Pituitary (2026) 29:76
https://doi.org/10.1007/s11102-026-01639-z

REVIEW

Consensus on acromegaly complications: an update

Andrea Giustina[1] · Luigi di Filippo[1] · Maria Fleseriu[2] · Rosario Pivonello[3] · Stephan Petersenn[4] · John Wass[5] · Susan L. Samson[6] · Alberto M. Pereira[7] · Raúl M. Luque[8] · Betina Biagetti[9] · Maria Chiara Zatelli[10] · Ken K Y Ho[11] · Cesar L. Boguszewski[12] · Aart Jan van der Lely[13] · Mark Gurnell[14] · Nienke Biermasz[15] · Katharina Schilbach[16] · Diego Ferone[17] · Monica R. Gadelha[18] · Adriana G. Ioachimescu[19] · Ezio Ghigo[20] · Christian J. Strasburger[21] · Pinar Kadioglu[22] · Pietro Maffei[23] · Niki Karavitaki[24] · Mónica Marazuela[25] · Michael Buchfelder[26] · Sabrina Chiloiro[27] · Anton Luger[28] · Yona Greenman[29] · Elena Valassi[30] · Ignacio Bernabeu[31] · Stefano Frara[32,33] · Philippe Chanson[34] · Thierry Brue[35] · John Ayuk[36] · Felipe F Casanueva[37] · Annamaria Colao[38] · Pietro Mortini[39] · Sebastian Neggers[40] · Manel Puig-Domingo[41] · Meliha Melin Uygur[1,42] · Shlomo Melmed[43]

Received: 2 December 2025 / Accepted: 12 January 2026

Abstract
The 16th Acromegaly Consensus Conference in September 2024 updated recommendations on diagnosis and treatment of acromegaly comorbidities. Since the 2020 acromegaly comorbidity management guideline was published, new evidence has emerged on novel and known comorbidities and new treatment approaches. Forty-three experts in the management of acromegaly reviewed the current literature and assessed changes in clinical practice standards and management. Current outcome goals were considered and updated, with a focus on the impact of current and emerging treatments of these comorbidities. Participants assessed factors that determine pharmacological choices, as well as use of specific agents in the management of the most relevant acromegaly comorbidities. We present consensus recommendations highlighting optimization of evidence-based acromegaly comorbidities management.

Keywords Pituitary adenoma · Growth hormone · IGF1 · Somatostatin receptor ligand · GH receptor antagonist · Transpenoidal surgery · Diabetes · Arthritis · Acral changes · Hypertension

Introduction

Acromegaly arises from autonomous growth hormone (GH) hypersecretion leading to excess circulating insulin-like growth factor 1 (IGF-I) concentrations, causing adverse effects on peripheral organs and physiologic processes [1, 2]. Patients commonly experience abnormal growth of bone and soft tissue, dysregulated glucose and lipid metabolism with increased risk for cardiovascular disease [3, 4], and consequent increased mortality risk [5]. The main treatment goal is to control excessive IGF-I concentrations, as well as signs and symptoms of the disease [6–9]. Early diagnosis and patient-centered management of comorbidities are important for optimal long-term outcomes.

The Acromegaly Consensus Group published the first set of recommendations on diagnosis and treatment of disease complications in 2003 [10, 11] and updated them in 2013 [12], and 2020 [13]. Given development of new management protocols [8], and conceptualization of the Pituitary Tumor Center of Excellence (PTCOE) [14], the field has focused on definition and optimization of management strategies for comorbidities and disease-related sequelae [15]. In September 2024, 43 experts in acromegaly management reviewed the literature and critically evaluated novel research findings and changes in clinical practice standards and opinion since the 2020 consensus. Updated recommendations focused on cardiovascular, respiratory, metabolic, and oncologic comorbidities, and bone and joint disorders,

Extended author information available on the last page of the article

Published online: 29 April 2026

as well as the impact of this disease on kidney function, quality of life (QoL) and mortality.

Materials and methods

Forty-three worldwide recognized experts in acromegaly management were assigned specific topics by the Consensus Co-Chairs (SM and AG) related to comorbidities and conducted comprehensive literature searches for English-language papers published between March 2018 and March 2024. In preparation of the manuscript, publications until March 2025 were also subsequently reviewed and included. Participants were selected based on their recognized expertise in the field as reflected by peer-reviewed publication records. Search terms included "acromegaly" and "comorbidities" as well as terms associated with each respective topic covered. After presentations to the entire group, parallel breakout sessions discussed current practice and recommendations, before providing summary reports back to the whole group. Consensus recommendations were based on all presentations and discussions, and participants voted on each recommendation. Divergent opinions were reconciled by voting, and all participants approved final statements included in the manuscript. Recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation system (GRADE; Table 1) [16, 17]. After the meeting, members of the Scientific Committee graded both the quality of the supporting evidence and consensus recommendations using the GRADE system. Evidence strength was graded as very low quality (VLQ), low quality (LQ), moderate quality (MQ), or high quality (HQ) [8]. Introductory sentences providing background evidence were graded with VLQ if based on expert opinion supported by one or few small uncontrolled studies; with LQ if supported by large series of small uncontrolled studies; with MQ if supported by one or few large uncontrolled studies or meta-analyses; with HQ if supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up. Consensus recommendations were classified as discretionary (DR) if based on VLQ or LQ evidence and as strong (SR) if based on MQ or HQ evidence.

Table 1 Grading of evidence and recommendations

Evidence	Recommendations
• Very low quality (VLQ): expert opinion supported by 1 or a few small uncontrolled studies • Low quality (LQ): supported by large series of small uncontrolled studies • Moderate quality (MQ): supported by 1 or a few large uncontrolled studies or meta-analyses • High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up	• Discretionary recommendation (DR): based on VLQ or LQ evidence • Strong recommendation (SR): based on MQ or HQ evidence

Recommendations were initially discussed by each topic's work-subgroup discussion and outcomes presented to the entire group for further discussion and consensus finalization [9]. Changes in current vs. 2020 key recommendations are summarized in Table 2. Main underlying mechanisms and clinical features as well as diagnostic approach for acromegaly comorbidities are reported in Fig. 1.

Determinants of acromegaly complications

Acromegaly signs and symptoms as well as comorbidities are mediated directly by either GH or IGF-I (HQ) (Fig. 1). Non-IGF-I mediated actions of GH include lipolysis, gluconeogenesis and glycogenolysis, together with decreased tissue glucose uptake and glucose oxidation [18] (MQ). GH directly inhibits insulin receptor signaling, attenuating suppression of hepatic glucose production and peripheral glucose utilization [18]. Stimulation of lipolysis by GH further hampers insulin sensitivity, impairs beta-cell function, and reduces whole-body fat [19]. GH also acts directly on epithelial channels in the distal nephron causing water and sodium retention (MQ) [20].

Glucose tolerance improves following successful surgical resection of the adenoma or with first-generation somatostatin receptor ligands (fg-SRLs), suggesting that reversal of GH excess ameliorates insulin sensitivity (HQ) [21]. Patients with hypertension and diabetes mellitus have more severely impaired cardiac performance than those without (MQ) [22]. GH excess reversibly reduces fat mass, increases extracellular water (ECW), and increases resting energy expenditure. GH promotes nephron sodium retain leading to expanded ECW [23] with soft tissue swelling, including tongue edema, with characteristic facial dysmorphism (MQ). Upper airway swelling may result in snoring or sleep apnea which improves following treatment (MQ). Myocardial edema may contribute to cardiomyopathy [24].

Prevalence and severity of disease complications arise from cumulative exposure to high IGF-I (MQ). Circulating IGF-I is the best marker of GH action, and its measurement by a validated assay with robust age-related reference ranges is the best biochemical marker of disease activity (MQ). IGF-I exerts anti-lipolytic effects on adipose tissue similar to that of insulin and opposite to GH effects (HQ) [25, 26]. Insulin sensitivity is reduced by GH while IGF-I increases insulin sensitivity (MQ) [27]. GH normalization is associated with improved life expectancy and ameliorates obstructive sleep apnea syndrome (OSAS) (MQ) [3]. IGF-I normalization leads to blood pressure (BP) lowering (in hypertensive patients), decrease in fasting plasma glucose (FPG), homeostatic model assessment for insulin resistance (HOMA-IR) and HOMA-B and increased HDL- cholesterol (C) but no change in LDL-C [28].

Table 2 Key changes from the 2020 to the 2024 consensus recommendations for diagnosis and follow-up of acromegaly comorbidities

Assessment	Frequency	
	2020	2024
Cardiovascular and respiratory disorders		
Blood pressure measurement	At baseline and every 6 months or upon change of antihypertensive treatment	Not modified ABMP is recommended over office measurements
Echocardiography	Annually, if abnormal	At diagnosis, annually if abnormal
CMRI	Not addressed	Consider at diagnosis, individualized follow-up
Electrocardiography	Annually, if abnormal	At diagnosis, individualized follow-up
Holter electrocardiography	Not addressed	In patients at high risk (history of syncope, abnormal ECG, structural abnormalities, heart failure)
Routine exercise program	Not addressed	In all patients without contraindication
Epworth scale and/or Polysomnography	Baseline or before surgery if OSAS is suspected	At diagnosis, individualized regular monitoring
Endocrine and metabolic disorders		
Fasting blood glucose, HbA1c	Fasting blood glucose every 6 months, particularly in uncontrolled disease and during SRL therapy; HbA1c every 6 months if diabetes or prediabetes is present	Glycemic status assessment every 6 months, more frequent (3 months) if out of target and/or after treatment modification
Lipid profile	Follow general guidelines	At diagnosis, every 8 ± 4 weeks after the treatment, annually after the achievement of target. Follow general guidelines for the treatment.
MASLD	Not addressed	Assessment in patients with risk factors (GHD)
Body Composition	Not addressed	Consider at diagnosis with DXA scans or BIA, individualized follow-up
Total testosterone, SHBG, and PRL (males)	Annually, consider testing free testosterone if there are doubts in interpretation of total testosterone	Not addressed
LH, FSH, 17β-estradiol, and PRL (females)	Annually, in premenopausal females with menstrual dysfunction and when pregnancy is desired	Not addressed
Serum free T4	Annually	Not addressed
Serum 8–9 am cortisol	If central adrenal insufficiency is suspected; cosyntropin stimulation test if serum cortisol is low	Not addressed
Musculoskeletal disorders		
Bone complications		
DXA	Every 2 years particularly if osteopenia/osteoporosis is present	Not modified
Vertebral morphometry on thoracic x-ray, thoracic and lumbar spine x-ray	Annually, particularly if history of vertebral fracture, decrease in BMD, kyphosis, symptoms of vertebral fracture, untreated hypogonadism, and no biochemical control of acromegaly	Not modified
TBS	Not addressed	When available, particularly in patients with high risk factors
Arthropathy	Early assessment is recommended	Early assessment of joints with specific questionnaires (e.g. WOMAC) and radiologic tools (e.g. X-Ray, MRI)
Other comorbidities		
Cancer		
Colonoscopy	Every 10 years; more frequently if IGF-I remains persistently elevated or if abnormal colonoscopy or family history of colon cancer	At diagnosis. During follow-up according to country-specific guidelines
Thyroid ultrasound	In patients with palpable thyroid nodules and/or with risk factors of thyroid cancer	Not modified
Kidney		
GFR	Not addressed	At diagnosis, annually thereafter
Renal ultrasound	Not addressed	Individualized at diagnosis and follow-up
Water and electrolyte balance	Not addressed	At diagnosis, annually thereafter

Table 2 (continued)

Assessment	Frequency	
	2020	2024
Quality of life		
AcroQoL	Annually	Not modified
Combination of PROMs (AcroQoL) and SAGIT/ACRODAT	Not addressed	Annually

Abbreviations: *BMD* bone mineral density, *DXA* dual-energy x-ray absorptiometry, *OSAS* obstructive sleep apnea syndrome, *PRL* prolactin, *SHBG* sex hormone binding globulin, *SRL* somatostatin receptor ligand, *GHD* growth hormone deficiency, *BIA* bioelectrical impedance analysis, *ABPM* ambulatory blood pressure monitoring, *GFR* glomerular filtration rate, *MRI* magnetic resonance imaging, *CMRI* cardiac MRI, *ECG* electrocardiography, *MASLD* metabolic dysfunction-associated steatotic liver disease, *TBS* trabecular bone score, *QoL* quality of life, *PROMs* patient-reported outcome measures, *HbA1c* hemoglobin A1C, *LH* Luteinizing Hormone, *FSH* follicle stimulating hormone, *T4* thyroxine, *IGF-I* insulin-like growth factor 1, *WOMAC* Western Ontario and McMaster universities osteoarthritis index

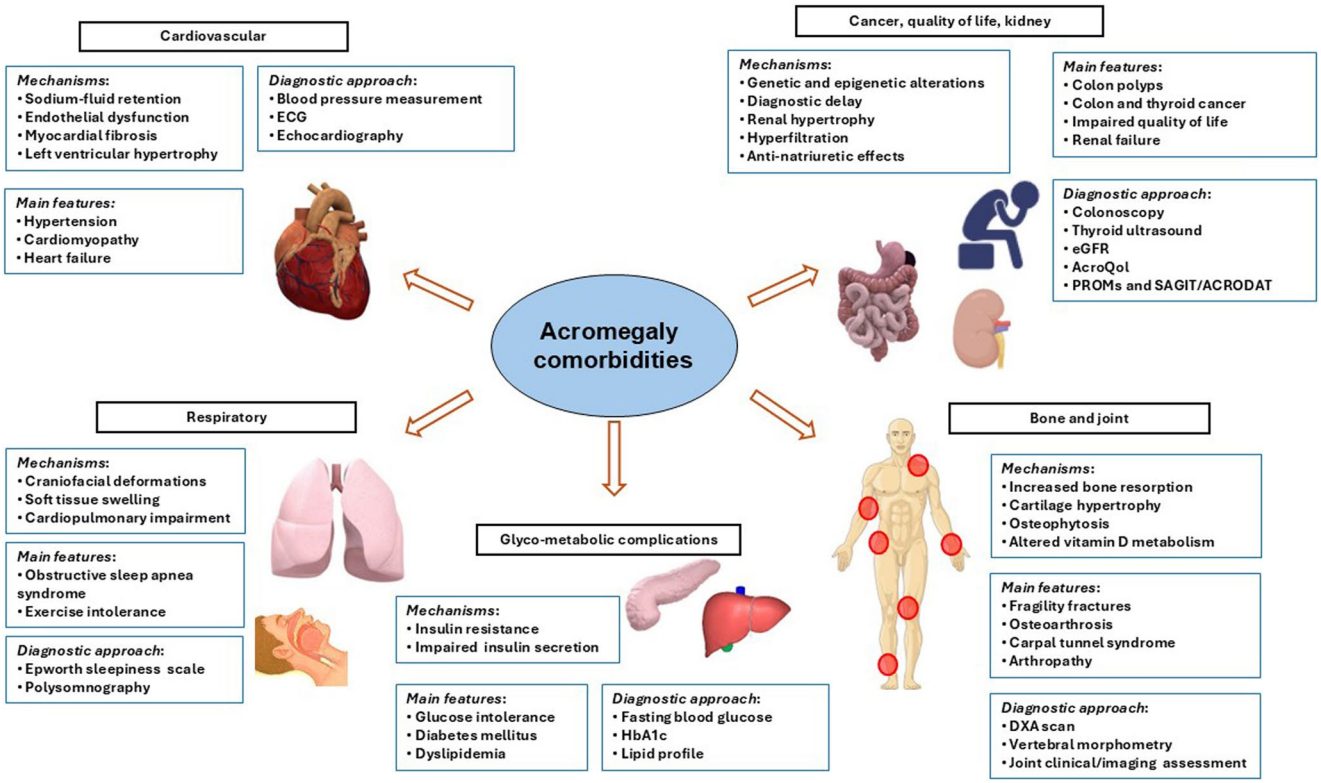

Fig. 1 Diagnostic approach and main underlying mechanisms and clinical features of acromegaly comorbidities

Successful surgery can reduce BP in patients with hypertension (LQ). FPG and HOMA-IR decreased following surgery since lowering GH per se improves insulin sensitivity [28]. SRLs may have overall neutral effects, as their suppression of insulin secretion may counterbalance the improvements in insulin sensitivity due to acromegaly control (MQ) [29]. IGF-I promotes vascular relaxation through modulation of sodium/potassium ATPase activity [30] with improved cardiac output, stroke volume, contractility, and ejection fraction (MQ). IGF-I receptors (IGF-IR) are abundantly expressed in cardiomyocytes, vascular endothelial cells, and smooth muscle cells [31], leading to vasodilatory effects primarily by enhancing endothelial nitric oxide synthase activity. IGF-I also improves lipid profile, lowers insulin concentrations, and increases insulin sensitivity [32].

