Growth Hormone Producing Adenomas: Acromegaly

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Abstract

Acromegaly is a rare disorder characterized by overproduction of growth hormone (GH) predominantly by a pituitary adenoma. Clinical features associated with acromegaly are a result of chronic excess GH and insulin-like growth factor-I (IGF-1) effects on tissue, bone, and other organs.

The disease is associated with increased mortality, chiefly from cardiovascular disease, but morbidity from associated comorbidities is also increased. Adequate control of growth hormone excess is paramount to controlling comorbidities.

The diagnosis is made by the biochemical confirmation of elevated GH and IGF-1 levels, the presence of clinical features, and evidence of a pituitary tumor based on MRI imaging. Transsphenoidal surgery, medical therapies, and radiation therapy are all options for disease control. Patients with acromegaly require long-term health surveillance, despite the fact that they may have normal GH and IGF-1 levels. Patients are monitored lifelong for disease recurrence, management of comorbidities and treatments to improve quality of life.

Keywords

Acromegaly · Growth hormone excess · Pituitary · Pituitary tumor · Insulin-like growth factor-1

Abbreviations

BMI	Body Mass Index
CHD	Congestive heart disease
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DI	Diabetes insipidus
GH	Growth hormone
GHRH	Growth hormone releasing hormone
IGF-1	Insulin-like growth factor-1
OGTT	Oral glucose tolerance test
OSA	Obstructive sleep apnea
SIADH	Syndrome of inappropriate antidiuretic hormone
SRIF	Somatostatin
SSA	Somatostatin analogue
SSRA	Somatostatin receptor analogue

Key Terms

- **Macroadenoma:** pituitary tumour >1.0 cm in any dimension.
- **Gigantism:** growth hormone excess occurring in childhood prior to the fusing of the long bone growth plates.
- **Somatotroph:** growth hormone secreting cell in the anterior pituitary.
- **Somatostatin:** a peptide hormone secreted by the hypothalamus that inhibits the production of growth hormone.
- **Ectopic Acromegaly:** growth hormone-releasing hormone (GHRH) secretion from neoplastic tissue that stimulates pituitary somatotrophs to inappropriately release growth hormone.

Key Points

- Acromegaly is an insidious disease caused by overproduction of growth hormone and insulin-like growth factor-1 (IGF-1) predominantly from a growth hormone producing adenoma in the pituitary gland.
- Hypersecretion of growth hormone may lead to disturbances in the musculoskeletal, cardiovascular, metabolic system as well as have implications for the development of other neoplasms.
- Early diagnosis and prompt treatment can prevent development of comorbidities and improve mortality and morbidity outcomes.
- Diagnosis is based on clinical and biochemical assessments and should include a screening IGF-1 with confirmation of the disease using an oral glucose tolerance test.
- Treatment of acromegaly includes surgery to remove the adenoma, medical therapy, pituitary irradiation, and/or combinations of each therapy.
- Quality of life may be adversely affected in chronic conditions like acromegaly and should be addressed by all care providers.

20.1 Introduction

Acromegaly is a disorder characterized by the overproduction of growth hormone (GH). Acromegaly comes from the Greek words for "extremities" (acro) and "big" (megaly), as one of the hallmark symptoms of this condition is abnormally large hands (Chanson and Salenave 2008). Growth hormone overproduction is usually from a benign tumor found in the pituitary gland. The pituitary gland is located at the base of the brain and directly below the hypothalamus (See Chap. 1).

GH-secreting pituitary adenomas are thought to arise from abnormal changes to somatotroph cells whose primarily role is to secrete GH. Although the reason GH producing tumors occur is unknown, most are the result of a genetic mutation in the replication of somatotroph cells. When GH hypersecretion occurs before the fusion of long bone growth plates in late adolescence, pituitary gigantism results, characterized primarily by excessive vertical growth (Chanson and Salenave 2008).

GH excess occurring during adulthood does not result in abnormal height, but rather is associated with slow insidious changes to the patient's physical appearance and alterations in body physiology. Hence, acromegaly often goes unrecognized in adults for many years. Many patients complain of non-specific symptoms for many years, seeking consultation from a number of medical specialties.

Early recognition of symptoms and treatment is paramount to limiting the impact of GH excess and subsequent comorbidities. A blood test for IGF-1 is recommended as a screening test when a patient presents with signs and symptoms of acromegaly. If elevated, referral to specialty centers versed in the diagnosis and treatment of pituitary diseases is highly recommended. Comprehensive care and access to health care professionals who are devoted to treating this disease is associated with best patient outcomes.

20.2 Epidemiology

Acromegaly is a slow, progressive disease. It may be up to 10 years (or more) before clear features of the disease emerge and are recognized by health care providers, necessitating a referral to an endocrinologist (Chanson et al. 2014; Nachtigall et al. 2008; Galoiu and Poiana 2015). This delay may largely be the result of the rarity of the disease.

Current population prevalence estimates range from 2.8 to 13.7 cases per 100,000 people with a yearly incidence of 0.2–1.1 cases per 100,000 population (Chanson et al. 2014; Gurel et al. 2014; Knutzen and Ezzat 2006; Lavrentaki et al. 2016). This is a significant increase over historical reports and may represent a true reflection of increased disease, increased awareness of the disease and earlier diagnosis, and/or patients more actively seeking medical attention for symptoms, particularly after internet research (Lavrentaki et al. 2016).

The median age of diagnosis is reported to be in the fifth decade of life, between 40.5 and 47 years of life (men: 36.5–48.5, females: 38–56) (Lavrentaki et al. 2016). Acromegaly generally affects both men and women equally. Over 65% of cases are associated with a pituitary macroadenoma at presentation (Nachtigall et al. 2008). If left untreated, disease comorbidities contribute significantly to increased mortality, which is 2–4 times higher than the general population (Beauregard et al. 2003; Colao et al. 2014a; Melmed 2017; Melmed et al. 2005).

Epidemiologic data is sparse regarding young-onset acromegaly, or gigantism, mainly due to the rarity of the cases. Reports indicate that only 2.4% of all cases of acromegaly were found in children between the ages of 0–19 years old (Daly et al. 2006). GH production from an ectopic source is very rare.

20.3 Pathophysiology

Growth hormone is a peptide hormone manufactured and secreted by somatotroph cells located in the anterior pituitary gland. Women secrete more GH than men, and overall GH production decreases with age. Under normal conditions, growth hormone is secreted in an episodic pulsatile manner and has a half-life of 11–19 min (Faria et al. 1989). GH production during the day is relatively low, but secretion and pulsatility increase at night in association with slow wave sleep (Melmed 2017). Approximately 70% of GH is produced at night, beginning within 2 h of the onset of sleep (Fig. 20.1). This circadian pattern is shifted in jet lag, but is unchanged in shift workers (Fig. 20.1) (Morris et al. 2012).

Episodic or pulsatile GH secretion and release is a complex process influenced by many factors. It is primarily under the central neurogenic control of two hormones released by the hypothalamus, growth hormone releasing hormone (GHRH), and somatostatin. GHRH stimulates (positive action) and somatostatin inhibits GH secretion (negative action) (Fig. 20.2). The alternating action of these hormones is largely responsible for GH pulsatility and the regulation of the appropriate concentration of growth hormone in the body (Bonert and Melmed 2017). Ghrelin is a peptide secreted from the gastrointestinal tract and stomach that modulates the release of GH at the levels of the hypothalamus and pituitary gland. GH and ghrelin have been found to be secreted simultaneously in humans with ghrelin amplifying GH pulses (Melmed et al. 2014). Exercise and stress also influences GH secretion (Melmed et al. 2014).

GHRH (positive stimulation) from hypothalamic neurons is released in response to sex steroids, neuropeptides, neurotransmitters, and opiates (Bonert and Melmed 2017). GHRH travels to the pituitary via the infundibulum and attaches to receptors on somatatroph cells. This process results in the synthesis of GH within these cells. GH is then distributed to receptor sites on target tissues throughout the body to affect nerves, muscles, bones, and other organ functions.

GHRH release and GH synthesis are stimulated by many factors. Leptin regulation of fat mass, food intake, and energy expenditure may provide a metabolic signal in fasting states triggering GH secretion in order to maintain meta-

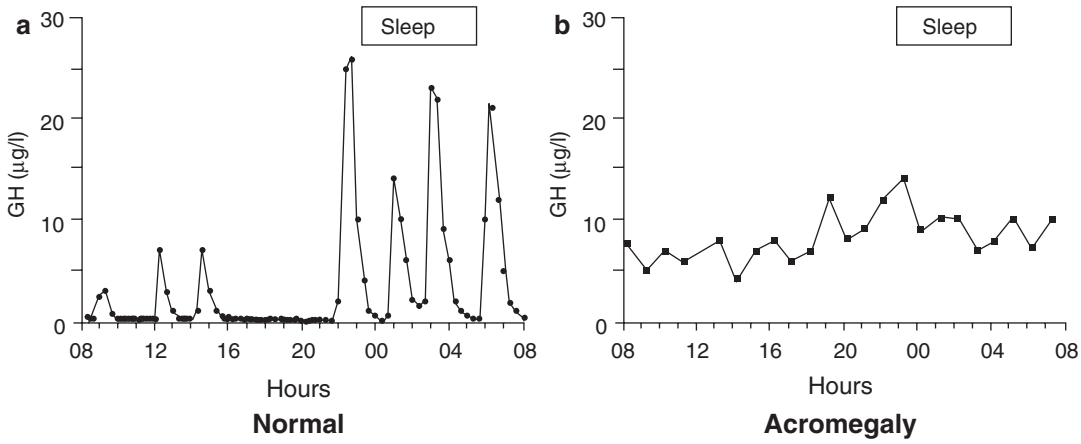

Fig. 20.1 GH circadian pulsatile production. (**a**) Normal subjects circadian pulsatile GH secretion with highest amplitude and frequency of pulses in slow wave sleep. GH levels are undetectable much of the time during the day. (**b**) Acromegaly subjects: Dysregulation of circadian frequency, and amplitude of GH pulses. Elevated baseline GH production. Ref: Chanson P, Salenave S: Acromegaly. Orphanet Journal of Rare Diseases. 3–17 (2008). Reproduced under creative commons license

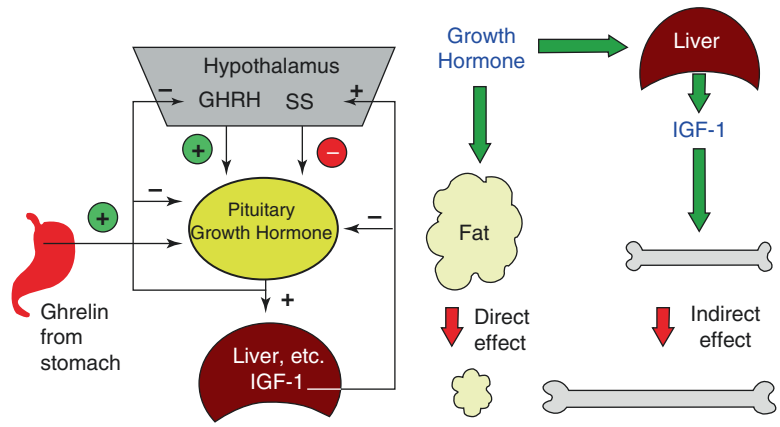

Fig. 20.2 Growth hormone physiology. Growth hormone (GH) or somatotropin secreted by the pituitary gland. Growth hormone releasing hormone (GHRH) stimulates anterior pituitary gland to release GH. The target of growth hormone: adipose tissue, liver, bone, and muscle. GH has direct effects and indirect effects on these targets. Reprinted with permission from http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/gh.html

bolic homeostasis (Bonert and Melmed 2017). Central dopamine and subsequent norepinephrine secretion stimulate GH secretion. Hypoglycemia also increases GH secretion via adrenergic stimulation while cholinergic and serotoninergic neurons have been associated with sleep-induced GH secretion (Bonert and Melmed 2017).

Somatostatin (Somatostatin Receptor Inhibiting Factor or SRIF) is a peptide that blocks GH secretion. SRIF can also inhibit adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), insulin, and glucagon secretion. Synthesized in the hypothalamus, SRIF travels down the infundibulum to the anterior pituitary, where it attaches to somatostatin receptors on somatotroph cells, thereby blocking GH secretion. It has similar actions at somatostatin receptors found throughout the body. Somatostatin attaches to five somatostatin subtype membrane receptors (SSTRs), SSTR 1, 2, 3, 4, and 5 (Bonert and

Melmed 2017). These subtypes have varying affinities for coupling with somatostatin (Bonert and Melmed 2017). SSTR 1, 3, and 5 are found on somatotrophs in the pituitary gland, whereas pituitary tumors express SSTR 1, 2, 3, and 5. These receptors provide a target for treatment of GH excess (Bonert and Melmed 2017). Other adrenergic pathways also inhibit GH release.

