A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update

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Abstract

Objective: The aim of the Acromegaly Consensus Group was to revise and update the consensus on diagnosis and treatment of acromegaly comorbidities last published in 2013.

Participants: The Consensus Group, convened by 11 Steering Committee members, consisted of 45 experts in the medical and surgical management of acromegaly. The authors received no corporate funding or remuneration.

Evidence: This evidence-based Consensus was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence following critical discussion of the current literature on the diagnosis and treatment of acromegaly comorbidities.

Consensus Process: Acromegaly Consensus Group participants conducted comprehensive literature searches for English-language papers on selected topics, reviewed brief presentations on each topic, and discussed current practice and recommendations in breakout groups. Consensus recommendations were developed based on all presentations and discussions. Members of the Scientific Committee graded the quality of the supporting evidence and the consensus recommendations using the GRADE system.

Conclusions: Evidence-based approach consensus recommendations address important clinical issues regarding multidisciplinary management of acromegaly-related cardiovascular, endocrine, metabolic, and oncologic comorbidities, sleep apnea, and bone and joint disorders and their sequelae, as well as their effects on quality of life and mortality.

Precis

The Acromegaly Consensus Group presents evidence-based recommendations for optimizing diagnosis and treatment of acromegaly comorbidities.

Introduction

Excess levels of circulating growth hormone (GH) and insulin-like growth factor (IGF)-I in acromegaly have deleterious effects on a wide range of tissues and physiologic processes (1,2). Patients commonly experience abnormal growth of bone and soft tissue (3,4) and have dysregulated glucose metabolism (5,6) with increased risk for cardiovascular disease (7), all of which may impact mortality risk (8). Treatment of patients with acromegaly is aimed at controlling excess GH and/or IGF-I levels, but signs and symptoms of the disease often persist despite achievement of biochemical control (1,9,10). The diagnosis and optimal management of acromegaly comorbidities is critical to ensuring the best long-term outcome for this chronic illness.

The Acromegaly Consensus Group published the first set of recommendations on diagnosis and treatment of disease complications in 2003 (11), and updated them in 2013 (12). In concert with development of new disease management protocols (9), and the conceptualization of the Pituitary Tumor Center of Excellence (13), investigators have increasingly been focusing on defining and optimizing management strategies for acromegaly comorbidities and disease-related sequelae. In June 2018, 45 experts in acromegaly management reviewed the literature and critically assessed new research findings and changes in clinical practice standards and clinical opinion since the 2013 consensus publication. Discussions focused on: cardiovascular, endocrine, metabolic, and oncologic comorbidities, sleep apnea, and bone and joint disorders, as well as the impact of these disease sequelae on quality of life (QoL) and mortality. Updated consensus recommendations on diagnosis and treatment of acromegaly comorbidities were graded using the Grading of Recommendations Assessment, Development and Evaluation

system (GRADE; Table 1) (14,15) and key consensus recommendations are presented in Table 2.

Materials and Methods

The process for development of consensus recommendations by Acromegaly Consensus Group participants before and during the meeting has been described (9). Briefly, participants were assigned specific topics related to acromegaly complications and conducted comprehensive literature searches for English-language papers published between March 2011 and May 2018. Search terms included "acromegaly" and "comorbidities" as well as terms associated with each respective topic covered. After brief presentations to the entire group on each topic, breakout groups discussed current practice and recommendations, and a summary of the findings reported back to the entire group. Consensus recommendations were developed based on all presentations and discussions and all participants voted on each recommendation. After the meeting, members of the Scientific Committee graded both the quality of the supporting evidence and the consensus recommendations using the GRADE system (Table 1). Evidence was graded by strength as very low quality (VLQ), low quality (LQ), moderate quality (MQ), or high quality (HQ). Recommendations were classified as discretionary (DR) or strong (SR).

Cardiovascular Disease

Although cardiovascular morbidity has improved significantly, cardiovascular disease is still an important cause of mortality among patients with acromegaly, despite the recent shift to cancer as the leading cause of mortality (16-18) and rates among those with well-controlled acromegaly now closely approximating that of the normal aging population (MQ). It remains unclear how

much of this shift is due to improved treatment of acromegaly and its comorbidities versus overall improved cardiac care and more stringent cardiovascular risk management; further studies are needed to distinguish between these factors.