GH stimulates transepithelial sodium transport in the distal nephron through activation of epithelial sodium channels (ENaC) in the collecting duct (MQ). IGF-I enhances sodium reabsorption by activating serum- and glucocorticoid-induced kinase 1 (Sgk1) increasing the membrane residency of active ENaCs. IGF-I may also cooperate with GH to regulate ENaC gene expression.

IGF-I is essential for differentiation and maturation of growth plate chondrocytes, promoting linear bone growth and osteoblastogenesis, enhancing collagen production, and supporting bone matrix mineralization, thereby contributing

to bone formation. In genetically modified mouse models circulating IGF-I is critical for cortical bone integrity, while locally produced skeletal IGF-I is required for the maintenance of cancellous (trabecular) bone. Together, these findings underscore the dual systemic and local roles of IGF-I in preserving both bone architecture and function (MQ) [33–35]. On the other hand, GH exerts direct anabolic actions on bone through its receptor (GHR), independent of hepatic IGF-I production. GHR is expressed in multiple skeletal compartments, including growth plate chondrocytes, osteoblasts, and mesenchymal stromal cells (MSCs). GH binding to GHR activates intracellular signaling cascades, primarily the JAK-STAT signaling pathway (especially STAT5), but also MAPK and PI3K/Akt pathway which promote chondrocyte proliferation, osteoblast differentiation, and anti-apoptotic effects in bone-forming cells. In animal models, local GH administration stimulates longitudinal bone growth even in the absence of IGF-I receptor activity, confirming an IGF-independent effect. GH directly increases bone formation parameters, enhances mineral apposition, and maintains cortical and trabecular bone mass. At the marrow level, GH favors osteoblastogenesis over adipogenesis by modulating MSC commitment and inhibiting adipogenic differentiation. These direct skeletal actions are essential for bone growth, microarchitectural integrity, and homeostasis throughout life [36].

Cardiorespiratory complications

Consensus recommendations

Diagnosis:

- *At diagnosis, an ECG assessment is recommended in all patients (SR).*
- *Ambulatory Blood Pressure Monitoring (ABPM) is recommended for the diagnosis of hypertension (DR).*
- *Assessment of cardiac function and morphology should be performed, at diagnosis including an echocardiography (DR).*
- *Specialized imaging techniques (e.g., speckled tracking echocardiography, CMRi) are not currently recommended (DR).*
- *In newly diagnosed patients, polysomnography should be systematically performed at diagnosis (even in the absence of symptoms) to properly identify and manage obstructive sleep apnea syndrome (OSAS) (DR).*

Therapy:

- *Patients with congestive heart failure require adequate therapy, and prevention of cardiac arrhythmia (SR).*
- *Hypertension may persist despite acromegaly control, and current guidelines for the general population should be followed (DR).*
- *Regardless of acromegaly control, treatment of OSAS should be instituted (DR).*
- *Continuous positive airway pressure with a specially fitted mask is recommended for patients with OSAS and atypical facial morphometry (DR).*
- *An individualized exercise program to improve exercise tolerance should be considered if there are no contraindications (DR).*

Follow up:

- *Follow-up echocardiography should be performed as clinically indicated (DR).*
- *ABPM is recommended for following patients with hypertension (DR).*
- *Patients at risk for arrythmias (history of syncope, abnormal ECG, structural abnormalities, heart failure) may benefit from ambulatory ECG monitoring (DR).*
- *Regular monitoring with polysomnography is recommended because OSAS may persist or worsen despite appropriate acromegaly therapy (DR).*

Mortality rates have decreased in well-controlled acromegaly closely approximating that of the general population (HQ) [37, 38]. Cardiovascular disease is an important cause of mortality in patients with acromegaly despite the recent shift to age-related cancers as the leading cause of death (MQ) [37, 39–43]. It remains unclear how much of this shift is due to improved treatment of acromegaly versus overall improved cardiac care.

Hypertension

The prevalence of hypertension is estimated at approximately 40% [4, 44–47], reaching up to 60% in some series, with higher rates in patients with biochemically active acromegaly and may occur at a younger age than in the general population (HQ) [48, 49]. Hypertension significantly increases mortality, particularly when accompanied by cardiovascular disease highlighting the critical importance of prompt screening and management of cardiovascular complications to reduce morbidity and mortality (HQ) [49]. Hypertension is related to insulin resistance, expansion of ECW, increased peripheral vascular resistance, and sleep apnea [45], and these effects may not be fully reversible. Importantly, hypertension may persist despite biochemical remission [50], particularly in older patients [45, 48].

The 24 h-ambulatory blood pressure monitoring (ABPM) is recommended over office measurements for the diagnosis

and follow-up of hypertension (DR) [51, 52]. Sodium overload may be prevented by the ENaC blocker amiloride and other diuretics if needed [53]. Surgical resection of the GH-secreting adenoma was demonstrated to reduce BP after 3- and 6-months post-surgery (MQ). 24 h-ABPM also confirmed a significant decrease in BP, with restoration of normal circadian BP rhythms (MQ). The benefits were more evident in patients with controlled IGF-1 concentrations, and not in those with uncontrolled acromegaly [45, 54–57]. In some studies, successful control of GH and IGF-I concentrations with fg-SRLs was associated with improved control of hypertension (LQ) [45, 54, 58]. However, a meta-analysis of 16 studies including 190 patients did not demonstrate direct effect of fg-SRLs on BP [59]. These findings suggest that the antihypertensive benefit sometimes observed with fg-SRLs is likely an indirect consequence of GH and IGF-I normalization, rather than a direct pharmacodynamic effect of the drugs themselves (LQ). Improved BP following pegvisomant treatment could support a direct pathogenic role of GH/IGF-I excess in hypertension development (LQ) [49].

Cardiomyopathy and heart failure

Cardiomyopathy has been considered a hallmark morbidity of acromegaly due to the impact of GH and IGF-I on the heart (HQ). GH enhances cardiomyocyte sensitivity and content of myofilament calcium, L-type calcium channels, and collagen deposition. In addition, cardiac hypertrophy might be induced by pressure or volume overload [4].

Cardiomyopathy may occur early in the course of the disease with specific cardiac alterations, mainly characterized by a reversible hyperkinetic left ventricle (LV) in the first stage; followed by a second stage of progressive hypertrophy leading to diastolic dysfunction and, a third stage of both diastolic and systolic dysfunction (MQ). Cardiomyopathy occurs independently of hypertension and diabetes but worsens with disease duration and other cardiovascular risk factors (HQ) [60–62]. The prevalence of LV hypertrophy (LVH) ranged between 11% and 78% and diastolic dysfunction between 11% and 58% of patients with this wide variation in percentages among the series due to different study design or overestimation of LVH with echocardiography [4]. Recently, speckle tracking echocardiography (STE) and cardiac magnetic resonance imaging (CMRi) have been used for definition of cardiac abnormalities (VLQ). However, there is currently insufficient research on STE to explore myocardial strain parameters in acromegaly [63]. Non-invasive CMRi is not routinely used in clinical practice but it may have advantages in the assessment of cardiac abnormalities with respect to echocardiography. In fact, it revealed lower frequency (5%) of LVH supporting overestimation of LV hypertrophy with echocardiography [64]. CMRi with late gadolinium enhancement enables direct visualization of myocardial fibrosis. T1 mapping and ECV quantification are advanced CMRi techniques allowing for precise, non-invasive assessment of myocardial tissue. T1 mapping correlates with myocardial collagen content, supporting their role as surrogate markers of fibrosis [64]. A multicenter case-control study using CMRi imaging demonstrated that compared to age-, sex-, and body mass index (BMI)-matched controls with similar cardiometabolic risk profiles, acromegaly patients exhibited increased biventricular volumes even with biochemical control, higher left ventricular mass (LVM), and reduced right ventricular systolic function [65].

Structural heart disease may improve with biochemical control of the disease (MQ). Surgical adenoma resection leads to rapid normalization of GH and IGF-I and reduced LVM, improved diastolic function, and resulted in partial or complete reversal of LVH (MQ). Postoperatively, BP normalization, reduced heart rate and increased left ventricular ejection fraction (LVEF) during exercise have been demonstrated [4, 66]. A meta-analysis showed that both lanreotide and octreotide reduced LVM in patients achieving disease control [59], with improved mitral inflow and better diastolic function (HQ). Compared with surgical remission, SRL therapy similarly decreased LVM, diastolic BP, with the added benefit of a modest increase in LVEF, despite normal baseline values (VLQ) [58]. Pegvisomant was associated with gradual improvements in cardiac comorbidities alongside suppressed IGF-I concentrations (MQ). Systolic dysfunction (defined as LVEF < 60%) improved with pegvisomant, and LVEF normalized in patients with hyperkinetic syndrome (LVEF > 70%). LVH also improved with pegvisomant treatment, as demonstrated by a decrease in LVM index in patients with the most severe LVH [67].

Baseline assessment of cardiac function and morphology should be conducted at diagnosis and individualized based on clinical characteristics. Prompt achievement of biochemical control is a primary therapeutic goal. Although treatment of acromegaly improves cardiac function in the short term, it probably has little or no effect on longstanding myocardial hypertrophy, ventricular dilation, or the long-term prognosis in patients with congestive heart failure, as myocardial damage is irreversible at this late stage of cardiomyopathy [68].

The pathogenesis of arrhythmias might be related to structural cardiomyopathy (LQ) [61]. The prevalence varies reaching up to 40% in older studies [69]. In contrast, a prospective study showed no sustained arrhythmias [70]. Notably, a recent cohort study found an increased atrial fibrillation risk during the first four years after diagnosis of acromegaly, although this association lost significance over

time [46]. Patients with acromegaly may rarely exhibit prolonged QT interval [71]. Elevated beat-to-beat short-term QT interval variability and higher prevalence of late potentials may underly arrythmia [72, 73]. Treatment selection of acromegaly should consider potential effects on QT interval i.e., the possible risk of QT interval prolongation with pasireotide [74, 75]. Therefore, QT interval monitoring before and during treatment is advisable [76]. Also, bradycardia is commonly observed with all SRLs [59, 77]. Long-term treatment with pegvisomant could improve rhythm abnormalities [78]. In patients at risk for arrythmias (history of syncope, abnormal baseline ECG, structural abnormalities, heart failure) Holter ambulatory ECG monitoring may be indicated (DR).

Heart failure is rare now in acromegaly, ranging between 1% and 4% [46, 79] and is likely influenced by disease duration and severity, the presence of cardiovascular risk factors and family history (LQ) [80]. Valvular dysfunction is reported in up to 86% of patients, but very rarely of clinical significance, most commonly affecting the mitral and aortic valves, and is irreversible despite successful biochemical control [61].

Obstructive sleep apnea syndrome

The prevalence of OSAS is very high in acromegaly, in up to 80% of newly diagnosed patients. OSAS results mainly from characteristic pharyngeal soft tissue swelling (HQ) (81). OSAS impact on multiple comorbidities is significant (HQ), i.e. representing an independent risk factor for ischemic heart disease, arrhythmia, and cardiomyopathy (HQ) (82, 83). Poor sleep quality adversely affects QoL, and cognitive function (84). Acromegaly treatment improves OSAS in most patients, but it might persist even in controlled patients, requiring close monitoring (MQ) (85-89). Preoperative treatment with SRLs may improve pharyngeal swelling and facilitate intubation during surgery. Patients should undergo OSAS assessment at diagnosis, with a thorough questioning of spouse/partner, and use of a sleep questionnaire, such as the Epworth sleepiness scale or the STOP-BANG questionnaire, although it is important to be aware that such questionnaires may underestimate the presence or severity of sleep disordered breathing (90). Accordingly, polysomnography or respiratory polygraphy should be systematically performed at baseline (even in the absence of symptoms), with regular monitoring recommended thereafter because OSAS may persist or worsen despite appropriate acromegaly therapy (DR) (91, 92). Continuous positive airway pressure with a specially fitted mask may be necessary for patients with atypical facial morphometry (DR).

Exercise intolerance

Patients with acromegaly may have decreased exercise tolerance due to cardiopulmonary impairment, muscle weakness, physical changes and hypopituitarism (LQ) [62, 93].

Studies found decreased LVEF at peak exercise, and an inverse correlation with both disease duration and age, while positively correlating with peak left ventricular filling rate [94]. In patients with preserved LV systolic function at rest, the LVEF response during physical exercise may still be impaired, likely due to underlying LV diastolic dysfunction. These findings highlight the relevance of diastolic abnormalities in limiting exercise capacity in acromegaly (VLQ) [95]. Respiratory complications, including altered craniofacial bones and soft tissues, respiratory mucosa, and cartilage, as well as increased lung volume, modified rib cage geometry, reduced lung elasticity, and increased distensibility contribute to impaired ventilatory efficiency (LQ). Patients often exhibit inadequate ventilatory response to increased exercise demand, with reduced workload capacity at both the anaerobic threshold and peak exertion [62]. Cardiopulmonary impairment is characterized by decreased maximal oxygen consumption (VO_2max) [62, 81]. Aerobic capacity typically reaches only 60–85% of age- and sex-adjusted normative values [96].

Decrease of GH and IGF-I concentrations with fg-SRLs was shown to improve exercise time, cardiac and ventilatory performance (LQ) [97, 98]. Following octreotide, increases in workload and oxygen consumption are observed at both anaerobic threshold and maximal effort. Importantly, after treatment, cardiopulmonary performance is partially restored [97]. Octreotide decreased GH and IGF-I concentrations and improved exercise performance, with an increase in exercise time until exhaustion or reaching age-related predicted target heart rate is reached during treadmill testing [99]. Reduced heart rate at peak exercise with octreotide was observed exclusively in younger patients. Normalization of LVEF response to exercise was achieved in 69.2% of patients overall, with a higher prevalence in younger (80%) compared to middle-aged patients (50%) [98]. Treatment with octreotide for 6 months led to significant improvements in ventilation threshold (VeT) and perceived vigor, accompanied by a modest increase in VO_2max as assessed during treadmill testing. Reduced serum IGF-I concentrations correlated with changes in VeT and subjective vigor scores. Taken together, these findings reinforce that maintaining physiologic GH/IGF-I concentrations is crucial for preserving optimal physical function (MQ) [100]. Short-term regular exercise improves cardiopulmonary function and exercise time and reduces heart rate during warm-up [101].

