertension remain to be evaluated; however, its modulatory effects on other relevant CV parameters are relevant. Pasireotide increases FPG and leads to a rise in diabetes prevalence, but on the other hand, improves the lipid profile by increasing HDL cholesterol and decreasing triglyceride levels (224-227). Clinically non-relevant QT interval prolongations have also been reported with pasireotide (228).

Given the pathophysiology of hypertension in acromegaly, it is not surprising that the prevalence is significantly higher in biochemically uncontrolled patients (172, 229). This was observed in a retrospective observational multicenter study evaluating BP changes in 105 hypertensive acromegalic patients at diagnosis and after 24 months (230). In this study, no difference was found in GH/IGF-1 levels between patients with mild or severe hypertension. While diastolic BP and left ventricular mass index improved in all patients under acromegaly treatment, systolic BP and cardiac function improved only in the patients who achieved biochemical control. Moreover, it was noted that uncontrolled acromegaly patients required significantly more antihypertensive medication (230).

Several studies evaluated the effect of different GH/IGF-1-lowering treatments on BP and CV morbidity. Surgical intervention has been shown to have the fastest effect, improving hypertension within 3 to 6 months and restoring a normal circadian BP rhythm (15, 231, 232). Significant improvements in both systolic BP (15, 231, 232) and diastolic BP (16, 233) have been described following adequate treatment of acromegaly.

A meta-analysis dated from 2007 showed no significant decrease in BP in patients under fgSRL treatment (16). This contrasts with data from two prospective studies where a reduction in BP in patients treated for at least 12 months has been shown (234, 235). While some studies describe a decrease in systolic BP under combined treatment (236, 237), other studies reported an effect only in biochemically controlled patients (229) or no effect (12). The importance of biochemical control was also shown in a retrospective study including 30 hypertensive and 28 normotensive patients with acromegaly. Biochemical control of acromegaly after 24 months with fgSRLs in monotherapy or in combination with pegvisomant had a beneficial effect on BP regulation (135). In addition, less progression of LVH and improved markers of structural cardiac dysfunction were observed in biochemically controlled patients in other studies (16, 238). Overall, the positive effect of fgSRLs and pegvisomant on BP appears to be dependent on long-term control of acromegaly. There is no data on the impact of cabergoline or radiotherapy on BP values in acromegalic patients. However, a recent study

described a weight and BMI reduction in acromegaly patients treated with cabergoline. Although BP was not studied, the weight loss related to the use of cabergoline in acromegaly may, in theory, improve the BP.

The impact of hypertension on clinical outcomes was demonstrated in the ACROSTUDY involving 2090 patients with acromegaly, 1344 of whom had hypertension. Although the mortality rate did not differ from the general population with hypertension (239), patients with hypertension had a 3.3-fold increased mortality rate compared to the normotensive patients (240).

Effects on cardiovascular complications

Treatment with fgSRLs can reduce cardiac dysrhythmia in some cases by reducing heart rate, premature ventricular beats, and QT interval (241, 242). Pegvisomant reduces the mean heart rate and reduces the risk of arrhythmias. In the Auriemma et al study, pegvisomant reduced the prevalence of arrhythmias from 15 down to 7.7%, and its complete disappearance was observed in one patient after 18 months of pegvisomant treatment (243). Pasireotide is associated with QT prolongation (2). In relation to cabergoline, the CV effects of this drug on acromegaly remain unclear, as it may be dose and duration dependent. Maione et al (244) compared patients treated with a median cumulative dose of 203 mg of cabergoline during 35 months vs patients never treated with cabergoline and found no differences in the incidence of new valve regurgitation (40.0 vs 45.8%, respectively) and disease control. Some studies did not observe changes in the frequency of ventricular arrhythmias after successful treatment of acromegaly (245).