Once secreted, GH circulates in the blood stream attaching to peripheral receptors inducing specific cellular changes. In the liver, IGF-1 is synthesized via the JAK/STAT signaling pathway (Morris et al. 2012; Burton et al. 2012). IGF-1 is essential for promoting developmental growth activities, but also provides inhibition of GH and GHRH production via negative feedback mechanisms (Melmed et al. 2014).

GH and IGF-1 excess induces multiple downstream physiologic changes. Bone metabolism is increased with periosteal new bone formation and skeletal overgrowth (Bonert and Melmed 2017). Simultaneously, bone resorption is accelerated, increasing the risk of fracture in the presence of GH excess. There is an associated increase in soft tissue growth, adipose tissue, lipolysis, increased muscle and liver uptake of triglycerides (Bonert and Melmed 2017). GH excess antagonizes both insulin action and carbohydrate metabolism, resulting in hyperglycemia.

Pituitary GH producing adenomas are largely thought to be the result of a genetic mutation leading to autonomous GH secretion and proliferation of somatotroph cells. However, some tumors may also result from GHRH synthesis or secretory dysfunction. Most GH adenomas are monoclonal, leading to abnormal proliferation of cells that only produce GH. However, up to 25% of GH producing tumors contain cells that co-secrete GH and prolactin (Melmed et al. 2014). Rare tumors also contain cells that can produce both GH and prolactin from the same cell (Chanson and Salenave 2008). Familial genetic acromegaly syndromes or familial isolated pituitary adenomas (FIPA) associated with acromegaly are rare and include McCune–Albright syndrome, multiple endocrine neoplasia type 1 (MEN-1), and Carney Complex (Melmed et al. 2014). (See Chap. 9).

Histopathology of GH-secreting tumors demonstrates distinct cell cytoplasmic staining for GH granules and may reflect tumor activity (Melmed 2017). These include: sparsely granulated or rapidly growing tumor cells or densely granulated or slowly growing tumor cells (Melmed 2017). Cell proliferation markers Ki67 (a nuclear protein associated with proliferation) and p53 (a tumour antigen and marker of mitotic activity) are usually quantified are considered of concern if elevated. A Ki67 > 3%, mitotic activity in >10% of cells, and positive nuclear staining for p53 (>10 strongly positive nuclei per 10 high power fields) are indicative of more aggressive tumors (Raverot et al. 2017). Higher expression of SSTR2 and p21 (inhibiting cell proliferation) are associated with lower likelihood of tumor aggression and recurrence (Cuevas-Ramos et al. 2015). Two classification systems have been proposed in an effort for early prediction of treatment response, and/or tumor recurrence or progression. Raverot et al. focused primarily on histopathology and tumor invasion, prospectively evaluating a grading system from 1 to 3 for all pituitary adenomas (Raverot et al. 2017) (Table 20.1). Tumors graded as 2b were found to have a 3.7 times higher risk of recurrence or progression than grade 1 tumors. Others examined clinical, radiologic, histopathologic, and outcome characteristics in order to develop a system of risk specifically for patients with acromegaly (Cuevas-Ramos et al. 2015) (Table 20.2). In this tool, level 1 is considered to have minimal risk of recurrence and is most likely to respond to monotherapy, whereas level 3 characteristics carry a significant risk of recurrence and poorer outcomes. This tool is pending further validation.

Table 20.1 Grading system for prediction of tumour recurrence

Grade	Description
1a	Non-invasive, no or low proliferative indicators
1b	Non-invasive but proliferation
2a	Invasive
2b[a]	Invasive with proliferation
3	Malignant

[a]2b had a 3.7 times higher risk of recurrence or progression over 1a (Raverot et al. 2017)

Table 20.2 Characteristics of aggressive GH producing tumors

Type 1	Older age at diagnosis Longer disease duration before diagnosis (less symptomatology) Nadir GH and IGF-1 lower Smaller tumor volumes but both micro- and macroadenomas Tumors extend toward sphenoid Densely granulated cells on histopathology Ki67 < 3% p16 low or undetectable Highest proportion of cells with SSRT2 staining May respond to dopamine agonists as monotherapy
Type 2	Less symptomatology than type 3 Fewer microadenomas than type 1. Some invasive macroadenomas Higher nadir GH and IGF-1 Invasive macroadenomas Similar proportion of densely and sparsely granulated cells on histopathology KI67 > 3% p16 low or undetectable High p21 immunoreactivity Lower SSRT2 staining More likely to require 2 or more surgeries
Type 3	Younger age at diagnosis Macroadenomas all invasive Nadir GH and IGF-1 higher than type 1 and 2 Higher prolactin levels (p = 0.01) than Most aggressive tumors Sparsely granulated cells Ki67 > 3% p16 low or undetectable Low expression of p21 and alpha subunit Negative or low SSRT2 staining More likely to require 2 or more surgeries More likely to require radiotherapy More commonly require combination medical therapy or modalities for control More likely to be medication resistant

Adapted from Cuevas-Ramos et al. (2015)

20.4 Clinical Symptoms

The presenting manifestations of acromegaly may be a reflection of disease progression and the time to diagnosis. Since the diagnosis is frequently delayed, it may account for the predominance of macroadenomas (tumors >1 cm) found in the majority of patients with acromegaly and the extent of the observed phenotypic changes (Nachtigall et al. 2008).

The most commonly reported symptoms at presentation are headaches, as well as menstrual disturbances in women and hypogonadism in men (Chanson and Salenave 2008; Chanson et al. 2014). The most prominent physical changes in appearance include acral enlargement (78–85%) and course facial features (70%) (Chanson and Salenave 2008; Melmed 2017).

Excess GH and IGF-1 act at multiple receptor sites on body organs, tissues and bone and muscle that ultimately produce the clinical characteristics and morbidity associated with acromegaly. In bone, high levels of IGF-1 increase chondrocyte and osteocyte activity, stimulating excess skeletal bone and cartilage formation (Chanson et al. 2014). Over time, overgrowth of bone and cartilage results in acral changes (enlargement of the hands and feet) and changes in facial features such as frontal bossing and jaw growth. Joint laxity and remodeling is associated with soft tissue changes and boney overgrowth eventually resulting in arthritis and/or joint deterioration (Chanson et al. 2014). Vertebral fractures occur up to 6.9 times more frequently in patients with acromegaly, particularly in association with hypogonadism (Chanson et al. 2014; Mazziotti et al. 2013). Increases in facial soft tissues result in changes in features, such as a bulbous nose, thickened lips, and enlarged tongue. Increases in peripheral tissue and edema result in enlargement of hands (leading to symptoms of carpal tunnel syndrome) and feet. Skin changes, including oily skin with large pores, excessive hair growth, excessive sweating, and skin hyperpigmentation are observed (Chanson and Salenave 2008; Chanson et al. 2014; Melmed 2017; Melmed et al. 2014). Multiple skin tags may be found under arms and on the trunk (Ben-Shlomo and Melmed 2006; Capatina and Wass 2015). Elevated GH levels are also associated with organ tissue hypertrophy and enlargement. This can promote the development of a goiter and colon polyps. Airway obstruction results from tongue enlargement and hypertrophy of pharyngeal tissue leading to sleep apnea and poor oxygenation (Capatina and Wass 2015). IGF-1 production overstimu-

lates myocyte activity, resulting in ventricular hypertrophy, compounding hypertension, cardiomegaly and congestive heart disease (CHD) (Melmed 2017) (Fig. 20.3).

Other pituitary hormonal changes in acromegaly are common and include hyperprolactinemia, which is seen in about 25–30% of patients with acromegaly (Abreu et al. 2016). In the presence of a large tumor, this may be associated with pituitary stalk compression, but co-secretion of prolactin, either from a single cell type or two different cell types, is possible and may be confirmed on histopathology (Melmed 2017). Patients frequently present with symptoms or a history of hypogonadism, menstrual abnormalities, and infertility (Melmed 2017). Hypopituitarism can be due to mass effect on the pituitary, or damage of the pituitary gland from surgical tumor excision or radiotherapy.

On presentation, patient reported symptoms include frontal headaches, increase in ring and shoe size, weight gain, excessive sweating, difficulty with speech, snoring and breathlessness, deepening voice, coarse oily skin, multiple joint pains and carpel tunnel symptoms, hirsutism, fatigue, poor endurance, infertility, plus difficulty

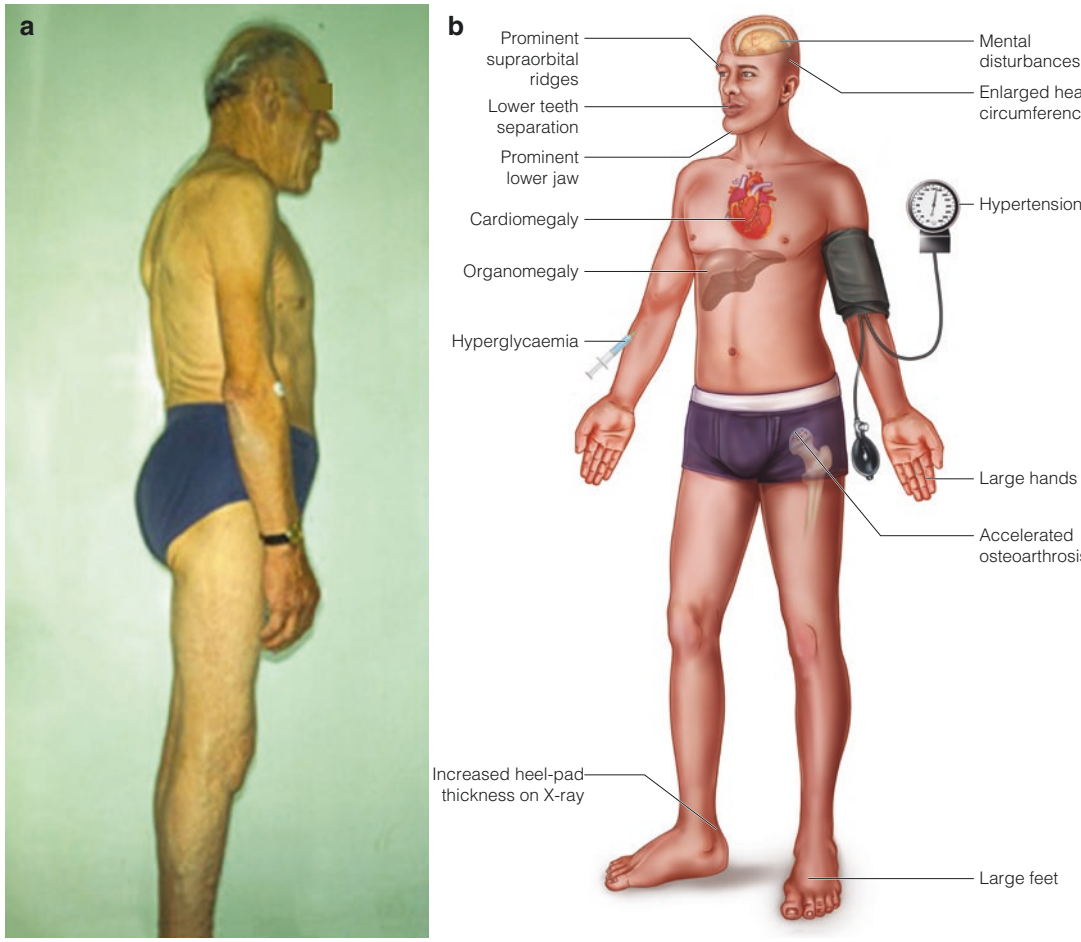

Fig. 20.3 Clinical features of acromegaly. (**a**) Clinical characteristics, (**b**) common morphological changes and comorbities. (**c**) Hand swelling and enlargement (right) (**d**) feet enlargement (left) (**e**) gaps between teeth particularly on mandible (**f**) broadening of nose and jaw enlargement (**g**) frontal bossing and jaw enlargement. Adapted from: Chanson P, Salenave S: Acromegaly. Orphanet J Rare Dis 3, 17 (2008)

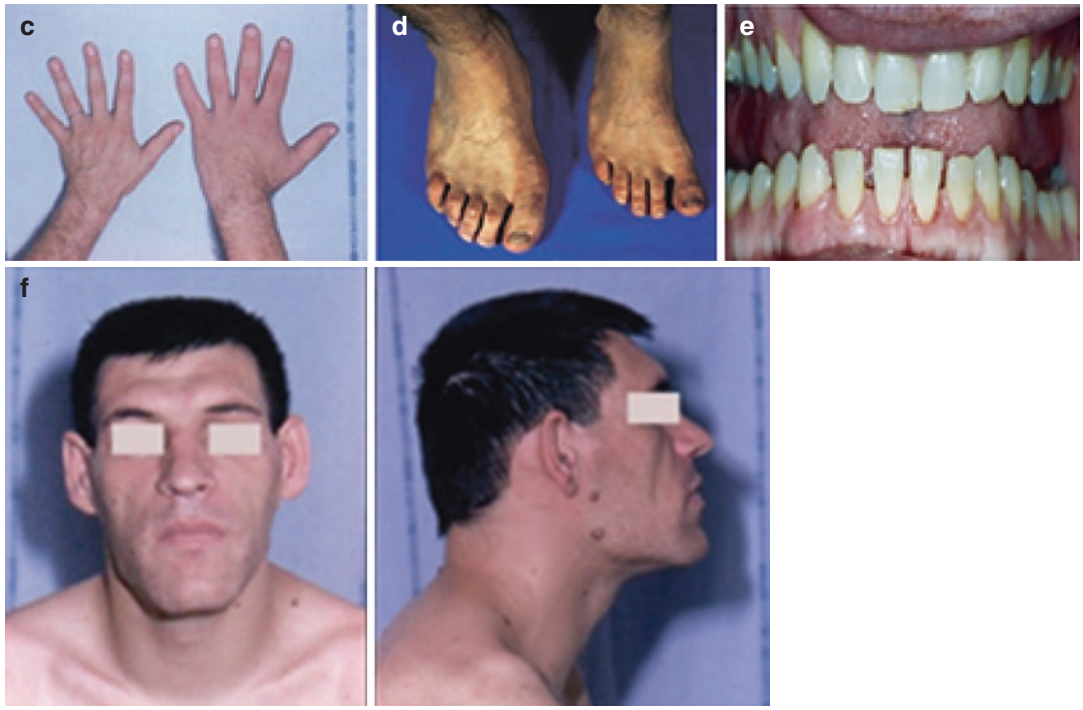

Fig. 20.3 (continued)

with cognition and memory. Patients may also have changes in vision, particularly peripheral vision and acuity when large tumors are present (Chanson and Salenave 2008; Chanson et al. 2014; Melmed 2017).

