Endocrine (2020) 68:16–31
https://doi.org/10.1007/s12020-020-02206-7

REVIEW

Check for updates

Acromegaly in the elderly patients

Maria Rosaria Ambrosio[1] · Irene Gagliardi[1] · Sabrina Chiloiro[2] · Ana Gonçalves Ferreira[3] · Marta Bondanelli[1] · Antonella Giampietro[2] · Antonio Bianchi[2] · Laura De Marinis[2] · Maria Fleseriu[4] · Maria Chiara Zatelli[1]

Received: 25 October 2019 / Accepted: 14 January 2020 / Published online: 14 February 2020

Abstract

Background Acromegaly is a rare disease characterized by a chronic exposition to growth hormone (GH) and insulin-like growth factor-1 (IGF-1), caused in most cases by a pituitary GH-secreting adenoma. Chronic GH excess induces systemic complications (metabolic, cardiovascular, respiratory, neoplastic, and musculoskeletal) and increased mortality if not appropriately treated. Recent epidemiological data report an improved life span of patients with acromegaly probably due to better acromegaly management; additionally, the number of pituitary incidentaloma in general population also increased over time due to more frequent imaging. Therefore, the number of elderly patients, newly diagnosed with acromegaly or in follow-up, is expected to grow in the coming years and clinicians will need to be aware of particularities in managing these patients.

Purpose This review aims to explore different aspects of acromegaly of the elderly patients, focusing on epidemiology, diagnosis, clinical presentation, complications, and management options.

Methods Available literature has been assessed through PubMed (data until August 2019) by specific keywords.

Conclusions Available data on acromegaly in the elderly patient are sparse, but point to important differences. Further studies are needed comparing elderly with younger patients with acromegaly to better define a tailored diagnostic and therapeutic management.

Keywords Acromegaly · Elderly · Epidemiology · Diagnosis · Comorbidities · Management

Introduction

Acromegaly is a clinical syndrome characterized by growth hormone (GH) and insulin-like growth factor-1 (IGF-1) excess, generally due to a GH secreting pituitary adenoma [1]. Chronic GH excess induces progressive somatic changes and is associated with multiple complications (cardiovascular, respiratory, metabolic, neoplastic, musculoskeletal) that are responsible for increased mortality and compromised quality of life [2–4]. Recent studies have reported an increase in acromegaly prevalence, but also survival, most likely due to improvement in diagnostic approaches, surgical techniques, and medical therapies. Data is also increasingly available due to large national databases [5–10]. Furthermore, general population survival is increasing. According to data from the U.S. Census Bureau the number of patients aged >65 years is estimated to increase by 2.9% annually from 562 million in 2012 to ~1.6 billion in 2050 (https://www.census.gov/en.html). Therefore, the number of elderly patients with acromegaly, newly diagnosed or in follow-up, is expected to grow in the coming years and clinicians will need to be aware of particularities of treating these patients. Definition of elderly also varies in studies, but usually includes patients over 60, 65, or 70 years old. In this review, we consider different aspects of acromegaly in the elderly: epidemiology, diagnosis, clinical presentation, complications, and management options.

✉ Maria Chiara Zatelli
ztlmch@unife.it

1 Section of Endocrinology & Internal Medicine, Dept of Medical Sciences, University of Ferrara, Ferrara, Italy

2 Pituitary Unit, Department of Endocrinology, Fondazione A Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

3 Endocrinology and Diabetes Department, Garcia de Orta Hospital, Almada, Portugal

4 Northwest Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA

Methods

We conducted a literature search (up to August 2019) on the topic "Acromegaly in the elderly" in English language. For this purpose, we performed an electronic search using MEDLINE (PubMed database) in August 2019 with the following database-specific keywords: "Acromegaly" AND "aging"; "Acromegaly" AND "elderly"; "Acromegaly" AND "Age"; "Pituitary adenoma" AND "Elderly"; "Pituitary Adenoma" AND "aging". In particular, we found: four retrospective studies [11–14] dealing with elderly acromegaly patients (elderly was considered >64 [12], 65 [11, 14], and 70 [13] years old]; one retrospective study which compared younger acromegaly patients vs. older acromegaly patients (elderly was considered >65 years old) [15]; one retrospective study which compared aged acromegaly patients vs. aged healthy controls (elderly was considered >60 years old) [16]; one cross-sectional study which compared aged acromegaly patients vs. aged healthy controls (elderly was considered >60 years old) [17]. Since the number of articles derived from this research was limited, data related to elderly patients with acromegaly were extracted from the population of recent epidemiological, clinical, and surgical studies focused on acromegaly. The reference section of selected studies was examined to detect other potentially suitable articles. In total, 117 articles were reviewed.

Epidemiology

Acromegaly is an overall rare disease and available data related to elderly patients with acromegaly is limited. A recent review, mostly from European population studies, found a total acromegaly prevalence of 2.8–13.7 cases per 100,000 people [5]. In a large US population Broder et al. found a prevalence of 7.10–8.78 cases per 100,000 people with higher values (11.5–15.2 cases per 100,000 inhabitants) in people aged 55–64 years old, without any significant gender differences [7]. Burton et al. confirmed an age-related increase in prevalence with an estimated 2.9–3.7 cases/100,000 inhabitants among 0–17 years old people and of 14.8–18.2 among >65 years old people [6]. Gatto et al. analyzed an Italian database reporting a significant increase in acromegaly prevalence between 2000 (4.7 per 100,000 people) and 2014 (6.9 per 100,000 people): 46% of patients were over 67 years old, with the 7th decade (67–78 years) the most represented (31.25%) [18]. Data derived by Caputo et al. from a regional Italian Database (2012–2016) confirmed a prevalence rate that increased with age until 79 years old and remarkably dropped thereafter. Prevalence was higher in women than in men aged between 40–80 years old [9]. The increase in prevalence could be explained by improved diagnostic and therapeutic management of acromegaly, but also by a larger availability of national patient databases [2]. Annual acromegaly incidence is 0.2–1.1 cases per 100,000 inhabitants, equally distributed between males and females. Frequently, diagnosis occurs in the 5th decade with a delay of 4.5–5 years that sometimes reaches up to 15–25 years [5]. Petrossian et al. evaluated 3173 patients with acromegaly from 10 different countries and observed an increasing age at diagnosis (41.8 years pre-1990 vs. 48.79 post-2010) in both sexes, and fortunately diagnosis delay got shorter. The median age at first symptoms of acromegaly also increased over time (24.6 years pre-1990 vs. 41.7 years post-2010) [19]. Broder et al. considering a population <65 years old, estimated an acromegaly incidence of 0.8–1.17 cases per 100,000 inhabitants with higher values between 35–64 years old (1.67 per 100,000) and lower under 17 years old (1.8 per 100,000) [7]. Burton et al. reported an annual incidence rate increasing with age (0.3–0.8 cases per 100,000 0–17 years old; 0.9–1.8 cases per 100,000 >65 years) [6]. Caputo et al. reported an overall incidence of acromegaly of 0.53 cases per 100,000 people and confirmed an increasing trend of incidence with age. Mean age at the diagnosis was 50.9 years old. Compared with Burton and Broder studies in an US population, Caputo found a lower incidence rate most likely explained by different study methods and real geographic discrepancies [9]. Data derived from surgical databases revealed that elderly patients with acromegaly represent 3 to 5% of cases [11, 15, 20]. Colao et al. identified GH-secreting adenomas as the second most frequent tumor (33.5%) in a series of 170 patients >60 years old [16]. The retrospective study of Arosio et al. based on the Italian population highlighted new acromegaly diagnosis in about 3% of males and 5% of females >65 years old [8]. The increase in acromegaly incidence with age in likely due to the increased diagnostic sensitivity of clinicians, who may be more aware of the disease in the recent times as compared with the past and therefore have a higher clinical suspicion when facing cases evocative of acromegaly [21]. Recent data suggest that a reduction in acromegaly mortality is likely due to the introduction of transsphenoidal surgery (since the 1970s), somatostatin receptor ligands (SRLS, since 1980s), and stricter criteria of disease remission [4, 10]. It seems that the increased life span has brought about a change in mortality causes in acromegaly, that now are more similar to those of the general population of corresponding age (cardiovascular diseases vs. cancer diseases) [10, 22]. Improvements in acromegaly management and therapies over the years allowed a greater life span of patients with acromegaly who can reach older ages.

Clinical presentation

Acromegaly has systemic involvement and, consequently, a large spectrum of presenting signs and symptoms. These include complaints related to GH hypersecretion and tumor mass effects, including visual field defects, headache, and hypopituitarism. There are very few data concerning acromegaly clinical presentation in elderly patients in comparison with younger subjects. It is generally assumed that older patients might have a milder phenotype [16, 23, 24], due to either smaller and enclosed tumors [25–27] and/or lower GH and IGF-1 levels [16, 27, 28] as compared with younger patients. An analysis of 1485 patients from the German Acromegaly Registry showed that secondary gonadal insufficiency was less frequent in older patients, but no correlation was found for ACTH deficiency. The Authors suggest that pituitary insufficiency might be less frequent in this group of patients because they usually have smaller tumors. Lower frequency of hypopituitarism in elderly patients seems plausible, but remains speculative [27]. Both GH hypersecretion and hypopituitarism symptoms can be difficult to identify in elderly patients because they can overlap with ageing features [24]. As a consequence, diagnosis can be delayed longer than in younger subjects, as was seen by Nabarro et al. [29]. Study included 256 patients and found a mean delay in diagnosis of 12.3 years in 82 patients >50 years while shorter time-periods were found in younger age groups (<31 years ($n = 58$): 6.0 years; 31–40 years ($n = 60$): 7.2 years; 41–50 years ($n = 56$): 10.2 years). Few studies specifically describe acromegaly signs and symptoms in elderly patients. Colao et al. [16] evaluated a cohort of 57 newly diagnosed acromegalic patients >60 years old and besides hypertension and glucose metabolism abnormalities, they describe the frequency of joint complaints and goiter, which were present in all the patients. In particular, euthyroid goiter occurred in 65% of patients and subclinical toxic/toxic goiter in 35%. However, there is no comparison with younger patients. Surgical series that specifically evaluated elderly patients with acromegaly also report preoperative data on signs and symptoms or hypopituitarism. Minniti et al. [11] studied 22 acromegalic patients aged over 65 years old and did not find patients with visual field defects and only two patients with pituitary hormone deficits. Puchner et al. [12] evaluated 15 patients that were 65 years or older and all of them had acromegaly typical features, namely, acromegalic habitus, enlarged hands, feet, and tongue, hyperhidrosis and arthralgia. Six patients had headaches and one had progressive visual loss. In the surgical series by Arita et al. [13], all nine evaluated patients that were 70 years old or more had typical acromegaly features, namely, enlarged hands and feet, frontal bossing, and coarse facial features. None of these series, however, compared elderly patients against nonelderly. Silverstein et al. [30] used electronic records to characterize acromegalic patients in the USA, including 367 subjects, 63 of whom aged 65 years or older. They found that carpal tunnel syndrome, panhypopituitarism, and depression were equally frequent when comparing these to younger patients, while esophageal reflux and arthralgia were more frequent ($P = 0.0033$ and $P = 0.032$, respectively), and headaches less frequent ($P = 0.0013$). In conclusion, more comparative studies are necessary to clarify this issue.