Hypertension is a major contributor to cardiovascular mortality in acromegaly (HQ) (8), but recent reports have indicated the positive impact of effective medical control. Prevalence is estimated at approximately 30% and may be as high as 60% in some series (19,20), with markedly higher rates seen in patients with biochemically uncontrolled acromegaly (MQ) (7,21). Excess GH leads to insulin resistance, endothelial dysfunction, and increased sodium and water retention resulting in increased plasma volume and leading to hypertension (22), but these effects may not be fully reversible, and hypertension may persist despite biochemical control of acromegaly (MQ) (23). Management of hypertension in acromegaly should be consistent with guidelines for the general population (SR).

Arrhythmia is relatively uncommon (24), and, when present, is likely related to structural heart disease, particularly cardiomyopathy (LQ) (25). However, patients may exhibit a prolonged QT interval (MQ) (26). Treatment selection for acromegaly should therefore consider potential effects on QT interval (SR). Study data suggest a possible risk of QT interval prolongation with pasireotide (27). Although the clinical relevance of this effect is unclear, monitoring prior to and during treatment is advisable (28). Retrospective data on octreotide/lanreotide in acromegaly patients do not suggest similar effects (27,29). Contributing risk from concomitant therapies that prolong QT interval should also be evaluated (DR).

As subclinical cardiomyopathy may be present (30), baseline echocardiogram is indicated (SR). Although prevalence of left ventricular hypertrophy (LVH) may be lower than earlier reports suggested, due to overdiagnosis, earlier diagnosis of acromegaly, and/or overestimation

of damage by echocardiography (LQ) (31), assessment of changes in cardiac structure is important for long-term management. Magnetic resonance imaging is not required to determine the most appropriate treatment (DR).

Heart failure occurs uncommonly in acromegaly, and is likely influenced by risk factors such as disease duration and severity, the presence of hypertension and diabetes mellitus, and family history (MQ) (32). The significance of cardiac valve disease with regurgitation specific to acromegaly is difficult to assess as tricuspid insufficiency is relatively common in the general population and other factors, such as hypertension, likely influence its risk (LQ).

Prevalence of ischemic heart disease is not increased due to acromegaly per se (33,34). Risk is likely more related to common risk factors such as hypertension, hyperlipidemia, disturbed glucose homeostasis, and smoking (LQ).

Biochemical control of acromegaly with SRLs and pegvisomant reduces LVH progression and improves other markers of structural cardiac dysfunction, including left ventricular ejection fraction (MQ) (35,36). By contrast, the incidence of valvular abnormalities and the risk for further progression of valvulopathy remain unchanged (LQ) (37). Data are reassuring regarding the risk for cardiac valve disease in patients with acromegaly treated with cabergoline (38) but additional studies are needed (VLQ).

Endocrine and Metabolic Disorders

Diabetes mellitus

Impaired glucose tolerance and diabetes mellitus (DM) are the most frequent metabolic comorbidities and are present in 30% to 50% of patients at diagnosis (HQ) (39,40). This rate is

expected to rise further as the prevalence of DM continues to increase in the general population (VLQ).

Acromegaly patients develop insulin resistance due to GH excess, and in those with longstanding disease, insulin insufficiency with impaired glucose tolerance may also occur (MQ) (41). Accordingly, if antidiabetic therapy is necessary, DM should be managed as for the general population and metformin considered as first-line therapy (SR). Tighter HbA1c control is recommended for younger patients (DR). Glucagon-like peptide (GLP)-1 agonists and dipeptidyl peptidase (DPP-4) inhibitors are largely untested and should be considered as second-line treatment on an individualized basis (DR). Sodium-glucose cotransporter (SGLT)-2 inhibitors may be a less favorable option due to increased risk for ketoacidosis in patients with acromegaly (DR) (42).

Importantly, the presence of DM influences the choice of acromegaly medical therapy (MQ). Octreotide and lanreotide generally have a neutral effect on glucose control (MQ) (43), although monitoring of glycemia is advisable (SR). Pasireotide is not recommended in patients with uncontrolled DM due to the high risk for developing hyperglycemia (SR) (9,44,45). The decision to continue pasireotide in a patient who develops hyperglycemia should be individualized. If the benefits of continuing pasireotide outweigh hyperglycemic risk, data from healthy subjects suggest that treatment with concomitant GLP-1 agonists or DPP-4 inhibitors may be useful in minimizing the hyperglycemic effect (DR) (46), but real-world applicability to acromegaly patients on long-term pasireotide remains unknown. Pegvisomant treatment improves glucose metabolism in acromegaly patients (47,48) and should be considered in patients with partial or no response to first-line medical therapy for whom glycemic control is challenging (SR) (9).

