Clinical, quality of life, and economic value of acromegaly disease control

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Abstract Although acromegaly is a rare disease, the clinical, economic and health-related quality of life (HRQoL) burden is considerable due to the broad spectrum of comorbidities as well as the need for lifelong management. We performed a comprehensive literature review of the past 12 years (1998–2010) to determine the benefit of disease control (defined as a growth hormone [GH] concentration $\leq 2.5$ µg/l and insulin-like growth factor [IGF]-1 normal for age) on clinical, HRQoL, and economic outcomes. Increased GH and IGF-1 levels and low frequency of somatostatin analogue use directly predicted increased mortality risk. Clinical outcome measures that may improve with disease control include joint articular cartilage thickness, vertebral fractures, left ventricular function, exercise capacity and endurance, lipid profile, and obstructive apnea events. Some evidence suggests an association between controlled disease and improved HRQoL. Total direct treatment costs were higher for patients with uncontrolled compared to controlled disease. Costs incurred for management of comorbidities, and indirect cost could further add to treatment costs. Optimizing disease control in patients with acromegaly appears to improve outcomes. Future studies need to evaluate clinical outcomes, as well as HRQoL and comprehensive economic outcomes achieved with controlled disease.

Keywords Acromegaly · Somatostatin analogues · Octreotide · Lanreotide · Quality of life · Morbidity · Mortality

Introduction

Acromegaly is a chronic, debilitating disorder caused by excessive growth hormone (GH) production predominantly due to a benign pituitary adenoma [1]. The overall annual incidence of acromegaly is approximately 3.3 cases/million, with a prevalence of 58–130 cases/million people [2, 3]. Diagnosing acromegaly is hampered by several factors, including the slow, insidious onset of the disease, and variability of biochemical assays beset by inappropriate reference ranges and conversion factors for GH and insulin-like growth factor (IGF)-1 laboratory tests. Reports in the literature suggest that the mean time from symptom onset to diagnosis is 3–7 years [4, 5].

Treatment options for patients with acromegaly include surgery, radiotherapy, and pharmacologic therapies. A cost-effective treatment strategy appears to be first-line surgery followed when needed by second-line octreotide LAR [6]. The goals of treatment are to achieve disease control, while minimizing adverse effects [1]. Disease control for this paper is defined as a GH concentration less than 2.5 µg/l and a normal, age-adjusted IGF-1 level. Many studies report outcomes for patients not achieving disease control using this definition. Therefore, comparison of study results is difficult.

Unfortunately, disease control is elusive for many patients with acromegaly. Data from registry studies show
that patients with acromegaly are not effectively treated (Table 1). Specifically, less than 50% of patients in these registry studies achieved disease control [7–9]. Two of these studies exclusively assessed patients treated with medical therapy. In these two studies, only 7 and 24% of patients achieved disease control with primary medical therapy and up to 42% with secondary medical therapy [8, 9].

In these registry studies, patients treated with radiotherapy either alone or with surgery or medical therapy were most likely to achieve disease control [8, 9]. However, the disadvantages of radiotherapy must be considered when evaluating these results. These include a lag time to response (>6 years in most patients), the development of hypopituitarism in over 50% of patients, and the risk of cerebrovascular events/stroke (21% at 20 years) and secondary brain tumors (2% at 20 years) [10–13].

In general, study results suggest an improvement in several outcomes in patients who lower their GH and/or IGF-1 concentrations with treatment compared to baseline. Less clear is the impact of disease control on health-related quality of life (HRQoL) and economic outcomes. A clear understanding of the potential benefits of disease control, and how this may translate into policy, reimbursement, and clinical decision-making, could improve outcomes for patients with acromegaly. Therefore, we conducted a study to determine the clinical, HRQoL, and economic benefits of achieving disease control in patients with acromegaly. To our knowledge, this is the first attempt to systematically review the impact of disease control defined as both a GH < 2.5 μg/l and normal age-adjusted IGF-1 levels on these outcomes. We sought to answer the following questions: Do patients with controlled disease live longer than patients with uncontrolled disease? Are comorbidities decreased in patients with controlled compared to uncontrolled disease? Is HRQoL improved in patients with controlled compared to uncontrolled disease? Finally, is there an economic benefit associated with disease control?

### Methods

A comprehensive literature review of the past 12 years (1998–2010) was conducted in MEDLINE, EMBASE, Econlit, and PsychInfo using the search terms acromegaly AND epidemiology, morbidity, mortality, complications, long-term outcomes, costs, economics, QoL, and utilities. Additional searches were conducted to identify clinical trials that evaluated somatostatin analogue, dopamine agonist, or pegvisomant administration on disease control and outcomes. Additional abstracts were identified through article bibliographies and searches in conference proceedings (2003–2009). Prospective or retrospective and cross-sectional studies or meta-analyses that reported on the relationship of comorbidity, long-term outcomes, economic factors, or HRQoL and disease control in adults with acromegaly were retained. Figure 1 summarizes the literature review selection process.

