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REVIEW

Gender differences in the glycometabolic and cardiovascular features of acromegaly

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Abstract

Introduction Gender medicine focuses on disease differences between females and males regarding symptoms, treatment, prognosis, psychosocial effects and prevention. Acromegaly is a rare endocrine disorder caused by excessive growth hormone (GH) production, in the vast majority of cases due to the presence of a GH-secreting pituitary adenoma. Chronic GH elevation leads to increased insulin-like growth factor-1 (IGF-1), resulting in tissue overgrowth and a number of comorbidities. Among these, patients with acromegaly can experience various issues of the cardiovascular and metabolic system, including glucose metabolism unbalance, diabetes mellitus, arterial hypertension and cardiomyopathy.

Aim and methods This narrative review discusses the impact of gender differences on glycometabolic and cardiovascular comorbidities in patients with acromegaly. We performed a detailed literature search, gathering scientific articles on this topic, including original research studies, case reports, reviews, systematic reviews, meta-analyses, guidelines, and consensus papers published in English from 1989 to early 2025.

Results A diagnostic delay between females and males is reported, together with a gender-related impact of the disease on body composition, lipid and glucose metabolism; gender differences in the development and progression of acromegaly cardiomyopathy are also described. In detail, females with acromegaly exhibit greater insulin resistance, increased adiposity, and higher risk of developing overt diabetes mellitus compared to males, along with milder cardiac abnormalities, despite experiencing higher cardiovascular mortality.

Conclusion Gender differences in metabolic and cardiovascular comorbidities of acromegaly need to be considered. Future studies should clarify the biological bases of these differences, to optimize treatment protocols and monitoring for our patients.

Keywords Gender medicine · Hyperglycaemia · Diabetes mellitus · Cardiovascular disease · Arterial hypertension · Cardiomyopathy

Abbreviation

ABPM	Ambulatory blood pressure monitoring
AUC	Area under the curve
BMC	Bone mineral content
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
ENaC	Epithelial sodium channel
FFAs	Free fatty acids
Fg-SRL	Second-generation somatostatin receptor ligand
FM	Fat mass
HDL-C	High-density lipoprotein cholesterol

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HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GLS	Global longitudinal strain
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor-1
IGF-1R	Insulin-like growth factor-1 receptor
IGT	Impaired glucose tolerance
IVS	Interventricular septa
LBM	Lean body mass
LV	Left ventricular
LDL-C	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMi	Left ventricular mass index
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
PAS	Pasireotide
PEG	Pegvisomant
PI3K	Phosphoinositide 3-kinase
OGTT	Oral glucose tolerance test
RhGH	Recombinant human growth hormone
ROCK	Rho-associated protein kinase
Sg-SRL	Second-generation somatostatin receptor ligand
SMR	Standardized mortality ratio
SRLs	Somatostatin receptor ligands
SSTR	Somatostatin receptor
ULN	Upper limit of normal

Introduction

Gender medicine (or gender-specific medicine) investigates how diseases differ between females and males in terms of clinical signs, therapeutic approaches, prognosis, as well as psychological, social impact and prevention strategies [1]. In the last decades, gender medicine has gained prominence as a research field aimed to improve the management of various diseases.

Acromegaly is a rare endocrine disorder caused by excessive growth hormone (GH) production, mainly due to the presence of a GH-secreting pituitary adenoma [2, 3] The chronic elevation of GH and the resulting increased secretion of insulin-like growth factor-1 (IGF-1) lead to the characteristic tissue overgrowth, to multiple comorbidities affecting various body districts such as the cardiovascular, osteoarticular, neurological, and pulmonary systems, as well as to a number of metabolic changes [2]. The clinical features of acromegaly develop insidiously over time, and its diagnosis is often delayed [4–6].

Among the above mentioned comorbidities, cardiovascular diseases represent one of the most common cause of death in patients with acromegaly [7]. Glucose intolerance and diabetes mellitus (DM) may occur in individuals with acromegaly due to either the direct effects of GH excess or the impact of specific medical therapies (e.g. second-generation somatostatin receptor ligand [sg-SRLs], pasireotide [PAS]) on glucose homeostasis [8]. Patients with untreated acromegaly have a 2–3 times increased mortality rate, while patients with controlled acromegaly have a life expectancy similar to that of the general population [9].

According to the latest consensus statement focused on diagnostic criteria [10], the diagnosis of acromegaly is confirmed in subjects with IGF-1 values > 1.3 × age-adjusted upper limit of normality (ULN) and the presence of characteristic clinical signs of the disease. Tailored ULN values based also on patient's sex, as indicated in previous consensus documents [11, 12], are no longer reported or recommended. Some studies reported that females have lower baseline IGF-1 levels but higher GH nadir after oral glucose tolerance test (OGTT) compared to males [13], while others did not find significant gender-related differences on GH nadir levels following OGTT [14].

In this literature review, we aim to highlight the impact of gender differences on glycometabolic and cardiovascular comorbidities in patients with acromegaly. By reporting data on insulin resistance, glucose metabolism, and related hormonal responses, we focus on the pathophysiological bases of these differences and their potential impact for disease management. Moreover, we aim to emphasize the importance of considering gender differences when assessing and treating patients with acromegaly.

Does the diagnostic delay impact gender differences in acromegaly?

1 As mentioned above, the diagnosis of acromegaly represents a significant challenge. In this context, a large multicenter European study (LAS database) and a recent survey suggest that female patients with acromegaly tend to be older at diagnosis and face longer diagnostic delay compared to males [15, 16]. This finding may stem from sex-specific differences in the clinical presentation. Indeed, while male patients often exhibit typical physical changes such as prognathism and enlargement of hands and feet, females are more likely to report symptoms like headache and musculoskeletal pain. Additionally, symptoms such as sweating and amenorrhea in females during their fourth-fifth decade may be misattributed to menopause, further delaying the

diagnosis [16, 17]. While oligomenorrhea is common among females with acromegaly [18], it is often mistakenly attributed to polycystic ovary syndrome, a more prevalent condition in the general population. Indeed, females with acromegaly may also present with clinical and biochemical signs of hyperandrogenism, polycystic ovarian morphology at ultrasound examination, as well as hypertension and glucose intolerance [17].