Considering the negative effects of disturbed glucose homeostasis on patient outcomes, including mortality risk (MQ) (8,49), all acromegaly patients should be screened for dysglycemia at diagnosis and during follow-up by fasting blood glucose or oral glucose tolerance and HbA1c assessment (SR). Consequent therapy for hyperglycemia is mandatory for optimizing outcome.

Hypopituitarism

Hypogonadism is detected in approximately 50% of patients and results from tumor mass effect, and/or concomitant hyperprolactinemia (MQ) (50,51). Hypogonadism may compromise sexual function, fertility, body composition, well-being, and bone health; proper assessment and adequate replacement of hormonal deficits is recommended (SR) (10). As acromegaly can lead to decreased sex hormone binding globulin (SHBG) levels (LQ) (52), free testosterone should be measured or free testosterone indices should be calculated to assess gonadal function in males with active acromegaly to avoid overdiagnosis of hypogonadism (DR).

Gonadal steroids significantly modulate the GH/IGF system. Testosterone enhances action of GH; estrogens, when taken orally, reduces hepatic IGF-I production, thereby indirectly attenuating GH action (LQ) (53). Therefore, the choice and route of gonadal steroid replacement can significantly affect underlying acromegaly disease activity. Selective estrogen receptor modulators (SERMs) are synthetic estrogen-like compounds with tissue-specific agonist and antagonist actions. As such, they may be used to modulate disease activity in acromegaly, improving gonadal activity via central antiestrogen action while also reducing hepatic IGF-I production via estrogen agonist action (VLQ) (54).

Insufficient replacement of other pituitary hormone deficiencies, such as in central hypothyroidism, or over-replacement of glucocorticoids in adrenal insufficiency may result in

dyslipidemia and increased cardiovascular risk (LQ) (55,56). High doses of glucocorticoid replacement have also been associated with increased mortality risk (VLQ) (57). However, as the GH/IGF-I axis affects cortisol metabolism (58), careful assessment of hormone replacement strategies is recommended (SR) (59).

Conventional radiation therapy increases risk for hypopituitarism and contributes to higher mortality rates (MQ) (57). These patients require careful long-term monitoring for the development of hormonal deficits. It is as yet unknown whether modern radiosurgical approaches are associated with a reduced impact on mortality compared with conventional radiotherapy (VLQ).

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is detected in up to 80% of newly diagnosed acromegaly patients (HQ) (40,60-62), and results mainly from pharyngeal soft tissue swelling characteristic of acromegaly (MQ) (63,64). OSA has well-described adverse effects on the cardiovascular system, and is an independent risk factor for ischemic heart disease, arrhythmia, cardiomyopathy, and other cardiovascular disorders (MQ).

Every patient should undergo careful assessment for OSA at diagnosis of acromegaly; this includes a thorough history, questioning of spouse/partner, and potentially use of a sleep questionnaire, such as the Epworth sleepiness scale (SR) (65). If OSA is suspected on screening, polysomnography could be considered before initial acromegaly surgery. In patients with severe pharyngeal swelling, polysomnography may be performed and pre-operative medical treatment with an SRL considered (DR).

Effective treatment of acromegaly, with reduction of GH/IGF-I, and concomitant reduction in soft tissue swelling, may significantly improve OSA. Nevertheless, because OSA may persist or worsen despite appropriate acromegaly therapy (MQ) (61,66,67), post-treatment evaluation is essential and regular monitoring recommended. Continuous positive airway pressure (CPAP) with a specially fitted mask may be necessary for patients with atypical facial morphometry due to acromegaly (SR). Management of disordered breathing should be undertaken jointly with a sleep physician.

Dyslipidemia

Prevalence of dyslipidemia in acromegaly is generally similar to that of the general population. Lipoprotein(a) may be elevated while HDL cholesterol may be lower (VLQ) (68,69), but the clinical significance of these findings is unclear. Diagnosis, treatment, and management of dyslipidemia should follow guidelines for the general population (SR), with treatment goals and regimens accounting for presence of other metabolic comorbidities of acromegaly, such as diabetes mellitus and hypertension (DR).