Diagnosis

Guidelines for diagnosis of acromegaly recommend assessment of circulating IGF-1 levels evaluated in relation to the normal age-adjusted value ranges according to the specific assay used. They also recommend performing the oral glucose tolerance test (OGTT) to confirm the diagnosis of acromegaly in patients with elevated or equivocal IGF-1 levels. The abnormal GH response to glucose load can be associated with an older age, female gender, obesity, and a high body mass index (BMI) [3]. An inverse correlation between basal GH levels at diagnosis and age was reported in a large multicenter international database of 3173 acromegalic patients [19]. In a series of untreated patients with acromegaly with clearly elevated GH values, an age-related reduction in basal GH secretion was found similarly to non-acromegalic controls ($r = -0.35$, $P < 0.001$) [31]. Arafat et al. evaluating the impact of assay methods on GH response to glucose, demonstrated that post-glucose GH-nadir values are assay-specific and correlate negatively with age and BMI. In multiple regression analysis, age, as well as BMI, and gender were predictors for both basal and nadir GH levels [32]. In 151 de novo patients with acromegaly (age ranges 19–77 years) basal GH and IGF-1 levels and GH nadir after OGTT were lower in elderly patients (age > 60 years) as compared with younger patients and negatively correlated with age [33]. In elderly patients, sometimes OGTT cannot be performed due to higher diabetes incidence and an alternative test could be the diurnal GH profile [34, 35]. Colao et al. evaluated the diagnostic accuracy of mean GH profile and nadir GH levels after OGTT in postoperative patients with acromegaly. In a cohort of 141 patients with acromegaly recruited over a 5-year period, different cutoffs in older patients were shown compared with younger and middle-aged patients to establish surgical remission. In patients with acromegaly older than 60 years, lower cut-off thresholds (1.4 µg/l for fasting GH and 0.5 µg/l for nadir GH after OGTT) predicted normal IGF-1 levels [34]. In the light of these data, age is an important factor to consider in the diagnosis and evaluation of acromegaly activity. Lower GH and IGF-1 levels in elderly acromegalic

patients than in young people may reflect the well known trend in GH and IGF-1 levels reduction in the general population. As in normal aging, this phenomenon could be related to a reduction in hypothalamic GHRH levels and to alterations in age-related plasma concentrations of sex steroids [32–34, 36]. A different tumor biology cannot be excluded [25]. Elderly acromegalic patients present smaller tumors that are more responsive to medical therapy with somatostatin analogs as compared with tumors in young patients (see below) [25, 37]. In addition, older patients usually display a higher body weight as compared with younger acromegalic patients, possibly negatively influencing GH response to OGTT.

After biochemical work-up, radiologic assessment of the sellar region is recommended to confirm the presence of a pituitary neuroendocrine tumor and to evaluate its size and invasiveness. Magnetic Resonance (MR) images are the gold standard and gadolinium injection could help to better define pituitary lesions [2, 3]. To date, there are no different recommendations for elderly patients but the higher frequency of renal failure in this population has to be taken in account before performing contrast-enhanced MR. Furthermore, there is recent concern of potential gadolinium accumulation in patients with normal kidney function [38], though no age differences have been specified. Regarding tumor size, data indicate a smaller tumor diameter in elderly patients with acromegaly compared with younger patients [11, 15]. Petrossian et al. reported in a large series that tumor size and invasiveness are inversely related to age and that there are no significant differences in tumor size between males and females in elderly patients [19]. Furthermore, in 57 acromegalic patients aged >60 years old, Colao et al. showed a greater prevalence of microadenomas and enclosed macroadenomas towards extrasellar/invasive macroadenomas (30, 49, and 21%, respectively) without gender differences [16]. Smaller tumor diameter and lower GH/IGF-1 levels may account for the generally milder clinical pictures of acromegaly in elderly vs. younger patients, but further studies are needed to support this hypothesis.

Comorbidities and complications

Metabolic complications

Acromegaly is associated with impaired glucose metabolism (IGM) and an altered lipid profile [38, 39], most frequently including hypertriglyceridemia, decreased HDL, elevated lipoprotein-a, and increased small dense LDL particles [4, 40–42]. The most important factors determining these changes are GH-induced insulin resistance and increased lipolysis, although pancreatic beta-cell dysfunction has also been described [39]. Older age has been associated to an increased IGM risk in acromegaly, although the evidence is not completely consistent. Bex et al. [43] performed a retrospective study including 418 acromegalic subjects, 25.3% of whom with diabetes. Median age at diagnosis was 42 years for men and 46 for women; patients with diabetes were on average 10 years older than nondiabetics. Arosio et al. [8] studied 1512 acromegalic patients with a mean age at diagnosis of 45 ± 13 years. Diabetes was diagnosed in 16.2% and older age was a significant predictive factor (OR 2.26; 95% CI 1.68–3.05; $P = 0.001$). Fieffe et al. [44] evaluated the French Acromegaly Registry records. Among 519 patients, diabetes was diagnosed in 22.3%, diabetic patients being significantly older at diagnosis than nondiabetics (mean age of patients with diabetes was 54 years vs. 44 years in nondiabetics; $P < 0.001$). They found a steady increasing diabetes rate with age, being the age-related risk of diabetes increased by 4.4% (OR 1.044). Dal et al. [45] in their cohort study included 405 patients with acromegaly (mean age at diagnosis 48.7 years). The study population was divided in two groups according to age—above and below the 50th percentile. Interestingly, diabetes risk was increased in both groups, but with a higher relative risk in younger patients (HR: 4.8; 95% CI 2.5–9.2 in the group <50th percentile vs. HR: 3.2; 95% CI 2.0–5.3 in the group >50th percentile). Conversely, five retrospective studies including a total of 964 patients have found a positive relationship between older age and diabetes in acromegalic patients [29, 46–49]. Diabetes prevalence varied between 18.8 and 52.5%. Espinosa et al. [49] specifically compared age between subjects with normal glucose metabolism, impaired fasting glucose, impaired glucose tolerance (IGT), and diabetes and found a significant difference only for diabetic patients against any of the others. Interestingly, Alexopoulou et al. [48] found that HOMA-B negatively correlated with age ($r = -0.253$; $P = 0.003$) in both uni- and multivariate analyses. Authors found no correlation with GH or IGF-1 levels, leading to the conclusion that ageing is associated to beta-cell reduced function. Therefore, this evidence could partially explain the higher likelihood of diabetes with older age. On the other hand, Kreze et al. [50] in a retrospective study of 43 patients with a mean age of 45.7 years found a prevalence of diabetes of 19%. When dividing the patients by age groups (≥40 vs. <40 years), although diabetes was more frequent in older subjects, the difference was not significant. Very few studies directly compared the prevalence of glucose metabolism abnormalities in elderly vs. nonelderly patients. Tanimoto et al. [26] retrospectively studied 87 newly diagnosed patients, and divided them by age groups: <30 years (young group, $n = 9$), 31–60 years (middle-aged group, $n = 62$), and ≥61 years (elderly group, $n = 16$). They found that 94% of the patients in the elderly

group were diagnosed with IGM (31% with diabetes and 63% with IGT), being significantly more frequent than in the other groups (72% in the middle aged and 33% in the young; $P < 0.001$). Silverstein et al. [30] found that diabetes occurred more often in elderly patients ($P = 0.013$). However, Sasagawa et al. [15] in their surgical series including 24 patients ≥65 years and 63 patients <65 years found that diabetes was slightly but not significantly more frequent in older patients (46 vs. 33%; $P = 0.20$). In conclusion, most evidence available so far suggests that older age might be a risk factor for diabetes, just as it is in the general population. This might be related to a progressive inability of ageing beta-cells to cope with the higher insulin resistance status that is a typical acromegaly feature. More studies comparing elderly against nonelderly patients are still needed to further elucidate this issue in this particular population.

Only few studies have evaluated the relationship between dyslipidemia and age in acromegaly. Ioaniţiu et al. [51] studied 43 acromegalic patients and found hyperlipidemia to be present in 55.8% of the cases, with no relationship to age. Colao et al. in their retrospective case control analysis in patients >60 years old showed how LDL, triglycerides, total cholesterol/HDL ratio were significantly increased in case group [16]. Conversely, Tanimoto et al. [26] found that hyperlipidemia was more frequent, but not significantly, with advancing age ($P = 0.47$). To the best of our knowledge, there are no other studies published in English literature evaluating the influence of age on lipid profile changes in patients with acromegaly. Therefore, once again, no definitive conclusions can be drawn on this issue, yet.