20.5 Comorbidities

National registries have been created in several countries to track comorbidities and mortality rates and also monitor the effects of treatment. Past reports from registries and other studies have indicated that life expectancy for a patient with untreated acromegaly is reduced by about 10 years compared to the general population. Cardiovascular disease is cited as the leading cause of death. However, in a recent analysis of the French Acromegaly Registry Group, better disease control reduced the incidence of comorbidities, bringing life expectancy close to that of the general population (Maione et al. 2017).

20.5.1 Cardiovascular Comorbidities

Cardiovascular disease (CVD) is the most prevalent comorbidity affecting people with acromegaly. Arrhythmias and sudden cardiac death represent the most common causes of mortality (Colao et al. 1999; Sharma et al. 2017). An increased risk of dilated cardiomyopathy, congestive heart failure (CHF), aortic and mitral valve disease, and coronary artery disease (CAD) are all reported (Sharma et al. 2017). Early studies (published prior to 1995) reported a standardized mortality risk associated with acromegaly of up to 3.31, or over 3 times higher than the general population. However, due to earlier diagnosis and disease control, mortality rates have improved with reported standardized mortality ratio now lower around 2.79 times that of the general population (Esposito et al. 2018). Some studies have found that coronary artery disease (CAD) risk is normalized with disease remission, whereas myocardial fibrosis, valvular dysfunction, and cardiac arrhythmias may be unchanged, despite

treatment for acromegaly (Sharma et al. 2017). CAD (stroke and myocardial infarction) risk remains unclear given concomitant risks from diabetes and hyperlipidemia, confounding morbidity and mortality statistics. However, encouraging data from a large German registry study demonstrated no increased risk of myocardial infarction (MI) or stroke in patients with acromegaly (Schöfl et al. 2017). Regardless, early recognition of CVD, treatment in specialty facilities, and pre-surgical treatment with somatostatin analogues have been shown to improve CVD outcomes (Sharma et al. 2017; Schöfl et al. 2017; Colao 2012).

Hypertension plays a significant role in development of cardiac hypertrophy or thickened heart chamber walls. It has been estimated that the incidence of hypertension in acromegaly is 18–60% and is associated with a significant increase in mortality (Pivonello et al. 2017). Pathogenic mechanisms of hypertension are unclear. However, it is postulated that GH and IGF-1 excess also act directly on the kidneys causing antidiuretic and antinatriuretic effects or by indirectly expanding plasma volume, resulting in increased peripheral resistance. Epithelial sodium channels (ENaC) are found in all cells and play a role in extracellular fluid volume and blood pressure. Excess GH stimulates sodium reabsorption in the distal nephrons, resulting in water retention and volume expansion (Kamenicky et al. 2008). Sleep apnea may also play a role (Sharma et al. 2017). Additionally, chronic GH exposure causes myocardial inflammation and fibrosis, hence tissue hypertrophy and loss of tissue elasticity. Using echocardiography, it has been reported that up to 85% of patients with acromegaly have left ventricular hypertrophy (Sharma et al. 2017). Thus, hypertension in acromegaly is multifactorial.

Cardiomyopathy in acromegaly has been described as occurring in progressive stages (Sharma et al. 2017). Early stages involve increased myocardial performance and decreased peripheral vascular resistance progressing to cardiac hypertrophy associated with myocardial inflammation and fibrosis. These early changes can progress to congestive heart failure, primarily through severe systolic and diastolic dysfunction and increased peripheral vascular resistance (Sharma et al. 2017). Dysfunctional changes in the cardiac valves, particularly in the mitral and aortic valves, are also a common feature in cardiomyopathy (Sharma et al. 2017). All patients presenting with acromegaly should be assessed with echocardiography and referred to cardiology as appropriate.

20.5.2 Metabolic Comorbidities

Disorders of glucose metabolism are frequently reported in patients with acromegaly. IGF-1 regulates carbohydrate metabolism and insulin sensitivity, manifesting in a range of comorbidities such as heart disease, hypertension, and diabetes (Galoiu and Poiana 2015; Melmed 2017). Studies have reported variable rates of impaired glucose tolerance (16–46%) and overt diabetes mellitus type II (19–56%) in patients with acromegaly (Alexopoulou et al. 2013). Chronic GH excess is known to lead to insulin resistance in the liver and peripheral tissues. Impaired beta cell function has also been implicated in hyperglycemia. Severity of impairment in this patient population is also influenced by IGF-1 levels, age, and increased BMI (Alexopoulou et al. 2013) (Fig. 20.4). Links have been shown between glucose intolerance, hypertension, and acromegalic cardiomyopathy (Chanson and Salenave 2008).

20.5.3 Respiratory Comorbidities

The most notable respiratory comorbidity in acromegaly is obstructive sleep apnea syndrome (OSA). Risk factors include: anatomical changes in the craniofacial bones, posterior pharyngeal soft tissue thickening, and soft palate hypertrophy and tongue enlargement. These changes lead to airway impairment (Guo et al. 2018).

Sleep apnea affects up to 80% of patients with acromegaly and is a common cause of daytime sleepiness, snoring, sleep hypoxia, headache, and memory dysfunction (Guo et al. 2018; Attal and Chanson 2018; Grunstein 1991). Obesity, particularly in males over 50 years, is a significant risk factor for OSA. Screening for sleep apnea is

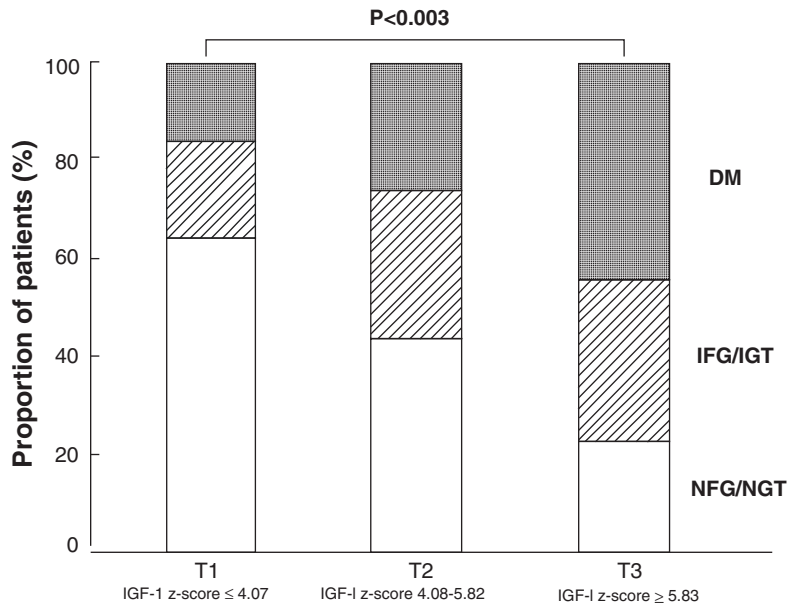

Fig. 20.4 Relationship of acromegaly: Glucose intolerance. Proportion of patients with NFG/NGT, IFG/IGT and DM within groups subdivided according to IGF-I z-score tertiles T1-T3. *NFG* normal fasting glucose, *NGT* normal glucose tolerance, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *DM* diabetes mellitus. Ref: Alexopoulou O, Bex M, Kamenicky P et al. 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. Creative commons License with permission

recommended for all patients with active and controlled acromegaly.

Lung function changes are also apparent in acromegaly patients, with rib cage remodeling, changes in cartilage and soft tissue that decrease elasticity and shorten inspiratory time (Chanson and Salenave 2008). Although alveolar volume may be increased, subclinical hypoxemia may be present (Chanson and Salenave 2008).

20.5.4 Neoplasia and Malignancies

Higher risk of developing neoplasms and some forms of cancers has been reported in patients with acromegaly. In a large Italian study, renal, thyroid, and colon cancer risk was significantly higher than in the general population (Terzolo et al. 2017). Pre-cancerous adenomatous colorectal polyps have been reported in upwards of 28% of acromegaly patients (Chanson and Salenave 2008; Abreu et al. 2016). Overexpression of GH in the colon was shown to increased epithelial cell proliferation and decreased apoptosis rates predisposing the development of polyps (Chesnokova et al. 2016). Thyroid nodules appear to be common and are found in up to 90% of patients with acromegaly. These patients have a greater likelihood of developing multinodular goiter when there is a longer interval between onset of symptoms and diagnosis (Chanson and Salenave 2008). However, some studies report the incidence of thyroid cancer does not appear to be different from the general population. A meta-analysis indicated that the overall cancer incidence for acromegaly patients was only slightly higher than the general population particularly for colorectal, breast, urinary, prostate, and hematologic cancers (Dal et al. 2018). No difference was found with respect to lung or gastric cancers. This emphasizes the need for ongoing cancer surveillance in patients diagnosed with acromegaly.

20.5.5 Arthropathies

Arthralgias and myalgias are reportedly experienced by about 70% of patients with acromegaly. Arthropathies develop after an average of 10 years of excess GH exposure, and can affect

all joints, causing progressive pain and dysfunction (Chanson and Salenave 2008; Melmed 2017; Abreu et al. 2016). Carpal tunnel syndrome and hip osteoarthropathy are commonly reported. Range of movement may be limited secondary to mechanical, non-inflammatory etiologies and/or hypermobility and tenderness. On radiographic images, joint spaces are seen to be widened (Melmed 2017). Osteocyte formation and uneven chondrocyte formations are thought to cause joint changes and osteoarthritis. In general, joint degeneration has been found to be irreversible and has been reported to impair activities of daily living and quality of life (Melmed 2017). Neurological conditions in the spine are thought to be associated with neural thickening and nerve entrapment, while disc space widening has been implicated in the development of kyphosis and scoliosis seen in these patients (Melmed 2017). Vertebral fractures have been reported in about 10% of patients (Abreu et al. 2016; Mazziotti et al. 2008).

20.5.6 Other Comorbidities

A higher incidence of asymptomatic cholelithiasis and gallbladder polyps is found in patients with untreated acromegaly (Annamalai et al. 2011; Montini et al. 2010). In addition, the treatment with somatostatins has also been associated with the development of gallstones and gallbladder sludge (Melmed 2017).

20.6 Diagnosis

The diagnosis of acromegaly is made through the clinical assessment of features and the measurement of biochemical parameters. Clinical findings unique to acromegaly, such as changes in facial features, enlarged hands (rings no longer fitting), and an increase in shoe size raise suspicions of acromegaly. Old photographs may be useful in determining changes in facial features (such as a driver's license photograph if taken 5–10 years previously). Other presenting symptoms may include headaches, joint aches or cardiovascular findings and hypogonadism (Chanson and Salenave 2008; Melmed 2017).

Biochemical confirmation of autonomous GH oversecretion is needed to make the diagnosis of acromegaly (Melmed 2017). A screening IGF-1 level should be performed if acromegaly is suspected. An elevated level should prompt a referral to a pituitary specialist or a general endocrinologist if a pituitary specialist is not available. Due to the pulsatile nature of GH secretion, a random GH level to confirm elevated GH is not useful, and is not recommended for diagnosis (Katznelson et al. 2014). According to internationally recognized guidelines, the gold standard test for confirming acromegaly is an oral glucose tolerance test (OGTT/GH suppression test). In this test, an oral glucose load of 75 g is given to the patient and GH levels are monitored every 30 min for 2 h. GH nadir of <1 μg/l (3 mIU/l) at any time point rules out the diagnosis of acromegaly (See Chapter: Provocative Investigations). The diagnosis may be complicated by variability in laboratory assays. Results must be interpreted in the context of the patient's age, BMI, and nutritional status. The presence of diabetes mellitus, renal and liver disease also spuriously alters results (Melmed 2017). Repeat sampling is recommended to confirm biochemical findings (Katznelson et al. 2014).