Skeletal muscle is a primary target tissue for GH and IGF-I and increased fatty infiltration (ectopic fatty deposition) and reduced muscle performance are seen in acromegaly (LQ). These alterations appear to be further exacerbated by active disease [102]. A recent study reported a high prevalence of sarcopenic obesity among patients with acromegaly, which may contribute to impaired exercise performance [103].

Endocrine and metabolic disorders

Consensus recommendations

Diagnosis:

- *Glucose metabolism should be investigated at diagnosis and during follow-up with fasting glucose concentrations and HbA1c assessment (SR).*
- *Since BMI does not reflect body composition alterations, evaluation should be undertaken by DXA or multifrequency bioimpedance at baseline and during disease treatment if available (DR).*

Therapy:

- *Alterations in glucose metabolism and diabetes should be restored with acromegaly disease control (DR).*
- *Treatment of impaired glucose tolerance and diabetes mellitus should entail biochemical control of acromegaly while following the general principles of management of diabetes mellitus (DR).*
- *A personalized, shared approach should be used to select glucose-lowering medications, considering effectiveness, comorbidities, side effects, and patient preference (DR).*
- *Metformin is the first treatment choice (DR).*
- *Risks and benefits of SGLT2 inhibitors should be balanced in uncontrolled acromegaly between the cardiovascular and renal protection and the potential risk of euglycemic ketoacidosis (DR).*
- *GLP-1 receptor agonists may be used in selected patients offering benefits beyond glycemic control, including improved cardiovascular and renal outcomes (DR).*
- *Correction of dyslipidemia is recommended by specific treatment, due to detrimental effects on cardiovascular co-morbidities (DR).*

Follow up:

- *Patients with metabolic syndrome require increased awareness and intensive treatment of dyslipidemia, insulin resistance, prediabetes, all typically observed in acromegaly (DR).*
- *GH deficiency (GHD) may be associated with an increased risk of metabolic dysfunction-associated steatotic liver disease and therefore overtreatment of acromegaly causing GHD should be avoided. If GHD develops, GH replacement therapy should be considered (DR).*
- *Patients with GHD may require more frequent liver function monitoring than recently suggested by MASLD guidelines (DR).*

Diabetes mellitus

Incidence of diabetes mellitus is increased, potentially affecting survival (HQ). Altered glucose metabolism is a common complication, with a reported diabetes mellitus prevalence of 30%, typically present at the time of diagnosis [104–107]. Patients with acromegaly have an increased risk of developing diabetes mellitus (HR: 4.0; 95% CI: 2.7–5.8), being most pronounced in the three years preceding diagnosis [79], primarily due to GH-induced insulin resistance. GH also directly impairs insulin signaling and stimulates lipolysis, leading to elevated free fatty acids (FFAs) that enhance hepatic gluconeogenesis and reduce glucose uptake [108]. Diabetes significantly increases mortality, with a 60% higher overall risk and a 2-fold increase in cardiovascular mortality (HQ) [108]. Patients should be evaluated for glycemic status both at diagnosis and during the follow-up using FPG and hemoglobin A1c (HbA1c) [13, 109, 110].

To optimize outcomes, hyperglycemia should be closely managed (Table 2) and targeting biochemical acromegaly remission should be the fist-step (DR) [107]. Improvement is seen after pituitary surgery, especially in patients with preserved β-cell function (HQ) [111–113]. After surgical remission, and in patients with preserved anterior pituitary function, a multicenter study reported remission of diabetes in 20% of patients; especially in the elderly [113]. Octreotide and lanreotide rarely impair glucose homeostasis, and generally have an overall neutral effect on FPG and HbA1c [114], mainly related to disease control, however glucose metabolism monitoring is essential, with emphasis on post prandial glucose (MQ) [115]. In contrast, pasireotide may have a detrimental effect on glucose metabolism, driven by its suppressive effect on insulin and incretin secretion [116], therefore it is not recommended in patients with poor glycemic control particularly if not treated with insulin (MQ) [8, 117]. The side effect usually manifests early during treatment and is usually manageable with appropriate treatment with incretin-based therapies and is reversible upon discontinuation [118–121]. Pegvisomant improves glucose metabolism (MQ) with a positive impact on insulin resistance, partially independently of disease control and may be considered as a valuable option either as monotherapy or in

combination with SRLs, in patients with severely impaired glucose metabolism (MQ) [8, 122].

A personalized, shared decision-making approach should be used to select glucose-lowering medications, considering effectiveness, comorbidities, side effects, and patient preference (DR) [123]. The initial step for mild glucose abnormalities is lifestyle interventions, diet, physical activity and weight loss (MQ). Metformin is the first-choice medical therapy if not contraindicated (LQ). Sodium–glucose cotransporter 2 (SGLT2) inhibitors may exert favorable effects on acromegaly disease control and might be useful, particularly in patients with cardiovascular and renal comorbidities, although they must be used with caution due to the risk of ketoacidosis, especially in patient with active acromegaly and insufficient pancreatic β-cell reserve (LQ) [123–125]. Decreased insulin secretion leads to reduced paracrine inhibition of glucagon release, further promoting ketogenesis. In the context of acromegaly, GH excess independently promotes lipolysis, which can further drive ketogenesis. Despite this theoretical risk, diabetic ketoacidosis has rarely been reported during SGLT2 inhibitor treatment. A recent study showed no reported adverse effects related to these medications which support the cautious use of SGLT2 inhibitors as a potential treatment option in patients with well-controlled acromegaly [107]. Pasireotide treatment could be a contraindication for SGLT2 inhibitor use due to its inhibitory effects on pancreatic β-cell function, which may exacerbate hyperglycemia and increase the risk of diabetic ketoacidosis (VLQ) [116]. Additionally, in patients treated with SGLT2 inhibitor osmotic diuresis might be enhanced resulting in impairment of renal function which should initially be closely monitored, particularly in older patients and those receiving GH receptor antagonists, as this class of drugs opposes the sodium-retaining effects of GH [24, 118]. Dual GIP/GLP-1 receptor agonist should be used with caution, since GIP has been implicated in paradoxical GH response glucose being clinical impact of this not yet known (VLQ) [126].

Dyslipidemia

Acromegaly is often associated with an atherogenic dyslipidemia patterns (MQ) which should be checked at baseline and appropriately monitored during follow-up (Table 2). The prevalence of dyslipidemia is 30% [105], potentially driven by GH excess, glucose intolerance, diabetes mellitus, and metabolic syndrome (MQ). Acromegaly is also associated with mild to moderate hypertriglyceridemia. Compared to healthy controls, acromegaly patients have elevated concentrations of triglycerides (TG) and lipoprotein(a) [Lp(a)], with reduced total cholesterol (TC), HDL-C, LDL-C, apolipoprotein A1, and apolipoprotein B in the acromegaly cohort compared to controls [127]. Elevated Lp(a) concentrations may contribute to atherosclerotic cardiovascular disease [128]. Insulin resistance impacts the metabolism of TGs, HDL-C, LDL-C, and very low-density lipoprotein cholesterol [129]. Elevated concentrations of FFAs due to increased lipolysis, the most prominent metabolic effect of GH, increase the risk of development of insulin resistance [130, 131].

Acromegaly treatment has inconsistent effects on lipid profile (LQ). Surgery generally lowers TGs, and LDL-C and increases HDL-C [111]. Octreotide and lanreotide decrease TGs and raise HDL-C [132, 133]. LDL-C may increase with pegvisomant treatment whereas LP(a) concentrations decrease after surgery and SRL treatment [28]. The diagnosis, treatment, and management of dyslipidemia to prevent cardiovascular disease should adhere the current evidence-based lipid guidelines [134–136].

Metabolic dysfunction-associated steatotic liver disease (MASLD)

MASLD may have relevant cardiovascular implications in patients with acromegaly (VLQ). GH promotes lipolysis and mobilizes FFAs into the circulation while also enhancing FFA β-oxidation, expected to reduce hepatic lipid accumulation (HQ). GH suppresses hepatic de novo lipogenesis. Interestingly, despite significant insulin resistance in acromegaly, hepatic lipid concentrations are reduced [137]. This paradox may be explained by increased hepatic mitochondrial activity [138] or decreased FGF21 [139, 140]. Nevertheless, genetic predisposition driven by the PNPLA3 susceptibility allele has been identified as a contributing risk factor for hepatic steatosis in acromegaly [141]. Moreover, combination with pegvisomant and a reduced-dose SRL, has been associated with increased intrahepatic lipid compared to SRL in monotherapy [142]. In contrast, GH deficiency (GHD) is strongly associated with an increased prevalence of MASLD [143, 144]. Therefore, patients with GHD may require more frequent liver function monitoring than recently suggested by MASLD guidelines (DR) [145].

Body composition

GH and IGF-I regulate body composition (HQ). Patients with acromegaly exhibit fluid retention and low-fat mass and a specific type of lipodystrophy (MQ) which is characterized by reduced adiposity despite significant insulin resistance (LQ). Visceral adipose tissue (VAT) and subcutaneous adipose tissue are decreased, while intermuscular adipose tissue increases [146]. Recently, a high prevalence of sarcopenic obesity has been demonstrated, although one study

reported no differences in sarcopenic obesity in patients with acromegaly compared to control group [103, 147]. After successful somatotroph adenoma resection, central adiposity increases, including VAT and intrahepatic lipid, while insulin sensitivity improves [148]. VAT increases in the short-term treatment with pegvisomant, however, this finding plateaus during long-term treatment [149].

Lean body mass (LBM), as estimated by dual-energy x-ray absorptiometry (DXA) is typically increased in acromegaly, likely due to excess ECW compartment rather than increased skeletal muscle (MQ) [15]. Similarly, reduced LBM during octreotide treatment have been attributed to decreases in soft tissue fluid rather than true muscle loss [150]. Skeletal muscle mass did not change with long-term pegvisomant [149]. Measuring BMI is of limited diagnostic utility due to the unique pattern of acromegaly body composition changes. Since BMI does not reflect body composition, it should be assessed with DXA or bioelectrical impedance analysis when clinically indicated at diagnosis and follow-up (DR). Skeletal muscle estimates from DXA-adjusted limb tissue strongly concurred with MRI measurements, validating the use of DXA prediction equations for assessing skeletal muscle [150]. While data on muscle mass are conflicting, higher fatty atrophy and lower muscle performance was demonstrated with a further detrimental effect of active acromegaly (VLQ) [102].

Bone complications

Consensus recommendations

Diagnosis:

- *Vertebral morphometry using spine X-ray or latero-lateral scan during DXA should be performed at diagnosis (SR).*
- *As BMD measured by DXA and FRAX score are not reliable parameters to predict vertebral fracture (VF) risk, assessment of bone quality* with *DXA-derived trabecular bone score (TBS) is recommended (DR).*
- *Vitamin D status should be evaluated at diagnosis (DR)*

Therapy:

- *Bone fracture preventing agents should be initiated based on clinical judgment and available guidelines (DR).*
- *Cholecalciferol supplementation should be recommended in acromegaly patients with low vitamin D concentrations and/or high risk of fractures (DR).*

Follow-up:

- *Patients without VFs should be monitored by DXA-derived BMD and TBS (DR)*
- *In patients with prevalent vertebral fractures and/or decreased BMD and/or bone quality, persistently active disease or untreated hypogonadism, monitoring with morphometry should be recommended (DR).*

Clinical assessment

Skeletal fragility is a frequent complication of acromegaly (HQ). GH and IGF-I directly and/or indirectly regulate bone metabolism; excess concentrations lead to increased bone turnover and deteriorated trabecular and cortical bone microarchitecture, as determined by changes in biochemical markers and calcium kinetics, leading to bone loss [151–155].

Vertebral fractures (VFs) are highly prevalent in acromegaly and contribute significantly to reduced QoL (HQ). Morphometric VFs represent an early and frequent sign of impaired bone health, with a median prevalence of 40% [142]. The risk of VFs is particularly high in patients with prior VFs [140, 143], more active disease at diagnosis, greater diagnostic delay, hypogonadism, or vitamin D deficiency [144–146] (MQ). Patients with acromegaly demonstrated a significantly increased risk of hip fractures in addition to clinical VFs compared with controls. This excess fracture risk was time-dependent and became evident early during the follow-up period [156]. Preexisting diabetes mellitus, GHD, and overtreatment of secondary adrenal insufficiency and hypothyroidism are also contributory factors [154, 157–159]. VFs are related to further fracture risk, decreased survival, and lower QoL in the general population [160]. Bone mineral density (BMD) using DXA has limited value for fracture risk prediction, as VFs may occur despite normal or increased BMD due to predominant deterioration in bone quality [161, 162]. An overestimation of lumbar spine (LS) BMD in acromegaly may result from joint degenerative changes, including osteophyte formation, facet joint hypertrophy, and bone enlargement (MQ). Since VFs are often silent and underdiagnosed, their radiological screening (spine X-ray or latero-lateral scan with DXA or chest X-ray) is important at diagnosis.

Bone quality is compromised despite preserved BMD, with altered structure at trabecular and cortical components (MQ). While BMD often remains normal, TBS and 3D-SHAPER analyses consistently show lower trabecular integrity. Postsurgical remission appears to partially restore TBS, whereas pituitary radiotherapy may worsen it. High-resolution peripheral quantitative computed tomography

and high-resolution cone-beam CT may show increased cortical porosity, reduced trabecular number, and impaired cortical strength, even in eugonadal or biochemically controlled patients. These changes are more pronounced in patients with VFs. Additionally, microindentation and quantitative ultrasound studies demonstrate persistent deficits in cortical bone properties and mechanical competence. Collectively, these findings support the need for advanced imaging modalities beyond BMD to assess bone fragility and suggest that fracture risk may be more accurately predicted by bone quality parameters than by BMD alone [152, 163, 164].

Vertebral fractures monitoring

A high prevalence of radiological VFs has been reported in newly diagnosed patients supporting the notion that VFs may represent an early skeletal complication of the disease (MQ). Notably, presurgical GH concentrations predict VF risk, as assessed by morphometric vertebral evaluation highlighting the importance of incorporating VF screening into the initial diagnostic workup, especially in patients presenting with random GH concentrations > 12 ng/mL at diagnosis [165]. Incident VFs (i-VFs) occurred in 34.3% of acromegaly patients, with a diagnostic delay of > 10 years associated with a 1.5-fold increased risk of developing i-VFs [166]. Early identification of VFs can facilitate personalized GH-lowering therapies and consideration of bone-targeted treatments. A prospective longitudinal cohort study revealed VF progression in 35% of patients over a 9-year follow-up period [167]. Notably, progression occurred more frequently among patients not receiving ongoing medical therapy. Previous studies have reported VF progression in 20–25% of treated acromegaly patients during shorter follow-up periods [158, 168]. Interestingly, patients receiving SRLs, were less likely to experience VF progression in contrast with previous observations suggesting increased risk of arthropathy progression in patients treated with SRLs, highlighting a potential divergence in skeletal outcomes based on the mechanism of medical treatment [167]. Moreover, SRLs may confer bone-protective effects since they are associated with a reduced risk of hypopituitarism compared with surgical or radiation approaches [167, 169]. Evaluation of VFs at follow-up should be patient-centered guided by symptoms and back pain, prior VFs, previous diagnosis of osteoporosis, presence of diabetes mellitus, disease activity [152, 161]. Vertebral morphometry should be performed on spine X-ray or lateral scans during DXA, or using chest X-ray performed for other clinical indications if available, particularly in high-risk patients (SR). DXA BMD measurement can still have a role, as femoral neck BMD is reduced, especially in patients experiencing i-VFs [158]. In the presence of low BMD, DXA measurements should be performed every 18–24 months depending on patient characteristics, in line with most guidelines [170–172]. DXA-derived bone quality measurements may provide valuable insights for predicting fracture risk and optimizing management of skeletal complications [152]. The FRAX score calculation, an objective quantitative estimate for fracture risk, was not useful for fracture prediction in patients with acromegaly [103, 173].