Glycometabolic features

1 The GH/IGF-1 axis plays a crucial role in regulating glucose and lipid metabolism. GH promotes anabolic actions in most tissues except adipose tissue, where its catabolic actions cause the breakdown of stored triglycerides into free fatty acids (FFAs) [8]. The chronic exposure to elevated GH levels antagonizes the antilipolytic action of insulin and increases FFA flux into the systemic circulation, thereby promoting lipotoxicity, which causes insulin resistance [19].
Although both females and males with acromegaly experience the impairment of glucose metabolism, such as increased insulin resistance and an elevated risk of DM, evidence suggests significant gender-specific differences [20, 21]. These are caused by the interaction between GH/IGF-1 axis, sex hormones, and body composition, ultimately leading to distinct metabolic profiles [22].
Impaired glucose metabolism and overt DM are known complications in patients with acromegaly: the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and DM ranges between 7 to 22%, 6 to 45% and 19 to 56%, respectively [23].

At the time of diagnosis, female patients present with a worse metabolic profile compared to males, despite exhibiting similar GH and IGF-1 levels [24]. This discrepancy includes insulin resistance and various features of metabolic syndrome, which have been attributed to visceral fat dysfunction [24]. Data from an Italian retrospective, comparative, multicenter study (Table 1) report no significant gender differences in body mass index (BMI, men: 25.54 ± 3.43 kg/m^2 vs women: 25.80 ± 3.59 kg/m^2, $p = 0.512$) and fasting glucose levels (5.44 ± 0.90 mmol/L vs 5.97 ± 0.92 mmol/L, $p = 0.755$) [24]. However, females exhibit a higher prevalence of DM compared to men (51.3% vs 19.1%, $p < 0.001$), along with a significantly greater insulin resistance as indicated by elevated Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score (5.08 ± 2.84 vs 3.59 ± 2.24, $p < 0.001$) and higher fasting insulin levels (21.25 ± 12.08 IU/mL vs 15.14 ± 8.45 IU/mL, $p < 0.001$) [24].

A recent cross-sectional, multi-center study reported that in patients with controlled disease (i.e. normal age-adjusted IGF-1 values) HOMA-IR and HOMA-beta indexes were comparable in females and males [16]. During OGTT, no difference was observed between females and males in glucose parameters (area under the curve [AUC] of glucose, fasting glucose and glucose after 120 min); however, a higher insulin response was found in female patients compared to males (insulin 120 min: 173 pmol/L vs 129 pmol/L, $p = 0.01$) [16].

The increased metabolic burden observed in females may be attributed to the direct role of estrogens in glucose metabolism and lipid storage, to their impact in the regulation of the GH/IGF-1 axis, as well as to a potential greater predisposition to adiposity and the associated insulin resistance [13]. A well-known gender-specific difference in patients with active acromegaly is the presence of lower IGF-1 values with respect to a given GH value in females compared to males [25]. This discrepancy has been mainly attributed to the inhibitory effect of circulating estrogens on hepatic IGF-1 production. However, the underlying mechanisms driving gender differences in GH secretion, particularly in postmenopausal women, may involve a paracrine action of estrogens at the central level. This hypothesis is supported by evidence showing that blocking estrogen receptor action with tamoxifen reduces GH secretion in postmenopausal women but not in men, underscoring the sex-specific influence of estrogens and their receptors on the GH/IGF-1 axis [26].

Of note, gender-specific GH responses to OGTT have been reported (Table 1) [13]: females have higher GH nadir levels (27.5 ± 3.8 µg/L vs 18.5 ± 2.3 µg/L, $p = 0.04$), while males demonstrate a greater percentage reduction (−45.1 ± 4.7% vs −17.5 ± 5.9%, $p = 0.0005$) [13]. In the specific cohort considered, males had also slightly higher basal IGF-1 levels compared to females (755.9 ± 32.9 µg/L vs 664.9 ± 24.9 µg/L, $p = 0.03$) [13], in line with the findings of a more recent meta-analysis [27].

Lipid metabolism (Table 1) also differs between genders: in biochemically controlled patients, females exhibit higher fasting FFAs levels (0.44 vs 0.37 mmol/L, $p = 0.03$), although their drop is more consistent at 120 min during OGTT (0.03 vs 0.05 mmol/L, $p = 0.02$) [16]. These differences might influence the overall metabolic risk profile, since elevated FFA levels are linked to insulin resistance and cardiovascular (CV) complications. These findings underscore a gender-specific dynamic in lipid metabolism, possibly due to differences in insulin sensitivity and body composition.