A pituitary MRI scan should be performed to determine the presence of a pituitary adenoma once an elevated IGF-1/GH is confirmed (Melmed 2017; Katznelson et al. 2014). Given that the majority of GH producing pituitary tumors are macroadenomas (>1 cm) and can impinge on the optic nerves, it is also recommended that these patients undergo ophthalmologic and visual field testing as a component of the initial examination (Katznelson et al. 2014).

20.7 Treatment Options

Treatment goals are to suppress or normalize GH and IGF-1, manage symptoms, and reduce tumor mass without compromising pituitary function (Melmed 2017; Katznelson et al. 2014).

If surgical resection fails to achieve GH control, or if the patient is not a candidate for sur-

gery, medical therapies and/or radiation therapy may be indicated (See Chapter: Pituitary Radiation) (Fig. 20.5).

20.7.1 Transsphenoidal Surgery

First-line treatment where a pituitary tumor is evident on MRI is selective transsphenoidal surgical resection. Success in achieving the aforementioned goals is dependent on a variety of factors, such as tumor size and location and presence of the tumor in the cavernous sinuses (Chanson et al. 2014). If the tumor is a microadenoma (<1.0 cm), surgical remission is achieved in approximately 70% of cases versus <50% for those with macroadenomas (>1.0 cm) (Melmed 2017). The best outcomes are achieved by experienced pituitary neurosurgeons. Both microscopic and endoscopic approaches are currently used, along with sophisticated intraoperative tumor localizing technologies (See Chap. 22).

Post-surgically, new onset hypopituitarism and secondary empty sella may occur (Melmed 2017). Surgical risks and complications include vision loss, cerebral spinal fluid (CSF) leak and epistaxis and hormonal dysfunction. The most common disturbances in hormones following surgery include diabetes insipidus, syndrome of inappropriate antidiuretic hormone (SIADH) and adrenal insufficiency.

Recurrence rates of pituitary tumors postoperatively range from 2 to 8% at 5 years post-op, with reports of up to 10% by 10 years postoperatively (Katznelson et al. 2014; Swearingen et al. 1998). This may be related to residual tumor from incomplete resection with subsequent growth or true recurrence. Re-operation is indicated for patients who experience visual impairment or if there is a high probability for substantial debulking or completely removing

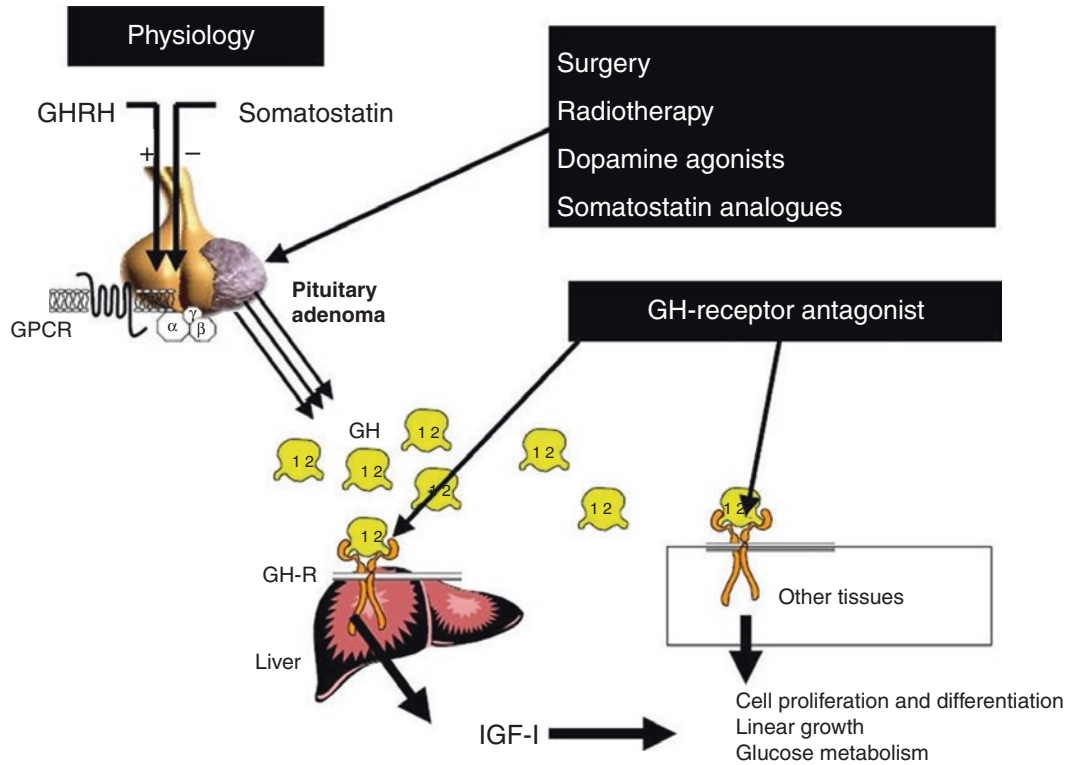

Fig. 20.5 Acromegaly treatments. Chanson P, Salenave S: Acromegaly. Orphanet Journal of Rare Diseases. 3–17 (2008). Reproduced under creative commons license

the tumor. With the potential to either remit disease or lower GH levels, re-operation is thought to be a viable, safe option and may achieve remission in up to 50% of cases (Heringer et al. 2016; Wilson et al. 2013).

20.7.1.1 Nursing Role in Transsphenoidal Surgery (Also See Chap. 23)

Preoperatively, the surgical procedure is reviewed with the patient. Patient needs, tolerance, and desire for specific surgical details vary. An overall description of the procedure itself, the risks, and what is to be expected following surgery are usually included. It is important to review the recommended lifestyle restrictions immediately postoperative, and when it is safe to return work or their previous lifestyle. Depending on the neurosurgeon and the health care system policy, the patient can be expected to stay inpatient for 1–3 days. This may vary based on specific postoperative complications such as CSF leak, diabetes insipidus, or signs of infection.

Immediately postoperatively, patients are monitored for pituitary hormone disturbances, with the most common one being transient diabetes insipidus. Sodium levels will be monitored to detect diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH). Both conditions are usually transient. Discharge instructions may include activity restrictions for 2–4 weeks, with gradual participation in more strenuous activity over the next several months. Lifting is usually restricted and the use of CPAP for sleep apnea is not recommended for the first 2 or more weeks. Surgical and endocrine follow-up is generally performed 2–12 weeks (practice dependent), at which all the pituitary hormones will be evaluated and MRI is performed.

20.7.1.2 Postoperative Testing

There has been some debate as to the definition of "cure" or disease remission. The Endocrine Society guidelines define postoperative "cure" as a suppressed GH level < 1 ng/ml following a glucose load and normalization of IGF-1 levels (Katznelson et al. 2014). A random GH/IGF-1 and oral glucose for GH suppression (OGTT) is recommended at 12 weeks or later postoperatively. MRI to evaluate any residual tumor is also recommended at 12 weeks postoperatively (Katznelson et al. 2014).

If biochemical testing demonstrates the patient has persistent acromegaly, then further therapy is needed. If the MRI scan shows a residual tumor that is surgically approachable, then re-exploration may be considered. If re-exploration is not an option, then the next line of therapy is medical management.

20.7.2 Medical Management

Medical management should be considered for those patients who did not achieve surgical cure, for whom surgery is contraindicated or in patients who elect not to undergo surgery. There are three classes of medical therapy which may be considered: (1) somatostatin analogues, (2) growth hormone receptor antagonist, and (3) dopamine agonists. These medications are used to decrease the production of growth hormone or block the action of growth hormone on target tissues. Patients with microadenomas are more likely to normalize GH and IGF-1 levels than those with macroadenomas (Melmed 2017).

20.7.2.1 Somatostatin Analogues

The native peptide, somatostatin, circulates throughout the body and attaches to one or more of five somatostatin receptor (SSR) sites found in various central and peripheral tissue. This peptide inhibits growth hormone secretion and regulates a number of gastrointestinal secretions and functions (Melmed 2017). Synthetic somatostatin ligands or analogues (SRL) that mimic the effect of native somatostatins have been developed for clinical use. SSR types 2 and 5 are expressed on somatotroph cells, particularly in GH-secreting adenomas. SRLs octreotide and lanreotide bind to somatostatin receptors, which in turn inhibit the production of growth hormone. Downstream effects include decreasing glucagon, increasing insulin secretion, suppressing pancreatic secretions, and increasing gastrointestinal motility

(Melmed 2017). The latter may lead to a side effect of transient diarrhea in some patients.

Octreotide was the first synthetic somatostatin that suppressed GH and decreased GH and IGF-1 levels in up to 90% of patients in clinical trials. Dosing is by subcutaneous injection every 8 h. Subsequently, somatostatin LAR, a long-acting formulation, given intramuscularly in doses of 20–40 mg every 4 weeks, was found to be safe and effective.

Lanreotide autogel (Somatuline) is another SRL, given as a deep subcutaneous injection in doses of 60, 90, or 120 mg every 28 days. It has been shown to be safely administered at home in some cases, and is approved in the USA for an extended dosing interval of up to 8 weeks (Salvatori et al. 2009).

Most patients will have some response to somatostatin analogues, demonstrated by a drop in GH and IGF-1 levels. However, many patients do not achieve normalization of either marker. Overall, the data suggest that approximately 57% of subjects on octreotide LAR normalize GH levels, and 67% normalize IGF-1 levels, but some studies indicate response rates as low as 41%. Similarly, only 44% of subjects on lanreotide may have normalization of IGF-1 levels (Colao et al. 2015). While the efficacy of somatostatin analogues is sub-optimal, an important characteristic of this class of medication is its effect on tumor shrinkage. About 30% of patients had reduction in tumor size by 20–50% (Colao et al. 2015).

Pasireotide is a somatostatin ligand with a broader affinity to the receptor subtypes over octreotide and lanreotide, and maybe slightly more effective in normalizing GH and IGF-1 levels (Colao et al. 2014a). However, in one head to head study, long-acting formulation of pasireotide achieved biochemical control in 31.3% of the patients compared to 19.2% of the patients treated with octreotide LAR (Colao et al. 2014b). Long-acting pasireotide is given as a once a month, intramuscular injection. One drawback of this medication is its impact on glucose metabolism. New onset diabetes was observed in 19–26% of treated patients, as compared to 4–8% of those treated with long-acting octreotide (Colao et al. 2014b).

Owing to the action of SRLs on pancreatic secretions and gastric motility, the most common side effects in more than 50% of patients are loose stools or diarrhea, nausea and abdominal cramping and gas. These side effects generally occur shortly after initial administration of the medication, and are most often transient in nature and gradually diminish or resolve over time. Biliary tract abnormalities including gallstone formation, biliary sludge and cholelithiasis occur in about 30% of patients, although most patients remain asymptomatic (Freda 2002). Abnormalities in glucose metabolism, hypo- and hyperglycemia, occur in about 2% and 15%, respectively, with up to 26% seen with pasireotide. Other less common side effects include hair loss and hypothyroidism. With the depot preparations, injection site reactions are also common (Freda 2002). Lipodystrophy, sterile abscess, and skin irritations have been reported.

20.7.2.2 Growth Hormone Receptor Antagonist

Pegvisomant is a growth hormone receptor antagonist that blocks the activity of growth hormone. By preventing dimerization at the growth hormone receptor, the critical process of transport of GH into the cell is blocked. Without dimerization, the effect of growth hormone on the cell cannot take place. While systemic GH levels remain elevated in the presence of pegvisomant, due to the nature of the compound's actions, IGF-1 levels are lowered. Initial studies demonstrated normalization of IGF-1 levels in 89% of treated patients (Trainer et al. 2000). There has been some concern that tumor growth may occur in 3–5% of the patients, but it is unclear whether this is due to the nature of the tumor, or due to persistent elevation in systemic GH (Frohman and Bonert 2007).

Pegvisomant is self-administered as a daily injection, and its effectiveness is dependent on patient adherence. It is available in 5 mg incremental doses ranging from 10 to 30 mg. Monitoring of biochemical effects is done through IGF-1 testing, as GH values are expected to be elevated and are therefore not informative (Trainer et al. 2000).

Side effects of pegvisomant can include injection site reactions, including local discomfort and reversible lipoatrophy, abnormal liver function tests, fatigue, and headache.