Pharmacological antiosteoporosis therapy should be considered individually based on clinical and biochemical findings, due to limited data elucidating prevention of fractures in active acromegaly (LQ) [174]. Current evidence does not allow for rigorous recommendations on the choice of medical acromegaly treatment in relation to bone health. Results from a limited number of patients revealed less frequent i-VFs with pasireotide compared to pegvisomant in patients resistant to SRLs [175]. As pegvisomant alone has no impact on osteoblast functions [176–178] the observation that the addition of pegvisomant to pasireotide therapy prevented occurrence of VF suggests that disease control could be important for skeletal health besides the effect of individual medications [179, 180].

Vitamin D balance

Active acromegaly is a risk factor for vitamin D deficiency correlating with IGF-I levels (LQ) [181]. Increased vitamin D binding protein likely reduces free vitamin D concentrations [182]. Low vitamin D concentrations might be associated with increased risk of i-VFs and supplementation with cholecalciferol may be protective from VF occurrence [183].

Other comorbidities

Consensus recommendations

Diagnosis:

- *Colonoscopy is recommended at diagnosis per country-specific general guidelines (SR)*
- *Screening for cancers, including thyroid, should follow country-specific general protocols (DR).*
- *Early joint clinical assessment is crucial to guide further radiological evaluation if needed (SR).*
- *Renal function (GFR) should be assessed at diagnosis (SR)*
- *QoL should be assessed with dedicated symptoms questionnaires (DR)*

Therapy:

- *In addition to normalizing biochemical parameters, improvement in QoL should be addressed, using a multidisciplinary, patient-centered approach which specifically addresses burden of treatment complications, and maladaptive coping (DR).*
- *Physiotherapy and other patient-centered approaches to improve joint function and QoL should be integrated in the multidisciplinary management of arthropathy (DR).*
- *Joint prostheses might be considered in specific patients (DR)*

Follow up:

- *Follow-up with colonoscopy is recommended as per country-specific general guidelines (SR).*
- *Patient-reported outcome measures (PROMs), symptom burden and QoL and clinician-reported outcome tools (SAGIT instrument and Acromegaly Disease Activity Tool) have shown different relationships with biochemical outcomes and should be assessed during follow-up (DR).*

Cancer

A priori, GH and IGF-I play important roles in cancer development and progression (MQ) [184]. Genetic and/or epigenetic alterations in acromegaly, presence of comorbidities (insulin resistance and diabetes), and aging of this population due to increased survival rates also predispose to cancer risk (MQ) [185, 186]. However, there has been a long-standing debate as to whether acromegaly has a higher risk of malignancy compared to general population.

Improved overall survival rates have led to an increased incidence of reported age-related malignancies (LQ). The incidence of cancer, particularly colon and thyroid cancers has increased mainly according to different reports which might have selection biases [185, 187, 188]. Population-based studies with lesser bias also revealed inconsistent results, some with no increase in cancer incidence [189] as opposed to others with a slight increase [187, 190]. However, large-scale studies show increased cancer incidence [39, 191]. In contrast, no increased incidence was found in malignancy-associated mortality [39]. In a recent, prospective, longitudinal large cohort study, cancer incidence was increased and cumulative exposure to IGF-I excess was a cancer predictor [192]. The total number of cancer cases observed was 156 and the expected number of cases was 87, yielding an increased standardized incidence ratio (SIR) of 1.78 (95% CI, 1.51–1.81). The SIR was increased for thyroid, 6.87 (4.3-10.05); breast, 1.67 (1.16–2.26); and colorectal, 2.65 (1.41–4.29) cancers. Trends for increases in SIR were found for renal, 1.67 (0.59–3.27); and prostate, 1.5 (0.89–2.27) cancers. Population-based genetic, geographic, and other factors may explain the heterogeneity of the results [192].

Quality of life

Despite advances in diagnostic modalities, a significant delay in acromegaly diagnosis persists, with patients often experiencing symptoms for several years prior to diagnosis (HQ). This latency contributes to irreversible acromegaly-associated cardiovascular disease, secondary diabetes mellitus, hypopituitarism, arthropathy, VFs, and psychological disorders [193, 194] (HQ). Impaired QoL and disease activity do not correlate. Dissociated biochemical outcomes and PROMs is present in approximately one-third of patients (MQ).

Many of the acromegaly complications are associated with increased mortality and substantial impairment in QoL [195]. The use of the *Acromegaly Quality of Life questionnaire* (AcroQoL) and simultaneous generic questionnaires with normative data has confirmed that QoL is impaired and largely independent of biochemical outcomes, although an improvement was seen after optimal treatment of acromegaly [196]. AcroQoL impairment correlated with adverse psychological well-being and advancing age. Musculoskeletal disorders, arthropathy, and muscle weakness are particularly linked to impaired QoL (MQ).

QoL improves after long-term biochemical control, regardless of the treatment modality (HQ). In addition, optimizing treatment of hormone deficiencies improves QoL (MQ). Surgical adenoma resection is associated with greater improvements in QoL. While pharmacological treatment ameliorates both acromegaly-related comorbidities and QoL, the chronic requirement for monthly SRL injections is an adverse subjective perception of well-being [197]. Most patients treated with injectable SRLs and classified as well-controlled persistently experience acromegaly-related symptoms (MQ). Furthermore, most patients reported that these symptoms interfered with daily functioning and adversely affected both leisure and occupational activities. Gastrointestinal side effects and injection site reactions were also frequently reported, highlighting the persistent treatment burden associated with long-term injectable therapy [198]. Addition of pegvisomant to long-acting SRL therapy improved GH-dependent parameters of QoL and reported headache, soft-tissue swelling, and the physical domain of AcroQoL, irrespective of IGF-I control [196, 197, 199–201]. Impaired QoL determinants include longer disease duration, GHD, conventional radiotherapy, pain (mainly due to arthropathy), anxiety, depressive symptoms,

impairments in cognitive functioning, and individual characteristics including older age at onset, female gender, and higher BMI (MQ) [196, 201].

Perceived discordance in patient- and physician-reported symptom frequency and severity, and injection site reactions which may not be relevant particularly with oral therapies [202, 203], underscore the need for better communication to improve care (LQ) [204]. PROMs (symptom burden and QoL) and clinician-reported outcome tools (SAGIT instrument and Acromegaly Disease Activity Tool) [205] which evaluate treatment efficacy and support shared decision making, have shown different relationships with biochemical outcomes [200]. Novel PROMs or combination of pre-existing generic and disease specific PROMs are necessary for a patient-centered approach to achieve optimal QoL outcomes [206]. Patient-centered care requires acknowledging patients' perspectives and promoting shared decision-making. Anxiety and depression should be assessed and monitored [195, 207].

Arthropathy

Joint pain, stiffness, and functional impairment are closely associated with reduced QoL (HQ). The prevalence of arthropathy is 4–12 fold higher in acromegaly and GH and IGF-I excess is associated with specific joint changes and arthropathy (HQ) [79, 208]. Therefore, early assessment of joints is recommended (SR). Arthropathy pathogenesis involves both GH and IGF-I excess which promotes chondrocyte DNA synthesis, cell replication, proteoglycan, and glycosaminoglycan synthesis [209]. Initially, elevated GH and IGF-I concentrations induce cartilage hypertrophy and ligamentous laxity, joint hypermobility, joint space widening, and periarticular soft tissue hypertrophy, that may be partially reversible with treatment. With prolonged GH excess, a degenerative phase ensues, with osteophyte and cyst formation, fibrocartilage overgrowth, and irreversible joint damage, often unresponsive to medical therapy [210]. The unique imaging phenotype of arthropathy in acromegaly differs from that of primary osteoarthritis (OA) and is characterized by osteophytosis with widened joint spaces reflecting cartilage hypertrophy [208, 210, 211]. It is predominantly characterized by thicker cartilage and changes in biochemical cartilage composition [210]. Persistent acromegaly shows joint space narrowing (JSN) with more severe joint complaints [212]. JSN affects 10–15% of patients with controlled acromegaly, especially women and older patients. JSN occurs in active disease, characterized by higher pretreatment IGF-I and longer exposure to hormonal excess [213]. Prompt diagnosis and earlier treatment may improve arthropathy reversibility (MQ). SRLs may reverse joint thickening in the early stages of disease [214]. Over time, however, joint degeneration may progress despite biochemical control, with radiological progression seen even after long-term disease control (LQ). These observations could be the consequence of smoldering or residual disease activity, or perhaps a direct effect of SRLs since SSTR are expressed in joint and cartilage cells [211].

Degenerative and inflammatory joint diseases should be distinguished at diagnosis. Arthropathy pain is a prominent symptom adversely affecting QoL and can result in significant deterioration of function over time [213, 215]. Acromegaly patients displayed significantly worse scores in all Western Ontario and McMaster universities osteoarthritis index (WOMAC) items, and these correlate strongly with other disability questionnaires, with QoL, percentage of worktime loss and perceived impact on work productivity and on regular daily activities [213]. The high prevalence of depression is associated with female sex, and particularly the presence of arthropathy, which independently impairs QoL [215].

Persistence and progression of arthropathy occur despite sustained long-term disease management (MQ). Arthropathy should be treated as in general population. However, clinical and radiological findings of acromegaly-associated arthropathy differ from those of primary OA [210], and should prompt patient-centered approaches such as occupational health service for job reclassification, supervised appropriate physical activity and consideration by disability services. For persistent, disabling end-stage arthropathy, joint replacement or other surgical interventions may be considered, if the patient is in remission or well controlled biochemically (DR).

Kidney

Acromegaly is associated with renal hypertrophy, renal cysts, elevated glomerular filtration rate (GFR) due to hyperfiltration, and microalbuminuria (HQ). Acromegaly is characterized by changes in renal structure and function, including variable expression of GH receptor, IGF-I, IGF-IR, and IGF-I-binding proteins variably expressed in anatomically and functionally different kidney segments [216]. Exposure to chronic GH and IGF-I excess increases renal plasma flow, GFR, and renal size [216]. These alterations may revert only partially after correction of GH and IGF-I excess (MQ). There is an increased prevalence of renal cysts and kidney length compared to the age-sex matched healthy population [217]. A 4.35-fold higher risk of developing end-stage kidney disease (ESKD) has been shown [218], also mediated by associated diabetes and hypertension. These reports underscore the need for timely, comprehensive management and long-term follow-up to mitigate ESKD risk. Increased risk of renal impairment and renal/ureteric cancer

is reported (LQ). Few studies reported increased risk of kidney cancer [186, 219].

GH exerts an anti-natriuretic effect leading to sodium and water retention with consequent increase in extracellular water (MQ). Mechanisms underlying antinatriuretic action of the GH/IGF-I axis include renal artery stenosis, changes in antinatriuretic peptides, and ENaC regulation (MQ). Sodium overload may be alleviated by coadministration of the ENaC blocker amiloride [24]. Increased body water and sodium, responsible for soft tissue swelling, leads to a broad spectrum of complications and may lead to high mortality in untreated patients (LQ).

Increased calcitriol and direct effect of IGF-I on the proximal tubule predispose to hyperphosphatemia (MQ). Hypercalciuria, mild hyperphosphatemia, and mild rise in plasma calcium are observed in active vs. treated acromegaly (MQ). Decreased fractional sodium and potassium excretion, hypercalciuria, hyperphosphaturia, microalbuminuria and high prevalence of micronephrolithiasis typically occur [220]. IGF-I-mediated and PTH-independent increased in calcitriol concentrations enhances intestinal calcium absorption and elevated fasting plasma calcium concentrations, the latter linked to increased distal tubular calcium reabsorption via the TRPV5 epithelial calcium channel [221]. Increased plasma phosphate concentrations are associated with both increased calcitriol-driven dietary phosphate absorption and direct antiphosphaturic action of IGF-I in the proximal tubule [24].

Effective treatment of acromegaly leads to rapid improvements in fluid retention, myocardial and peripheral nerve edema, improved cardiac function and reduction of misdiagnosed neuropathies (MQ). OSAS, partly due to soft tissue swelling, also improves with biochemical control (MQ). Since dysmorphic features may improve promptly after successful surgery or medical treatment, underlying the importance of water retention in the acromegaly phenotype (MQ) [24].

Treatment impacts on acromegaly complications

Surgery

If surgery is performed in dedicated neurosurgical centers by experienced neurosurgeons [14], beneficial effects are prompt (HQ). Surgery improves metabolic and cardiorespiratory disorders [88, 111, 222]. Postoperative remission is more common in older patients and those with preserved anterior pituitary function [113]. After surgery, improved glucose tolerance was observed in 87.3% of patients with impaired glucose tolerance and in 66.7% of those with diabetes mellitus. In contrast, deterioration in glucose tolerance occurred in 14.3% of patients with normal glucose tolerance. Improvement was more likely in individuals with lower preoperative FPG, 2-hour blood glucose, and HbA1c concentrations, as well as HOMA-β and insulinogenic index to insulin resistance ratio [112, 223]. Headache, visual acuity compromise, visual field impairment and cranial nerve palsies also ameliorate or resolve completely [224].

Successful transsphenoidal surgical resection improves ventricular mass and diastolic function, and modestly decreases BP and, in some cases, normalizes circadian BP rhythm [55]. Improved OSAS severity evaluated by polysomnography after surgery was associated with decreased IGF-I concentrations [88]. Surgery also ameliorates synovial thickening, bone marrow lesions [225], and peripheral nerve compression (carpal tunnel syndrome) [226, 227]. In experienced neurosurgical centers, regaining normal anterior pituitary function after surgery occurs more often than induction of new pituitary deficiency [228].

Pituitary adenectomy was more effective than SRLs in reducing mortality [229]. The concurrent presence of at least three cardiovascular risk factors was more frequently observed in patients receiving SRLs compared to those undergoing surgical remission [230]. QoL improvement is more pronounced with surgery compared to SRLs [212].

Somatostatin receptor ligands

Information on long-term efficacy and safety is derived from studies investigating the use of long-acting octreotide and lanreotide preparations which improve LVM, LVEF, heart rate and arrhythmias (HQ) [222, 231]. Fg-SRLs have both positive and negative impacts on glucose metabolism, because in addition to inhibiting GH, they may also suppress glucagon, gastrointestinal glucose absorption, hepatic glucose production, and insulin secretion (MQ) [230]. While these agents have a generally neutral effect on glucose metabolism [114], post glucose insulin suppression occurs and may lead to progressive glucose tolerance impairment, independently of the degree of GH/IGF-I control. Improved insulin sensitivity and reduced insulin secretion may lead to hypoglycemic and/or hyperglycemic episodes, highlighting the importance of glucose monitoring [4, 230]. OSAS resolves or improves in patients achieving biochemical remission with fg-SRLs [85, 87], most significantly within the first year of treatment [89]. Although partial reversibility of cartilage hypertrophy after short-term fg-SRL therapy was shown, arthropathy usually persists despite long-term biochemical remission in most patients [212].

Pasireotide is slightly more effective in normalizing GH and IGF-I concentrations improving headache and reducing adenoma-size (MQ). Pasireotide reduces insulin and

incretin secretion, with impaired glucose tolerance sometimes warranting diabetic medication initiation or dose change (MQ) [117]. In patients with active disease, incidental VFs occurred less frequently with pasireotide compared to pegvisomant, despite similar IGF-I concentrations [175].