Table 1 Parameters of metabolic features in patients with acromegaly according to gender

	Study design	n. of patients	Parameter	Males	Females	*p*-value
Ciresi et al. [24] [a]	retro-spective, comparative, multicenter study	F = 150, M = 157	BMI (Kg/m^2)	25.54 ± 3.43	25.80 ± 3.59	0.512
			Fasting glucose (mmol/L)	5.44 ± 0.90	5.97 ± 0.92	0.755
			DM	19.1	51.3	< 0.001
			Family history for DM	33.8	48	0.011
			Increased WC	7	38	< 0.001
			MS	19.1	51.3	< 0.001
			Fasting insulin (IU/mL)	15.14 ± 8.45	21.25 ± 12.08	< 0.001
			HOMA-IR	3.59 ± 2.24	5.08 ± 2.84	< 0.001
			AUC insulin	7578 ± 3383	9127 ± 4622	0.02
Colao et al. [13] [b]	open retrospective multicenter cohort study	F = 79, M = 72	GH nadir after glucose load (µg/L)	18.5 ± 2.3	27.5 ± 3.8	0.04
			GH change after glucose load (%)	−45.1 ± 4.7	−17.5 ± 5.9	0.0005
			Basal IGF-I levels (µg/L)	755.9 ± 32.9	664.9 ± 24.9	0.03
Dal et al. [16][c]	cross-sectional, multi-centre study	F = 43, M = 41	FFA AUC (mmol/L)	22 (17–31)	26 (16–37)	n.s
			FFA fasting (mmol/L)	0.37 (0.22–0.48)	0.44 (0.34–0.59)	0.03
			FFA 120 min (mmol/L)	0.05 (0.03–0.09)	0.03 (0.01–0.07)	0.02
			Glucose AUC (mmol/L)	910 (800–1122)	882 (773–1152)	n.s
			Glucose fasting (mmol/L)	5.5 (5.1–5.9)	5.0 (4.7–5.7)	n.s
			Glucose 120 min (mmol/L)	6.3 (5.2–8.5)	6.8 (5.2–8.8)	n.s
			Insulin AUC (pmol/L)	15,863 (9210–23996)	20,303 (15,473–29,265)	0.04
			Insulin fasting (pmol/L)	25 (20–48)	25 (18–39)	n.s
			Insulin 120 min (pmol/L)	129 (82–203)	173 (122–342)	0.01
			Homa-Beta	46 (30–81)	54 (35–85)	0.72
			Homa-IR	1.2 (0.8–2.1)	0.9 (0.6–1.5)	0.09
			Adipo-IR	10 (6–19)	11 (5–20)	0.76

Legend: F, female; M, male; BMI, body mass index; DM, diabetes mellitus; WC, waist circumference; MS, metabolic syndrome; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; AUC, area under the curve; GH, growth hormone; IGF-1, insulin-like factor 1; FFA, free fatty acids; min, minutes; IR, insulin resistance; N, number; n.s., not significant

[a]Data are expressed as number of subjects (percentage) or mean ± SD

[b]Data are expressed as mean ± SD

[c]Data are expressed as median (interquartile range)

Differences in body composition between patients with acromegaly and healthy subjects have been widely reported, and gender-differences have been highlighted within acromegaly patients [28–31].

Males with acromegaly (including both those with controlled and active disease) have greater total body mass (89 ± 13 vs 76.5 ± 15.3 kg, $p < 0.001$), lean body mass (LBM; 64.6 ± 8.7 vs 56.4 ± 5.8 kg, $p < 0.001$), and bone mineral content (BMC; 2.9 ± 0.5 vs 2.6 ± 0.3 kg, $p < 0.05$) compared to healthy controls, but no statistically significant differences were observed in total and trunk fat mass (FM) [28]. These differences were not found in females with acromegaly (including both controlled and active disease) compared to healthy controls.

Furthermore, controlled male (but not female) patients had more total mass than controls (89 ± 14.7 vs 76.5 ± 15.3 kg, $p < 0.05$), but no statistically significant difference was noted between subjects with active and controlled disease. Active male patients had significantly more LBM (68.1 ± 6.8 kg, $p < 0.001$) than controls (56.4 ± 5.8 kg), while biochemically controlled male patients showed only a trend towards higher LBM (61.8 ± 9.4 kg, $p < 0.065$) (Table 2) [28]. In females there is a different scenario, since patients with active acromegaly had similar LBM compared to healthy subjects. This gender difference could be mediated by testosterone, which is known to modulate the metabolic effects of GH [32]. A decrease in FM was observed only in active disease, compared with both biochemically controlled patients and control subjects (males: 19.5 ± 5.3 vs 27 ± 6.2 vs 25.9 ± 4%, $p < 0.001$; females: 30.3 ± 6.7 vs 37.1 ± 5.8 vs 36.5 ± 6.6%, $p < 0.01$) [28]. The reduction in FM in active acromegaly is due to inhibition of lipogenesis and stimulation of lipolysis caused by GH excess, as well as increased energy expenditure [33, 34]. Notably, at multiple linear regression analysis, GH independently predicted total and trunk FM only in female patients. This finding suggests a potential causal relationship between GH and FM in females, whereas in males, the negative correlation may be influenced by other

Table 2 Body composition parameters in patients with controlled and active acromegaly according to gender [28]

	Parameter	Controlled disease	Active disease	Controls
Males	Total mass (kg)*	89 ± 14.7	89 ± 11	76.5 ± 15.3
	Total fat mass (%)†	27 ± 6.2	19.5 ± 5.3	25.9 ± 4
	Trunk fat mass (%)†	30 ± 7.9	20.6 ± 7.2	28.3 ± 7.5
	LBM (kg)‡	61.8 ± 9.4	68.1 ± 6.8	56.4 ± 5.8
	BMC (Kg)§	2.7 ± 0.4	3.2 ± 0.5	2.6 ± 0.3
Females	Total mass (kg)°	72.2 ± 12.7	66.2 ± 13	67.5 ± 12.6
	Total fat mass (%)+	37.5 ± 5.8	30.3 ± 6.7	36.5 ± 6.6
	Trunk fat mass (%)×	37.5 ± 7.1	27.4 ± 8.2	35.9 ± 8.6
	LBM (kg)°	41.7 ± 10	43.5 ± 7	40.2 ± 5.4
	BMC (Kg)°	2.1 ± 0.3	2.2 ± 0.8	2 ± 0.3

Legend: LBM, lean body mass; BMC, bone mineral content

Data are expressed as mean ± SD. *Controlled patients had more total mass than controls ($p < 0.05$). †Active disease patients had less total and trunk FM than controlled patients and controls ($p < 0.001$ and $p < 0.01$ respectively). ‡Active disease patients had more LBM than controls ($p < 0.001$). §Active disease patients had more BMC than controlled acromegalic patients and controls ($p < 0.01$ and $p < 0.001$ respectively). +Active disease patients had less total FM than controlled patents and controls ($p < 0.05$). ×Active patients had less trunk FM than controlled patients and controls ($p < 0.005$ and $p < 0.05$ respectively). °No statistically significant

factors such as gonadal status (i.e. testosterone levels), more active lifestyle, or the inclusion of a younger patient population [28].