20.7.2.3 Dopamine Agonist

Dopamine agonists bind to dopamine receptor subtypes, D1 and D2 that are widely found throughout the nervous system and gastrointestinal tract. In healthy individuals, binding will result in stimulation of GH secretion (Jaffe and Barkan 1992). However, in individuals with acromegaly, dopamine agonist binding to these receptors results in an inhibition of GH secretion. The advantage of this class of medication is it's oral administration, and it's relatively lower cost. However, efficacy is low, limiting its use as a monotherapy. Data from several studies show that bromocriptine, the first dopamine agonist to be used in acromegaly, is effective in normalizing IGF-1 in only about 10% of patients (Jaffe and Barkan 1992). Newer dopamine agonists, such as cabergoline and quinagolide, have a greater efficacy rate of between 30 and 44% and are often better tolerated (Abs 1998; Sandret et al. 2011). With such low efficacy rates, dopamine agonists may be used in combination with other medicalx therapies for acromegaly or in those patients with modest elevations in GH or IGF-1 levels. Conversely, dopamine agonists have been used successfully in pituitary tumors which oversecrete prolactin (prolactinomas). Therefore, those patients with acromegaly who have a pituitary tumor that co-secretes GH and prolactin may benefit from medical therapy consisting of combination therapy (dopamine agonist and somatostatin analogue or dopamine agonist and pegvisomant) (Jaffe and Barkan 1992).

Side effects of dopamine agonists include gastrointestinal upset, nausea, headache, postural hypotension, fatigue, nasal congestion, and inhibition of impulse control in some cases. High doses of dopamine agonist used for patients with Parkinson's disease have also resulted in cardiac valve abnormalities (Valassi et al. 2010). However, these abnormalities have not been observed in patients where conservative doses of cabergoline have been used (≤2.0 mg/week) (Valassi et al. 2010). Additionally, no increased risk of valve abnormalities was seen in one study of 42 patients with acromegaly treated with cabergoline for a median of 34 months (Maione et al. 2012).

20.7.2.4 Combination Therapy

Combination therapy, although not FDA approved in the USA, has been used in patients who are not responsive to monotherapy. The combination of somatostatin analogues and dopamine agonists is relatively expensive, and recent studies suggest that IGF-1 levels normalized in about 30–40% of patients (Lim and Fleseriu 2016). This combination therapy is appealing for those patients with mild elevations in IGF-1 levels on somatostatin alone. Additionally, combination of a somatostatin analogue and growth hormone receptor antagonist has been reported to normalize IGF-1 levels in 80–97% of previously uncontrolled patients on monotherapy (Lim and Fleseriu 2016). Although this may achieve biochemical control, the cost of this combination therapy is expensive and requires extra monitoring for elevations in liver function.

20.7.3 Emerging Therapies

New formulations of oral octreotide are currently in clinical trials. One formulation is combined with a transient permeability enhancer (TPE) to allow octreotide absorption by temporarily opening the gap junctions in gut epithelial cells (Melmed et al. 2014). Patients must refrain from eating within 2 h of dosing. The most commonly reported side effect is diarrhea that usually resolves within 2 weeks of starting drug therapy. Efficacy is reported as similar to that of subcutaneous injections of octreotide (Melmed et al. 2014). Additionally, just completed phase 1 clinical trials, CRN00808 is an oral octreotide with a half-life of 42–50 h. Efficacy trials are ongoing (clinical trials.gov).

There are several early stage investigations of molecules designed to block the GH receptors (GHr), resulting in lowering of circulating levels of GH and IGF-1 expression. In recently completed phase 2 clinical trials, ATL1103 administered subcutaneously to two cohorts

(once or twice weekly administration) achieved a median fall in IGF-1 of 27.8% from baseline. It was well tolerated in trials with few injection site reactions reported (Trainer et al. 2018). Phase 3 trials are anticipated. Another molecule, ISIS766720 (IONIS GHR-LRX), is an antisense oligonucleotide that also acts to reduce the GHr expression, thus decreasing circulating IGF-1 levels (www.ionispharma.com). Phase 2 studies are planned in patients with acromegaly (clinicaltrials.gov, www.clinicaltrialsregister.eu).

20.7.4 Radiation Therapy

Radiation therapy in acromegaly is primarily used as adjunctive therapy in patients who have not achieved full control through surgical resection, lack of adequate response to medical therapy or with demonstrated tumor growth. Radiation therapy may also be considered to alleviate the burden of lifelong medical therapy (See Chapter: Radiation therapy).

Stereotactic radiotherapy was developed to deliver more focused radiation so as to spare surrounding tissue damage (Minniti et al. 2011). The two types of radiation therapy used to treat acromegaly are conventional fractionated or single dose stereotactic radiosurgery. In conventional fractionated radiation therapy, carefully calculated radiation doses are delivered to a precise area from several angles in divided doses over a period of about 6 weeks (Melmed 2017; Minniti et al. 2011). Patients are usually immobilized in a mask that is placed over the face. GH control is reported in 90% of patients 10 years after treatment. The most rapid decline of around 50% of pre-treatment levels is usually achieved by 2 years after treatment (Minniti et al. 2011). Fractionated treatments are well tolerated and without evidence of cognitive dysfunction, particularly in children after treatment (Minniti et al. 2011). However, there is a risk of optic damage, neurotoxicity, a higher incidence of CVAs, and secondary brain malignancies (2.4% at 20 years) post radiation.

In single dose stereotactic radiosurgery, one high dose is delivered to a single target while the patient is immobilized in a frame. This results in 30–60% of patients achieving remission at 5 years, but may incur a higher risk of radiation-induced side effects (Minniti et al. 2011; Gheorghiu 2017).

It is important to note that patients with active acromegaly continue to require treatment with medical therapy until the radiation takes effect. As GH levels usually fall slowly (over 1–10 years), interim medical therapy is required in over half of post radiation patients (Melmed 2017). Secondary brain neoplasms and radionecrosis may also occur post radiation therapy. Radiation therapy may also be associated with new onset hypopituitarism, requiring ongoing monitoring and initiation of treatment as needed. Regular symptom monitoring, pituitary testing, and MR imaging is indicated post therapy.

20.8 Quality of Life (QoL)

In recent years, the importance of quality of life has become a significant parameter in assessing the overall success in the long-term treatment and management of acromegaly. QoL is recognized by the World Health Organization as one of three patient-related outcome goals along with mortality and morbidity (Geraedts et al. 2017). QoL is multidimensional, comprised of parameters of function such as physical, social, and emotional well-being, and is assessed from the patient perspective. There are multiple general and disease specific tools available for assessment of QOL.

Many studies have demonstrated a decline in QoL in patients with acromegaly despite biochemical disease remission, although results of systematic reviews are inconclusive (Geraedts et al. 2017; Szczesniak et al. 2015; Webb 2006; Webb and Badia 2007). This may be related to factors such as assessments being performed during different stages of the disease, study design, treatment modalities, or differences in parameters assessed. Although drug studies report QoL improvement with currently used medical therapies, significant disease-related decline in QoL

compared to the general population persists (Geraedts et al. 2017; Adelman et al. 2013). Significant treatment burdens remain and include: lifestyle restrictions, pain associated with injections, family issues and high economic burden from loss of wages and productivity, medication and health care insurance costs, in some countries (Liu et al. 2017; Yedinak et al. 2018).

Many structural skeletal changes in acromegaly are permanent. Up to 90% of patients with acromegaly report musculoskeletal pain which has a negative correlation on quality of life (Wassenaar et al. 2010). Decreased mobility from increased joint pain and BMI impacts physical functioning and social activities. BMI and boney changes are also associated with changes in body image, contributing to increased anxiety, depression, decreased motivation, and increased social isolation (Biermasz et al. 2004; Conaglen et al. 2015; Crespo et al. 2016; Pantanetti et al. 2002). Osteoarthritic changes and joint space widening may only be partially improved after treatment, contributing to chronic pain and dysfunction (Claessen et al. 2017). Referrals to, and care coordination with, appropriate specialists such as orthopods, counselors and/or psychiatrists and/or rheumatologists should be encouraged.

Cognitive dysfunction is reported to be more prevalent in patients with acromegaly compared to both those with non-functioning pituitary adenomas and the general population. Executive functions of attention, memory, and new learning are affected, particularly when GH and IGF-1 levels are high and may persist, to some extent, despite treatment (Shan et al. 2017; Yedinak and Fleseriu 2013). Cognitive therapy has been demonstrated to improve associated depression, with concomitant improvement in patients perception of QoL (Kunzler et al. 2018). Long-term outcomes and the impact of more specific cognitive training remain unclear.

Comorbidities also play a role in QoL for this patient population. Headaches may improve after treatment but not resolve and may impact many aspects of functioning (Webb and Badia 2007). Screening for other comorbidities such as oncologic diseases, cardiovascular, respiratory (sleep apnea), metabolic (dyslipidemia and diabetes), osteoarticular, and hypopituitarism is recommended pre and post disease remission (Bernabeu et al. 2018). Some studies have suggested that hypopituitarism does not negatively affect QoL (Geraedts et al. 2017). However, other concomitant diseases may all contribute to a decline in QoL (Fig. 20.6).

20.9 Nursing Management Considerations

In addition to medical assessments, nurses must assess physiological, psychological, sociocultural, spiritual, economic, and lifestyle function. As previously discussed, substantial physiologic changes are usually apparent at the time of presentation, with implications for all functional

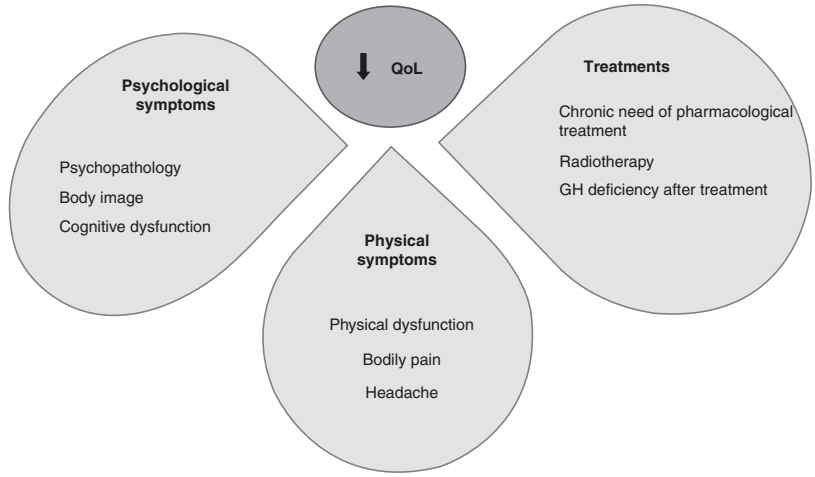

Fig. 20.6 Factors that can affect quality of life (QoL) in patients with acromegaly. From: Crespo, I., Valassi, E. & Webb, S.M. Update on Quality of Life in Patients with Acromegaly. Pituitary (2017) 20: 185. https://doi-org.liboff.ohsu.edu/10.1007/s11102-016-0761-y with permission

domains. Assessment should include family involvement or the patients support structure at diagnosis, as involvement of family/support has shown benefit in treatment adherence and long-term outcomes (Andela et al. 2017; Yedinak 2014). Assessment of memory, coping skills, and mood at baseline can provide direction in the care of these patients. All have been shown to be altered in acromegaly, particularly in the presence of high GH/IGF-1. Baseline assessment alerts the nurse to the potential need for additional resource needs or referrals (Webb and Badia 2007; Yedinak 2014).

Learning styles may also be impacted and require evaluation, although no data was found in the literature in this regard. It is important to note that re-assessment is required as the patient's phase of treatment progresses and life stage needs change.

Medical diagnosis can generate considerable anxiety and relief. Anxiety has been shown to impair memory and patients with acromegaly have also been found to have impaired verbal memory (Crespo et al. 2015). Patients express relief that their symptoms are legitimized with a diagnosis, but the patient may not have realistic posttreatment expectations. Therefore, it is vital to explore the patients' perception of treatment outcomes.

Much disease related information is now freely available on the internet, although not all information is accurate. Determination of the level of patient knowledge and the source of the patient's information can help frame patient and family education needs.

Key issues from patient assessment to address in care planning include: patient and family knowledge regarding acromegaly, the learning style of the patient; how realistic are treatment expectations; resource deficits, particularly with respect to accuracy of information sources; economic and social support; geographic limitations; the patient's level of anxiety and depression; local health care provider availability. Disturbed body image and uncompensated or deficient coping skills will need to be considered in treatment planning.

Care planning is patient centered and goal directed toward self-efficacy. In this model of care, the patient and family are involved in all care decisions. Motivational interviewing is a useful technique when mutually establishing measurable and achievable short- and long-range goals is based on the patient needs assessment. Goals must be meaningful to the patient for best adherence (Hall et al. 2012).

Planning involves multiple phases of care. Beginning with the execution of appropriate testing, preparation for hospitalization progresses through discharge planning and postoperative workup to determine remission versus the need for long-term therapy, medical and or radiologic treatments.