Musculoskeletal Disorders

Arthropathy

Acromegaly is associated with specific GH- and IGF-I induced joint changes that increase the risk for arthropathy (HQ) (3,70,71). Cartilage hypertrophy and osteophyte formation contribute to joint space narrowing that may initially be reversible (VLQ) (3). Over time, however, joint degeneration may progress despite biochemical control, with radiological progression seen in the

majority of patients even after long-term disease control (MQ) (72). Early diagnosis and treatment of acromegaly may therefore improve reversibility of arthropathy (SR).

Arthropathy pain is one of the most prominent symptoms negatively affecting QoL in patients with acromegaly, and can result in significant deterioration of function over time (MQ) (73). Treatment of arthropathy should follow guidelines as for the general population (SR). However, clinical and radiological findings of acromegaly-associated arthropathy differ from those of primary osteoarthritis (74), and should be considered when selecting an intervention approach (DR).

Carpal tunnel syndrome

Carpal tunnel syndrome in acromegaly is caused by median nerve enlargement and resultant delayed conduction velocity that correlates with disease duration and IGF-I level (MQ) (75,76). Most patients show symptomatic improvement with acromegaly control, although increased nerve diameter may not be reversible despite treatment (LQ) (76,77). Depending on the severity of symptoms, nerve conduction and imaging studies and decompression surgery may be warranted (DR).

Vertebral fractures

Fractures of the vertebrae detected with vertebral morphometry, particularly of the thoracic spine, are highly prevalent in acromegaly patients with active disease, reported to affect up to 60% of patients (HQ) (78,79). Estimates from available data suggest a 3-fold to 8-fold higher prevalence than in the general population, and a slight predominance in males vs females (LQ) (80). Excess GH and IGF-I, which play key roles in bone metabolism, lead to increased bone

turnover and deterioration of cortical and trabecular bone structure (MQ) (80-83). Accordingly, fracture risk is highest in patients with long-standing active acromegaly. Biochemical control corrects bone turnover defects and protects against fracture risk (MQ) (81,84-86). Lumbar spine trabecular bone score, related to bone microarchitecture, provides information on bone strength independent of BMD (80). However, some patients with biochemically controlled acromegaly may still have a higher risk of vertebral fracture as a result of permanent or irreversible alterations in bone structure (MQ) (78,82,87). Notably, although prevalence of vertebral fracture is higher in eugonadal men with acromegaly than in healthy controls (78), hypogonadism is a significant independent risk factor for increased incidence and adverse outcome of fracture (MQ) (87) and androgen replacement therapy should be considered in hypogonadal men and estrogen substitution considered in postmenopausal women (SR).

Because the presence of a vertebral fracture is a strong predictor of subsequent fractures, and because optimization of biochemical control as well as correction of other risk factors (eg, hypogonadism) may reduce these events (80), imaging studies to assess bone morphometry are suggested in all patients at diagnosis, regardless of disease status (SR), with follow-up studies repeated as appropriate to clinical disease activity, hypogonadism, and comorbid skeletal disorders (DR) (71). Bone mineral density is not a good reflection of bone quality in acromegaly, and may be normal as assessed on standard dual X-ray absorptiometry (MQ) (78,81,88-90). Further studies are needed to determine the role of vitamin D supplementation and bone-targeting agents and other interventions in the prevention and treatment of vertebral fractures in acromegaly (DR).

Cancer

The raw incidence of cancer, specifically colon and thyroid, appears to be increased in patients with acromegaly (MQ) (91). However, intensity of screening can influence reported incidence rates and confound efforts to reduce cancer incidence through routine screening (LQ) (92). Excess GH and IGF-I have been linked to colon epithelial transformation and polyposis, respectively (LQ) (93,94). These observations would suggest that acromegaly patients undergo screening colonoscopy at diagnosis (DR), although there are no conclusive data linking screening frequency to colon cancer mortality rates (LQ) (95), and cancer-specific mortality rates in acromegaly are generally similar to those observed in the general population (MQ) (16). In addition, increased life expectancy of acromegaly patients has been associated with more deaths due to malignancies that are not normally related to GH/IGF-I excess. Thus, cancer incidence in acromegaly seems to be more related to age than to GH excess as observed in the general population (96).