The observed gender differences in glycometabolic parameters among patients with acromegaly can be attributed to various pathophysiological mechanisms involving the complex interplay between GH/IGF-1 axis, sex hormones, as well as muscle and adipose tissues.

The differential action of GH and IGF-1 among genders plays a central role. As previously mentioned, females exhibit higher GH nadir levels and a reduced capacity to suppress GH after glucose load [13], suggesting a less effective feedback mechanism. Moreover, females experience a significantly longer diagnostic delay compared to males [27], resulting in an extended period without specific treatments. The duration and severity of the disease can contribute to the observed gender differences. Prolonged exposure to elevated GH levels amplifies metabolic alterations; females who already exhibit a higher prevalence of comorbidities such as DM [24] may experience more severe long-term metabolic complications. Sex hormones further impact on these differences. Estrogens, predominant in females, promote fat deposition, particularly in subcutaneous and visceral regions, and can worsen insulin resistance. Conversely, testosterone in men supports higher LBM, which is metabolically active and improves glucose utilization, offering some protection against insulin resistance. Differences in body composition are another key factor. Males generally have higher LBM and lower FM percentages, while females exhibit higher total and trunk FM [28]. These differences significantly impact metabolic health, as visceral fat, more prevalent in females, is linked to insulin resistance and systemic inflammation.

Gender differences in glycometabolic outcomes after medical therapy

According to the most recent consensus statement on acromegaly treatment outcomes, medical therapy is mainly recommended in case of disease persistence after surgical resection of the pituitary adenoma, although pre-operative SRL treatment can be considered in selected cases with mild disease activity [8].

Following surgery, first-line, second-line and third-line medical approaches can be proposed based on the peculiar patients and adenoma characteristics. These pharmacological therapies include first- and second-generation somatostatin receptor ligands (fg-SRLs: octreotide and lanreotide; sg-SRL: PAS), the GH receptor antagonist pegvisomant (PEG) and the dopamine agonist cabergoline (this latter as off-label treatment) [35]. Different factors must be taken into account when considering a pharmacological treatment for acromegaly, including patient metabolic profile at baseline, with particular attention to glucose homeostasis [8, 36, 37]. Several studies have investigated potential predictive factors of glycometabolic impairment after medical therapy [38]; however, studies assessing the influence of gender are still lacking.

Fg-SRLs are generally considered neutral with respect to their impact on glucose metabolism, although meta-analyses describe a slight increase in HbA_{1c} levels after prolonged treatment; however, no specific data on gender differences are currently available [39, 40].

Few literature data investigate the effects of dopamine agonist treatment on glycometabolic parameters in patients with acromegaly. Early studies on bromocriptine and more recent reports on cabergoline show an overall improved glucose tolerance during dopamine agonist treatment, which seems not always correlated with the reduction of GH and/or IGF-1 levels [41, 42]. However, also in this context, no data on the potential gender differences occurring by use of these medical therapies are available. Intriguingly, bromocriptine has been approved for the treatment of type 2 DM and in a randomized controlled trial, it determined a relative risk reduction in CV adverse events regardless age, sex, race, body mass index, duration of diabetes, or preexisting cardiovascular disease [43].

Impairment of glucose balance is the most common adverse event correlated with PAS therapy [44, 45]. Interestingly, a recent study showed a higher prevalence of DM in female patients with acromegaly after six-month therapy

with PAS as compared to males, regardless of age [46]. Females exhibited higher FPG and HbA_{1c} levels at baseline than males, and the prevalence of DM at the last follow-up visit remained significantly higher in the female group. Potential causes include a sexual dimorphism in the sensitivity of pancreatic somatostatin receptors (SSTR) subtype 1, 3 and 5 to PAS, which could result in a differential effect of the compound on insulin secretion between the two sexes [47, 48].

A recent meta-analysis by Esposito and colleagues has further explored the impact of PAS therapy on lipid metabolism in acromegaly. No significant changes in total cholesterol, low-density lipoprotein cholesterol (LDL-C) or triglycerides were observed, while a modest but significant increase in high-density lipoprotein cholesterol (HDL-C) was reported (MD + 6.2 mg/dL, 95% CI 1.4–10.9]) [49]. Unfortunately, sample size limitations prevented the Authors to perform a proper subgroup analyses on sex [49].

PEG has been reported to significantly improve fasting glucose, insulin and HbA_{1c} levels in patients with acromegaly, directly through the blockade of GH receptor on peripheral tissues (mainly muscle and adipose tissue) and indirectly through IGF-1 normalization [50]. A better therapeutic response to PEG has been reported in males by Marazuela and colleagues [51]; however, this finding has not been confirmed by a post-hoc analysis of a recent ACROSTUDY report [52]. To date, differences in the glycometabolic outcomes among the two sexes following PEG treatment remain to be investigated.

In conclusion, although several studies have assessed the effect of different medical therapies for acromegaly on lipids, glucose metabolism and cardiac outcomes [38, 53], there is a general lack of evidence as concerns gender differences.