Care planning is complex, requires multidisciplinary collaboration, and must be adaptable. Patient needs change with phase of treatment, age, and life stage, with social and economic changes requiring ongoing adaptation. At each visit it is recommended that the patients' clinical condition, and their geographic, economic, and psychological concerns, treatment expectations and goals be addressed (Plunkett and Barkan 2015). It is estimated that 17–21% of patients with acromegaly are lost to follow-up with around 88% of these patients thought to have uncontrolled disease (Kasuki et al. 2012; Scott et al. 2004). Outcomes must be regularly reviewed and a plan revised to achieve better patient continuity and outcomes.

20.10 Long-Term Management

All patients with a history of acromegaly require periodic evaluations lifelong. The joint European and US Endocrine Societies clinical guidelines recommend a definition of remission as an IGF-1 in normal range for age and gender and a GH of <1 μg/L with glucose suppression. However, an undetectable GH (<0.04 μg/L) along with a normal IGF-1 is thought to be a more rigorous indicator of remission (Katznelson et al. 2014). Using the same GH/IGF-1 assay throughout treatment is advised. Monitoring comorbidities, thyroid studies, and assessment for

hypopituitarism is indicated (Katznelson et al. 2014). Follow-up MRI is the suggested imaging modality, but there is no guideline for follow-up imaging beyond 12 weeks postoperatively. Others recommend varying intervals from 20 to 12 months for the first 5 years and then every 5 years lifelong (Fig. 20.7).

Recurrence rates are low, but may be higher in young patients with larger tumors found to be sparsely granulated on pathology (Melmed 2017; Swearingen et al. 1998). Close and long-term monitoring is necessary. Treatment modalities, particularly transsphenoidal surgery and radiation therapy, may result in damage to the pituitary gland which may lead to the development of hypopituitarism. Hypopituitarism requires frequent biochemical testing and replacement of the missing or decreased pituitary hormones particularly post radiation therapy. Post radiation therapy, ongoing imaging is also recommended for

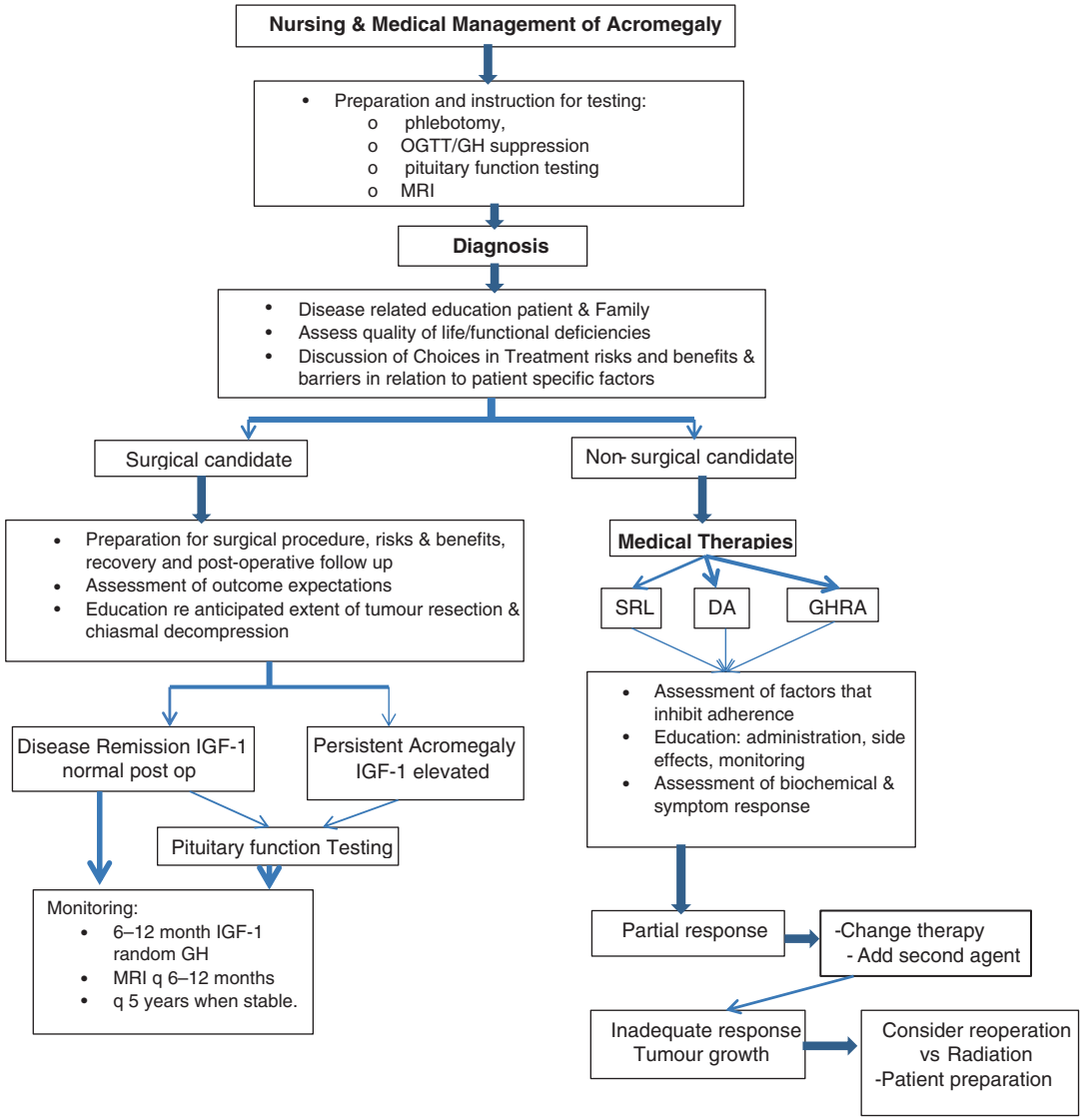

Fig. 20.7 Acromegaly management algorithm. Adapted from: Acromegaly: An Endocrine Society Clinical Practice Guideline J Clin Endocrinol Metab. 2014;99(11):3933–3951. doi:https://doi.org/10.1210/jc.2014-2700. Copyright © 2014 by the Endocrine Society. This article is published under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License (CC-BY-NC-ND; http://creativecommons.org/licenses/by-nc-nd/4.0/)

secondary tumors that may develop in the field of radiation (Minniti et al. 2011).

Guidelines also recommend monitoring for comorbidities, and for the development or worsening of cardiovascular diseases such as coronary artery disease, cardiomyopathy, and hypertension (Katznelson et al. 2014). Respiratory dysfunction and sleep apnea may persist despite disease remission. Since exposure to elevated IGF-1 levels have been implicated in the development of certain malignancies, routine screening tests for the detection of cancer should be performed on a regular basis and should include colonoscopies for the detection of cancerous colon polyps.

Finally, since there are many clinical features of acromegaly that do not improve with remission of the disease, health care providers should not hesitate to refer a patient to a specialist if needed. Many patients will still have clinical conditions associated with changes to bone and cartilage, such as the development of arthritis or joint issues that require referral to appropriate specialists.

20.11 Home Care Educational Programme

Starting a new medicine solicits many questions about the underlying diagnosis, symptoms, complications, and expected outcomes. A new medicine also means another responsibility for the patient, subcutaneous injections that are to be self administered. Patients have high expectations when a new drug has been introduced. However, they lack confidence in using unfamiliar equipment, substances, and techniques. They are particularly concerned about accuracy in drug preparation, administration, and side effects. The home care educational programme was developed to address these questions and concerns.

20.11.1 Programme Goals

(a) Assist the patient to become confident in self-injection technique.
(b) Provide the support of a trained specialist endocrine nurse.
(c) To improve adherence to drug administration schedules.
(d) To support self-care and improve quality of life.
(e) To provide patient focused education, with an emphasis on self-care, tailored to the specific needs of the individual patient.

20.11.2 Role of the Specialist Endocrine Nurse in Home Care

- Highly valued by patients
- Provides support as needed
- Provides personal contact
- Time to listen
- Knowledgeable about acromegaly
- Respects patient autonomy
- Available to answer questions
- Provide consistent follow-up
- Understand the emotional aspects of disease and diagnosis (Scott et al. 2004).
  - Phase 1: first symptoms, patient worried, feel misunderstood, very eager to find a "cure" or an answer. Risk of being lost to follow-up.
  - Phase 2 Diagnosis: patients are relieved when receiving a correct, final diagnosis.
  - Phase 3 Start of treatment: patients are unaware of the complexity of treatment and the implications of the disease.
  - Phase 4 Follow-up: patients accept the situation as it is, yet are sometimes unaware that follow-up and prevention are needed.

20.11.3 Method: A Home Care Programme

This programme is modeled after successful home care programmes for diabetes and CHD (Scott et al. 2004; Corbett 2003). The key to a successful programme is mutual goal setting.

The programme is divided into four face-to-face visits during the first week (day 1–2–3–7), and after 1 month, there are regular phone calls to

answer questions or titrate dose. Visits are scheduled when needed.

20.11.4 Programme Content

Week 1 (Day 1, 2, 3, and 7).

- Explanation of the disease and the chosen medical therapy.
- Description of the importance of adherence to prescription (dose and frequency).
- Outline of possible side effects
- Demonstration of use of injection technique and patient practice manipulating equipment.
- Description of drug dose and titration protocol.
- Day 7 patient reviewed in autonomous drug administration.
- Questions are answered by specialist endocrine nurse as they arise.
- Observations reported to patient's endocrinologist.

20.11.5 Programme Conclusion

This home care programme assigns one nurse who coaches a group of patients for an introductory week and at regular intervals thereafter. The programme improves patient satisfaction, assists patient adherence to treatment, and improves quality of life by attaining rapid IGF-1/GH normalization.

Patient feedback is positive. They are grateful for the education and training, feel independent and motivated by improved biochemical results, and have a sense of security by establishing direct communication with their endocrine team.

A home care programme for patients with acromegaly was initiated in 2011 at the Ghent University Hospital in Belgium. The protocol was approved by the ethical committee. The programme has since been expanded to 20 hospitals in Flanders, Belgium.

20.12 Conclusions

Patients with acromegaly suffer from physical, social, and psychological challenges related to the disease, many of which can persist during and after treatment and significantly modify quality of life. The nurses' role is critical in addressing and managing these issues through collaborative medical management, disease-related education, promotion of treatment adherence and lifestyle modifications, coordination of management of comorbidities and more. Multiple studies have shown that assessing and addressing known quality of life indicators in this population should be incorporated into the regular care of patients with acromegaly for best outcomes.

20.13 Patient Case Studies

Case Study 1

A 59-year-old man was referred for further assessment and treatment of suspected acromegaly. Symptoms include aching in his fingers, shoulders, hips, and knees, as well as snoring. On physical examination, his blood pressure is 150/95 mm Hg, he had acromegalic facies, wide fingers and toes, and crepitation on flexion and extension of both knees. His serum IGF-1 level is 753 ng/mL (98.6 nmol/L), (reference range, 41–279 ng/mL [5.4–36.5 nmol/L]) and his fasting blood glucose level is 142 mg/dL (7.9 mmol/L). His baseline GH is 11.7 ng/ml (11.7 μg/L). MRI was obtained and an 11 mm mass on the right side of the sella was visible. Transsphenoidal surgery is recommended. He asks if any of his abnormalities will persist even if the surgery is successful.

Question: what is this patient's morbidity and mortality risk?

Case Study 2

A 23-year-old man is referred for acromegaly. His height is 74 in. (188 cm), and his weight is 210 lb. (95.5 kg). His hands and feet are enlarged, and he has prognathism. A paternal uncle was thought to have had a pituitary adenoma of uncertain type. There is no known family history of calcium disorders or kidney stones. A random GH level is 33 ng/mL (33 μg/L), and his serum IGF-1 concentration is 811 ng/mL (106.2 nmol/L) (reference range, 147–527 ng/mL [19.3–69.0 nmol/L]). His serum calcium level is nor-

mal. MRI shows a 4.3-cm pituitary adenoma with suprasellar extension.

Question: Does this patient have a genetic risk?

20.14 Patient Stories

Patient 1

In 2014, at the age of 36, I had been having irregular periods. I would alternate having one every other month. Since I had always been regular in the past, I tracked my periods for several months and discussed the pattern with my primary doctor at my annual appointment in December, 2014. Lab work found that my prolactin was high at 59.7 ng/mL (normal 3–13 ng/ml).

She scheduled an MRI with contrast in January 2015, and there was a 1.1 cm tumor on my pituitary. It was assumed to be a prolactinoma. I was referred to an endocrinologist, and in March, 2015, my prolactin was still elevated, but my IGF-1 was also high (432 ng/mL) (reference range 128–291 ng/mL). Looking at the MRI, she said that the tumor was pressing against the pituitary stalk, so the elevated prolactin was likely a product of "stalk effect."

A glucose suppression test in April 2015 showed baseline GH was 1.1 ng/mL, which did not suppress to a level of less than 1.0. This confirmed that I had acromegaly.