Pegvisomant

Pegvisomant reduces cardiovascular complications and OSAS prevalence (HQ). In two large registries, pegvisomant improved BP, reducing the risk for coronary heart disease [232], as well as increased LVEF and decreased LVM index (MQ) [67]. The prevalence of cardiac rhythm disturbances decreased from 15% to 7.7% after long-term pegvisomant [78]. Treatment with pegvisomant reduces tongue volume and the severity of OSAS, which resolves in around 50% of patients [67, 86]. Pegvisomant uniquely improves insulin sensitivity, independently of disease control and reduces the need for antidiabetic medications (MQ) [233]. Pegvisomant significantly decreased FPG, HbA1c, fasting plasma insulin, and HOMA-IR. Addition of pegvisomant to SRLs alleviates adverse SRL effects on glucose metabolism [122].

Conclusion

Contemporary management of acromegaly and its comorbidities has yielded lower mortality rates, approaching those of the general population. Early diagnosis and prompt achievement of biochemical remission are *sine qua non* for improved QoL, especially at experienced centers with dedicated neurosurgeons at a PTCOE [14, 15]. These centers provide multimodal management with a personalized approach to medical treatment options, as well as access to specialists for diagnosis, monitoring, and treatment of disease related comorbidities [216, 217]. Specific and effective treatments for systemic comorbidities of the disease play a key clinical role in all patients with acromegaly [218].

Acknowledgements This work is partially supported by PREF (Pituitary Research and Education Foundation).

Author contributions A.G., S.M. contributed to all aspects of the article. L.d.F. and M.M.U. wrote the article and reviewed and/or edited the manuscript before submission. All authors researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Funding Open access funding provided by SCELC, Statewide California Electronic Library Consortium. This work is partially supported by PREF (Pituitary Research and Education Foundation).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests A.G. has occasionally consulted for Amolyt, Abiogen, Alexion, Crinetics, Ipsen, Pfizer and Recordati Rare Diseases, and received research grants to the Istitution by Recordati Rare Diseases. L.d.F. received a research grant to their institution from Abiogen Pharma S.p.A. and his research activities are partly supported by Glucocorticoid induced Osteoporosis Skeletal (GIOSEG). M.F. received grants to their institution from Amryt, Crinetics, Ionis and Recordati Rare Diseases, received occasional consulting fees or has served as occasional Advisory Board Member for Amryt, Crinetics, Camurus, Ipsen, and Recordati Rare Diseases. S.P. has been a speaker at workshops and/or advisory board member for HRA Pharma, Ipsen, Lilly, Novo Nordisk, Pfizer, and Recordati Rare Diseases. S.L.S. is principal investigator for Chiasma (Chiesi) and Pasireotide (Novartis, now Recordati Rare Diseases). C.L.B. has received speaking fees from Ipsen, consulting fees from Ipsen, Recordati Rare Diseases and Novo Nordisk, and is a principal investigator of clinical trials of Crinetics. A.J.v.d.L. has received consulting and speaking fees from Amolyt Pharma, Pfizer. M.G. has received speakers honoraria from Ipsen and Pfizer. K.S. has received honoraria for consulting, speaking and scientific projects from the following companies: Pfizer, Recordati Rare Diseases, Camurus, Crinetics, Novo Nordisk, Ascendis. D.F. received fees for lecture and advisory boards from Novartis, Camurus, Recordati Rare Diseases. M.R.G. has received speaker fees from Recordati Rare Diseases, Ipsen and Novo Nordisk, is member of the advisory board of Recordati Rare Diseases, Ipsen, Novo Nordisk and Crinetics, is principal investigator in clinical trials from Recordati Rare Diseases and Crinetics. A.G.I. occasionally consults for Crinetics, Camurus and Xeris, has received research grants to their institution from Recordati Rare Diseases, Xeris, Chiesi. C.J.S. is an advisory board member or recipient of speaker's fees from NovoNordisk, Amolyt, Pfizer, Crinetics, Sandoz-Hexal, Recordati Rare Diseases, Debiopharm and ConsilientHealth. P.K. participated in clinical trials of Carmus and Recordati Rare Diseases. . P.M. has been a principal investigator in clinical trials of Ipsen, Pfizer, Camurus, received consultation fee and research support from Pfizer, Recordati Rare Diseases. N.K. has been a speaker for Pfizer, Ipsen, Recordati Rare Diseases, investigator for Pfizer, Ipsen, scientific advisory board for Pfizer, Ipsen, Recordati Rare Diseases. S.C. has received lecture and advisory fees and grants from Ipsen, Recordati Rare Diseases. A.L. has received lecture fees from Ipsen and served as consultant for NovoNordisk. Y.G. participated in clinical trials of Crinetics, Cortendo, Debiopharm and Ascendis. E.V. is on the advisory board for Recordati Rare Diseases, HRA pharma, received speaker fees from Recordati Rare Diseases, HRA Pharma, Ipsen. S.F. has received consultancy and speaker fees from Ipsen and Pfizer, consultancy fee from Novartis, is an advisory board member for Recordati Rare Diseases and Novo Nordisk, and has received grants to their institution from Abiogen Pharma S.p.A. P.C. has received unrestricted research and educational grants from Ipsen, Recordati Rare Diseases, Advanz and Pfizer, is an investigator (principal or coordinator) for clinical trials funded by Chiasma, Recordati Rare Diseases, Pfizer, Crinetics and Debiopharm, is a member of Advisory Boards from Pfizer, Crinetics, Recordati Rare Diseases and Amolyt, lectures for Ipsen, Recordati Rare Diseases and Pfizer. T.B. is clinical trial investigator for Xeris, Crinetics, Debiopharm, Recordati Rare Diseases, is on advisory boards for Pfizer, Recordati Rare Diseases, Novo-Nordisk, received speaker fees from Pfizer, Recordati Rare Diseases, Novo-Nordisk and received research grants from Pfizer. A.C. is a principal investigator of research studies for Novartis, Ipsen, Pfizer, a consultant for Novartis, Ipsen, Pfizer, received honoraria from Novartis, Ipsen and Pfizer. S.N. has received consulting, research and speaking fees from Novo Nordisk, Crinetics, Recordati Rare Diseases, Pfizer. M.P.-D. received funding for advisory board or lectures given at symposia organized by Recordati Rare Diseases, Pfizer, Novartis and Ipsen. S.M. received

a research grant to their institution from Recordati Rare Diseases; is a consultant to Ionis, Camurus, NovoNordisk, Chiesi. A.G. is Editor in Chief of Pituitary. L.D.F, R.P. and A.G.I., are Associate Editors of Pituitary. The other authors declare no competing interests.

References

1. Giustina A, Colao A, Acromegaly (2025) N Engl J Med 393(19):1926–1939
2. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S (2022) Acromegaly: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol 10(11):804–826
3. Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM et al (2019) Acromegaly Nat Rev Dis Primers 5(1):20
4. Gadelha MR, Kasuki L, Lim DST, Fleseriu M (2019) Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr Rev 40(1):268–332
5. Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC et al (2010) Mortality in patients with pituitary disease. Endocr Rev 31(3):301–342
6. Giustina A, Biermasz N, Casanueva FF, Fleseriu M, Mortini P, Strasburger C et al (2024) Consensus on criteria for acromegaly diagnosis and remission. Pituitary 27(1):7–22
7. Katznelson L, Laws ER Jr., Melmed S, Molitch ME, Murad MH, Utz A et al (2014) Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 99(11):3933–3951
8. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH et al (2018) A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol 14(9):552–561
9. Giustina A, Barkan A, Chanson P, Grossman A, Hoffman A, Ghigo E et al (2008) Guidelines for the treatment of growth hormone excess and growth hormone deficiency in adults. J Endocrinol Invest 31(9):820–838
10. Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA et al (2003) Diagnosis and treatment of acromegaly complications. J Endocrinol Invest 26(12):1242–1247
11. Melmed S, di Filippo L, Fleseriu M, Mercado M, Karavitaki N, Gurnell M et al (2025) Consensus on acromegaly therapeutic outcomes: an update. Nat Rev Endocrinol 21(11):718–737
12. Melmed S, Casanueva FF, Klibanski A, Bronstein MD, Chanson P, Lamberts SW et al (2013) A consensus on the diagnosis and treatment of acromegaly complications. Pituitary 16(3):294–302
13. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C et al (2020) A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. J Clin Endocrinol Metab 105(4):e937–e946
14. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS et al (2017) Criteria for the definition of pituitary tumor centers of excellence (PTCOE): A pituitary society statement. Pituitary 20(5):489–498
15. Giustina A, Uygur MM, Frara S, Barkan A, Biermasz NR, Chanson P et al (2024) Standards of care for medical management of acromegaly in pituitary tumor centers of excellence (PTCOE). Pituitary 27(4):381–388
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926
17. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH et al (2008) A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab 93(3):666–673
18. Olarescu NC, Bollerslev J (2016) The impact of adipose tissue on insulin resistance in acromegaly. Trends Endocrinol Metab 27(4):226–237
19. Vila G, Jørgensen JOL, Luger A, Stalla GK (2019) Insulin resistance in patients with acromegaly. Front Endocrinol (Lausanne) 10:509
20. Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M et al (2008) Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. Endocrinology 149(7):3294–3305
21. Ho KK, Jenkins AB, Furler SM, Borkman M, Chisholm DJ (1992) Impact of octreotide, a long-acting somatostatin analogue, on glucose tolerance and insulin sensitivity in acromegaly. Clin Endocrinol (Oxf) 36(3):271–279
22. Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P et al (2000) Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. J Clin Endocrinol Metab 85(1):193–199
23. O'Sullivan AJ, Kelly JJ, Hoffman DM, Freund J, Ho KK (1994) Body composition and energy expenditure in acromegaly. J Clin Endocrinol Metab 78(2):381–386
24. Kamenický P, Mazziotti G, Lombès M, Giustina A, Chanson P (2014) Growth Hormone, Insulin-Like growth Factor-1, and the kidney: pathophysiological and clinical implications. Endocr Rev 35(2):234–281
25. UNDERWOOD LE, HINTZ RL, VOINA SJ, VAN WYK JJ (1972) Human Somatomedin, the growth Hormone-Dependent sulfation Factor, is Anti-Lipolytic. J Clin Endocrinol Metabolism 35(2):194–198
26. Kopchick JJ, Berryman DE, Puri V, Lee KY, Jorgensen JOL (2020) The effects of growth hormone on adipose tissue: old observations, new mechanisms. Nat Rev Endocrinol 16(3):135–146
27. Zapf J, Froesch ER, Schmid C (1999) Metabolic effects of IGFs. In: Rosenfeld RG, Roberts CT (eds) The IGF system: molecular Biology, Physiology, and clinical applications. Humana, Totowa, NJ, pp 577–616
28. Briet C, Ilie MD, Kuhn E, Maione L, Brailly-Tabard S, Salenave S et al (2019) Changes in metabolic parameters and cardiovascular risk factors after therapeutic control of acromegaly vary with the treatment modality. Data from the Bicêtre cohort, and review of the literature. Endocrine 63(2):348–360
29. Frara S, Maffezzoni F, Mazziotti G, Giustina A (2016) Current and emerging aspects of diabetes mellitus in acromegaly. Trends Endocrinol Metab 27(7):470–483
30. Obradovic M, Zafirovic S, Soskic S, Stanimirovic J, Trpkovic A, Jevremovic D et al (2019) Effects of IGF-1 on the cardiovascular system. Curr Pharm Des 25(35):3715–3725
31. Yan Z, Xing Z, Xue T, Zhao J, Li G, Xu L et al (2024) Insulin-like growth factor-1 in myocardial ischemia-reperfusion injury: A review. Med (Baltim) 103(9):e37279
32. Macvanin M, Gluvic Z, Radovanovic J, Essack M, Gao X, Isenovic ER (2023) New insights on the cardiovascular effects of IGF-1. Front Endocrinol (Lausanne) 14:1142644

33. Yakar S, Werner H, Rosen CJ (2018) Insulin-like growth factors: actions on the skeleton. J Mol Endocrinol 61(1):T115–t37
34. Werner H, Sarfstein R, Laron Z (2021) The role of nuclear insulin and IGF1 receptors in metabolism and cancer. Biomolecules 11(4):531
35. Frara S, Acanfora M, Franzese V, Brandi ML, Losa M, Giustina A (2024) Novel approach to bone comorbidity in resistant acromegaly. Pituitary 27(6):813–823
36. Bolamperti S, Villa I, di Filippo L (2024) Growth hormone and bone: a basic perspective. Pituitary 27(6):745–751
37. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS (2018) Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur J Endocrinol 179(1):59–71
38. Rosendal C, Arlien-Søborg MC, Nielsen EH, Andersen MS, Feltoft CL, Kistorp C et al (2024) The changing landscape of acromegaly – an epidemiological perspective. Reviews Endocr Metabolic Disorders 25(4):691–705
39. Orme S, McNally R, James PW, Davis J, Ayuk J, Higham C et al (2024) Increased mortality in acromegaly is due to vascular and respiratory disease and is normalised by control of GH levels-A retrospective analysis from the UK acromegaly register 1970–2016. Clin Endocrinol (Oxf) 100(6):558–564
40. Biagetti B, Iglesias P, Villar-Taibo R, Moure MD, Paja M, Araujo-Castro M et al (2023) Mortality in acromegaly diagnosed in older individuals in Spain is higher in women compared to the general Spanish population. J Clin Endocrinol Metab 108(9):2193–2202
41. Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F et al (2017) Changes in the management and comorbidities of acromegaly over three decades: the French acromegaly registry. Eur J Endocrinol 176(5):645–655
42. Ritvonen E, Löyttyniemi E, Jaatinen P, Ebeling T, Moilanen L, Nuutila P et al (2016) Mortality in acromegaly: a 20-year follow-up study. Endocr Relat Cancer 23(6):469–480
43. Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros AL, Sosa E et al (2014) Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab 99(12):4438–4446
44. Del Corso LM, Mesa Junior CO, Andrade VFC, Fidalski SZK, Boguszewski CL (2024) Diagnostic, therapeutic, and prognostic characteristics of patients with acromegaly according to tumor size at diagnosis. Pituitary 27(5):537–544
45. Puglisi S, Terzolo M (2019) Hypertension and acromegaly. Endocrinol Metab Clin North Am 48(4):779–793
46. Hong S, Kim KS, Han K, Park CY (2022) Acromegaly and cardiovascular outcomes: a cohort study. Eur Heart J 43(15):1491–1499
47. Araujo-Castro M, García-Centeno R, González L, Lacerda Nobre E, de Griné Severino M, Goi J et al (2025) Prevalence and evolution of hypertension in a large Iberian cohort of patients with acromegaly. Pituitary 28(6):119
48. Sardella C, Cappellani D, Urbani C, Manetti L, Marconcini G, Tomisti L et al (2016) Disease activity and lifestyle influence comorbidities and cardiovascular events in patients with acromegaly. Eur J Endocrinol 175(5):443–453
49. Vila G, Luger A, van der Lely AJ, Neggers S, Webb SM, Biller BMK et al (2020) Hypertension in acromegaly in relationship to biochemical control and mortality: global ACROSTUDY outcomes. Front Endocrinol (Lausanne) 11:577173
50. González B, Vargas G, de Los Monteros ALE, Mendoza V, Mercado M (2018) Persistence of diabetes and hypertension after multimodal treatment of acromegaly. J Clin Endocrinol Metab 103(6):2369–2375
51. Rocha P, Barroso J, Carlos F, Muxfeldt E, Gadelha M, Kasuki L (2023) Importance of 24 h ambulatory blood pressure monitoring in patients with acromegaly and correlation with cardiac magnetic resonance findings. Pituitary 26(4):402–410
52. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M et al (2025) AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension 2025;82(10):e212-e316
53. Kamenicky P, Blanchard A, Frank M, Salenave S, Letierce A, Azizi M et al (2011) Body fluid expansion in acromegaly is related to enhanced epithelial sodium channel (ENaC) activity. J Clin Endocrinol Metabolism 96(7):2127–2135
54. Colao A, Pivonello R, Galderisi M, Cappabianca P, Auriemma RS, Galdiero M et al (2008) Impact of treating acromegaly first with surgery or somatostatin analogs on cardiomyopathy. J Clin Endocrinol Metabolism 93(7):2639–2646
55. Minniti G, Moroni C, Jaffrain-Rea ML, Esposito V, Santoro A, Affricano C et al (2001) Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. Clin Endocrinol (Oxf) 55(3):307–313
56. Reyes-Vidal C, Fernandez JC, Bruce JN, Crisman C, Conwell IM, Kostadinov J et al (2014) Prospective study of surgical treatment of acromegaly: effects on ghrelin, weight, adiposity, and markers of CV risk. J Clin Endocrinol Metab 99(11):4124–4132
57. Serri O, Beauregard C, Hardy J (2004) Long-term biochemical status and disease-related morbidity in 53 postoperative patients with acromegaly. J Clin Endocrinol Metab 89(2):658–661
58. Colao A, Auriemma RS, Galdiero M, Lombardi G, Pivonello R (2009) Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and Insulin-Like growth Factor-I Levels, tumor Shrinkage, and cardiovascular disease: A prospective study. J Clin Endocrinol Metabolism 94(10):3746–3756
59. Maison P, Tropeano A-I, Macquin-Mavier I, Giustina A, Chanson P (2007) Impact of somatostatin analogs on the heart in acromegaly: A metaanalysis. J Clin Endocrinol Metabolism 92(5):1743–1747
60. Ramos-Leví AM, Marazuela M (2019) Bringing cardiovascular comorbidities in acromegaly to an Update. How should we diagnose and manage them? Front Endocrinol 10:120
61. Sherin RPV, Vietor NO, Usman A, Hoang TD, Shakir MKM (2024) Cardiovascular disorders associated with acromegaly: an update. Endocr Pract 30(12):1212–1219
62. Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25(1):102–152
63. Huang R, Jin J, Zhang P, Yan K, Zhang H, Chen X et al (2023) Use of speckle tracking echocardiography in evaluating cardiac dysfunction in patients with acromegaly: an update. Front Endocrinol (Lausanne) 14:1260842
64. dos Santos Silva CM, Gottlieb I, Volschan I, Kasuki L, Warszawski L, Balarini Lima GA et al (2015) Low frequency of cardiomyopathy using cardiac magnetic resonance imaging in an acromegaly contemporary cohort. J Clin Endocrinol Metab 100(12):4447–4455
65. De Alcubierre D, Feola T, Cozzolino A, Pofi R, Galea N, Catalano C et al (2024) The spectrum of cardiac abnormalities in patients with acromegaly: results from a case-control cardiac magnetic resonance study. Pituitary 27(4):416–427
66. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM et al (2001) Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalization of growth hormone and insulin-like growth factor I levels on cardiac performance. J Clin Endocrinol Metab 86(4):1551–1557
67. Kuhn E, Maione L, Bouchachi A, Rozière M, Salenave S, Brailly-Tabard S et al (2015) Long-term effects of Pegvisomant on comorbidities in patients with acromegaly: a retrospective single-center study. Eur J Endocrinol 173(5):693–702