All stages of acromegaly-related cardiomyopathy and cardiac morpho-functional parameters can improve during successful treatment of acromegaly, although more significant improvements are seen in earlier disease stages. Conversely, the cardiac output of patients with congestive heart failure may benefit from effective acromegaly treatment, particularly their systolic function. Still, full recovery is not possible, and long-term prognosis remains poor (16, 246). The cardiac improvements following GH/IGF-1 normalization can be observed regardless of the type of acromegaly treatment (14-17). Combined therapy with pegvisomant and fgSRLs may also improve the cardiac structure and function, notably the diastolic dysfunction, in acromegaly patients resistant to isolated therapy with fgSRLs (237). In order to achieve the maximal improvement of the acromegalic cardiomyopathy, GH/IGF-1-lowering treatments must be combined with efforts and therapies to optimize other coexisting CV risk factors (50). Popielarz-Grygalewicz et al (247) suggested that fgSRLs may restore disturbed coronary function in patients with acromegaly.

Effects on diabetes

The different medical therapies for acromegaly may impact the glycemic status variably. FgSRLs (octreotide, lanreotide), despite improving disease control, can mildly reduce insulin secretion, leading to a slight increase in HbA1c and postprandial glucose levels, without significantly affecting FPG levels (248). Those patients with pre-existing impaired glucose tolerance or diabetes are more prone to glycemic deterioration during treatment with fgSRLs (249). In contrast, pasireotide has a reversible negative impact on glycemic control due to its high potency in

suppressing endogenous insulin secretion, resulting in increased FPG, HbA1c, and diabetes (250). A recent meta-analysis with 20 real-world studies comprising 409 patients, reported a significant increase in FPG (SMD -0.8 mg/dL [95% CI: -1.0 to -0.5 , $P < .01$]), HbA1c (SMD -0.5% [95% CI: -0.7 to -0.2]) and type 2 diabetes prevalence (SMD -11.5% [95% CI: -17.5 to -5.5]) after pasireotide initiation (250). Similar results were reported from another recent meta-analysis describing a higher frequency of diabetes after pasireotide treatment (OR 3.7, 95% CI 2.9-4.7) (205). According to the data from the main clinical trials, the rates of hyperglycemia and diabetes with pasireotide treatment were approximately 41.5-42.4% and 23.6-24.2% respectively (251, 252). The hyperglycemic effect of pasireotide is mainly attributed to an impairment in insulin secretion, while insulin sensitivity remains unaffected (253). The main risk factors of hyperglycemia with pasireotide are older age, the presence of previous impaired glucose tolerance, elevated HbA1c, a history of dyslipidemia or hypertension, and BMI ≥ 30 kg/m² (254). These glucose disturbances typically appear shortly after pasireotide initiation and tend to improve once the therapy is withdrawn (254, 255).

Pegvisomant has a favorable effect on carbohydrate metabolism by decreasing FPG and HbA1c, as well as improving insulin sensitivity (256-258). A meta-analysis of 30 studies with pegvisomant in monotherapy and 5 with pegvisomant in combination with fgSRLs showed a significantly decrease of FPG [effect size (ES) -0.80 mmol/L (95% CI, -1.06 to -0.55); $P = .000$], of HbA1c [ES -0.43% (95% CI, -0.56 to -0.31); $P = .000$], of fasting plasma insulin [ES -5.31 mU/L (95% CI, -10.23 to -0.39); $P = .034$], and of HOMA-IR [ES -0.61 (95% CI, -1.17 to -0.04); $P = .034$] (256). It should be noted that the combination of pegvisomant with fgSRLs mitigates the negative impact of fgSRLs on glucose metabolism, producing an overall neutral effect (256).

Dopamine agonists seem to improve insulin sensitivity and may exert a positive effect on carbohydrate metabolism (259). A study of 12 patients with acromegaly treated with bromocriptine showed a significant decrease in basal and glucose-stimulated insulin levels in all patients after treatment (260). The addition of cabergoline to pegvisomant decreases the postprandial glucose rise (261). However, a recent study aimed to evaluate the effect of cabergoline on weight and glucose metabolism in patients with acromegaly, failed to demonstrate a marked benefit on glucose metabolism (262).

Effects on dyslipidemia

Achieving biochemical control of acromegaly positively affects cardiometabolic parameters, including the lipid profile (108). Transsphenoidal surgery has been associated with improvements in lipid levels, including reduction of triglyceride levels and an increase in HDL cholesterol levels following normalization of serum GH and IGF-1 (263). FgSRLs, particularly octreotide long-acting release demonstrated significant reductions in triglycerides, total cholesterol/HDL ratio, and Lp(a), and led to an increase in HDL cholesterol levels (264). Similarly, lanreotide has been shown to lower triglycerides and increase HDL cholesterol in non-diabetic acromegaly patients (264). However, pegvisomant has mixed effects on lipids, as it reduces Lp(a) levels but may increase total cholesterol and triglycerides in some cases (265). Pasireotide has been studied mostly in healthy volunteers, showing dose-dependent reductions in serum cholesterol and

triglycerides (108). Pasireotide also seems to have a beneficial effect on the lipid profile of patients with Cushing's disease (266), but evidence concerning acromegaly is limited.