Cardiovascular complications

Cardiovascular disease (CVD) is a frequent comorbidity in patients with acromegaly [2] affecting morbidity and increasing all causes-mortality. Leading risk factors involved in CVD onset and progression are GH/IGF-1 hypersecretion, long-standing disease, and age in addition to typical cardiovascular risk factors (smoking, obesity, dyslipidemia) [52]. Hypertension is more frequent in patients with acromegaly (about 35%, ranging from 18 to 60%) than in general population and generally, it occurs at an earlier age and in early phases of the disease. Patients are often non-dippers and diastolic pressure is mostly affected [53]. Hypertension in acromegaly is not related to gender and it is less frequently related to a family history of hypertension [52–54]. Acromegaly treatment seems to improve hypertension in most patients [4, 55]. Arosio et al. demonstrated with a multivariate model that older age and higher IGF-1 levels at diagnosis were significant predictors of hypertension [8]. Typical hypertrophic cardiomyopathy could be already present at the time of acromegaly diagnosis, but it is generally asymptomatic. Rarely, it presents with severe heart failure. Age, hypertension, disease activity, and duration are considered as potential risk factors for cardiomyopathy [52]. In a study performed by Colao et al. left ventricular (LV) mass index significantly increased from young (<30 years) to elderly (>60 years) patients and the prevalence of LV hypertrophy (LVH) was higher in patients aged >50 year (74.3%) than in younger ones (35–57%) [39]. Indeed, in a logistic regression model, Maione et al. showed that ULN IGF-1 and GH levels at baseline were associated with myocardial hypertrophy/valvulopathy and heart failure respectively; this association disappeared after age adjustment [56]. This evidence may support the hypothesis that aging may negatively influence clinical manifestations of GH excess. The prevalence of cardiac valve diseases, arrhythmias, peripheral vascular diseases, ischemic heart diseases are variable. Carotid atherosclerosis and endothelial dysfunction are related to classic cardiovascular risk factors in acromegaly [38]. The retrospective analysis of Colao et al. is currently the only study that considers exclusively elderly patients (57 patients, >60 years old) with acromegaly compared with a nonacromegaly control group. Hypertension and LVH were found to be more frequent in acromegaly group (82 vs. 67% and 96 vs. 16%). Furthermore, patients had higher systolic and diastolic blood pressure, heart rate, and LV mass index than controls. Diastolic and systolic dysfunction was significantly more prevalent in patients vs. controls (82 vs. 2% and 51 vs. 2%) [16]. Minniti et al. focused on the perioperative cardiovascular status of 22 patients with acromegaly >65 years old. Hypertension and LVH were found in 54.2 and 63.6% of cases, respectively. Pituitary surgery normalized GH excess in 68% patients and among them, a significant improvement in cardiovascular abnormalities was achieved within 6 months. Lower blood pressure and a significant reduction in cardiac mass were observed in cured people, confirming the role of GH/IGF-1 exposure in determining cardiac hypertrophy also in elderly people [11]. In conclusion, LVH should be considered in an elderly patient with acromegaly [16]. Indeed, hypertension and long-standing GH excess could contribute to the hypertrophic effect. To date, however, spare data are available about CD in elderly patients with acromegaly.

Cancer

Cancer has become the first cause of death among acromegalic patients [4, 56]. A recent meta-analysis reported a Standardized incidence ratio (SIR) of overall cancer of 1.5 (95% CI 1.2–1.8) and in detail SIRs were elevated for colorectal cancer, 2.6 (95% CI 1.7–4.0), thyroid cancer, 9.2 (95% CI 4.2–9.9), breast cancer, 1.6 (95% CI 1.1–2.3), gastric cancer, 2.0 (95% CI 1.4–2.9) and urinary tract cancer, 1.5 (95% CI 1.0–2.3) [57]. Cancer is an age-dependent disease

and its increased incidence in acromegaly might be due to a longer survival of these patients in recent years. However, even if studies on animal models [58] and epidemiological data seem to define a potential association between acromegaly and cancer, the exact pathogenesis is still not clear. Noteworthy, acromegaly-related morbidities such as obesity and diabetes are known factors associated with increased incidence and mortality from malignancies and they may amplify cancer risk [59]. Age and family history of cancer remain significant independent factors associated to cancer risk also in acromegalic patients [22].

Respiratory complications

Acromegaly is a condition that increases sleep apnea syndrome (SAS) risk, which prevalence in these patients is much higher than in general population. SAS in acromegaly is predominantly obstructive, although in some cases it has a central or mixed etiology [4]. Obstructive apnea syndrome is usually related to changes in bone and soft tissues of the skull and face and structural changes in the upper airways that lead to their narrowing. Central apnea syndrome is caused by central inhibition of the respiratory center [38, 60, 61]. Older age is a risk factor for SAS in the general population. This might be explained by age-related weakening of the upper airway musculature [62–64]. The latter has also been described as a risk factor for SAS in acromegaly, although evidence is controversial. Six retrospective studies including a total of 209 patients with acromegaly found a positive relationship between age and SAS, with this comorbidity being statistically significantly related to a higher mean age [60, 61, 64–67]. In these studies, all types of SAS were considered, except in the one by Dostalova et al. [61], that included only patients with obstructive SAS. They found a prevalence of SAS varying between 39 and 87.5% in these subjects. In the study by Chevallier et al. [66], higher age was also significantly related to SAS severity. Dal et al. found an increased SAS risk in both age groups, with a higher hazard ratio (HR) in the older age group (HR 13.3; 95% CI 5.5–21.2 vs. HR 10.8; 95% CI 5.9–30.0) [45]. On the other hand, Weiss et al. [63] and Turan et al. [68] in their retrospective analyses of 55 and 30 acromegalic patients, respectively, found that mean age of SAS subjects was higher, but the difference was not statistically significant. Conversely, Vannuci et al. [69] showed in a retrospective study of 25 patients with acromegaly that older age is not a risk factor for SAS (prevalence was 56%). Indeed, these patients had a lower mean age, but the difference was not statistically significant. In these studies [63, 64] all types of SAS were considered. Some limitations exist with the available data so far, such as differences in study design (i.e., disease functional status from the patients enrolled and SAS parameters). In addition, these studies included elderly patients, but did not specifically compare them with younger age groups. Altogether, most of the evidence is in favor of older age being a risk factor for SAS in acromegalic patients, just as it is in the general population. It is advisable to evaluate patients for SAS at diagnosis and during treatment, and also when acromegaly is biochemically controlled to select the patients eligible to specific treatment with continuous positive airway pressure [70].

Skeletal system complications

Joint and bone complications, more specifically, secondary osteoarthritis (OA) and skeletal fragility with increased risk of vertebral fractures (VF) are frequent in acromegaly [71–73]. Arthropathy is common in all patients and can cause significant disability [74]. Higher age is considered to be a risk factor for primary OA, which might be present in up to 30% of people over 60 years. Few studies have evaluated if this was also true for acromegaly-related arthropathy, with inconsistent findings [74–76]. Claessen et al. prospectively studied a cohort of 58 patients (with long-term remission; mean age of 62 ± 10.9 years) for arthropathy radiological progression at hand, knee, and hip joints. After a mean follow-up of 2.6 years, they found higher age to be associated with joint space narrowing (OR 1.10; $P = 0.01$) but not with osteophyte progression. Considering joints separately, in the hip joint space narrowing was related to older age (OR 1.1, $P = 0.047$) and in the hands both joint space narrowing and osteophyte progression were related to older age ($P < 0.001$ and $P = 0.02$, respectively). The Authors conclude that this predictive factor for primary OA also applies for patients with acromegaly despite long-term controlled disease. However, results were inconsistent with a relationship between older age and joint space narrowing at patient level, but not in all joints and not in osteophyte progression [75]. On the other hand, Kropf et al. in their study of 71 patients (with active and controlled disease) with a mean age of 49.5 ± 14.5 years, evaluated the presence of arthropathy in large peripheral joints (knees, hips, and shoulders) and found that it was significantly related to older age at diagnosis (47.2 ± 15 years with arthropathy vs. 40.3 ± 13.8 years without arthropathy; $P = 0.044$), but not at current age [74]. Furthermore, Biermasz et al. studied 67 patients (mean age of 56.8 ± 1.5 years), in remission from acromegaly, for the presence of radiological OA, and found a positive correlation, though weak, between older age at diagnosis and OA (adjusted regression coefficient for total body OA was 0.37; 95% CI 0.24–0.52) [76]. In the nationwide cohort study by Dal et al. older patients had a higher risk of arthropathy (HR 2.3; 95% CI 1.8–3.4 vs. HR 1.6; 95% CI 1.1–2.4) [45]. Altogether, the data available so far are insufficient to draw specific conclusions on this

Table 1 Summary of the main characteristics and findings of studies evaluating surgical treatment in acromegaly elderly patients