Arterial hypertension

Arterial hypertension, defined as a confirmed office systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg [54], is one of the most frequent CV complications in acromegaly. It has a prevalence averaging 33% [55], thus being more frequent than in the general population [56]. As reported by Costenaro and colleagues [57], a higher prevalence of hypertension was observed when evaluating office BP measurements rather than with ambulatory blood pressure monitoring (ABPM), with a prevalence of 23% with ABPM vs. 32% with clinical measurements.

Acromegaly-associated hypertension presents with peculiar characteristics. Higher diastolic BP and lower systolic BP levels have been observed in acromegalic compared to non-acromegalic hypertensive patients [56, 58], as well as a higher prevalence of non-dippers in hypertensive patients with acromegaly [58]. The onset of hypertension occurs earlier in patients with acromegaly than in general population and it is less frequently related to family history of hypertension [56]. In a variable percentage of patients, biochemical control of acromegaly leads to an improvement or even a remission of hypertension. If biochemical control is not achieved or it does not impact on BP, antihypertensive drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended [59].

The pathogenic mechanisms underlying acromegaly-associated hypertension remain not fully understood; however, it appears that the primary mechanism involves an increase in plasma volume secondary to the antidiuretic and antinatriuretic effects of hormone hypersecretion on the kidney distal tubule [60]. This results from the prolonged exposure to elevated GH and IGF-1 levels, which stimulate the epithelial sodium channel (ENaC)-dependent sodium reabsorption [59]. A direct stimulation of the renin–angiotensin–aldosterone system, secondary to the action of GH/IGF-1, is still controversial [59]. Furthermore, other complications of acromegaly, including insulin resistance and DM, may promote renal sodium reabsorption, thereby contributing to the onset of hypertension [53].

To date, the relationship between hypertension and gender differences remains inconsistent. Some studies have indicated that hypertension is more prevalent among females than males [27]: the Mexican Acromegaly Registry analyzed data from 2,057 patients treated in 24 centers across Mexico and reported a diagnosis of hypertension in 32.4% of females compared to 23.7% of males with acromegaly ($p < 0.0001$) [61]. In line with this finding, a retrospective multicenter epidemiological study conducted in Italy (1512 patients from 24 tertiary referral centers) reported a similar trend (age-standardized rate: 33.7% in females vs 28.7% in males), although these numbers did not reach statistical significance [62]. Other registry studies on acromegaly did not find a different prevalence of hypertension between males and females [56, 63–68]. Therefore, further studies to examine the potential implications of gender differences on diagnostic and therapeutic strategies for the management of hypertension in patients with acromegaly are needed.

Cardiovascular features

Cardiovascular diseases (CVD) still represent relevant causes of death in patients with acromegaly, accounting for approximately 44% of mortality in the first decade following diagnosis. However, as time goes on, cancer-related deaths become more prevalent, increasing to about 35% in later decades [7]. Interestingly, CV mortality is higher in female patients with acromegaly compared to their male

counterparts. Several epidemiological studies show a significantly increased standardized mortality ratio (SMR) [9] of female patients compared to their controls, while males with acromegaly show survival rates comparable to the general population [7, 9, 69]. The elevated mortality observed in females with acromegaly has been attributed to several factors. Firstly, females are often diagnosed at an older age, reflecting a longer diagnostic delay [15] and a more prolonged exposure to elevated GH and IGF-1 levels [27]. This is likely due to a more insidious disease onset, as previously described [16]. Secondly, as mentioned in the previous chapters, several studies have reported a higher prevalence of metabolic syndrome [24], hypertension, and DM in female patients with acromegaly at the time of diagnosis [5, 21], along with a worse metabolic profile, including greater insulin resistance, even after achieving disease control [16]. Lastly, hypogonadism can further impact CV risk factors, such as hypertension and metabolic syndrome, which are already common in patients with acromegaly [5, 21]. This is particularly significant for females, who may experience complications from estrogen deficiency, leading to increased CV morbidity and mortality. Overall, the interplay between diagnostic delay, hypogonadism, and the cardiometabolic comorbidities of acromegaly can increase the risk of CV mortality in females, highlighting the need to consider gender-specific factors when evaluating and managing these patients.

Cardiomyopathy

Acromegalic cardiomyopathy represents a distinct form of heart disease associated with acromegaly, characterized by cardiac dysfunction, which progresses through three different phases [70, 71]. The early stage is characterized by hyperkinetic heart function and the development of concentric left ventricular (LV) hypertrophy (LVH); the intermediate stage presents with impaired diastolic function and symptoms such as exertional dyspnea; the late stage leads to severe systolic dysfunction and heart failure, often irreversible despite treatment [70, 71]. Key factors contributing to the development of acromegalic cardiomyopathy include patient's age and other CV risk factors, including hypertension, obesity, and DM [72, 73]. Moreover, the severity of cardiac alterations has also been associated with a longer disease duration and a more severe disease activity [73], suggesting that prolonged exposure to elevated GH and IGF-1 levels is directly detrimental to cardiac health. Supporting this hypothesis, patients with acromegaly can develop significant cardiac changes even in the absence of traditional CV risk factors, underscoring the unique nature of acromegalic cardiomyopathy as a hallmark of the disease itself.