I was then referred to a neurologist at the University Pituitary Clinic. Surgery was in June 2015, and the neurosurgeon was fairly sure that she had been able to remove the entire tumor. My prolactin levels immediately went back to normal. About a week after surgery, my sodium levels were low (119 mMol/L). I was readmitted to the hospital and placed on a one liter a day fluid restriction. After 2 days, my sodium levels went back to normal, and I was discharged.

At my 1-month follow-up in July 2015, my IGF-1 was still elevated (403 ng/mL). They decided to re-test in a few months. In September 2015, my IGF-1 had decreased to 346 ng/mL, but was still high. Finally, in November 2015, my IGF-1 had fallen into normal range—283 ng/mL!! What a relief! In December 2015, I repeated the glucose suppression test, and my GH level suppressed to 0.3 ng/mL, indicating remission!

I am happy to report that my IGF-1 levels and MRI results have continued to be normal over the last few years since surgery: September 2016/205 ng/mL, and September 2017/150 ng/mL (range 57–241).

I have noticed a decrease in swelling of my face, hands, and tongue as well as less joint pain since surgery. My cholesterol levels have also improved.

Patient 2

I was diagnosed with acromegaly in October of 2010. My condition, like many, if not most of the stories I read and hear about, was missed for many years. In my case, doctors estimated probably around 30 years.

When I look back, it is difficult to isolate many of the symptoms that now clearly were due to the overproduction of growth hormone. Now, hindsight being 20–20, it all makes sense. I am now 63 years old and was diagnosed with acromegaly at age 56. In retrospect, the signs started in my early to mid-30s. My physical characteristics kept changing. I was getting bigger: my hands, my chest, my muscles, my feet, and even my head was growing. I thought it was the process of aging. It never occurred to me that this was not normal. I clearly remember my dentist noticing bottom teeth separation and my primary care physician noticing my blood pressure was consistently higher than normal. I was put on mild hypertension medication in my late 30s to early 40s. By my mid to late 40s my blood sugars started to rise. Sleep apnea was another tail-tell sign. My wife noticed alarming sings of apneas (breathing stops while at sleep). In my early to mid 40s I started noticing marked pain in my leg joints specifically knees, ankles, and hips as well as a noticeable lack of energy.

I met my endocrinologist and neurosurgeon at the Center for Pituitary Disorders on a dreary, grey, drippy November San Francisco morning. "How fitting," I thought, you're going to get bad news on a miserable day! They were amazingly reassuring, particularly to my wife Carol, who

was very, very worried. After all, it is not every day you are told you have a tumor in your head. For some strange reason, I was as calm as I've ever been. Finally, knowing exactly what had been bothering me for so many years was like a 5000-pound rock lifted off my back. My first thought, as I was listening to their explanations, the surgery, medical treatment steps, and what the future would hold was: "these guys ooze competence." I was reassured with these two doctors and could not wait to get this thing out of my head.

Three months earlier I had gone to an orthopedic surgeon who recommended a hip replacement and, "by the way, I think you have a condition called Acromegaly." He told me what it was and what caused it. I must have looked at him in horror because immediately, he felt compelled to tell me I was not going to die. He had a colleague with acromegaly and a golf-ball-size pituitary tumor was removed.

At home I "googled" "Acromegaly" and THERE IT WAS!!!. "How is this possible" I thought. The screen was filled with people that looked like me. "I have almost every symptom listed" I screamed loud enough for my wife to hear me three rooms away. "You mean to tell me there are other people running around with this?" "I have most of the physical characteristics!", "Andre the Giant has this?. Don't any of these doctors I've been seeing for 30 years know about this?" "My grandmother could have diagnosed me. I could have diagnosed it," I thought angrily. It was so evident to me!

I felt ignorant, then angry, then depressed. But I also realized that as a patient I should have been more aware and perhaps, if I had been more aware of potential pituitary conditions, I could have asked better questions and help the doctors focus on a diagnosis earlier. I knew things would get better, but growing for 30 years had done irreversible damage to my bones and joints. That was the end of some of my favorite things: tennis, backpacking, hiking, even standing and walking for long periods of time. I was going to have to adjust to all of that.

During transsphenoidal surgery 95% of the pituitary adenoma was removed, but my determination to use my skills to help raise awareness of acromegaly and pituitary disorders so that people could be diagnosed early and properly, was peaked. The word about acromegaly is not getting out fast or efficiently enough.

I had developed an admiration and great friendship with my endocrinologist. We decided to move forward on a doctor–patient collaborative approach and communicate, not just the medical and scientific knowledge, but also what it is like to live with the chronic conditions associated with acromegaly. The eNews magazine Pituitary World News was the result.

Pituitary World News is a communication and publishing platform designed to encourage collaborations, innovation and creativity between industry experts, the healthcare community and patients and their families. Through awareness and communication strategies its mission is to reduce the time it take to diagnosis, improve knowledge and quality of life.

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20.15 Patient Advocacy Groups

The World Alliance of Pituitary Organizations (WAPO) is a self-governed non-profit organization created in order to unite the international pituitary patient community to push for optimal treatment and care for all patients with pituitary and related conditions worldwide. The goal of this organization is to share information, work together, and support all pituitary patients' advocates all around the world. WAPO believes in the strength of a global network of national pituitary patient organizations, which will lead to better outcomes worldwide (Fig. 20.8). The Acromegaly Community is a patient support and advocacy group for people affected by acromegaly patients,

Fig. 20.8 World Association of Pituitary Organization (WAPO)

their families and friends. Presently, the group has over 2000 members worldwide. They provide an emotional and communal support network for people touched by Acromegaly and offer information on issues of interest to people with the disease and provide a network of emotional support for Acromegaly patients, their friends and their family. The Acromegaly Community Website: https://www.acromegalycommunity.org

20.15.1 Best Practice "Bulgarian Association of Patients with Acromegaly"

One WAPO's member organization is the Bulgarian Association of Patients with Acromegaly (ABAB), who has been raising awareness for acromegaly for more than 7 years. For the last 5 years we have been involved in a court trial regarding "access to radiosurgery" and "parallel export or shortage of medicines." Both campaigns were widely spread by the Bulgarian media over a 5-year period. This amounted to an awareness campaign.

One of the most successful ABAB campaigns is the "Shoe Shop project" (Fig. 20.9). The Patient association contacted two Shoe Shop companies in Bulgaria who were already selling "big size shoes." Only one of the two stores accepted to meet and now supports the "Shoe Shop project." The patient advocacy group prepared information brochures, created from validated information on acromegaly. The brochure invited people to be alert for symptoms and encouraged them to be seen by a specialist. The material was translated and approved by a local endocrinology and used in the ABAB campaign (Acromegaly Shoe Shop Awareness). These brochures were distributed by the shoe shop in the boxes of purchased shoes. The shoe company made special boxes for display with a sign to their clients: "**If your feet and hands are growing, check for *acromegaly.***"

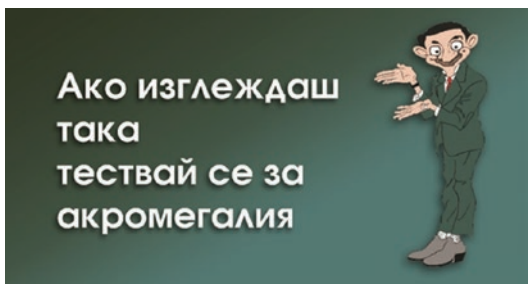

Fig. 20.9 Bulgarian Association of Patients with Acromegaly Email: acromegaly@abv.bgwebsite: http://www.pituitary-bg.com

The shoe shop entrepreneur also donated a pair of shoes to ABAB's tallest member and a journalist wrote an article about the support of the shoe shop, as well as highlighting the awareness campaign.

The next awareness campaigns will focus on access to expert diagnostic centers, medications, and reimbursement for treatment. The only center currently is in the capital city Sofia, and not accessible for rural patients.

As in Bulgaria, pituitary patients encounter similar problems in countries worldwide. The most important is late diagnosis. It takes on average 8–10 years to identify the pituitary diseases since their symptoms are not very specific and the cases are so rare. In some countries the situation is even worse and most patients either don't get treatment at all or get to the neurosurgeon when the adenoma is too large to operate. Even when diagnosed, in many countries, patients do not get appropriate treatment on time. Even when treated, patients still suffer from comorbidities, both physical and psychological.

The number or pituitary patients is relatively small but when they join their voices, they become a real power. To this end, patient groups and organizations appear in most countries. The main goals of a patient group are: (1) to represent patients in communication with health care authorities and policy makers, to advocate for patients, (2) to raise awareness about the pituitary diseases among health care professionals and general public, and (3) to empower patients so that they act in order to improve their own situation, either through better adherence, better communication, lifestyle change, or legal action.

Patient organizations are in most cases not-for-profit organizations acting in the best interest of the patients they represent. To make patient organization's activity most efficient, they try to co-operate with health care authorities, doctors, and nurses. Patient advocates are not doctors and cannot make prescriptions. However, patients tend to trust other patients so patient groups can spread the word about the importance of adherence, about patient rights and duties. Patient groups also raise awareness about the disease, thus improving the chances of undiagnosed patients to be diagnosed. These activities require support from all people involved with pituitary patient care including nurses and doctors.

There are patient groups or patient organizations active in most of the countries in the world. In some countries the organizations are well established, like the UK Pituitary Foundation. They have stable financial support from diverse base of sponsors and many fundraising events. In other countries patient groups are just starting their activities and trying to find their way to sustainability. It is not an easy path. In any case they both are ready to support patients and need your support and active involvement.

Some of the many projects in which member organizations are involved include: Acromegaly Community, US, the Vancouver Acromegaly Support Group, Canada are holding Acromegaly Awareness Days; Velikan, the Russian Pituitary Patient Organization, has launched a program for information and legal support for pituitary patients in Russia; The Spanish Association of People Affected by Acromegaly and the Pituitary Alliance of Latin America, jointly enacted a program of awareness of acromegaly; The dental school of Lima, Peru launched a program to educate dentists in signs an symptoms of acromegaly to promote early diagnosis.

To learn more about patient organizations in your region you can address to WAPO, the World Alliance of Pituitary Organizations (www.wapo.org and facebook.com/wapo.org). WAPO was created in 2016 after a series of annual meetings of patient advocacies from all over the world. The WAPO mission is to identify pituitary organizations, to guide the development of their organization, and to create an active global network (Fig. 20.10).

As of May 2017, WAPO membership included 33 organizations from 24 countries (see the map)

Fig. 20.10 World Membership WAPO

representing 30% of global population of patients with pituitary diseases.

If there is no patient group in your region, maybe you know active people that are ready to create one. Please introduce them to WAPO at mail@wapo.org. In this case WAPO will provide the activists with the best practices collected over the years and all possible support from its members.

Together we can improve the life of pituitary patients worldwide!

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References

Abreu A, Tovar AP, Castellanos R, Valenzuela A, Giraldo CMG, Pinedo AC, et al. Challenges in the diagnosis and management of acromegaly: a focus on comorbidities. Pituitary. 2016;19(4):448–57.

Abs R. Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab. 1998;83(2):374–8.

Adelman D, Liebert N, Lamerson BB. Acromegaly: the disease, its impact on patients, and managing the burden of long-term treatment. Int J Gen Med. 2013;6:31.

Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary. 2013;17(1):81–9.

Andela CD, Tiemensma J, Kaptein AA, Scharloo M, Pereira AM, Kamminga NGA, et al. The partner's perspective of the impact of pituitary disease: looking beyond the patient. J Health Psychol. 2017:135910531769542.

Annamalai AK, Gayton EL, Webb A, Halsall DJ, Rice C, Ibram F, et al. Increased prevalence of gallbladder polyps in acromegaly. J Clin Endocrinol Metab. 2011;96(7):E1120–E5.

Attal P, Chanson P. Screening of acromegaly in adults with obstructive sleep apnea: is it worthwhile? Endocrine. 2018;61(1):4–6.

Beauregard C, Truong U, Hardy J, Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol. 2003;58(1):86–91.

Ben-Shlomo A, Melmed S. Skin manifestations in acromegaly. Clin Dermatol. 2006;24(4):256–9.

Bernabeu I, Aller J, Álvarez-Escolá C, Fajardo-Montañana C, Gálvez-Moreno Á, Guillín-Amarelle C, et al. Criteria for diagnosis and postoperative control of acromegaly, and screening and management of its comorbidities: expert consensus. Endocrinol Diabetes Nutr (English ed). 2018;65(5):297–305.

Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JWA, et al. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab. 2004;89(11):5369–76.

Bonert VS, Melmed S. Growth hormone. In: Melmed S, editor. The pituitary. London: Elsevier; 2017. p. 85–127.

Burton T, Le Nestour E, Bancroft T, Neary M. Real-world comorbidities and treatment patterns of patients with acromegaly in two large US health plan databases. Pituitary. 2012;16(3):354–62.

Capatina C, Wass JAH. 60 YEARS OF NEUROENDOCRINOLOGY: Acromegaly. J Endocrinol. 2015;226(2):T141–T60.

Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3(1):17.

Chanson P, Salenave S, Kamenicky P. Acromegaly. Handb Clin Neurol. 2014;124:197–219. https://doi.org/10.1016/B978-0-444-59602-4.00014-9.

Chesnokova V, Zonis S, Zhou C, Recouvreux MV, Ben-Shlomo A, Araki T, et al. Growth hormone is permissive for neoplastic colon growth. Proc Natl Acad Sci. 2016;113(23):E3250–E9.

Claessen KMJA, Canete AN, de Bruin PW, Pereira AM, Kloppenburg M, Kroon HM, et al. Acromegalic arthropathy in various stages of the disease: an MRI study. Eur J Endocrinol. 2017;176(6):779–90.

Colao A. Improvement of cardiac parameters in patients with acromegaly treated with medical therapies. Pituitary. 2012;15(1):50–8.

Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Morte AMD, et al. Impact of patient's age and disease duration on cardiac performance in acromegaly: a radionuclide angiography study. J Clin Endocrinol Metab. 1999;84(5):1518–23.

Colao A, Vandeva S, Pivonello R, Grasso LFS, Nachev E, Auriemma RS, et al. Could different treatment approaches in acromegaly influence life expectancy? A comparative study between Bulgaria and Campania (Italy). Eur J Endocrinol. 2014a;171(2):263–73.

Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014b;99(3):791–9.

Colao A, Auriemma RS, Pivonello R, Kasuki L, Gadelha MR. Interpreting biochemical control response rates

with first-generation somatostatin analogues in acromegaly. Pituitary. 2015;19(3):235–47.
Conaglen HM, de Jong D, Crawford V, Elston MS, Conaglen JV. Body image disturbance in acromegaly patients compared to nonfunctioning pituitary adenoma patients and controls. Int J Endocrinol. 2015;2015:1–8.
Corbett CF. A randomized pilot study of improving foot care in home health patients with diabetes. Diabetes Educ. 2003;29(2):273–82.
Crespo I, Santos A, Valassi E, Pires P, Webb SM, Resmini E. Impaired decision making and delayed memory are related with anxiety and depressive symptoms in acromegaly. Endocrine. 2015;50(3):756–63.
Crespo I, Valassi E, Webb SM. Update on quality of life in patients with acromegaly. Pituitary. 2016;20(1):185–8.
Cuevas-Ramos D, Carmichael JD, Cooper O, Bonert VS, Gertych A, Mamelak AN, et al. A structural and functional acromegaly classification. J Clin Endocrinol Metab. 2015;100(1):122–31.
Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C, et al. Cancer incidence in patients with acromegaly: a cohort study and meta-analysis of the literature. J Clin Endocrinol Metab. 2018;103(6):2182–8.
Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the Province of Liège, Belgium. J Clin Endocrinol Metab. 2006;91(12):4769–75.
Esposito D, Ragnarsson O, Granfeldt D, Marlow T, Johannsson G, Olsson DS. Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study. Eur J Endocrinol. 2018;178(5):459–69.
Faria ACS, Veldhuis JD, Thorner MO, Vance ML. Half-time of endogenous growth hormone (GH) disappearance in normal man after stimulation of GH secretion by GH-releasing hormone and suppression with somatostatin. J Clin Endocrinol Metab. 1989;68(3):535–41.
Freda PU. Somatostatin analogs in acromegaly. J Clin Endocrinol Metab. 2002;87(7):3013–8.
Frohman LA, Bonert V. Pituitary tumor enlargement in two patients with acromegaly during pegvisomant therapy. Pituitary. 2007;10(3):283–9.
Galoiu S, Poiana C. Current therapies and mortality in acromegaly. J Med Life. 2015;8(4):411–5.
Geraedts VJ, Andela CD, Stalla GK, Pereira AM, van Furth WR, Sievers C, et al. Predictors of quality of life in acromegaly: no consensus on biochemical parameters. Front Endocrinol (Lausanne). 2017;8:40.
Gheorghiu ML. Updates in outcomes of stereotactic radiation therapy in acromegaly. Pituitary. 2017;20(1):154–68.
Grunstein RR. Sleep apnea in acromegaly. Ann Intern Med. 1991;115(7):527.
Guo X, Zhao Y, Wang M, Gao L, Wang Z, Zhang Z, et al. The posterior pharyngeal wall thickness is associated with OSAHS in patients with acromegaly and correlates with IGF-1 levels. Endocrine. 2018; https://doi.org/10.1007/s12020-018-1631-3.
Gurel MH, Bruening PR, Rhodes C, Lomax KG. Patient perspectives on the impact of acromegaly: results from individual and group interviews. Patient Prefer Adherence. 2014;8:53–62.
Hall K, Gibbie T, Lubman DI. Motivational interviewing techniques - facilitating behaviour change in the general practice setting. Aust Fam Physician. 2012;41(9):660–7.
Heringer LC, de Oliveira MF, Rotta JM, Botelho RV. Effect of repeated transsphenoidal surgery in recurrent or residual pituitary adenomas: a systematic review and meta-analysis. Surg Neurol Int. 2016;7:14.
Jaffe CA, Barkan AL. Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin N Am. 1992;21(3):713–35.
Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M, et al. Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. Endocrinology. 2008;149(7):3294–305.
Kasuki L, Marques NV, Nuez MJBL, Leal VLG, Chinen RN, Gadelha MR. Acromegalic patients lost to follow-up: a pilot study. Pituitary. 2012;16(2):245–50.
Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51.
Knutzen R, Ezzat S. The cost of medical care for the acromegalic patient. Neuroendocrinology. 2006;83(3–4):139–44.
Kunzler LS, Naves LA, Casulari LA. Cognitive-behavioral therapy improves the quality of life of patients with acromegaly. Pituitary. 2018;21(3):323–33.
Lavrentaki A, Paluzzi A, Wass JAH, Karavitaki N. Epidemiology of acromegaly: review of population studies. Pituitary. 2016;20(1):4–9.
Lim DST, Fleseriu M. The role of combination medical therapy in the treatment of acromegaly. Pituitary. 2016;20(1):136–48.
Liu S, Adelman DT, Xu Y, Sisco J, Begelman SM, Webb SM, et al. Patient-centered assessment on disease burden, quality of life, and treatment satisfaction associated with acromegaly. J Investig Med. 2017;66(3):653–60.
Maione L, Garcia C, Bouchachi A, Kallel N, Maison P, Salenave S, et al. No evidence of a detrimental effect of cabergoline therapy on cardiac valves in patients with acromegaly. J Clin Endocrinol Metab. 2012;97(9):E1714–E9.
Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, et al. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. Eur J Endocrinol. 2017;176(5):645–55.
Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A, et al. Prevalence of vertebral fractures

in men with acromegaly. J Clin Endocrinol Metab. 2008;93(12):4649–55.
Mazziotti G, Bianchi A, Porcelli T, Mormando M, Maffezzoni F, Cristiano A, et al. Vertebral fractures in patients with acromegaly: a 3-year prospective study. J Clin Endocrinol Metab. 2013;98(8):3402–10.
Melmed S. Acromegaly. In: Melmed S, editor. The pituitary. London: Elsevier; 2017. p. 423–66.
Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, et al. Consensus statement: medical management of acromegaly. Eur J Endocrinol. 2005;153(6):737–40.
Melmed S, Kleinberg DL, Bonert V, Fleseriu M. Acromegaly: assessing the disorder and navigating therapeutic options for treatment. Endocr Pract. 2014;20(Suppl 1):7–17; quiz 8–20
Minniti G, Scaringi C, Enrici R. Radiation techniques for acromegaly. Radiat Oncol. 2011;6(1):167.
Montini M, Gianola D, Paganl MD, Pedroncelli A, Caldara R, Gherardi F, et al. Cholelithiasis and acromegaly: therapeutic strategies. Clin Endocrinol. 2010;40(3):401–6.
Morris CJ, Aeschbach D, Scheer FAJL. Circadian system, sleep and endocrinology. Mol Cell Endocrinol. 2012;349(1):91–104.
Nachtigall L, Delgado A, Swearingen B, Lee H, Zerikly R, Klibanski A. Changing patterns in diagnosis and therapy of acromegaly over two decades. J Clin Endocrinol Metab. 2008;93(6):2035–41.
Pantanetti P, Sonino N, Arnaldi G, Boscaro M. Self image and quality of life in acromegaly. Pituitary. 2002;5(1):17–9.
Pivonello R, Auriemma RS, Grasso LFS, Pivonello C, Simeoli C, Patalano R, et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary. 2017;20(1):46–62.
Plunkett C, Barkan A. The care continuum in acromegaly: how patients, nurses, and physicians can collaborate for successful treatment experiences. Patient Prefer Adherence. 2015;9:1093.
Raverot G, Dantony E, Beauvy J, Vasiljevic A, Mikolasek S, Borson-Chazot F, et al. Risk of recurrence in pituitary neuroendocrine tumors: a prospective study using a five-tiered classification. J Clin Endocrinol Metab. 2017;102(9):3368–74.
Salvatori R, Nachtigall LB, Cook DM, Bonert V, Molitch ME, Blethen S, et al. Effectiveness of self- or partner-administration of an extended-release aqueous-gel formulation of lanreotide in lanreotide-naïve patients with acromegaly. Pituitary. 2009;13(2):115–22.
Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35.
Schöfl C, Petroff D, Tönjes A, Grussendorf M, Droste M, Stalla G, et al. Incidence of myocardial infarction and stroke in acromegaly patients: results from the German Acromegaly Registry. Pituitary. 2017;20(6):635–42.
Scott L, Setterkline K, Britton A. The effects of nursing interventions to enhance mental health and quality of life among individuals with heart failure. Appl Nurs Res. 2004;17(4):248–56.
Shan S, Fang L, Huang J, Chan RCK, Jia G, Wan W. Evidence of dysexecutive syndrome in patients with acromegaly. Pituitary. 2017;20(6):661–7.
Sharma MD, Nguyen AV, Brown S, Robbins RJ. Cardiovascular disease in acromegaly. Methodist Debakey Cardiovasc J. 2017;13(2):64–7.
Swearingen B, Barker FG, Katznelson L, Biller BMK, Grinspoon S, Klibanski A, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 1998;83(10):3419–26.
Szczesniak D, Jawiarczyk-Przybylowska A, Rymaszewska J. The quality of life and psychological, social and cognitive functioning of patients with acromegaly. Adv Clin Exp Med. 2015;24(1):167–72.
Terzolo M, Reimondo G, Berchialla P, Ferrante E, Malchiodi E, De Marinis L, et al. Acromegaly is associated with increased cancer risk: a survey in Italy. Endocr Relat Cancer. 2017;24(9):495–504.
Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7.
Trainer PJ, Newell-Price J, Ayuk J, Aylwin S, Rees DA, Drake W, et al. A randomised, open-label, parallel group phase 2 study of antisense oligonucleotide therapy in acromegaly. Eur J Endocrinol. 2018:EJE-18-0138.
Valassi E, Klibanski A, Biller BMK. Potential cardiac valve effects of dopamine agonists in hyperprolactinemia. J Clin Endocrinol Metab. 2010;95(3):1025–33.
Wassenaar MJE, Biermasz NR, Kloppenburg M, AAvd K, Tiemensma J, Smit JWA, et al. Clinical osteoarthritis predicts physical and psychological QoL in acromegaly patients. Growth Hormon IGF Res. 2010;20(3):226–33.
Webb SM. Quality of life in acromegaly. Neuroendocrinology. 2006;83(3–4):224–9.
Webb SM, Badia X. Quality of life in growth hormone deficiency and acromegaly. Endocrinol Metab Clin N Am. 2007;36(1):221–32.
Wilson TJ, McKean EL, Barkan AL, Chandler WF, Sullivan SE. Repeat endoscopic transsphenoidal surgery for acromegaly: remission and complications. Pituitary. 2013;16(4):459–64.
Yedinak C, editor Prevalence of depression in patients with pituitary tumors: association of depression with perceived social capital. In Sigma Theta Tau International's 25th International Nursing Research Congress; 2014 July 24–28; Hong Kong, China.
Yedinak CG, Fleseriu M. Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: a pilot study. Endocrine. 2013;46(3):585–93.
Yedinak C, Pulaski Liebert KJ, Adelman DT, Williams J. Acromegaly: current therapies benefits and burdens. Clin Pract. 2018;15(2)

Key Reading

1. Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3(1):17.
2. Melmed S, Casanueva F, Cavagnini F, Chanson P, et al. Consensus statement: medical management of acromegaly. Eur J Endocrinol. 2005;153(6):737–40.
3. Melmed S, Kleinberg DL, Bonert V, Fleseriu M. Acromegaly: assessing the disorder and navigating therapeutic options for treatment. Endocr Pract. 2014;20(Suppl 1):7–17; quiz 8–20
4. Plunkett C, Barkan A. The care continuum in acromegaly: how patients, nurses, and physicians can collaborate for successful treatment experiences. Patient Prefer Adherence. 2015;9:1093.