Authors/ Ref.	Study design	Study population (*n*/age/FU)	Mean adenoma size ± SD (m—micro; M—macroadenoma)	Mean pre-op GH ± SD (ng/mL)	Mean pre-op IGF-1 ± SD (ng/mL)	Preoperative comorbidities	Surgery	Peri-operative complications	Remission of disease/clinical improvement	Mortality (related to procedure)
Sasagawa et al. [15]	Retrospective	$n = 87$ ≥65 y: 24 (27.6%) Mean age: 68 y (65–75) <65 y: 63 (72.4%) Mean age: 53 y (30–64) FU: 6 m	≥65 y: 9.6 ± 4.3 mm <65 y: 12.6 ± 6.4 mm (p 0.056) ———————— ≥65 y: m: 16 (67%) M: 8 (33%) (no data <65 y)	≥65 y: 7.05 ± 7.6 <65 y: 8.15 ± 31.2 (p 0.357)	≥65 y: 456.4 ± 192.6 <65 y: 603.1 ± 310.7 (p 0.002) IGF-1 SD 5.5 (≥65 y) vs. 6.9 (<65 y) (p 0.058)	≥65 y: HT: 15 (63%) DM: 11 (46%) DCV: 7 (29%) C: 8 (33%) <65 y: HT: 29 (46%) p 0.128 DM: 21 (33%) p 0.020 DCV: 5 (8%) p 0.017 C: 6 (10%) p 0.011 ASA-PS ≥65 y: 2: 6 (25%) 3: 18 (75%) <65 y: 2: 61 (97%) 3: 2(3%) (p 0.00001)	TSS	≥65 y: 4 (17%) (Angina, HF, renal dysfunction, cerebral infarction) <65 y: 4 (6%) (2 CSF leaks, cerebral infarction, difficult endotracheal intubation) (p 0.142) Hypopituitarism: ≥65 y: 1 (4%) <65 y: 2 (3%) (p 0.625)	GH < 1.0 ng/mL and normal IGF-1: ≥65 y: 16 (67%) <65 y: 45 (71%) (p 0.426) HT and DM discontinuing or reducing treatment dose: HT ≥65 y: 4/15 (27%) <65 y: 10/29 (34%) (p 0.432) DM ≥65 y: 4/11 (35%) <65 y: 9/21 (43%) (p 0.513)	None
Arita et al. [13]	Retrospective	$n = 7$ ≥70 y Mean age: 74 y (70–82) Mean FU: 73 m (11–145 m)	16.3 ± 6.3mm m: 1 (14%); M: 6 (86%)	39.8 ± 44.7	381.3 ± 294.4	HT: 5 (71%) DM: 6 (100%) DCV: 2 (29%) Dislipidemia: 2 (29%) C: 2 (29%) ASA-PS: 2: 7 (100%)	TSS	No imediate postoperative complications Transient polyuria: 3 (43%) No new-onset hypopituitarism	GH < 1.0 ng/mL: 5 (71.4%) Normal IGF-1: 4 (57.1%)[a] HT Reducing medication: 3/5 (60%) DM Cured: 5/6 (83%)	None
Minniti et al. [11]	Retrospective	$n = 22$[b] ≥ 65 y Mean age 68.3 y (65–74) Mean FU (cured patients): 5.2 ± 2.1 y	Size data not available m:4 (18%); M: 18 (82%)	33.1 ± 29.9	568.2 ± 138.9	HT: 11 (50%) DM: 4 (18%) IGT: 5 (23%) ASA-PS: 2: 9 (41%) 3: 7 (32%)	TSS	Difficult intubation: 3 (14%) Transient DI: 4 (18%) CSF leak suspected in 4 (18%), only 1 needed surgery Partial hypopituitarism: 3 (14%)	GH < 1.0 ng/mL and normal IGF-1: 15 (68%) No relapse during FU HT Reduction in mean BP in the cured (SBP: 138 vs.	None

Table 1 (continued)

Authors/ Ref.	Study design	Study population (*n*/age/FU)	Mean adenoma size ± SD (m—micro; M—macroadenoma)	Mean pre-op GH ± SD (ng/mL)	Mean pre-op IGF-1 ± SD (ng/mL)	Preoperative comorbidities	Surgery	Peri-operative complications	Remission of disease/clinical improvement	Mortality (related to procedure)
									130 mmHg, $p < 0.05$; DPB: 89 vs. 84 mmHg, $p < 0.05$) DM 2 DM + 3 IGT cured (56%)	
Puchner et al. [12]	Retrospective	$n = 15$[c] ≥65 y Mean age 68.3 y (65–81) FU: 4.2 y (2weeks–13 y)	Size data not available m: 4 (27%) M: 11 (73%)	47.4 ± 64.2	1112 ± 501	HT: 9 (60%) DM: 4 (27%) DCV: 3 (20%) ASA-PS: 1: 2 (13%) 2: 5 (33%) 3: 8 (53%)	Transnasal microsurgery	No intra-op complications Post-op: Transient DI: 1 (7%) Epistaxis: 1 (7%) No hypopituitarism	GH < 4.5 ng/mL + IGF-1 < 380 mcg/L in all patients (100%) No relapse during FU HT 3 patients improved BP DM 2 cured (50%) 2 controled only with diet (50%)	None

FU follow-up, *y* years, *TSS* transsphenoidal surgery, *HT* hypertension, *DM* diabetes mellitus, *DCV* cardio/cerebrovascular disease, *C* cancer, *ASA-PS* American Society of Anesthesiologists physical status, *HF* heart failure, *CSF* cerebrospinal fluid, *IGT* impaired glucose tolerance, *DI* diabetes insipidus, *BP* blood pressure

[a]In one case with associated bromocriptine

[b]Six pre-treated with SSA for a period ranging from 2 to 6 months before surgery

[c]Nine treated previously with DA and four with octreotide

matter. In addition, none of the evaluated studies specifically compared elderly vs. nonelderly patients. To the best of our knowledge, there are no studies specifically addressing this issue in English literature.

Bone abnormalities related to GH excess include high bone turnover and deteriorated microarchitecture with an overall increased VF risk, especially (although not exclusively) in patients with active disease [72, 73]. Bone mineral density measurement might be normal or even increased, not being a reliable marker of bone disease in this context and FRAX score is unreliable [77]. Importantly, these patients frequently have other negative impact factors on bone health, namely, diabetes mellitus, hypogonadism and replacement glucocorticoid and l-thyroxine treatment [72, 78]. The role of age as a predictive factor for VF risk in acromegaly has been investigated with variable results. Eight studies including a total of 477 patients with acromegaly have found a VF prevalence between 10.6 and 63.8%, and no relationship with age. Instead, the long duration of active acromegaly was associated to an increased fracture risk [73, 79–85]. In one study (Dal et al.) fractures risk was not increased in any age group [45]. However, Wassenaar et al. evaluated 89 patients with acromegaly. Interestingly, VF prevalence was higher in the groups >65 years (67–88 vs. 44–59%) [82]. On the other hand, Bonadonna et al. retrospectively studied 36 postmenopausal women with acromegaly with a median age of 60.5 years (range 44–79) to evaluate VF predictive factors. Importantly, hypopituitary women or those on any treatment possibly influencing bone health were excluded. They found that women with VF ($n = 19$) were significantly older (mean age 65 years (range 49–79) vs. 54 years (range 44–74); $P = 0.004$). Furthermore, age was not significantly different between women with controlled against active disease [86]. In conclusion, most of the available evidence seems to be in favor of age not being a predictive factor of VF risk in acromegalic patients per se, although not all data are consistent. Again, studies specifically designed to address this issue in the elderly population are lacking.

Aging and quality of life

Acromegaly itself could interfere in physiological aging process. Hatipoglu et al. in a comparative cross-sectional study, concluded that acromegaly could worsen cognitive functions, functional mobility, instrumental daily living activities, and increase malnutrition risk [17]. Conversely, in a large systematic review [87] on quality of life in acromegaly, while higher depression scores and BMI correlated with negative impact on QoL, other factors, including age and gender were not relevant and more studies are needed to determine the impact of acromegaly or its treatment on QoL in elderly patients.

Surgical treatment

Surgery is recommended as first line treatment for acromegaly in most patients [3, 88]. In the elderly, there are some concerns about a higher risk of perioperative complications, because these patients usually have associated comorbidities [15]. In addition, there might be specific features that can increase the risk of complications during and after surgery, namely, narrow upper airways, CVD, heart failure, hypertension, diabetes, and cancer [15]. Preoperative treatment has been suggested to decrease surgical risk in selected patients [3, 89]. Few studies have specifically evaluated surgical treatment in this age group [11–13, 15], and only one included a control group of nonelderly patients [15]. A total of 68 elderly patients were included. Table 1 summarizes the main characteristics and findings of these studies; there was a higher anesthesia risk according to ASA-PS score due to the presence of comorbidities. However, there were no severe perioperative complications and in the only study that included a control group, they were not significantly more frequent vs. nonelderly patients [15]. Notably, there was no mortality related to the surgical procedure [11–13, 15]. Most patients achieved disease remission and preoperative comorbidities (diabetes mellitus and hypertension), improved significantly after surgery. Recently, Spina et al. in an Italian surgical series of pituitary tumor aged >65 years report a surgical remission rate of 73.7% in patients with acromegaly [14]. High remission rates can be explained by the fact that somatotroph tumors are usually smaller and less aggressive in older patients, as previously stated, and consequently more likely to be totally removed in the surgical procedure. Indeed, in those studies with data concerning tumor size and invasiveness most of the patients had relatively small, non-invasive, or minimally invasive adenomas [11, 13, 15]. Only two studies reported relapse rate that was null during a mean follow-up period of 4.2 [12] and 5.2 years [11], respectively. There are some limitations in these studies, all with a retrospective design and a small sample size. The absence of a control group in most also limits the result interpretation. Different age criteria have been used to define the elderly group, as well as remission. Furthermore, some patients had been preoperatively treated with SRL or dopamine agonist (DA). Other studies did not specifically evaluate elderly patients, but studied age as a potential predictive factor for surgical remission [90–94] with conflicting results. Sun et al. [90] found that mean age of 59 patients with surgical remission was significantly higher compared with non-remission patients. The same trend was described by Taghvaei et al. [91] in their cohort of 73 patients. However, other series totalizing altogether 413 patients did not find age to be predictive of surgical remission [92–94]. Jane et al. in their series of 62 patients found that those over 65 years ($n = 9$] had higher surgical

remission rates, but in the overall analysis concluded that age was not predictive of remission [95]. In conclusion, surgery might be regarded as a safe procedure in elderly patients [at least if ASA-PS score is ≤3) and it has been associated with high rates of remission and significant metabolic improvement in this population. Proper anesthesia risk must be evaluated preoperatively and surgery must be performed by an expert pituitary neurosurgical team. Post-operative close monitoring is also mandatory and surgery should be performed when possible in a specialized center of excellence [96]. Influence of age as potentially predictive of surgical remission has not been consistent, but study design and different proportion of included elderly patients may explain the discrepancies. Evidence from larger studies including control groups is lacking. Further stratification of age groups in elderly patients would also bring important data on our knowledge in this matter.