Effect on sleep apnea syndrome

Overall, the treatment of acromegaly improves SAS in a substantial number of patients, but biochemical control does not reliably predict remission of SAS. Some studies showed that 40% of patients with controlled acromegaly have persistent SAS after treatment (118, 120, 267). In an Italian study including 36 acromegaly patients (18 active and 18 controlled), the prevalence of SAS was 56% in the active group and 39% in the controlled one, and in the longitudinal evaluation available in 6 patients, 5 showed improvement of SAS, but none recovered (118). A recent prospective study with 35 patients found that after surgery (with a remission rate of 91.4%), 20 of the 24 patients diagnosed with obstructive SAS preoperatively had an respiratory event index <5/hour postoperatively (267). SRLs may have a positive impact on obstructive SAS (118, 268, 269). Herrmann *et al* described a significant tongue volume decrease in patients with controlled acromegaly (120+/-14 mL, $P < .05$) in comparison with the persistent uncontrolled group of patients (137+/-10 mL, $P =$ not significant) after treatment with octreotide (268). In the same line, one prospective study with 30 patients with newly diagnosed acromegaly concluded that presurgical therapy with lanreotide autogel lowers GH and IGF-1 concentrations, induces tumor shrinkage, and ameliorates/reverses cardiac, vascular, and sleep complications in many patients with acromegaly (270). However, they found that unexpectedly, despite almost universal improvements in biochemical control (GH and IGF1 reductions in 93% of the cases), apnea hypopnea index responses to SRL therapy varied markedly among individuals: 14 (61%) exhibited an improvement and 2 (8.7%) showed no change, but 7 (30.4%) manifested a significant deterioration in obstructive SAS. Thus, although in general improvement of obstructive SAS is expected, it is difficult to identify which patients will improve. Nevertheless, the current guidelines support the use of presurgical therapy with SRLs for patients with severe pharyngeal thickness and sleep apnea, or high-output heart failure, with the aim of reducing surgical risk from severe comorbidities (1). There is no available information about the impact of pasireotide on SAS, but due to the mechanism of action, a similar or even higher effect than first generation SRL should be expected. Another study with 12 patients treated with pegvisomant reported that tongue volume decreased (105+/-33 to 83+/-33 mL; $P = .007$) as well as the apnea-hypopnea index (23+/-22 to 18+/-18/h; $P = .0066$) after treatment with pegvisomant (271).

Management of cardiovascular and metabolic comorbidities in acromegaly

General recommendations: lifestyle and non-pharmacological interventions

As there is no specific recommendation for patients with acromegaly, lifestyle, and non-pharmacological interventions in

acromegaly patients should follow the general recommendations as for any patient with increased CV risk (142): sodium restriction (<2.3 g/day) and increased potassium intake, except in patients with chronic kidney disease; weight management is essential, particularly after successful acromegaly treatment, to prevent metabolic complications; aerobic and resistance exercise (≥ 150 minutes/week of moderate intensity) to improve endothelial function and reduce BP; management of obstructive SAS, which is highly prevalent in acromegaly and can contribute to BP elevation and smoking cessation. As recommended for patients with diabetes in general, lifestyle interventions are essential for proper control of acromegaly-related diabetes or glucose abnormalities. These positive health behaviors include diabetes self-management education and support, medical nutrition therapy, routine physical activity, adequate quality sleep, support for cessation of tobacco products, health behavior counseling, and psychosocial care (272).

Management of hypertension

There are no studies specifically addressing the medical treatment of hypertension in acromegaly. Thus, the selection of antihypertensive medications should follow similar principles as for the general population, with no specific antihypertensive drug class being universally recommended in acromegaly (Table S5 and Fig. 6) (58, 141).