68. Bihan H, Espinosa C, Valdes-Socin H, Salenave S, Young J, Levasseur S et al (2004) Long-term outcome of patients with acromegaly and congestive heart failure. J Clin Endocrinol Metab 89(11):5308–5313
69. Ramos-Leví AM, Marazuela M (2017) Cardiovascular comorbidities in acromegaly: an update on their diagnosis and management. Endocrine 55(2):346–359
70. Warszawski L, Kasuki L, Sá R, Dos Santos Silva CM, Volschan I, Gottlieb I et al (2016) Low frequency of cardniac arrhythmias and lack of structural heart disease in medically-naïve acromegaly patients: a prospective study at baseline and after 1 year of somatostatin analogs treatment. Pituitary 19(6):582–589
71. Unubol M, Eryilmaz U, Guney E, Ture M, Akgullu C (2013) QT dispersion in patients with acromegaly. Endocrine 43(2):419–423
72. Maffei P, Martini C, Milanesi A, Corfini A, Mioni R, de Carlo E et al (2005) Late potentials and ventricular arrhythmias in acromegaly. Int J Cardiol 104(2):197–203
73. Orosz A, Csajbók É, Czékus C, Gavallér H, Magony S, Valkusz Z et al (2015) Increased Short-Term Beat-To-Beat variability of QT interval in patients with acromegaly. PLoS ONE 10(4):e0125639
74. Breitschaft A, Hu K, Darstein C, Ligueros-Saylan M, Jordaan P, Song D et al (2014) Effects of subcutaneous Pasireotide on cardiac repolarization in healthy volunteers: a Single-Center, phase I, Randomized, Four-Way crossover study. J Clin Pharmacol 54(1):75–86
75. MacKenzie Feder J, Bourdeau I, Vallette S, Beauregard H, Ste-Marie LG, Lacroix A (2014) Pasireotide monotherapy in cushing's disease: a single-centre experience with 5-year extension of phase III trial. Pituitary 17(6):519–529
76. Drugs@FDA: FDA approved drug products. Pasireotide (2018). Accessed 1 May . https://www.accessdata.fda.gov/
77. Parolin M, Dassie F, Vettor R, Steeds RP, Maffei P (2021) Electrophysiological features in acromegaly: re-thinking the arrhythmic risk? J Endocrinol Investig 44(2):209–221
78. Auriemma RS, Pivonello R, De Martino MC, Cudemo G, Grasso LF, Galdiero M et al (2013) Treatment with GH receptor antagonist in acromegaly: effect on cardiac arrhythmias. Eur J Endocrinol 168(1):15–22
79. Dal J, Feldt-Rasmussen U, Andersen M, Kristensen L, Laurberg P, Pedersen L et al (2016) Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur J Endocrinol 175(3):181–190
80. Lombardi G, Galdiero M, Auriemma RS, Pivonello R, Colao A (2006) Acromegaly and the cardiovascular system. Neuroendocrinology 83(3–4):211–217
81. Pivonello R, Auriemma RS, Grasso LF, Pivonello C, Simeoli C, Patalano R et al (2017) Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary 20(1):46–62
82. Cao W, Wang X, Luo J, Huang R, Xiao Y (2021) Impact of obstructive sleep apnea on cardiovascular risk in patients with acromegaly. Sleep Med 80:193–198
83. Filchenko I, Korostovtseva L, Bochkarev M, Tsoy U, Sviryaev Y (2023) Cardiovascular remodeling in active and controlled acromegaly: association with sleep-disordered breathing. Sleep Breath 27(6):2305–2314
84. Wennberg A, Lorusso R, Dassie F, Benavides-Varela S, Parolin M, De Carlo E et al (2019) Sleep disorders and cognitive dysfunction in acromegaly. Endocrine 66(3):634–641
85. Annamalai AK, Webb A, Kandasamy N, Elkhawad M, Moir S, Khan F et al (2013) A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. J Clin Endocrinol Metab 98(3):1040–1050
86. Berg C, Wessendorf TE, Mortsch F, Forsting M, Teschler H, Weischer T et al (2009) Influence of disease control with Pegvisomant on sleep Apnoea and tongue volume in patients with active acromegaly. Eur J Endocrinol 161(6):829–835
87. Parolin M, Dassie F, Alessio L, Wennberg A, Rossato M, Vettor R et al (2020) Obstructive sleep apnea in acromegaly and the effect of treatment: A systematic review and Meta-Analysis. J Clin Endocrinol Metab 105(3):e23–e31
88. Cho J, Kim JH, Kim YH, Lee J (2024) Obstructive sleep apnea screening and effects of surgery in acromegaly: A prospective study. Endocrinol Metab (Seoul) 39(4):641–652
89. Wolters TLC, Roerink S, Drenthen LCA, van Haren-Willems J, Wagenmakers M, Smit JWA et al (2020) The course of obstructive sleep apnea syndrome in patients with acromegaly during treatment. J Clin Endocrinol Metab 105(1):290–304
90. Powlson AS, Annamalai AK, Moir S, Webb AJ, Bala L, Graggaber J et al (2024) High prevalence of severe sleep cycle disruption in de Novo acromegaly and underdiagnosis by common clinical screening tools: A prospective, observational, cross-sectional study. Clin Endocrinol (Oxf) 100(3):251–259
91. Chemla D, Attal P, Maione L, Veyer AS, Mroue G, Baud D et al (2014) Impact of successful treatment of acromegaly on overnight heart rate variability and sleep apnea. J Clin Endocrinol Metab 99(8):2925–2931
92. Davi MV, Dalle Carbonare L, Giustina A, Ferrari M, Frigo A, Lo Cascio V et al (2008) Sleep Apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. Eur J Endocrinol 159(5):533–540
93. Clayton RN (2003) Cardiovascular function in acromegaly. Endocr Rev 24(3):272–277
94. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Morte AMD et al (1999) Impact of patient's age and disease duration on cardiac performance in acromegaly: A radionuclide angiography study. J Clin Endocrinol Metabolism 84(5):1518–1523
95. Spinelli L, Petretta M, Verderame G, Carbone G, Venetucci AA, Petretta A et al (2003) Left ventricular diastolic function and cardiac performance during exercise in patients with acromegaly. J Clin Endocrinol Metabolism 88(9):4105–4109
96. Woodhouse LJ, Mukherjee A, Shalet SM, Ezzat S (2006) The influence of growth hormone status on physical Impairments, functional Limitations, and Health-Related quality of life in adults. Endocr Rev 27(3):287–317
97. Giustina A, Boni E, Romanelli G, Grassi V, Giustina G (1995) Cardiopulmonary performance during exercise in acromegaly, and the effects of acute suppression of growth hormone hypersecretion with octreotide. Am J Cardiol 75(15):1042–1047
98. Colao A, Marzullo P, Cuocolo A, Spinelli L, Pivonello R, Bonaduce D et al (2003) Reversal of acromegalic cardiomyopathy in young but not in middle-aged patients after 12 months of treatment with the depot long-acting somatostatin analogue octreotide. Clin Endocrinol (Oxf) 58(2):169–176
99. Padayatty SJ, Perrins EJ, Belchetz PE (1996) Octreotide treatment increases exercise capacity in patients with acromegaly. Eur J Endocrinol 134(5):554–559
100. Thomas SG, Woodhouse LJ, Pagura SM, Ezzat S (2002) Ventilation threshold as a measure of impaired physical performance in adults with growth hormone excess. Clin Endocrinol (Oxf) 56(3):351–358
101. Hatipoglu E, Topsakal N, Erkut Atilgan O, Camliguney AF, Ikitimur B, Ugurlu S et al (2015) Physical and cardiovascular performance in cases with acromegaly after regular short-term exercise. Clin Endocrinol (Oxf) 83(1):91–97
102. Milioto A, Corica G, Nista F, Wildemberg LEA, Rossi F, Bignotti B et al (2024) Skeletal muscle evaluation in patients with acromegaly. J Endocr Soc 8(4):bvae032

103. Rocha CPS, Hupalowski NN, Andrade VFC, Boguszewski CL, Borba VZC (2025) Assessment of sarcopenic obesity in patients with acromegaly. Pituitary 28(1):25
104. Petrossians P, Daly AF, Natchev E, Maione L, Blijdorp K, Sahnoun-Fathallah M et al (2017) Acromegaly at diagnosis in 3173 patients from the Liège acromegaly survey (LAS) database. Endocr Relat Cancer 24(10):505–518
105. Slagboom TNA, van Bunderen CC, De Vries R, Bisschop PH, Drent ML (2023) Prevalence of clinical signs, symptoms and comorbidities at diagnosis of acromegaly: a systematic review in accordance with PRISMA guidelines. Pituitary 26(4):319–332
106. Fauchier G, Laurent E, Maione L, Lecuyer AI, Herbert J, Pierre-Renoult P et al (2024) Acromegaly: Incidence, patient characteristics and treatment patterns in a 10-year nationwide retrospective hospital cohort study. Ann Endocrinol (Paris) 85(6):589–595
107. Esposito D, Boguszewski CL, Colao A, Fleseriu M, Gatto F, Jørgensen JOL et al (2024) Diabetes mellitus in patients with acromegaly: pathophysiology, clinical challenges and management. Nat Rev Endocrinol 20(9):541–552
108. Esposito D, Olsson DS, Franzén S, Miftaraj M, Nåtman J, Gudbjörnsdottir S et al (2022) Effect of diabetes on morbidity and mortality in patients with acromegaly. J Clin Endocrinol Metab 107(9):2483–2492
109. Committee ADAPP (2024) 6. Glycemic goals and hypoglycemia: standards of care in Diabetes—2025. Diabetes Care 48(Supplement1):S128–S45
110. Biagetti B, Araujo-Castro M, Marazuela M, Puig-Domingo M (2024) Treatment of acromegaly-induced diabetes: an updated proposal. Pituitary 28(1):15
111. Cozzolino A, Feola T, Simonelli I, Puliani G, Hasenmajer V, Minnetti M et al (2020) Metabolic complications in acromegaly after neurosurgery: a meta-analysis. Eur J Endocrinol 183(6):597–606
112. Kinoshita Y, Fujii H, Takeshita A, Taguchi M, Miyakawa M, Oyama K et al (2011) Impaired glucose metabolism in Japanese patients with acromegaly is restored after successful pituitary surgery if pancreatic {beta}-cell function is preserved. Eur J Endocrinol 164(4):467–473
113. Pascual-Corrales E, Biagetti B, Marazuela M, Asensio-Wandosel D, Rodríguez Berrocal V, Irigaray Echarri A et al (2024) Glucose metabolism outcomes after pituitary surgery in patients with acromegaly. Pituitary 27(5):497–506
114. Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P, Giustina A (2009) Effects of somatostatin analogs on glucose homeostasis: A metaanalysis of acromegaly studies. J Clin Endocrinol Metabolism 94(5):1500–1508
115. Cozzolino A, Feola T, Simonelli I, Puliani G, Pozza C, Giannetta E et al (2018) Somatostatin analogs and glucose metabolism in acromegaly: A Meta-analysis of prospective interventional studies. J Clin Endocrinol Metab 103(6):2089–2099
116. Biagetti B, Araujo-Castro M, Tebe C, Marazuela M, Puig-Domingo M (2025) Real-world evidence of effectiveness and safety of Pasireotide in the treatment of acromegaly: a systematic review and meta-analysis. Rev Endocr Metab Disord 26(1):97–111
117. Gadelha M, Marques NV, Fialho C, Scaf C, Lamback E, Antunes X et al (2023) Long-term efficacy and safety of Pasireotide in patients with acromegaly: 14 years of Single-Center Real-World experience. J Clin Endocrinol Metab 108(12):e1571–e9
118. Samson SL, Gu F, Feldt-Rasmussen U, Zhang S, Yu Y, Witek P et al (2021) Managing pasireotide-associated hyperglycemia: a randomized, open-label, phase IV study. Pituitary 24(6):887–903
119. Gadelha MR, Gu F, Bronstein MD, Brue TC, Fleseriu M, Shimon I et al (2020) Risk factors and management of pasireotide-associated hyperglycemia in acromegaly. Endocr Connect 9(12):1178–1190
120. Feldt-Rasmussen U, Bolanowski M, Zhang SL, Yu Y, Witek P, Kalra P et al (2024) Predictive factors and the management of hyperglycemia in patients with acromegaly and cushing's disease receiving Pasireotide treatment: post hoc analyses from the SOM230B2219 study. Front Endocrinol (Lausanne) 15:1250822
121. Colao A, Bronstein MD, Brue T, De Marinis L, Fleseriu M, Guitelman M et al (2020) Pasireotide for acromegaly: long-term outcomes from an extension to the phase III PAOLA study. Eur J Endocrinol 182(6):583
122. Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E et al (2019) Pegvisomant improves glucose metabolism in acromegaly: A Meta-Analysis of prospective interventional studies. J Clin Endocrinol Metab 104(7):2892–2902
123. Committee ADAPP (2024) 9. Pharmacologic approaches to glycemic treatment: standards of care in Diabetes—2025. Diabetes Care 48(Supplement1):S181–S206
124. Quarella M, Walser D, Brändle M, Fournier J-Y, Bilz S (2017) Rapid onset of diabetic ketoacidosis after SGLT2 Inhibition in a patient with unrecognized acromegaly. J Clin Endocrinol Metabolism 102(5):1451–1453
125. Adnan Z (2019) Sodium glucose Co-transporter inhibitors in patients with acromegaly and diabetes. Trends Endocrinol Metabolism 30(2):77–79
126. Jensen MH, Gasbjerg LS, Skov-Jeppesen K, Jacobsen JCB, Poulsen SS, Zhou C et al (2024) GIP receptor antagonism eliminates Paradoxical growth hormone secretion in some patients with acromegaly. J Clin Endocrinol Metab 110(3):715–729
127. Wang M, Guo S, He M, Shao X, Feng L, Yu Y et al (2020) High-Performance liquid Chromatography-Mass Spectrometry-Based lipid metabolite profiling of acromegaly. J Clin Endocrinol Metabolism 105(4):e1075–e84
128. Newman CB (2023) Effects of endocrine disorders on lipids and lipoproteins. Best Pract Res Clin Endocrinol Metab 37(3):101667
129. Bjornstad P, Eckel RH (2018) Pathogenesis of lipid disorders in insulin resistance: a brief review. Curr Diab Rep 18(12):127
130. Chueire VB, Muscelli E (2021) Effect of free fatty acids on insulin secretion, insulin sensitivity and incretin effect - a narrative review. Arch Endocrinol Metab 65(1):24–31
131. Møller N, Jørgensen JOL (2009) Effects of growth hormone on Glucose, Lipid, and protein metabolism in human subjects. Endocr Rev 30(2):152–177
132. Shao XQ, Chen ZY, Wang M, Yang YP, Yu YF, Liu WJ et al (2022) Effects of Long-Acting somatostatin analogues on lipid metabolism in patients with newly diagnosed acromegaly: A retrospective study of 120 cases. Horm Metab Res 54(1):25–32
133. Caron PJ, Petersenn S, Houchard A, Sert C, Bevan JS (2017) Glucose and lipid levels with Lanreotide autogel 120 mg in treatment-naïve patients with acromegaly: data from the PRIMARYS study. Clin Endocrinol (Oxf) 86(4):541–551
134. Patel SB, Wyne KL, Afreen S, Belalcazar LM, Bird MD, Coles S et al (2025) American association of clinical endocrinology clinical practice guideline on Pharmacologic management of adults with dyslipidemia. Endocr Pract 31(2):236–262
135. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al (2019) 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European society of cardiology (ESC) and European atherosclerosis society (EAS). Eur Heart J 41(1):111–188
136. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A, Fein HG et al (2020) Lipid management in patients with endocrine disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 105(12):3613–3682
137. Fellinger P, Beiglböck H, Semmler G, Pfleger L, Smajis S, Baumgartner C et al (2023) Increased GH/IGF-I axis activity