Gender may play a significant role in the development and progression of acromegalic cardiomyopathy. To date, most studies investigating changes in cardiac structure and function have been conducted using echocardiography [74, 75]. However, data regarding gender-specific characterization of cardiac parameters in echocardiographic studies are still lacking. Only one study has directly compared LV systolic function between male and female patients newly diagnosed with acromegaly using 2D speckle tracking echocardiography, which allows the evaluation of longitudinal, radial, and circumferential deformation, thus offering a more sensitive assessment of myocardial contractility. Despite exhibiting similar LV mass (LVM), females displayed a more favorable global longitudinal strain (GLS) at diagnosis than males [76]. Notably, GLS is a critical parameter for assessing LV systolic function and has a particular value in detecting subtle systolic dysfunctions, even in patients with preserved ejection fraction, making it a crucial tool for early diagnosis and management of cardiac conditions [77]. Although these findings may suggest that females with acromegaly experience less severe subclinical systolic dysfunction, it might be partially due to the lower BMI and body surface area (BSA) values observed in females, since GLS values were not adjusted by these parameters, as for standard echocardiographic parameters [76]. Moreover, it should be noted that, even in the general population, females exhibit better GLS, along with larger ejection fractions and smaller cardiac outputs [78], compared to males, making it difficult to ascertain the specific impact of the disease on the observed differences. This underscores the need to establish distinct cut-off points for GLS in females and males, similarly to the different normal ranges used for other echocardiographic parameters.

Cardiac magnetic resonance imaging (cMRI) has emerged in recent years as the gold standard method for the morphological and structural assessment of the heart in patients with acromegaly due to its superior reproducibility and accuracy, enabling to detect early and more subtle changes than echocardiography [79]. Notably, comparative studies between these two modalities in patients with acromegaly have yielded inconsistent results, showing both higher [80] and lower [81] prevalence of LVH as determined by cMRI analysis compared with standard echocardiography studies. In this context, several cMRI studies have indicated significant sex-related differences in cardiac features between male and female patients. A recent study investigating cardiac morphology, function and myocardial tissue characterization via cardiac MRI observed that patients with acromegaly exhibit a disease-specific type of myocardial hypertrophy, characterized by an increase in both intracellular and extracellular LVM [82]. Interestingly, male gender was identified as an independent predictor for

LV myocardial mass, exhibiting a significant association with higher indexes of both intracellular and extracellular mass [82]. In line with this finding, male patients with acromegaly had higher LVM indices, increased thickness of the interventricular septa (IVS), and reduced left and right ventricular ejection fractions than female patients [83]. Finally, a recently published cMRI study evaluated cardiac morphology and function in 20 patients with acromegaly (13 males, 7 females). Male patients exhibited higher IVS thickness and BSA-corrected LVM, even after adjusting for population age and sex reference ranges [84], supporting a possible involvement of sexual hormones in cardiac disease progression in acromegaly-related cardiomyopathy, as documented in other CV diseases [85, 86].

The underlying reasons for the observed gender differences are not fully understood, but they may be related to the modulating effects of sex hormones on the somatotropic axis. Sex differences in GH and IGF-1 secretory patterns are well-established and have already been discussed [21, 27, 87, 88], with premenopausal females showing higher basal and pulsatile GH levels than males [89]. Interestingly, this secretory phenotype has only been observed in premenopausal women and those undergoing estradiol treatment, suggesting a direct involvement of circulating estrogens [90].

Sex hormones may influence cardiac morpho-functional changes induced by GH and IGF-1 excess [82, 91], as lower IGF-1 levels could underlie the improved cardiac morphology and structure observed in females with acromegaly [76, 84, 92]. Recent studies have identified IGF-1, rather than GH, as an independent predictor of myocardial LVM, irrespective of other common cardiometabolic comorbidities, suggesting that a more severe degree of hormone excess might directly affect cardiomyocytes [84]. In patients with acromegaly, both GH and IGF-1 exert direct effects on cardiomyocytes, contributing to cardiac remodeling and dysfunction [93, 94]. Upon binding of its receptor (IGF-1R), IGF-1 enhances cardiac contractility by increasing calcium influx and peak calcium levels in cardiomyocytes. Through the activation of the PI3K/protein kinase B (Akt), MAPK and Rho-associated protein kinase (ROCK) pathways, IGF-1 also stimulates the synthesis of contractile proteins and promotes cardiomyocyte growth, resulting in cardiomyocyte hypertrophy. GH similarly affects cardiomyocyte function by enhancing contractility and promoting cardiac tissue growth, primarily by activating PI3K/AKT/mTOR and MAPK signaling pathways [95]. However, while short-term exposure to elevated GH and IGF-1 levels can have beneficial effects on cardiac function, prolonged exposure can lead to maladaptive changes, including myocardial fibrosis and inflammation, which ultimately increase the risk of heart failure and other cardiovascular complications in patients with acromegaly [95, 96]. Nevertheless, a recent study has confirmed that gender differences are one of key clinical factors affecting the prevalence of cardiac abnormalities in naïve patients with acromegaly, as well as age, BMI, disease duration, and hypertension, rather than GH or IGF-1 levels [83]. This highlights the need for further prospective studies with larger cohorts to define the causative factors of acromegalic cardiomyopathy and their correlation with gender differences.

Gender differences in CV outcomes after medical therapy

Cardiac alterations have generally been reported to improve or completely reverse [97] after effective management of GH and IGF-1 levels, either through transsphenoidal surgery [98, 99] or medical treatment with fg-SRLs [99–101]. While more significant benefits have been observed in patients of younger age and achieving complete GH and IGF-1 normalization [102], cardiac improvements are also seen in patients with partial biochemical improvement [74, 99], suggesting that the biochemical target for reducing CV complications may differ from full biochemical normalization [17, 103]. Moreover, the occurrence of cardiac improvements in patients who do not achieve disease control, along with preclinical data reporting SSTR expression in cardiomyocytes [104, 105], supports the hypothesis that SRLs might also exert direct beneficial effects on cardiac muscle, irrespective of GH and IGF-1 normalization. Data regarding a potential gender-dependent response to SRLs on CV outcomes in patients with acromegaly remain limited, with only one study reporting more marked reductions in LVM and improvements in diastolic function in males compared to females after treatment [83]. The reduction in GH and IGF-1 levels correlates with improvements in LV function. In males, successful treatment may lead to more pronounced reductions in LVM and improvements in diastolic function; in females, who typically present with better-preserved systolic function at diagnosis, more subtle enhancements in cardiac function could be observed after treatment.