The primary antihypertensive drug classes with strong evidence for reducing CV events through BP control in the general population include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs), thiazide or thiazide-like diuretics (such as hydrochlorothiazide, chlorthalidone, and indapamide), and β -blockers (142). ACEi are a good option for those patients with LVH or proteinuria, and ARBs are an alternative to ACEi with similar benefits. Moreover, they are effective in reducing LVH, a frequent complication in patients with acromegaly (7). The first four medications are normally recommended as first-line, while β -blockers are recommended in specific circumstances, such as angina, heart failure, post-myocardial infarction, or heart rate control. Additionally, β -blockers and diuretics may increase the risk of new-onset diabetes mellitus in predisposed patients, such as acromegaly patients (273). However, it is worth noting that some experts recommend diuretics (mainly ENaC-targeting agents) and β -blockers as a first choice in acromegaly, based on the pathophysiological mechanisms unique to this condition (42, 274). Another promising antihypertensive medication for patients with acromegaly are sodium-glucose co-transporter 2 (SGLT2) inhibitors, especially for those cases with diabetes and metabolic syndrome (275). However, SGLT2 inhibitors should be considered cautiously among partially controlled acromegaly patients and not recommended in poorly controlled patients due to the risk of diabetic ketoacidosis (276).

Real-world data from the recent Iberian acromegaly study showed that the most used drug classes were ACEi (40.2%) and ARBs (37.3%), followed by thiazide diuretics (34.9%) and CCBs (22.5%), while β -blockers were used in 18.2% of the cases, mirroring the above-mentioned recommendations concerning first-line antihypertensive drugs (122).

In addition, as recommended for the general hypertensive population (142), combined antihypertensive therapy may be also advisable for acromegaly patients with hypertension, except in specific situations detailed in Fig. 6. This approach enhances treatment efficacy, likely due to the ability of targeting multiple physiological mechanisms underlying acromegaly-related hypertension, as well as it minimizes the occurrence of side effects as lower doses of individual antihypertensive drugs are used (142).

Management of cardiovascular disease

In relation to cardiomyopathy, it is reported that it can be reversed if the diagnosis is made early in the course of the disease. The management of heart failure should follow standard guidelines for heart failure, and thus, ACEi, ARBs, β -blockers, and mineralocorticoid receptor antagonists are useful (9, 161). For arrhythmia management, it is important to ensure optimal control of heart rate and consider the use of devices such as implantable automatic defibrillators or pacemakers, especially for patients with advanced atrioventricular block. Moreover, catheter ablation should be considered in patients with atrial fibrillation to improve symptoms, quality of life, and ventricular function (39, 161).

Atherosclerosis may be better managed by targeting commonly recognized CV risk factors (smoking status, insulin resistance, hypertension, etc.) (9). The main therapeutic interventions focused on improving CV prognosis in acromegaly patients are described in Table S6 (58). However, it should be noted that those patients with clinically relevant heart failure, arrhythmia or CAD, should be referred to and treated by a dedicated cardiologist.

Management of diabetes and dyslipidemia

The management of diabetes in acromegaly presents unique therapeutic challenges, requiring individualized approaches that consider the underlying pathophysiology of GH/IGF-1 excess (98, 99). First-line treatment should aim at achieving biochemical control of GH and IGF-1, as normalization of hormonal excess has been shown to improve insulin sensitivity and glucose metabolism (103). However, certain considerations are necessary when surgery fails to achieve GH and IGF-1 normalization. In such cases, the choice of pharmacologic therapy for acromegaly should take into account the potential metabolic impact, as some agents may negatively affect glucose homeostasis (250, 277). When antihyperglycemic therapy is required, the treatment approach generally follows standard diabetes guidelines for the general population (278). Metformin remains the preferred first-line option due to its effectiveness in lowering hepatic glucose production, improving insulin sensitivity, and a favorable cost-effectiveness profile (98, 99). Newer agents such as glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors may provide similar cardiometabolic important benefits as in type 2 diabetes. However, the distinct metabolic characteristics of acromegaly, including increased ketogenesis and potential interactions between incretins and GH secretion, should be taken into account, as they may influence therapeutic responses and safety (99).