relates to lower hepatic lipids and phosphor metabolism. J Clin Endocrinol Metab 108(10):e989–e97
138. Fellinger P, Wolf P, Pfleger L, Krumpolec P, Krssak M, Klavins K et al (2020) Increased ATP synthesis might counteract hepatic lipid accumulation in acromegaly. JCI Insight 5(5)
139. Uygur MM, Dereli Yazıcı D, Gogas Yavuz D (2022) Low serm fibroblast growth Factor-21 levels is not associated with carotid intima-media thickness in acromegaly patients. J Endocrinol Invest 45(7):1405–1412
140. Eroğlu İ, Iremli BG, Idilman IS, Yuce D, Lay I, Akata D et al (2023) Nonalcoholic fatty liver Disease, liver Fibrosis, and utility of noninvasive scores in patients with acromegaly. J Clin Endocrinol Metab 109(1):e119–e29
141. Koutsou-Tassopoulou A, Papapostoli-Sklavounou I, Krawczyk M, Friesenhahn-Ochs B, Weber SN, Lammert F et al (2019) Hepatic steatosis in patients with acromegaly. Endocrinol Diabetes Metabolism 2(4):e00090
142. Madsen M, Krusenstjerna-Hafstrøm T, Møller L, Christensen B, Vendelbo MH, Pedersen SB et al (2012) Fat content in liver and skeletal muscle changes in a reciprocal manner in patients with acromegaly during combination therapy with a somatostatin analog and a GH receptor antagonist: a randomized clinical trial. J Clin Endocrinol Metab 97(4):1227–1235
143. Hutchison AL, Tavaglione F, Romeo S, Charlton M (2023) Endocrine aspects of metabolic dysfunction-associated steatotic liver disease (MASLD): beyond insulin resistance. J Hepatol 79(6):1524–1541
144. Nishizawa H, Iguchi G, Murawaki A, Fukuoka H, Hayashi Y, Kaji H et al (2012) Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. Eur J Endocrinol 167(1):67–74
145. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D et al (2023) AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):1797–1835
146. Freda PU, Shen W, Heymsfield SB, Reyes-Vidal CM, Geer EB, Bruce JN et al (2008) Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with growth hormone and insulin-like growth factor I excess due to acromegaly. J Clin Endocrinol Metab 93(6):2334–2343
147. Inojosa AC, Hirt AV, Araújo T, Ferreira ME, Andrade L, Cunha V et al (2025) Sarcopenic obesity and physical function in acromegaly: impact of disease control and evaluation using dual X-ray absorptiometry and multifrequency bioelectrical impedance analysis. J Endocrinol Investig 48(9):2027–2039
148. Reyes-Vidal CM, Mojahed H, Shen W, Jin Z, Arias-Mendoza F, Fernandez JC et al (2015) Adipose tissue redistribution and ectopic lipid deposition in active acromegaly and effects of surgical treatment. J Clin Endocrinol Metab 100(8):2946–2955
149. Kuker AP, Shen W, Jin Z, Singh S, Chen J, Bruce JN et al (2021) Body composition changes with Long-term Pegvisomant therapy of acromegaly. J Endocr Soc 5(3):bvab004
150. Freda PU, Shen W, Reyes-Vidal CM, Geer EB, Arias-Mendoza F, Gallagher D et al (2009) Skeletal muscle mass in acromegaly assessed by magnetic resonance imaging and dual-photon x-ray absorptiometry. J Clin Endocrinol Metab 94(8):2880–2886
151. Giustina A, Mazziotti G, Canalis E (2008) Growth Hormone, Insulin-Like growth Factors, and the skeleton. Endocr Rev 29(5):535–559
152. Uygur MM, Frara S, di Filippo L, Giustina A (2023) New tools for bone health assessment in secreting pituitary adenomas. Trends Endocrinol Metab 34(4):231–242
153. Mazziotti G, Frara S, Giustina A (2018) Pituitary diseases and bone. Endocr Rev 39(4):440–488
154. Kužma M, Vaňuga P, Ságová I, Pávai D, Jackuliak P, Killinger Z et al (2021) Vertebral fractures occur despite control of acromegaly and are predicted by cortical volumetric bone mineral density. J Clin Endocrinol Metab 106(12):e5088–e96
155. Kim J, Hong N, Choi J, Moon JH, Kim EH, Lee EJ et al (2023) Increased risk of hip fracture in patients with acromegaly: A nationwide cohort study in Korea. Endocrinol Metab (Seoul) 38(6):690–700
156. Kwon H, Han KD, Kim BS, Moon SJ, Park SE, Rhee EJ et al (2023) Acromegaly and the long-term fracture risk of the vertebra and hip: a National cohort study. Osteoporos Int 34(9):1591–1600
157. Kužma M, Vaňuga P, Pávai D, Killinger Z, Hans D, Binkley N et al (2024) Association of trabecular bone score corrected for tissue thickness with glucose metabolism in acromegaly. Front Endocrinol (Lausanne) 15:1448566
158. Mazziotti G, Bianchi A, Porcelli T, Mormando M, Maffezzoni F, Cristiano A et al (2013) Vertebral fractures in patients with acromegaly: A 3-Year prospective study. J Clin Endocrinol Metabolism 98(8):3402–3410
159. Mazziotti G, Mormando M, Cristiano A, Bianchi A, Porcelli T, Giampietro A et al (2014) Association between l-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism. Eur J Endocrinol 170(6):893–899
160. Giustina A (2020) Acromegaly and vertebral fractures: facts and questions. Trends Endocrinol Metabolism 31(4):274–275
161. Mazziotti G, Biagioli E, Maffezzoni F, Spinello M, Serra V, Maroldi R et al (2015) Bone Turnover, bone mineral Density, and fracture risk in acromegaly: A Meta-Analysis. J Clin Endocrinol Metabolism 100(2):384–394
162. Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A et al (2008) Prevalence of vertebral fractures in men with acromegaly. J Clin Endocrinol Metabolism 93(12):4649–4655
163. Giustina A (2023) Acromegaly and bone: an update. Endocrinol Metab (Seoul) 38(6):655–666
164. Bioletto F, Barale M, Prencipe N, Berton AM, Parasiliti-Caprino M, Gasco V et al (2023) Trabecular bone score as an index of bone fragility in patients with acromegaly: A systematic review and Meta-Analysis. Neuroendocrinology 113(4):395–405
165. Frara S, Melin Uygur M, di Filippo L, Doga M, Losa M, Santoro S et al (2022) High prevalence of vertebral fractures associated with preoperative GH levels in patients with recent diagnosis of acromegaly. J Clin Endocrinol Metab 107(7):e2843–e50
166. Chiloiro S, Giampietro A, Gagliardi I, Bondanelli M, Veleno M, Ambrosio MR et al (2022) Impact of the diagnostic delay of acromegaly on bone health: data from a real life and long term follow-up experience. Pituitary 25(6):831–841
167. Pelsma ICM, Biermasz NR, Pereira AM, van Furth WR, Appelman-Dijkstra NM, Kloppenburg M et al (2020) Progression of vertebral fractures in long-term controlled acromegaly: a 9-year follow-up study. Eur J Endocrinol 183(4):427–437
168. Claessen KM, Kroon HM, Pereira AM, Appelman-Dijkstra NM, Verstegen MJ, Kloppenburg M et al (2013) Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study. J Clin Endocrinol Metab 98(12):4808–4815
169. Mazziotti G, Maffezzoni F, Frara S, Giustina A (2017) Acromegalic osteopathy. Pituitary 20(1):63–69
170. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A et al (2020) American association of clinical Endocrinologists/American college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal Osteoporosis—2020 update. Endocr Pract 26:1–46
171. Fuggle NR, Beaudart C, Bruyère O, Abrahamsen B, Al-Daghri N, Burlet N et al (2024) Evidence-Based guideline for the management of osteoporosis in men. Nat Rev Rheumatol 20(4):241–251
172. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D (2019) Pharmacological management of osteoporosis in

postmenopausal women: an endocrine Society* clinical practice guideline. J Clin Endocrinol Metab 104(5):1595–1622
173. Brzana J, Yedinak CG, Hameed N, Fleseriu M (2014) FRAX score in acromegaly: does it tell the whole story? Clin Endocrinol (Oxf) 80(4):614–616
174. Mazziotti G, Battista C, Maffezzoni F, Chiloiro S, Ferrante E, Prencipe N et al (2020) Treatment of acromegalic osteopathy in Real-life clinical practice: the BAAC (Bone active drugs in Acromegaly) study. J Clin Endocrinol Metab 105(9):e3285–e3292
175. Chiloiro S, Giampietro A, Frara S, Bima C, Donfrancesco F, Fleseriu CM et al (2020) Effects of Pegvisomant and Pasireotide LAR on vertebral fractures in acromegaly resistant to First-generation SRLs. J Clin Endocrinol Metab 105(3):e100–e107
176. Vitali E, Grasso A, Schiavone ML, Trivellin G, Sobacchi C, Mione M et al (2024) The direct impact of Pegvisomant on osteoblast functions and bone development. J Endocrinol Invest 47(6):1385–1394
177. Kuker AP, Agarwal S, Shane E, Bicca J, Geer EB, Cremers S et al (2024) Long-term Pegvisomant therapy of acromegaly: effects on bone Density, turnover and microstructure using HRpQCT. J Endocr Soc 8(6):bvae079
178. Chiloiro S, Palumbo C, Giampietro A, De Marinis L, Bianchi A, Giustina A et al (2025) Acromegaly treatment and bone: a bidirectional relationship. Pituitary 28(6):124
179. Chiloiro S, Giampietro A, Infante A, Mattogno PP, Lauretti L, Olivi A et al (2024) Bone health and skeletal fragility in second- and third-line medical therapies for acromegaly: preliminary results from a pilot single center experience. Pituitary 27(3):303–309
180. Chiloiro S, Mazziotti G, Giampietro A, Bianchi A, Frara S, Mormando M et al (2018) Effects of Pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. Pituitary 21(3):302–308
181. Halupczok-Żyła J, Jawiarczyk-Przybyłowska A, Bolanowski M (2015) Patients with active acromegaly are at high risk of 25(OH) D deficiency. Front Endocrinol (Lausanne) 6:89
182. Altinova AE, Ozkan C, Akturk M, Gulbahar O, Yalcin M, Cakir N et al (2016) Vitamin D-binding protein and free vitamin D concentrations in acromegaly. Endocrine 52(2):374–379
183. Bilezikian JP, Formenti AM, Adler RA, Binkley N, Bouillon R, Lazaretti-Castro M et al (2021) Vitamin D: Dosing, levels, form, and route of administration: does one approach fit all? Rev Endocr Metab Disord 22(4):1201–1218
184. Basu R, Boguszewski CL, Kopchick JJ (2025) Growth hormone action as a target in cancer: Significance, Mechanisms, and possible therapies. Endocr Rev 46(2):224–280
185. Boguszewski CL, Ayuk J, MANAGEMENT OF ENDOCRINE, DISEASE (2016) Acromegaly and cancer: an old debate revisited. Eur J Endocrinol 175(4):R147–R156
186. Terzolo M, Reimondo G, Berchialla P, Ferrante E, Malchiodi E, De Marinis L et al (2017) Acromegaly is associated with increased cancer risk: a survey in Italy. Endocr Relat Cancer 24(9):495–504
187. Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C et al (2018) Cancer incidence in patients with acromegaly: A cohort study and Meta-Analysis of the literature. J Clin Endocrinol Metab 103(6):2182–2188
188. Xiao Z, Xiao P, Wang Y, Fang C, Li Y (2023) Risk of cancer in acromegaly patients: an updated meta-analysis and systematic review. PLoS ONE 18(11):e0285335
189. Petroff D, Tönjes A, Grussendorf M, Droste M, Dimopoulou C, Stalla G et al (2015) The incidence of cancer among acromegaly patients: results from the German acromegaly registry. J Clin Endocrinol Metab 100(10):3894–3902
190. Baris D, Gridley G, Ron E, Weiderpass E, Mellemkjaer L, Ekbom A et al (2002) Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control 13(5):395–400
191. Kim YS, Yun JS, Kim H, Jeun SS, Kim B, Lee SW et al (2025) Acromegaly and the risk of cancer: a nationwide population-based cohort study in Korea. Eur J Endocrinol 192(3):220–227
192. Freda PU, Bruce JN, Jin Z, Kostadinov J, Khandji AG, Cremers S et al (2024) Prospective, longitudinal study of cancer predictors and rates in a new York City cohort of 598 patients with acromegaly. J Clin Endocrinol Metab 110(5):1247–1257
193. Boguszewski CL (2020) Acromegaly: 'You must know it to think of it'. Eur J Endocrinol 183(1):C1–c4
194. Esposito D, Ragnarsson O, Johannsson G, Olsson DS (2020) Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality. Eur J Endocrinol 182(6):523–531
195. Coopmans EC, Andela CD, Claessen K, Biermasz NR (2022) Evaluating the impact of acromegaly on quality of life. Endocrinol Metab Clin North Am 51(4):709–725
196. Webb SM, Crespo I, Santos A, Resmini E, Aulinas A, Valassi E (2017) MANAGEMENT OF ENDOCRINE DISEASE: quality of life tools for the management of pituitary disease. Eur J Endocrinol 177(1):R13–r26
197. Crespo I, Valassi E, Webb SM (2017) Update on quality of life in patients with acromegaly. Pituitary 20(1):185–188
198. Fleseriu M, Molitch M, Dreval A, Biermasz NR, Gordon MB, Crosby RD et al (2021) Disease and Treatment-Related burden in patients with acromegaly who are biochemically controlled on injectable somatostatin receptor ligands. Front Endocrinol (Lausanne) 12:627711
199. Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X et al (2008) Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without Pegvisomant. J Clin Endocrinol Metab 93(10):3853–3859
200. van der Meulen M, Zamanipoor Najafabadi AH, Broersen LHA, Schoones JW, Pereira AM, van Furth WR et al (2022) State of the Art of Patient-reported outcomes in acromegaly or GH deficiency: A systematic review and Meta-analysis. J Clin Endocrinol Metab 107(5):1225–1238
201. Geraedts VJ, Andela CD, Stalla GK, Pereira AM, van Furth WR, Sievers C et al (2017) Predictors of quality of life in acromegaly: no consensus on biochemical parameters. Front Endocrinol (Lausanne) 8:40
202. Fleseriu M, Nachtigall LB, Samson SL, Melmed S (2024) Oral octreotide capsules for acromegaly treatment: application of clinical trial insights to real-world use. Expert Rev Endocrinol Metab 19(4):367–375
203. Wildemberg LE, Fialho C, Gadelha MR (2024) Treatment of acromegaly with the nonpeptide, highly selective somatostatin receptor type 2 agonist Paltusotine. Best Pract Res Clin Endocrinol Metab 38(4):101906
204. Geer EB, Sisco J, Adelman DT, Ludlam WH, Haviv A, Gelbaum D et al (2020) Observed discordance between outcomes reported by acromegaly patients and their treating endocrinology medical provider. Pituitary 23(2):140–148
205. Giustina A, Bronstein MD, Chanson P, Petersenn S, Casanueva FF, Sert C et al (2019) Staging and managing patients with acromegaly in clinical practice: baseline data from the SAGIT® validation study. Pituitary 22(5):476–487
206. Broersen LHA, Zamanipoor Najafabadi AH, Pereira AM, Dekkers OM, van Furth WR, Biermasz NR (2021) Improvement in symptoms and Health-Related quality of life in acromegaly patients: A systematic review and Meta-Analysis. J Clin Endocrinol Metab 106(2):577–587
207. Geraedts VJ, Dimopoulou C, Auer M, Schopohl J, Stalla GK, Sievers C (2015) Health outcomes in acromegaly: depression and anxiety are promising targets for improving reduced quality of life. Front Endocrinol 5:2014