Histopathology

GH-secreting adenomas are classically divided in two histological subtypes according to the amount of cytoplasmic secretory granules: densely granulated (DG) and sparsely granulated (SG), that are typically more aggressive [97, 98]. To our knowledge, there are no data available so far specifically comparing histopathological features of GH-secreting adenomas in elderly patients vs. nonelderly. However, a few studies evaluated age according to differences in histological subtype frequency of these tumors and, consequently, clinical behavior. In a retrospective study on 86 consecutive surgeries (70 patients overall), there was a trend towards younger diagnosis in SG adenomas compared with DG adenomas [98]. Kiseljak-Vassiliades et al. summarized in their review the evidence from five studies that evaluated the association between granulation pattern and age, including a total of 420 patients with acromegaly. In four of these studies (including 342 patients), the mean age of patients harboring SG tumors was lower as compared with patients with DG tumors. On the contrary, one study including 78 patients with acromegaly found no correlation between granulation pattern and age, but it included a small number of patients with SG tumors. Taken together, these data support a correlation of granulation pattern with age [99]. Subsequently, Kiseljak-Vassiliades et al. in a retrospective study including 101 patients confirmed that patients with SG tumors were younger as compared with those with DG (40.4 ± 13.7 vs 50.0 ± 12.8 years; $P = 0.001$) [100]. Cuevas-Ramos et al. [25] in a large retrospective study of 338 acromegaly patients, found a group of subjects with smaller, less aggressive DG tumors with a higher expression of SSTR2 and a higher mean age at diagnosis. These results are in keeping with the evidence that older age is related to smaller, less aggressive tumors, mainly with DG pattern and higher SSTR2 expression, thus, likely more responsive to treatment. Another recent large study from Mori et al. confirmed that SG cytokeratin pattern is more frequent in younger patients (also related to larger tumor size and higher Knosp grade) [101]. Table 2 summarizes those that seem to be the main histopathology findings in older subjects.

Table 2 Histopathology findings in older subjects with acromegaly

Characteristic	Older age
Dimensions	Smaller tumors
Histological subtype (granulation pattern)	Predominantly densely granulated
SSTR2 expression	Higher expression
Proliferative markers	Highest proportion of Ki-67 <3%

All these studies have a retrospective design, some have small sample sizes and results are not completely consistent, but when analyzed altogether, we can probably conclude that older patients are harboring more frequently DG, smaller lesions. However, none of these studies specifically evaluated elderly vs. nonelderly patients, therefore extrapolation of these data to this specific age group remains speculative.

Medical therapy

Medical therapy in acromegaly might be used as primary or adjuvant treatment. It includes SRLs, GH receptor antagonist (pegvisomant) and DA [102]. In elderly patients, few might argue that medical treatment should be used as primary therapy, considering that certain comorbidities can increase the risk of surgical complications. However, this treatment is not curative, requires lifelong expensive therapy and possible adverse events have to be taken into consideration, although they are generally well tolerated [11, 102]. Furthermore, as described before, surgery seems to be generally safe and effective in these patients. Concerning medical therapy, SRLs treatment is usually the first choice, especially in Europe [38]. Van der Lely et al. retrospectively evaluated the relationship between age and responsiveness to octreotide in 100 patients with acromegaly (age range 23–83 years). They found older people to have a higher sensitivity to octreotide in terms of GH release inhibition (especially in males) [28]. Colao et al. have prospectively studied a cohort of 99 patients aged 45.6 ± 17.9 years receiving SRLs therapy (octreotide and lanreotide] as primary and only treatment for at least 12 months. Unlike in the previous study, the percent decrease in tumor volume was inversely correlated with

age. Although statistically significant, the correlation coefficient was, however, weak ($r = -0.23$; $P = 0.023$) [37]. Altogether, there are not enough data to draw a conclusion about the influence of age in SRL treatment response. Scaroni et al. recently studied the paradoxical response of GH to hyperglycemia after OGTT in 496 patients with acromegaly with a mean age at diagnosis of 41.8 years (range 32–51 years). Patients who have a paradoxical response at diagnosis are older than the group without paradoxical response (44.1 vs. 40.5 years; $P = 0.006$), have smaller tumors and have a higher remission rate after treatment with SRL [103]. Older acromegalic patients are likely to have a better response to SRL due to the presence of smaller and less aggressive tumors, mainly with DG patterns and increased SSTR2 expression [28, 37]. Concerning Pasireotide LAR, development of hyperglycemia seems to be related to baseline glucose [104], thus we can envision a more pronounced incidence of hyperglycemia or diabetes under this treatment on elderly patients. Pegvisomant is another option for medical treatment in acromegaly, alone or in combination therapy. It is mainly indicated for patients partially or completely resistant to SRLs, though in US this drug is approved also as first line medical therapy [105]. Evidence about age as a predictive factor of response to pegvisomant is scarce and controversial. Parkinson et al. retrospectively studied 147 patients treated exclusively with pegvisomant (after washout of other medical treatments if previously ongoing), ranging from 20 to 78 years, and found no significant correlation between age and the dose needed to normalize IGF-1 ($P = 0.69$) [106]. Sievers et al. retrospectively studied 271 patients from the ACROSTUDY German cohort, with a mean age of 51.2 ± 13.9 years, and found that age was negatively associated with IGF-1 change after 1 year of pegvisomant therapy [107]. Kasuki et al. retrospectively evaluated 27 patients treated with pegvisomant (in a minority of patients as single agent, most in combination with SRLs and one with cabergoline), aged 20–82 years (at diagnosis), and found no association between age and IGF-1 reduction [108]. Many confounding factors exist in these studies, one of the most relevant being the fact that some patients were on other treatments, too. Currently, there is insufficient data to establish if age is truly a predictive factor of pegvisomant response. However, since pegvisomant has been shown to improve glucose control in some patients [109], use in elderly patients with glucose abnormalities and no other contraindications could be potentially beneficial as single therapy or in combination. The most frequently used DA in the treatment of acromegaly is cabergoline. It might be feasible as monotherapy in patients with slightly elevated IGF-1 levels (generally <1.5 times the upper limit of normal) or in combination therapy [110]. To our knowledge, no studies have specifically addressed the influence of age on DA response. An important consideration in patients on treatment with cabergoline is an increased risk of valvular heart disease [110]. Elderly patients with acromegaly have been described to have higher prevalence of cardiovascular risk factors, LV hypertrophy and lower LV ejection fraction than healthy age-matched controls [16]. Adding up a valvular disease might aggravate their cardiac condition. Closely monitoring these subjects should be warranted. With regard to Pasireotide LAR, a single case report described that this treatment was effective and safe in an elderly patient [111]. However, previous studies on the efficacy of Pasireotide LAR did not analyze the data according to age, although the patients' mean age in these studies ranged from 40.8 years to 45.5 years [112, 113]. Indeed, according to data derived from the PAOLA study, the percentage of patients aged >65 years ranged from 5 to 12% of Pasireotide treated patients [114]. Moreover, a single case of and elderly acromegaly patient treated with a combination therapy with Pasireotide LAR and Pegvisomant was also described, suggesting that this treatment choice can be useful and safe in case of aggressive acromegaly, also in elderly patients [115].

Radiotherapy

Although radiotherapy may be effective in selected cases, guidelines suggest that its use as a third line treatment in patients with tumor remnant following surgery or if medical therapy is not effective or is not tolerated [3]. Many studies reported the efficacy of radiotherapy for GH-secreting adenoma with hormonal remission rates of 30 and 80% depending on the different follow-up time and criteria used to define the "cure" of disease [116]. However, various complications have also been reported, such as hypopituitarism, visual deterioration, and radiation-induced brain necrosis [3]. In recent reports, Gamma Knife Radiosurgery (GKR) obtained hormonal normalization in about 30–60% of patients with GH-secreting adenomas. Kim et al. reported remission in 14 of 30 patients within a median period of 35 months (range, 12–129) after GKR [117]. However, there is no clear evidence supporting the superiority of innovative vs. conventional radiation techniques in terms of tumor control and faster biochemical control [116]. There are no data on radiotherapy in elderly acromegalic patients. In the elderly, patient life expectancy should also be considered when assessing the timing of biochemical and tumor control.

Conclusions

The number of elderly patients with acromegaly, both newly diagnosed and in follow-up, is expected to grow in

Table 3 Clinical features, complications and response to treatment of acromegalic elderly patients

Clinical phenotype [16, 23, 24]	Milder in elderly vs. younger patients
Tumor size [25–27]	Smaller and more frequently included tumors (Hardy grade 1) in elderly vs. younger patients
Basal GH and IGF1 levels and post-OGTT GH nadir levels [16, 19, 27, 28, 31–33, 37]	Lower in elderly vs, younger patients
Hypertension, glucose metabolism abnormalities, joint complaints and goiter [16]	More frequent in elderly patients vs. age matched controls
Left ventricular hypertrophy [39]	Characteristic of elderly patients
Risk of diabetes mellitus, hypertension, SAS and cancer [8, 16, 22, 26, 29, 30, 43, 44, 46–49, 60, 61, 64–67]	Age related
Arthropathy and VF risk [45, 73–76, 79–85]	Not age-related
Surgery [11–13, 15, 96]	Safe
SRL treatment [28, 37]	Better response in elderly vs. younger patients

the coming years and clinicians will need to be aware of particularities associated with age (Table 3).

We generally assume that older acromegalic patients might have a milder phenotype. Both GH hypersecretion and hypopituitarism symptoms can be difficult to identify in elderly patients because they can overlap with ageing features. As a consequence, diagnosis can be more delayed than in younger subjects. Age is an important factor to consider in the diagnosis and evaluation of acromegaly activity. Basal GH and IGF-1 levels and post-OGTT GH nadir seem to be lower in elderly patients than in younger patients. Most of the available evidence so far suggests that older age might be a risk factor for diabetes, hypertension, SAS, cancer, just as it is in general population. LV hypertrophy should be considered a characteristic of elderly acromegalic patients. Hyperlipidemia seems to be more frequent with advancing age but data are not significant. Arthropathy and VF risk in acromegalic patients seem not to be age-related, although data are controversial. Concerning treatment, surgery might be regarded as a safe procedure in elderly patients with high rates of remission and significant metabolic improvement. Proper anesthesia risk must be evaluated preoperatively and surgery must be performed by an expert pituitary neurosurgical team. Age is most likely related to histological subtype of GH-secreting tumors, with older patients having more frequently DG pattern and smaller lesions. Among medical therapy, SRLs treatment is usually the first choice. There is some evidence that older subjects might display a better response to this treatment. Currently, there is insufficient data to establish if age is truly a predictive factor of the response to pegvisomant. There are no data on radiotherapy in elderly patients with acromegaly and life expectancy must also be considered when assessing the timing of any disease control.