In patients not adequately controlled by SRLs, treatment with PEG has been shown to induce significant improvements of LVM index (LVMi) [106, 107], as well as diastolic and systolic function [106]. The observed correlation between cardiac improvements and the degree of IGF-1 reduction [106] suggests that the beneficial effects of PEG on cardiac function and structure can largely be attributed to its high efficacy in achieving IGF-1 normalization [106, 107]. However, considering that GH receptors are expressed in cardiomyocytes [93], a direct effect of PEG on cardiac muscle cannot be ruled out. To date, potential gender

differences in the cardiac response to PEG have not been investigated.

The CV effects of PAS, cabergoline, or pituitary radiotherapy on acromegalic cardiomyopathy have yet to be investigated.

Figure 1 and Fig. 2 summarize the peculiar characteristics of glucose and lipid metabolism, adipose tissue and muscle function, as well cardiovascular comorbidities in male and female acromegaly patients.

Conclusions

The impairment of glucose and lipid metabolism, together with arterial hypertension and CV diseases, are among the most common and impactful comorbidities associated with acromegaly. Beyond the biochemical control of GH and IGF-1 excess, a proactive management of these disease-related conditions is strongly recommended, in order to further improve patient's quality of life and to reduce mortality. In this context, the gender differences emerged from our review of available evidence highlight the need for a tailored sex-based approach to the management of patients with acromegaly. A longer diagnostic delay in females compared to males has been reported by many Authors, together with a worse glycometabolic profile characterized by a higher prevalence of insulin resistance, adiposity and DM [108]. On the other hand, females with acromegaly show milder cardiac abnormalities despite higher CV mortality, with smaller LVM indices, thinner IVS, and higher ejection fractions compared to males. Both males and females with acromegaly gain CV benefits from treatment, but male patients may see greater improvements, possibly due to a more severe baseline cardiac phenotype. Finally, the relationship between hypertension and gender remains inconsistent. All these findings underlie the need for a more focused gender-medicine approach in a complex systemic disease such as acromegaly, since the GH/IGF-1 axis is well-known to be affected by sex hormones and by gender itself.

Although the currently available level of evidence is generally "low", a gender-medicine driven approach to acromegaly management should be already taken into consideration in daily clinical practice. As an example, a more pro-active approach on treating glucose and lipids imbalance in female patients should be carried out, throughout a timely use of antidiabetic and lipid-lowering drugs. Similarly, the presence of glycometabolic impairment and hypertension should be carefully weighed in the screening

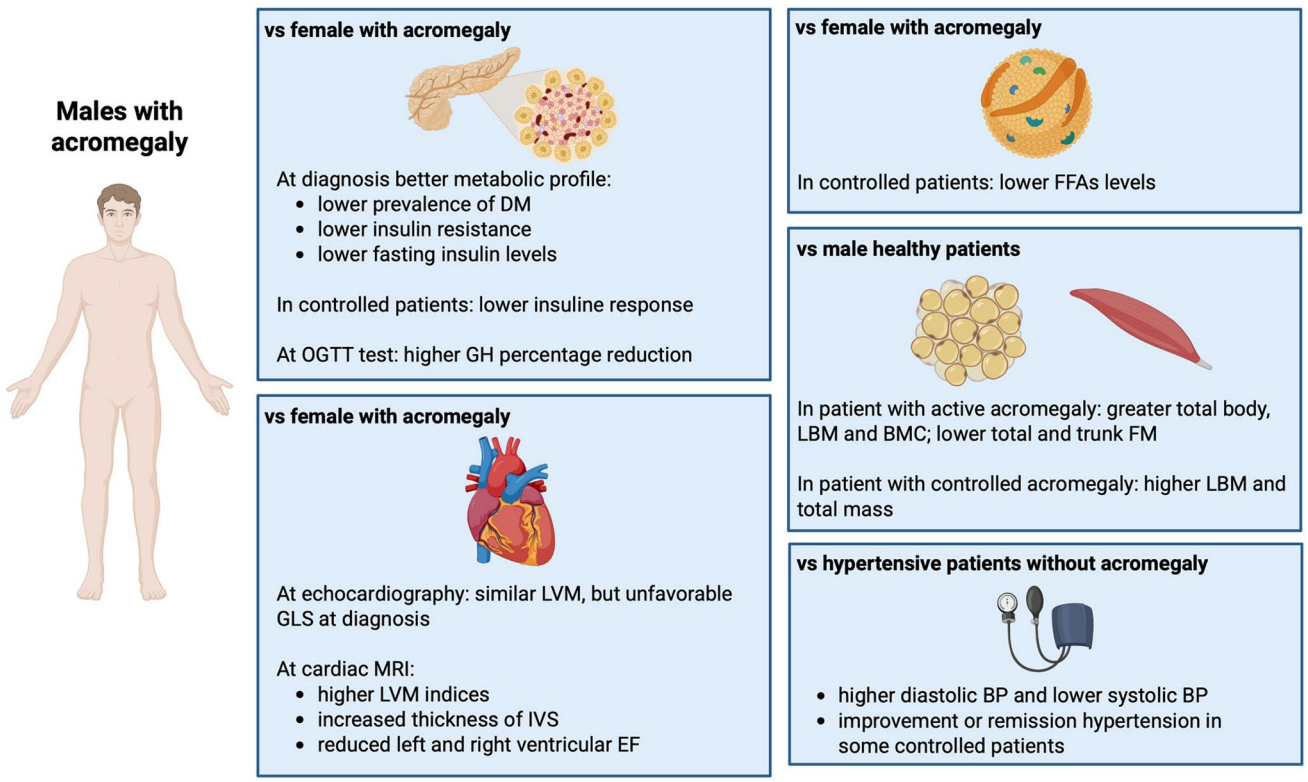

Fig. 1 Characteristics of glucose metabolism, lipid metabolism, adipose tissue, muscle and cardiovascular comorbidities in male acromegaly patients. Legend: BMC, bone mineral content; BP, blood pressure; DM, diabetes mellitus; EF, ejection fraction; FFAs, free fatty acids; FM, fat mass; GH, growth hormone; GLS, global longitudinal strain; IVS, interventricular septa; LBM, lean body mass; LVM, left ventricular mass; MRI, magnetic resonance imaging OGTT, oral glucose tolerance test. Created in https://BioRender.com