Current evidence does not support routine screening for thyroid cancer at acromegaly diagnosis (DR) (97,98). However, thyroid ultrasound and careful evaluation is recommended in those with palpable thyroid nodules and other risk factors for thyroid cancer, consistent with guideline recommendations for the general population (SR) (99).

Follow-up and screening for all other cancers should be performed according to national/regional guidelines for the general population (SR).

Impact of Comorbidities on Therapeutic Approaches

GH levels directly reflect somatotroph tumor secretory activity and IGF-I levels reflect peripheral disease activity (HQ). Thus, despite limitations due to assay variability, GH and age-

related IGF-I levels remain cornerstone biochemical targets for acromegaly management (SR) (2).

However, acromegaly has an adverse effect on QoL, largely due to musculoskeletal complications and persistent comorbidities (MQ) (100,101), and the economic burden of disease may further adversely affect QoL (LQ) (102). Although effective treatment of acromegaly may improve QoL, biochemical control does not necessarily correlate with clinical well-being and QoL impairments often persist despite biochemical control (MQ) (101,103). A patient-centered approach, accounting for biochemical parameters, comorbidities, treatment complications, and QoL measures, should all be considered in treatment decisions (SR) (102). Scoring systems such as SAGIT (104) and ACRODAT (105) are useful to assess overall disease activity and general and acromegaly-specific QoL instruments such as AcroQoL (106) can be helpful in identifying specific factors for follow-up (DR). When GH and IGF-I levels are discrepant, and when patients are only partially responsive to treatment, clinical factors, including disease-related symptoms, should be used to assess disease control and guide treatment decisions (SR) (9).

Conclusions

Recent advances in acromegaly disease control as well as improved management of comorbidities have led to lower mortality rates, approaching those of the general population. Integrated acromegaly management requires a personalized approach to treatment (SR) (107). Effective management of comorbidities should lead to further decreased morbidity and mortality and improved QoL (SR). Pituitary Tumor Centers of Excellence (13) provide multimodal management of both biochemical dysfunction and mass effects, as well as access to a wide range of specialists to diagnose, monitor, and treat disease-related comorbidities. Such a multimodal

approach appears effective in treating adverse comorbidities and is critical, as many patients with acromegaly will not achieve biochemical control and comorbidities may not remit even when full biochemical control is achieved (SR).

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Author contributions

AG and SM served as Program Coordinators of the 12th Acromegaly Consensus Conference. NB, MDB, FEC, DC, MF, CS, PM, JW, and AVDL served as Steering Committee Members. All authors researched data for the Conference. AG and SM wrote the manuscript and all authors reviewed and/or edited the manuscript before submission.

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Table 1. Grading of Evidence and Recommendations

Grading the evidence	Grading the recommendations
• Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies • Low quality (LQ): supported by large series of small uncontrolled studies • Moderate quality (MQ): supported by one or 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

Adapted with permission from Giustina et al (108)

Table 2. Key Consensus Recommendations for Diagnosis and Treatment of Acromegaly Complications

Assessment	Frequency
Cardiovascular Disorders	
Blood pressure measurement	At baseline and every 6 months or upon change of antihypertensive treatment
Echocardiography	Annually, if abnormal
ECG	Annually, if abnormal
Endocrine and Metabolic Disorders	
Epworth scale or sleep study	Annually Before surgery if OSA is suspected
Fasting blood glucose or OGTT	Fasting blood glucose every 6 months, particularly in uncontrolled disease and during SRL therapy; HbA1c every 6 months if diabetes or prediabetes is present
Total testosterone, SHBG, and PRL (males)	Annually; consider testing free testosterone if there are doubts in interpretation of total testosterone
LH, FSH, 17β-estradiol, and PRL (females)	Annually, in pre-menopausal females with menstrual dysfunction and when pregnancy is desired
Serum Free T4	Annually

Serum 8-9 AM cortisol	If central adrenal insufficiency is suspected; cosyntropin stimulation test if serum cortisol is low
Musculoskeletal Disorders	
DXA	Every 2 years particularly if osteopenia/osteoporosis is present
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
Cancer	
Colonoscopy	Every 10 years; more frequently if IGF-I remains persistently elevated or if abnormal colonoscopy or family history of colon cancer
Quality of life	
AcroQoL	Annually