Current literature data on the evaluated issue have some limitations. Studies concerning elderly patients with acromegaly are few, the series are limited and not selected, the definition of elderly is not unequivocal. Therefore, to increase knowledge on acromegaly in the elderly, further comparison studies are needed.

Funding This study was supported by funding from the University of Ferrara to MCZ and MRA (FAR2019).

Compliance with ethical standards

Conflict of interest MRA reports registration fees for scientific meetings from Ipsen, Novartis, Pfizer, and Savio Pharma. LDM reports that she has been Principal Investigator for clinical trials for Novartis, Ipsen, Pfizer, and Chiasma. MF has been a principal investigator for studies with research grants to Oregon Health & Science University from Chiasma, Crinetics, Ionis, Novartis, Pfizer and has been an occasional scientific consultant to Chiasma, Crinetics, Ipsen, Novartis, Pfizer. MCZ received consulting fees from Sanofi, Novartis and Ipsen; received financial support for scientific meetings and for research support from Itapharma, Abiogen, Sanofi, Novartis and Ipsen. IG, SC, AGF, MB, AG, AB have no actual or potential conflict of interest in relation to this paper.

References

1. S. Melmed, Acromegaly pathogenesis and treatment. J. Clin. Invest. **119**(11), 3189–3202 (2009)
2. A. Colao, L.F.S. Grasso, A. Giustina, S. Melmed, P. Chanson, A. M. Pereira et al. Acromegaly. Nat. Rev. Dis. Prim. **5**(1), 20 (2019)
3. L. Katznelson, E.R. Laws, S. Melmed, M.E. Molitch, M.H. Murad, A. Utz et al. Acromegaly: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **99**(11), 3933–3951 (2014)
4. M.R. Gadelha, L. Kasuki, D.S.T. Lim, M. Fleseriu, Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr. Rev. **40**(1), 268–332 (2019)
5. A. Lavrentaki, A. Paluzzi, J.A.H. Wass, N. Karavitaki, Epidemiology of acromegaly: review of population studies. Pituitary **20**(1), 4–9 (2017)

6. T. Burton, E. Le Nestour, M. Neary, W.H. Ludlam, Incidence and prevalence of acromegaly in a large US health plan database. Pituitary **19**(3), 262–267 (2016)
7. M.S. Broder, E. Chang, D. Cherepanov, M.P. Neary, W.H. Ludlam, Incidence and prevalence of acromegaly in the United States: a claims-based analysis. Endocr. Pract. J. Clin. Endocrinol. **22**(11), 1327–1335 (2016)
8. M. Arosio, G. Reimondo, E. Malchiodi, P. Berchialla, A. Borraccino, L. De Marinis et al. Predictors of morbidity and mortality in acromegaly: an Italian survey. Eur. J. Endocrinol. **167** (2), 189–198 (2012)
9. M. Caputo, A. Ucciero, C. Mele, L. De Marchi, C. Magnani, T. Cena et al. Use of administrative health databases to estimate incidence and prevalence of acromegaly in Piedmont Region, Italy. J. Endocrinol. Investig. **42**(4), 397–402 (2019)
10. F. Bolfi, A.F. Neves, C.L. Boguszewski, V.S. Nunes-Nogueira, Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur. J. Endocrinol. **179**(1), 59–71 (2018)
11. G. Minniti, M.-L. Jaffrain-Rea, V. Esposito, A. Santoro, C. Moroni, J. Lenzi et al. Surgical treatment and clinical outcome of GH-secreting adenomas in elderly patients. Acta Neurochir. **143** (12), 1205–1211 (2001)
12. M.J.A. Puchner, U.J. Knappe, D.K. Lüdecke, Pituitary surgery in elderly patients with acromegaly. Neurosurgery **36**(4), 677–684 (1995)
13. K. Arita, H. Hirano, S. Yunoue, S. Fujio, A. Tominaga, T. Sakoguchi et al. Treatment of elderly acromegalics. Endocr. J. **55** (5), 895–903 (2008)
14. A. Spina, M. Losa, P. Mortini, Pituitary adenomas in elderly patients: clinical and surgical outcome analysis in a large series. Endocrine **65**(3), 637–645 (2019)
15. Y. Sasagawa, Y. Hayashi, O. Tachibana, A. Nakagawa, M. Oishi, T. Takamura et al. Transsphenoidal surgery for elderly patients with acromegaly and its outcomes: comparison with younger patients. World Neurosurg. **118**(Oct), e229–e234 (2018)
16. A. Colao, R. Pivonello, L. Spinelli, M. Galderisi, R.S. Auriemma, M. Galdiero et al. A retrospective analysis on biochemical parameters, cardiovascular risk and cardiomyopathy in elderly acromegalic patients. J. Endocrinol. Invest. **30**(6), 497–506 (2007)
17. E. Hatipoglu, M. Yuruyen, E. Keskin, H. Yavuzer, M. Niyazoglu, A. Doventas et al. Acromegaly and aging: a comparative cross-sectional study. Growth Horm. IGF Res. **25**(1), 47–52 (2015)
18. F. Gatto, G. Trifirò, F. Lapi, F. Cocchiara, C. Campana, C. Dell'Aquila et al. Epidemiology of acromegaly in Italy: analysis from a large longitudinal primary care database. Endocrine **61** (3), 533–541 (2018)
19. P. Petrossians, A.F. Daly, E. Natchev, L. Maione, K. Blijdorp, M. Sahnoun-Fathallah et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) database. Endocr. Relat. Cancer **24**(10), 505–518 (2017)
20. M.A. Azab, M. O'Hagan, H. Abou-Al-Shaar, M. Karsy, J. Guan, W.T. Couldwell, Safety and outcome of transsphenoidal pituitary adenoma resection in elderly patients. World Neurosurg. **122** (Feb), e1252–e1258 (2019)
21. L.B. Nachtigall, N. Karavitaki, K. Kiseljak-Vassiliades, L. Ghalib, H. Fukuoka, L.V. Syro et al. Physicians' awareness of gadolinium retention and MRI timing practices in the longitudinal management of pituitary tumors: a "Pituitary Society" survey. Pituitary **22**(1), 37–45 (2019)
22. M. Terzolo, G. Reimondo, P. Berchialla, E. Ferrante, E. Malchiodi, L. De Marinis et al. Acromegaly is associated with increased cancer risk: a survey in Italy. Endocr. Relat. Cancer **24** (9), 495–504 (2017)
23. N. Anoun, H. E. Ouahabi, L'acromégalie du sujet âgé: quelles particularités? Pan Afr. Med. J. 27 (2017) http://www.panafrican-med-journal.com/content/article/27/169/full/
24. G. Minniti, V. Esposito, M. Piccirilli, A. Fratticci, A. Santoro, M.-L. Jaffrain-Rea, Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur. J. Endocrinol. **153**(6), 723–735 (2005)
25. D. Cuevas-Ramos, J.D. Carmichael, O. Cooper, V.S. Bonert, A. Gertych, A.N. Mamelak et al. A structural and functional acromegaly classification. J. Clin. Endocrinol. Metab. **100**(1), 122–131 (2015)
26. K. Tanimoto, N. Hizuka, I. Fukuda, K. Takano, T. Hanafusa, The influence of age on the GH–IGF1 axis in patients with acromegaly. Eur. J. Endocrinol. **159**(4), 375–379 (2008)
27. S. Petersenn, M. Buchfelder, B. Gerbert, H. Franz, H.J. Quabbe, H.M. Schulte et al. Age and sex as predictors of biochemical activity in acromegaly: analysis of 1485 patients from the German acromegaly register. Clin. Endocrinol. **71**(3), 400–405 (2009)
28. A.J. van der Lely, A.G. Harris, S.W. Lamberts, The sensitivity of growth hormone secretion to medical treatment in acromegalic patients: influence of age and sex. Clin. Endocrinol. **37**(2), 181–185 (1992)
29. J.D. Nabarro, Acromegaly. Clin. Endocrinol. **26**(4), 481–512 (1987)
30. J.M. Silverstein, E.D. Roe, K.M. Munir, J.L. Fox, B. Emir, M. Kouznetsova et al. Use of electronic health records to characterize a rare disease in the u.s.: treatment, comorbidities, and follow-up trends among patients with a confirmed diagnosis of acromegaly. Endocr. Pract. **24**(6), 517–526 (2018)
31. A. Ribeiro-Oliveira, M.M. Abrantes, A.L. Barkan, Complex rhythmicity and age dependence of growth hormone secretion are preserved in patients with acromegaly: further evidence for a present hypothalamic control of pituitary somatotropinomas. J. Clin. Endocrinol. Metab. **98**(7), 2959–2966 (2013)
32. A.M. Arafat, M. Möhlig, M.O. Weickert, F.H. Perschel, J. Purschwitz, J. Spranger et al. Growth hormone response during oral glucose tolerance test: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age, and body mass index. J. Clin. Endocrinol. Metab. **93**(4), 1254–1262 (2008)
33. A. Colao, G. Amato, A.M. Pedroncelli, R. Baldelli, S. Grottoli, V. Gasco et al. Gender- and age-related differences in the endocrine parameters of acromegaly. J. Endocrinol. Invest. **25** (6), 532–538 (2002)
34. A. Colao, R. Pivonello, L.M. Cavallo, M. Gaccione, R.S. Auriemma, F. Esposito et al. Age changes the diagnostic accuracy of mean profile and nadir growth hormone levels after oral glucose in postoperative patients with acromegaly. Clin. Endocrinol. **65** (2), 250–256 (2006)
35. S. Grottoli, P. Razzore, D. Gaia, M. Gasperi, M. Giusti, A. Colao et al. Three-hour spontaneous GH secretion profile is as reliable as oral glucose tolerance test for the diagnosis of acromegaly. J. Endocrinol. Invest. **26**(2), 123–127 (2003)
36. E.C. degli Uberti, M.R. Ambrosio, S.G. Cella, A.R. Margutti, G. Trasforini, A.E. Rigamonti et al. Defective hypothalamic growth hormone (GH)-releasing hormone activity may contribute to declining gh secretion with age in man. J. Clin. Endocrinol. Metab. **82**(9), 2885–2888 (1997)
37. A. Colao, R. Pivonello, R.S. Auriemma, F. Briganti, M. Galdiero, F. Tortora et al. Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. J. Clin. Endocrinol. Metab. **91** (6), 2112–2118 (2006)