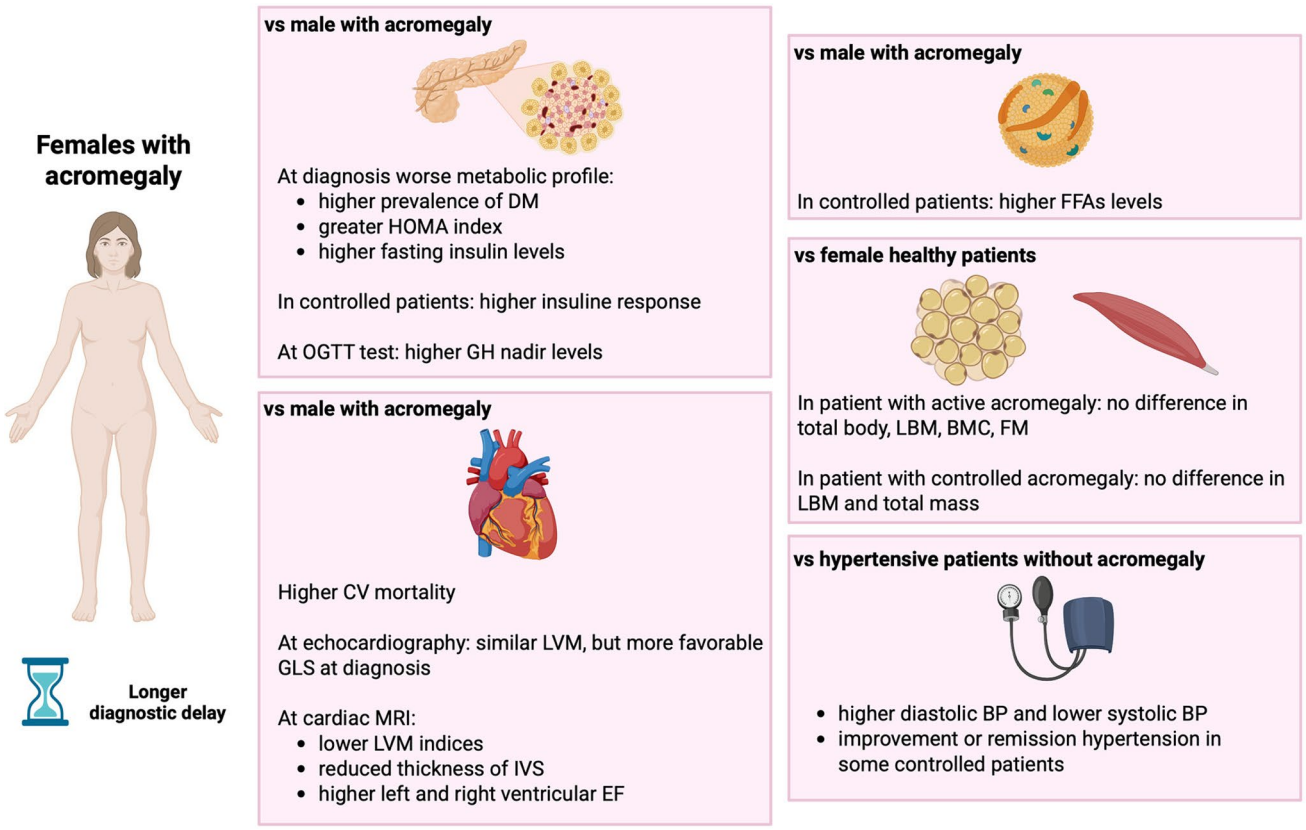

Fig. 2 Characteristics of glucose metabolism, lipid metabolism, adipose tissue, muscle and cardiovascular comorbidities in female acromegaly patients. Legend: BMC, bone mineral content; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; FFAs, free fatty acids; FM, fat mass; GH, growth hormone; GLS, global longitudinal strain; HOMA, Homeostasis Model Assessment; IVS, interventricular septa; LBM, lean body mass; LVM, left ventricular mass; MRI, magnetic resonance imaging OGTT, oral glucose tolerance test. Created in https://BioRender.com

phase of female patients with borderline-elevated IGF-1 levels, in order to attempt a decrease in the diagnostic delay of uncertain cases. All these aspects also play an important role in choosing the most appropriate medical treatment for acromegaly, including patient's gender as an additional characteristic to navigate the currently proposed treatment algorithms.

Therefore, future studies should be primarily focused on the better understanding of the pathophysiological bases of the above reported gender differences, in order to optimize treatment protocols, which (clearly) represent the first-step for a patient's tailored approach.

Authors' contributions F.G., S.F., F.F., R.S.A., and A.C. contributed to the study conception and design. Material preparation, data collection and analysis were performed by F.G., A.A., D.D.A., M.D.S., R.G., V.L., and F.P. The first draft of the manuscript was written by F.G., A.A., D.D.A., M.D.S., R.G., V.L. and F.P.; tables 1–2 and Figs. 1–2 were prepared by A.A. and F.G. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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