208. Claessen KM, Mazziotti G, Biermasz NR, Giustina A (2016) Bone and joint disorders in acromegaly. Neuroendocrinology 103(1):86–95
209. Barkan A (1997) Acromegalic arthropathy and sleep apnea. J Endocrinol 155(Suppl 1):S41–S44 discussion S5
210. Claessen K, Canete AN, de Bruin PW, Pereira AM, Kloppenburg M, Kroon HM et al (2017) Acromegalic arthropathy in various stages of the disease: an MRI study. Eur J Endocrinol 176(6):779–790
211. Pelsma ICM, Kroon HM, Andela CD, van der Linden EMJ, Kloppenburg M, Biermasz NR et al (2024) Approach to the patient with controlled acromegaly and acromegalic arthropathy: clinical diagnosis and management. Pituitary 27(6):824–836
212. Claessen KM, Ramautar SR, Pereira AM, Smit JW, Roelfsema F, Romijn JA et al (2012) Progression of acromegalic arthropathy despite long-term biochemical control: a prospective, radiological study. Eur J Endocrinol 167(2):235–244
213. Fatti LM, Cangiano B, Vitale G, Persani L, Mantovani G, Sala E et al (2019) Arthropathy in acromegaly: a questionnaire-based Estimation of motor disability and its relation with quality of life and work productivity. Pituitary 22(5):552–560
214. Colao A, Marzullo P, Vallone G, Marinò V, Annecchino M, Ferone D et al (1998) Reversibility of joint thickening in acromegalic patients: an ultrasonography study. J Clin Endocrinol Metabolism 83(6):2121–2125
215. Cangiano B, Giusti E, Premoli C, Soranna D, Vitale G, Grottoli S et al (2022) Psychological complications in patients with acromegaly: relationships with sex, arthropathy, and quality of life. Endocrine 77(3):510–518
216. Fujio S, Takano K, Arimura H, Habu M, Bohara M, Hirano H et al (2016) Treatable glomerular hyperfiltration in patients with active acromegaly. Eur J Endocrinol 175(4):325–333
217. Bostan H, Kizilgul M, Calapkulu M, Kalkisim HK, Topcu FBG, Gul U et al (2024) The prevalence and associated risk factors of detectable renal morphological abnormalities in acromegaly. Pituitary 27(1):44–51
218. Hong S, Kim KS, Han K, Park CY (2023) A cohort study found a high risk of end-stage kidney disease associated with acromegaly. Kidney Int 104(4):820–827
219. Esposito D, Ragnarsson O, Johannsson G, Olsson DS (2021) Incidence of benign and malignant tumors in patients with acromegaly is increased: A nationwide Population-based study. J Clin Endocrinol Metab 106(12):3487–3496
220. Auriemma RS, Galdiero M, De Martino MC, De Leo M, Grasso LF, Vitale P et al (2010) The kidney in acromegaly: renal structure and function in patients with acromegaly during active disease and 1 year after disease remission. Eur J Endocrinol 162(6):1035–1042
221. Kamenický P, Blanchard A, Gauci C, Salenave S, Letierce A, Lombès M et al (2012) Pathophysiology of renal calcium handling in acromegaly: what Lies behind hypercalciuria? J Clin Endocrinol Metab 97(6):2124–2133
222. Wolf P, Bouazizi K, Kachenoura N, Piedvache C, Gallo A, Salenave S et al (2023) Increase in intracellular and extracellular myocardial mass in patients with acromegaly: a cardiac magnetic resonance imaging study. Eur J Endocrinol 189(2):199–207
223. He W, Yan L, Wang M, Li Q, He M, Ma Z et al (2019) Surgical outcomes and predictors of glucose metabolism alterations for growth hormone-secreting pituitary adenomas: a hospital-based study of 151 cases. Endocrine 63(1):27–35
224. Banerji D, Das NK, Sharma S, Jindal Y, Jain VK, Behari S (2016) Surgical management of acromegaly: long term functional outcome analysis and assessment of recurrent/residual disease. Asian J Neurosurg 11(3):261–267
225. Nezu M, Kudo M, Morimoto R, Ono Y, Omata K, Tezuka Y et al (2018) Effects of surgical treatment for acromegaly on knee MRI structural features. Endocr J 65(10):991–999
226. Berkmann S, Brun J, Schuetz P, Christ E, Mariani L, Mueller B (2021) Prevalence and outcome of comorbidities associated with acromegaly. Acta Neurochir (Wien) 163(11):3171–3180
227. Sasagawa Y, Tachibana O, Doai M, Tonami H, Iizuka H (2015) Median nerve conduction studies and wrist magnetic resonance imaging in acromegalic patients with carpal tunnel syndrome. Pituitary 18(5):695–700
228. Yedinak C, Hameed N, Gassner M, Brzana J, McCartney S, Fleseriu M (2015) Recovery rate of adrenal function after surgery in patients with acromegaly is higher than in those with non-functioning pituitary tumors: a large single center study. Pituitary 18(5):701–709
229. Bogazzi F, Colao A, Rossi G, Lombardi M, Urbani C, Sardella C et al (2013) Comparison of the effects of primary somatostatin analogue therapy and pituitary adenomectomy on survival in patients with acromegaly: a retrospective cohort study. Eur J Endocrinol 169(3):367–376
230. Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A et al (2006) Comparison between Six-Year therapy with Long-Acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. J Clin Endocrinol Metabolism 91(1):121–128
231. Heidarpour M, Shafie D, Aminorroaya A, Sarrafzadegan N, Farajzadegan Z, Nouri R et al (2019) Effects of somatostatin analog treatment on cardiovascular parameters in patients with acromegaly: A systematic review. J Res Med Sci 24:29
232. Berg C, Petersenn S, Lahner H, Herrmann BL, Buchfelder M, Droste M et al (2010) Cardiovascular risk factors in patients with uncontrolled and Long-Term acromegaly: comparison with matched data from the general population and the effect of disease control. J Clin Endocrinol Metabolism 95(8):3648–3656
233. Giustina A, Arnaldi G, Bogazzi F, Cannavò S, Colao A, De Marinis L et al (2017) Pegvisomant in acromegaly: an update. J Endocrinol Invest 40(6):577–589

Authors and Affiliations

Andrea Giustina[1] · Luigi di Filippo[1] · Maria Fleseriu[2] · Rosario Pivonello[3] · Stephan Petersenn[4] · John Wass[5] · Susan L. Samson[6] · Alberto M. Pereira[7] · Raúl M. Luque[8] · Betina Biagetti[9] · Maria Chiara Zatelli[10] · Ken K Y Ho[11] · Cesar L. Boguszewski[12] · Aart Jan van der Lely[13] · Mark Gurnell[14] · Nienke Biermasz[15] · Katharina Schilbach[16] · Diego Ferone[17] · Monica R. Gadelha[18] · Adriana G. Ioachimescu[19] · Ezio Ghigo[20] · Christian J. Strasburger[21] · Pinar Kadioglu[22] · Pietro Maffei[23] · Niki Karavitaki[24] · Mónica Marazuela[25] · Michael Buchfelder[26] · Sabrina Chiloiro[27] · Anton Luger[28] · Yona Greenman[29] · Elena Valassi[30] · Ignacio Bernabeu[31] · Stefano Frara[32,33] · Philippe Chanson[34] · Thierry Brue[35] · John Ayuk[36] · Felipe F Casanueva[37] · Annamaria Colao[38] · Pietro Mortini[39] · Sebastian Neggers[40] · Manel Puig-Domingo[41] · Meliha Melin Uygur[1,42] · Shlomo Melmed[43]

✉ Shlomo Melmed
melmed@csmc.edu

1 Institute of Endocrine and Metabolic Sciences, San Raffaele Vita-Salute University and IRCCS San Raffaele Hospital, Milan, Italy

2 Pituitary Center, Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA

3 Università Federico II di Napoli, Naples, Italy

4 ENDOC Center for Endocrine Tumors, Hamburg, Germany

5 Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals, Oxford, UK

6 Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Jacksonville, FL, USA

7 Amsterdam UMC, Department of Endocrinology and Metabolism, University of Amsterdam, Pituitary Center Amsterdam, Amsterdam, Netherlands

8 Department of Cell Biology, Physiology, and Immunology, Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBERobn), Maimonides Institute for Biomedical Research of Córdoba (IMIBIC), University of Cordoba, Cordoba, Spain

9 Endocrinology & Nutrition Department, Hospital Universitario Vall de Hebrón, Barcelona, Spain

10 Department of Medical Sciences, Section of Endocrinology, Geriatrics & Internal Medicine, University of Ferrara, Ferrara, Italy

11 Garvan Institute of Medical Research, St. Vincent's Hospital and the UNSW Sydney, Sydney, Australia

12 Department of Internal Medicine, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, Curitiba, Brazil

13 Pituitary Center Rotterdam, Erasmus University Medical Center, Rotterdam, Netherlands

14 Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

15 Division of Endocrinology, Department of Medicine, Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, The Netherlands

16 Medizinische Klinik und Poliklinik IV, LMU Klinikum, LMU Munich, Germany & Deggendorf Institute of Technology, Deggendorf, Germany

17 Endocrinology Unit, IRCCS Ospedale Policlinico San Martino, Università di Genova, Genova, Italy

18 Neuroendocrinology Research Center/Endocrinology Division, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

19 Department of Medicine, Division of Endocrinology and Molecular Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

20 Department of Medical Sciences, University of Turin, Turin, Italy

21 Department of Endocrinology and Metabolism, Charité-Universitätsmedizin Berlin, Berlin, Germany

22 Division of Endocrinology-Metabolism and Diabetes, Istanbul University - Cerrahpasa, Istanbul, Türkiye, Turkey

23 Department of Medicine, Padua University, Padua, Italy

24 Department of Metabolism and Systems Science, College of Medicine and Health, University of Birmingham, Birmingham, UK

25 Department of Endocrinology and Nutrition, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Madrid, Spain

26 Department of Neurosurgery, University Hospital Erlangen, 91054 Erlangen, Germany

27 UOC Endocrinology and Diabetology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

28 Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Vienna, Austria

29 Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv University, Tel Aviv-Yafo, Israel

30 Endocrinology Department, Germans Trias i Pujol Hospital and Research Institute, CIBERER Unit 747, Universitat Internacional de Catalunya, Barcelona, Spain

31 Endocrinology & Nutrition Department, Hospital Universitario de Santiago de Compostela, Santiago de Compostela, Spain

32 Department of Life Science, Health, and Health Professions, Link Campus University, Rome, Italy

[33] Department of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy

[34] Physiologie et Physiopathologie Endocriniennes, Reference Center for Rare Pituitary Diseases (CRMR HYPO), Université Paris-Saclay, Inserm, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin- Bicêtre, France

[35] AP-HM, Aix Marseille Univ, INSERM, MMG, MarMaRa, Marseille, France; Reference Center for Rare Pituitary Diseases (CRMR HYPO), La Conception University Hospital, Marseille, France

[36] University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

[37] Santiago de Compostela University, IDIS-Complejo Hospitalario Universitario de Santiago (CHUS), CIBERobn, Instituto Salud Carlos III, Santiago de Compostela, Spain

[38] Endocrinology Unit, Department of Clinical Medicine and Surgery, Federico II University, Napoli, Italy

[39] Department of Neurosurgery and Gamma Knife Radiosurgery, Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy

[40] Department of Medicine, Section Endocrinology, Erasmus MC, Rotterdam, Netherlands

[41] Department of Endocrinology & Nutrition, Germans Trias i Pujol University Hospital, Badalona, Spain and CIBER-ER, ISCIII, Badalona, Spain

[42] Department of Endocrinology and Metabolism Disease, School of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey

[43] Cedars-Sinai Medical Center, Los Angeles, CA, USA