38. R. Pivonello, R.S. Auriemma, L.F.S. Grasso, C. Pivonello, C. Simeoli, R. Patalano et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary **20** (1), 46–62 (2017)
39. A. Colao, D. Ferone, P. Marzullo, G. Lombardi, Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr. Rev. **25**(1), 102–152 (2004)
40. L. Vilar, C.F. Vilar, R. Lyra, R. Lyra, L.A. Naves, Acromegaly: clinical features at diagnosis. Pituitary **20**(1), 22–32 (2017)
41. K. Feingold, E. A Brinton, C. Grunfeld, *The Effect of Endocrine Disorders on Lipids and Lipoproteins*. K.R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman et al. (eds.) Endotext [Internet] (MDText.com, Inc., South Dartmouth, MA, 2000). http://www.ncbi.nlm.nih.gov/books/NBK409608/
42. S. Melmed, F.F. Casanueva, A. Klibanski, M.D. Bronstein, P. Chanson, S.W. Lamberts et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary **16**(3), 294–302 (2013)
43. M. Bex, R. Abs, G. T'Sjoen, J. Mockel, B. Velkeniers, K. Muermans et al. AcroBel – the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. Eur. J. Endocrinol. **157**(4), 399–409 (2007)
44. S. Fieffe, I. Morange, P. Petrossians, P. Chanson, V. Rohmer, C. Cortet et al. Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French acromegaly registry. Eur. J. Endocrinol. **164**(6), 877–884 (2011)
45. J. Dal, U. Feldt-Rasmussen, M. Andersen, L.Ø. Kristensen, P. Laurberg, L. Pedersen et al. Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur. J. Endocrinol. **175**(3), 181–190 (2016)
46. A.V. Dreval, I.V. Trigolosova, I.V. Misnikova, Y.A. Kovalyova, R.S. Tishenina, I.A. Barsukov et al. Prevalence of diabetes mellitus in patients with acromegaly. Endocr. Connect. **3**(2), 93–98 (2014)
47. H. Biering, G. Knappe, H. Gerl, H. Lochs, Prevalence of diabetes in acromegaly and Cushing syndrome. Acta Med Austriaca **27** (1), 27–31 (2000)
48. O. Alexopoulou, M. Bex, P. Kamenicky, A.B. Mvoula, P. Chanson, D. Maiter, Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary **17**(1), 81–89 (2014)
49. A.L. Espinosa-de-los-Monteros, B. González, G. Vargas, E. Sosa, M. Mercado, Clinical and biochemical characteristics of acromegalic patients with different abnormalities in glucose metabolism. Pituitary **14**(3), 231–235 (2011)
50. A. Kreze, E. Kreze-Spirova, M. Mikulecky, Risk factors for glucose intolerance in active acromegaly. Braz. J. Med Biol. Res **34**(11), 1429–1433 (2001)
51. D. Ioaniţiu, R. Bartoc, I. Ispas, M. Augustin, V. Dimitriu, D. Popovici et al. The dyslipemic syndrome in acromegaly. Endocrinologie **20**(1), 25–36 (1982)
52. A.M. Ramos-Leví, M. Marazuela, Bringing cardiovascular comorbidities in acromegaly to an update. How should we diagnose and manage them? Front Endocrinol. **10**(Mar), 120 (2019)
53. A.M. Ramos-Leví, M. Marazuela, Cardiovascular comorbidities in acromegaly: an update on their diagnosis and management. Endocrine **55**(2), 346–359 (2017)
54. M. Bondanelli, M.R. Ambrosio, E.C. degli Uberti, Pathogenesis and prevalence of hypertension in acromegaly. Pituitary **4**(4), 239–249 (2001)
55. C. Briet, M.D. Ilie, E. Kuhn, L. Maione, S. Brailly-Tabard, S. Salenave et al. 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 (2019)
56. L. Maione, T. Brue, A. Beckers, B. Delemer, P. Petrossians, F. Borson-Chazot et al. Changes in the management and comorbidities of acromegaly over three decades: the French acromegaly registry. Eur. J. Endocrinol. **176**(5), 645–655 (2017)
57. J. Dal, M.Z. Leisner, K. Hermansen, D.K. Farkas, M. Bengtsen, C. Kistorp et al. Cancer Incidence in patients with acromegaly: a cohort study and meta-analysis of the literature. J. Clin. Endocrinol. Metab. **103**(6), 2182–2188 (2018)
58. S. Melmed, Clinical perspective: acromegaly and cancer: Not a problem? J. Clin. Endocrinol. Metab. **86**(7), 2929–2934 (2001)
59. C.L. Boguszewski, J. Ayuk, Management of endocrine disease: acromegaly and cancer: an old debate revisited. Eur. J. Endocrinol. **175**(4), R147–R156 (2016)
60. M.V. Davi', L. Dalle Carbonare, A. Giustina, M. Ferrari, A. Frigo, V. Lo Cascio et al. 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 (2008)
61. S. Dostalova, K. Sonka, Z. Smahel, V. Weiss, J. Marek, D. Horinek, Craniofacial abnormalities and their relevance for sleep apnoea syndrome aetiopathogenesis in acromegaly. Eur. J. Endocrinol. **144**(5), 491–497 (2001)
62. M. Hein, J.-P. Lanquart, G. Loas, P. Hubain, P. Linkowski, Prevalence and risk factors of moderate to severe obstructive sleep apnea syndrome in insomnia sufferers: a study on 1311 subjects. Respir. Res. **18**(1), 135 (2017)
63. V. Weiss, K. Sonka, M. Pretl, S. Dostálová, J. Klozar, P. Rambousek et al. Prevalence of the sleep apnea syndrome in acromegaly population. J. Endocrinol. Invest. **23**(8), 515–519 (2000)
64. F.R.B. van Haute, G.F. Taboada, L.L. Corrêa, G.A.B. Lima, R. Fontes, A.P. Riello et al. Prevalence of sleep apnea and metabolic abnormalities in patients with acromegaly and analysis of cephalometric parameters by magnetic resonance imaging. Eur. J. Endocrinol. **158**(4), 459–465 (2008)
65. B.L. Herrmann, T.E. Wessendorf, W. Ajaj, S. Kahlke, H. Teschler, K. Mann, Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly. Eur. J. Endocrinol. **151**(3), 309–315 (2004)
66. M. Chevallier, S. Pontier, K. Sedkaoui, P. Caron, A. Didier, Characteristics of sleep apnea syndrome in a cohort of patients with acromegaly. Rev. Mal. Respir. **29**(5), 673–679 (2012)
67. F. Rosenow, S. Reuter, U. Deuss, B. Szelies, R.D. Hilgers, W. Winkelmann et al. Sleep apnoea in treated acromegaly: relative frequency and predisposing factors. Clin. Endocrinol. (Oxf.) **45** (5), 563–569 (1996)
68. O. Turan, B. Akinci, A.O. Ikiz, O. Itil, I. Oztura, E. Ada et al. Airway and sleep disorders in patients with acromegaly. Clin. Respir. J. **12**(3), 1003–1010 (2018)
69. L. Vannucci, P. Luciani, E. Gagliardi, S. Paiano, R. Duranti, G. Forti et al. Assessment of sleep apnea syndrome in treated acromegalic patients and correlation of its severity with clinical and laboratory parameters. J. Endocrinol. Invest. **36**(4), 237–242 (2013)
70. M.V. Davì, A. Giustina, Sleep apnea in acromegaly: a review on prevalence, pathogenetic aspects and treatment. Expert Rev. Endocrinol. Metab. **7**(1), 55–62 (2012)
71. K.M.J.A. Claessen, A.N. Canete, P.W. de Bruin, A.M. Pereira, M. Kloppenburg, H.M. Kroon et al. Acromegalic arthropathy in various stages of the disease: an MRI study. Eur. J. Endocrinol. **176**(6), 779–790 (2017)
72. G. Mazziotti, F. Maffezzoni, S. Frara, A. Giustina, Acromegalic osteopathy. Pituitary **20**(1), 63–69 (2017)
73. G. Mazziotti, A. Bianchi, T. Porcelli, M. Mormando, F. Maffezzoni, A. Cristiano et al. Vertebral fractures in patients with