Regarding dyslipidemia, while acromegaly is associated with altered lipoprotein metabolism (12), current treatment recommendations for managing dyslipidemia are largely based on

general cardiovascular risk management guidelines, as there are no acromegaly-specific lipid treatment protocols (209).

Gaps in current knowledge and future directions

Despite advances in understanding the CV burden of acromegaly, several important gaps remain. Most current recommendations are extrapolated from the general population, without specifically accounting for the unique pathophysiological features of GH/IGF-1 excess and the typical acromegaly-related CV phenotype. Prospective, longitudinal studies with well-defined CV endpoints are still lacking. In particular, there is a need for standardized protocols for cardiovascular screening across disease stages, especially for subclinical manifestations and for a better characterization of atherosclerotic risk, given the controversy in relation to the prevalence of CAD. In addition, a proper evaluation of the real risk of arrhythmia and sudden cardiac death of patients with acromegaly is needed, as there is no clear evidence between the link of GH/IGF-1 excess and the risk of arrhythmia and sudden cardiac death. Prospective studies focused on elucidating the real prevalence of cardiac valve disease and its clinical repercussion on patients with acromegaly should be performed, and randomized trials assessing CV outcomes in response to acromegaly-specific treatments (surgery, fgSRLs, pegvisomant, pasireotide) will be useful to determine the real impact of these therapies on CV comorbidities. We also consider that the identification of predictive biomarkers for CV complications and treatment response would help to stratify the CV risk of our patients with acromegaly and help to determine the most suitable treatment in each patient.

The future trajectory of clinical management for hypertension and associated CV complications in acromegaly necessitates a rigorous, multi-pronged research strategy. Moving beyond current generalized endocrinological and CV recommendations requires dedicated studies focusing on specific pathophysiological mechanisms, therapeutic efficacy, and risk stratification unique to this disorder. Prospective cohort studies are foundational for understanding the natural history of hypertension development, progression, and response to systemic control in acromegaly, which is often poorly captured by retrospective reviews. In addition, the temporal relationship between biochemical normalization and CV risk reduction is often assumed but requires precise longitudinal quantification. In this regard, studies must explicitly link the duration and stability of controlled disease status to hard cardiovascular endpoints. Furthermore, the identification of molecular biomarkers capable of predicting imminent CV decompensation or identifying responders to specific therapies is paramount for personalized medicine. Research initiatives and efforts covering these aspects will be essential to move from general recommendations to acromegaly-specific clinical algorithms regarding the management of hypertension and CV disease in acromegaly, which ultimately will improve the CV risk management and clinical outcomes of acromegaly patients with hypertension and/or cardiomyopathy.

Conclusions

CV disease remains a leading cause of morbidity and mortality in patients with acromegaly, necessitating a sophisticated

understanding of the interplay between hormonal excess and vascular pathology. Although the biochemical control of GH and IGF-1 significantly improves many cardiac and vascular abnormalities, a substantial residual CV risk persists. This ongoing vulnerability is frequently driven by permanent structural changes, the cumulative impact of long-standing comorbidities, and the deleterious effects of diagnostic delays that allow cardiovascular remodeling to become irreversible. Consequently, early and systematic screening, individualized treatment of CV comorbidities, and the implementation of rigorous multidisciplinary care are critical to optimizing patient outcomes. Ongoing research must now transition toward a more granular exploration of disease-specific CV pathways, moving beyond general population guidelines to address the unique pathophysiology of the acromegalic heart. To achieve this, the scientific community must prioritize the initiation of large-scale prospective cohort studies designed to track the natural history of vascular complications under modern therapeutic regimens. These longitudinal observations are essential for evaluating the long-term impact of stringent GH/IGF-1 control on systemic blood pressure and hard CV endpoints, such as myocardial infarction, heart failure, and stroke.

Furthermore, there is an urgent clinical requirement for targeted intervention trials specifically tailored to evaluate the efficacy of various anti-hypertensive classes within this population. Such trials will clarify whether certain pharmacological agents offer superior cardioprotection in the context of GH excess, thereby moving away from empirical prescribing. Parallel to these clinical trials, research efforts should be directed toward the identification and validation of novel biomarkers and clinical predictors. The discovery of these indicators is paramount for sophisticated cardiovascular risk stratification, allowing clinicians to distinguish between patients at low risk and those requiring intensive, early intervention.

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