acromegaly: a 3-year prospective study. J. Clin. Endocrinol. Metab. **98**(8), 3402–3410 (2013)
74. L.L. Kropf, M. Madeira, L. Vieira Neto, M.R. Gadelha, M.L.F. de Farias, Functional evaluation of the joints in acromegalic patients and associated factors. Clin. Rheumatol. **32**(7), 991–998 (2013)
75. K.M.J.A. Claessen, S.R. Ramautar, A.M. Pereira, J.W.A. Smit, F. Roelfsema, J.A. Romijn et al. Progression of acromegalic arthropathy despite long-term biochemical control: a prospective, radiological study. Eur. J. Endocrinol. **167**(2), 235–244 (2012)
76. N.R. Biermasz, M.J.E. Wassenaar, A.A. van der Klaauw, A.M. Pereira, J.W.A. Smit, F. Roelfsema et al. Pretreatment insulin-like growth factor-I concentrations predict radiographic osteoarthritis in acromegalic patients with long-term cured disease. J. Clin. Endocrinol. Metab. **94**(7), 2374–2379 (2009)
77. J. Brzana, C.G. Yedinak, N. Hameed, M. Fleseriu, FRAX score in acromegaly: does it tell the whole story? Clin. Endocrinol. (Oxf.) **80**(4), 614–616 (2014)
78. J.R. Anthony, A.G. Ioachimescu, Acromegaly and bone disease. Curr. Opin. Endocrinol. Diabetes Obes. **21**(6), 476–482 (2014)
79. L. Dalle Carbonare, V. Micheletti, E. Cosaro, M.T. Valenti, M. Mottes, G. Francia et al. Bone histomorphometry in acromegaly patients with fragility vertebral fractures. Pituitary **21**(1), 56–64 (2018)
80. S. Chiloiro, M. Mormando, A. Bianchi, A. Giampietro, D. Milardi, C. Bima et al. Prevalence of morphometric vertebral fractures in "difficult" patients with acromegaly with different biochemical outcomes after multimodal treatment. Endocrine **59**(2), 449–453 (2018)
81. K.M.J.A. Claessen, H.M. Kroon, A.M. Pereira, N.M. Appelman-Dijkstra, M.J. Verstegen, M. Kloppenburg et al. Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study. J. Clin. Endocrinol. Metab. **98**(12), 4808–4815 (2013)
82. M.J.E. Wassenaar, N.R. Biermasz, Na.T. Hamdy, M.C. Zillikens, J.B.J. van Meurs, F. Rivadeneira et al. High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly. Eur. J. Endocrinol. **164**(4), 475–483 (2011)
83. C. Battista, I. Chiodini, S. Muscarella, G. Guglielmi, M.L. Mascia, V. Carnevale et al. Spinal volumetric trabecular bone mass in acromegalic patients: a longitudinal study. Clin. Endocrinol. (Oxf.) **70**(3), 378–382 (2009)
84. S. Chiloiro, G. Mazziotti, A. Giampietro, A. Bianchi, S. Frara, M. Mormando et al. Effects of pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. Pituitary **21**(3), 302–308 (2018)
85. M. Madeira, L.V. Neto, C.H. Torres, L.M.C. de Mendonça, M.R. Gadelha, M.L.F. de Farias, Vertebral fracture assessment in acromegaly. J. Clin. Densitom. **16**(2), 238–243 (2013)
86. S. Bonadonna, G. Mazziotti, M. Nuzzo, A. Bianchi, A. Fusco, L. De Marinis et al. Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. J. Bone Min. Res. **20**(10), 1837–1844 (2005)
87. V.J. Geraedts, C.D. Andela, G.K. Stalla, A.M. Pereira, W.R. van Furth, C. Sievers et al. Predictors of quality of life in acromegaly: no consensus on biochemical parameters. Front. Endocrinol. 8 (2017). https://doi.org/10.3389/fendo.2017.00040/full
88. S. Melmed, M.D. Bronstein, P. Chanson, A. Klibanski, F.F. Casanueva, J.A.H. Wass et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat. Rev. Endocrinol. **14**(9), 552–561 (2018)
89. M. Fleseriu, I.A. Hashim, N. Karavitaki, S. Melmed, M.H. Murad, R. Salvatori et al. Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **101**(11), 3888–3921 (2016)
90. H. Sun, J. Brzana, C.G. Yedinak, S.H. Gultekin, J.B. Delashaw, M. Fleseriu, Factors associated with biochemical remission after microscopic transsphenoidal surgery for acromegaly. J. Neurol. Surg. Part B Skull Base **75**(1), 47–52 (2014)
91. M. Taghvaei, S.M. Sadrehosseini, J.B. Ardakani, M. Nakhjavani, M. Zeinalizadeh, Endoscopic endonasal approach to the growth hormone-secreting pituitary adenomas: endocrinologic outcome in 68 patients. World Neurosurg. **117**(Sep), e259–e268 (2018)
92. M. Shirvani, R. Motiei-Langroudi, Transsphenoidal surgery for growth hormone-secreting pituitary adenomas in 130 patients. World Neurosurg. **81**(1), 125–130 (2014)
93. X. Antunes, M.R. Gadelha, L. Kasuki, Reply to "Predictors of surgical outcome and early criteria of remission in acromegaly-some controversial issues". Endocrine **63**(1), 190–191 (2019)
94. D.B. Hazer, S. Işık, D. Berker, S. Güler, A. Gürlek, T. Yücel et al. Treatment of acromegaly by endoscopic transsphenoidal surgery: surgical experience in 214 cases and cure rates according to current consensus criteria. J. Neurosurg. **119**(6), 1467–1477 (2013)
95. J.A. Jane, R.M. Starke, M.A. Elzoghby, D.L. Reames, S.C. Payne, M.O. Thorner et al. Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J. Clin. Endocrinol. Metab. **96**(9), 2732–2740 (2011)
96. On behalf of The Pituitary Society, Expert Group on Pituitary Tumors, F.F. Casanueva, A.L. Barkan, M. Buchfelder, A. Klibanski, E.R. Laws et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a pituitary society statement. Pituitary **20**(5), 489–498 (2017)
97. M.B.S. Lopes, Growth hormone-secreting adenomas: pathology and cell biology. Neurosurg. Focus. **29**(4), E2 (2010)
98. J. Brzana, C.G. Yedinak, S.H. Gultekin, J.B. Delashaw, M. Fleseriu, Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. Pituitary **16**(4), 490–498 (2013)
99. K. Kiseljak-Vassiliades, S. Shafi, J.M. Kerr, T.L. Phang, B.K. Kleinschmidt-DeMasters, M.E. Wierman, Clinical implications of growth hormone-secreting tumor subtypes. Endocrine **42**(1), 18–28 (2012)
100. K. Kiseljak-Vassiliades, N.E. Carlson, M.T. Borges, B.K. Kleinschmidt-DeMasters, K.O. Lillehei, J.M. Kerr et al. Growth hormone tumor histological subtypes predict response to surgical and medical therapy. Endocrine **49**(1), 231–241 (2015)
101. R. Mori, N. Inoshita, J. Takahashi-Fujigasaki, T. Joki, H. Nishioka, T. Abe et al. Clinicopathological features of growth hormone-producing pituitary adenomas in 242 acromegaly patients: classification according to hormone production and cytokeratin distribution. ISRN Endocrinol. **2013**, 723432 (2013)
102. L.F.S. Grasso, R.S. Auriemma, R. Pivonello, A. Colao, Somatostatin analogs, cabergoline and pegvisomant: comparing the efficacy of medical treatment for acromegaly. Expert Rev. Endocrinol. Metab. **12**(1), 73–85 (2017)
103. C. Scaroni, N. Albiger, A. Daniele, F. Dassie, C. Romualdi, G. Vazza et al. Paradoxical GH increase during OGTT is associated with first-generation somatostatin analog responsiveness in acromegaly. J. Clin. Endocrinol. Metab. **104**(3), 856–862 (2019)
104. H.A. Schmid, T. Brue, A. Colao, M.R. Gadelha, I. Shimon, K. Kapur et al. Effect of pasireotide on glucose- and growth hormone-related biomarkers in patients with inadequately controlled acromegaly. Endocrine **53**(1), 210–219 (2016)
105. A. Giustina, G. Arnaldi, F. Bogazzi, S. Cannavò, A. Colao, L. De Marinis et al. Pegvisomant in acromegaly: an update. J. Endocrinol. Invest. **40**(6), 577–589 (2017)

106. C. Parkinson, P. Burman, M. Messig, P.J. Trainer, Gender, body weight, disease activity, and previous radiotherapy influence the response to pegvisomant. J. Clin. Endocrinol. Metab. **92**(1), 190–195 (2007)
107. C. Sievers, D.M. Baur, A. Schwanke, M. Buchfelder, M. Droste, K. Mann et al. Prediction of therapy response in acromegalic patients under pegvisomant therapy within the German ACROSTUDY cohort. Pituitary **18**(6), 916–923 (2015)
108. L. Kasuki, E. Machado, O. de, L.L. Ogino, M.C.A. Coelho, C.M. D.S. Silva, L.E.A. Wildemberg et al. Experience with pegvisomant treatment in acromegaly in a single Brazilian tertiary reference center: efficacy, safety and predictors of response. Arch. Endocrinol. Metab. **60**(5), 479–485 (2016)
109. T. Feola, A. Cozzolino, I. Simonelli, E. Sbardella, C. Pozza, E. Giannetta et al. Pegvisomant Improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. J. Clin. Endocrinol. Metab. **104**(7), 2892–2902 (2019)
110. E. Kuhn, P. Chanson, Cabergoline in acromegaly. Pituitary **20** (1), 121–128 (2017)
111. S. Chiloiro, A. Giampietro, A. Bianchi, T. Tartaglione, C. Bima, M.G. Vita et al. Acromegaly can be cured by first-line pasireotide treatment? Endocrine **64**(1), 196–199 (2019)
112. On behalf of the ACCESS Study Investigators, M. Fleseriu, E. Rusch, E.B. Geer, Safety and tolerability of pasireotide long-acting release in acromegaly—results from the acromegaly, open-label, multicenter, safety monitoring program for treating patients who have a need to receive medical therapy (ACCESS) study. Endocrine **55**(1), 247–255 (2017)
113. On behalf of the Pasireotide C2305 Study Group, M.D. Bronstein, M. Fleseriu, S. Neggers, A. Colao, M. Sheppard et al. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, phase III study. BMC Endocr. Disord. **16**(1), 16 (2016)
114. M.R. Gadelha, M.D. Bronstein, T. Brue, M. Coculescu, M. Fleseriu, M. Guitelman et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol. **2**(11), 875–884 (2014)
115. S. Chiloiro, C. Bima, T. Tartaglione, A. Giampietro, M. Gessi, L. Lauretti et al. Pasireotide and pegvisomant combination treatment in acromegaly resistant to second line therapies: a longitudinal study. J. Clin. Endocrinol. Metab. 2019. https://doi.org/10.1210/jc.2019-00825.
116. G. Minniti, J. Flickinger, The risk/benefit ratio of radiotherapy in pituitary tumors. Best Pract. Res. Clin. Endocrinol. Metab. **33**(2), 101269 (2019). https://doi.org/10.1016/j.beem.2019.04.003
117. E.H. Kim, M.C. Oh, J.H. Chang, J.H. Moon, C.R. Ku, W.-S. Chang et al. Postoperative gamma knife radiosurgery for cavernous sinus-invading growth hormone-secreting pituitary adenomas. World Neurosurg. **110**(Feb), e534–e545 (2018)