### Table 1

| Treatment | Bex et al. (2007) [8] | Peterse et al. (2008) [7] | Mestron et al. (2004) [9] |
|-----------|----------------------|--------------------------|--------------------------|
|           | Belgium and Luxembourg | Germany | Spain |
| n         | Normal IGF-1 (%) | GH < 2 μg/l (%) | Controlled (%) | n | Normal IGF-1 (%) | GH < 2.5 μg/l (%) | Controlled (%) | n | Controlled (%) | Active disease (%) |
| Surgery   | 125 | 36 | 34 | 554 | 54.3 | 67.3 | 246 | 46.3 | 19.5 |
| Radiotherapy | 20 | 50 | 50 | NR | NR | 29 | 34.5 | 44.8 |
| Primary medical therapy | 74 | 31 | 46 | NR | NR | 113 | 7.1 | 92.9 |
| SSA       | 57% | NR | NR | 28 | 145 | 36.3 | 30.5 |
| Dopamine agonist | 15 | NR | NR | 13 | NR | NR |
| Secondary medical therapy | 121 | 53 | 49 | 42 |
| Surgery   | 65 | 52 | 56 | 37 | 277 | 35.7 | 64.3 |
| Radiotherapy | 4 | 25 | 25 | 0 | NR | NR | 42 | 11.9 | 88.1 |
| Surgery + radiotherapy | 52 | 59 | 45 | 52 | 359 | 27.3 | 72.4 |
| SSA followed by surgery | 93 | 62.9 | 68.4 |
| Surgery followed by SSA | 34 | 24.1 | 45.5 |

GH growth hormone, IGF-1 insulin-like growth factor-1, NR not reported, SSA somatostatin analogue

* 68.3% of patients treated with SSA; 31.4% treated with dopamine agonists; bPercentages may not add up to 100% due to missing data; cTwo patients received dopamine agonists in conjunction with SSA
Do patients with controlled disease live longer?

Overall, mortality is increased in patients with acromegaly [14–22] (Fig. 2; [23, 24]). Results from two meta-analyses suggest that disease control is inversely related to mortality; as disease control improves mortality decreases [23, 24]. Factors found to decrease mortality included disease remission, decreased GH concentrations, normalized IGF-1 concentrations, and increased somatostatin analogue use (Table 2) [23]. These studies also suggest that achieving disease control has the potential to essentially normalize mortality in the acromegaly patient to that of the general population [24].

One exception may be when radiotherapy is included as part of treatment. The meta-analysis by Dekkers et al. found higher mortality in studies before 1995 when patients were more likely to receive radiotherapy as primary treatment [24]. Similarly, Sherlock et al. found a 2-fold increase in mortality in acromegaly patients treated with radiotherapy compared with the general population (SMR 2.1; 95% CI, 1.7–2.6; \( P = 0.006 \)) [25]. Specifically, in patients who received radiotherapy, there was a significantly higher increase in the risk of cerebrovascular deaths (SMR 4.1; 95% CI, 2.3–6.6; \( P = 0.034 \)) [25].

Are comorbidities decreased with controlled disease?

Many patients with acromegaly have untreated disease for several years prior to diagnosis and a spectrum of morbidities are apparent. In one study, 40% of patients at diagnosis had multiple comorbidities [4]. Some, but not all, of these comorbidities can be reversed upon cure or control of the patient’s condition [2]. Results from several studies show significant improvements in a number of key acromegaly comorbidities when disease control is achieved (Table 3).

Glucose metabolism

Altered glucose metabolism in patients with acromegaly varies from impaired glucose tolerance (16–46% of patients) to overt diabetes mellitus (19–56% of patients) [26]. Glucose-related metabolic abnormalities can be reversed in patients with acromegaly when GH and IGF-1 concentrations are controlled by either surgery or administration of pharmacologic therapy [33]. Surgery improves glucose tolerance and pegvisomant appears to improve insulin sensitivity and carbohydrate metabolism [26].
Table 2 Influence of disease control and somatostatin analogue use on mortality in patients with acromegaly [23]

| Acromegaly population | SMR (95% CI) | Risk ratio (P value) |
|------------------------|--------------|---------------------|
| Remission in >70% of patients | 1.2 (1.0–1.5) | 1.7 (<0.05) |
| Remission in <70% of patients | 2.0 (1.6–2.3) |                |
| GH < 2.5 μg/l | 1.1 (0.9–1.4) | 1.7 (<0.05) |
| GH > 2.5 μg/l | 1.9 (1.5–2.4) |                |
| Normal IGF-I | 1.1 (0.9–1.4) | 2.3 (<0.05) |
| Increased IGF-I | 2.5 (1.6–4.0) |                |
| Somatostatin analogue use in >30% of patients | 1.2 (1.0–1.5) | 1.7 (<0.001) |
| Somatostatin analogue use in <30% of patients | 2.0 (1.6–2.3) |                |

CI confidence interval, GH growth hormone, IGF-1 insulin-like growth factor-1, SMR standardized mortality ratio

Administration of a somatostatin analogue can improve insulin resistance induced by elevated GH levels [26], and may reduce insulin needs in overt diabetes. However, somatostatin therapy may also decrease islet cell insulin secretion thereby worsening glucose-related metabolic abnormalities [34]. Nevertheless, in most patients, these effects counterbalance each other and patients maintain an euglycemic state.

Cardiovascular effects/hypertension

The hallmark cardiac effect in patients with acromegaly is concentric biventricular hypertrophy due to thickened cardiac walls [26]. Cardiac hypertrophy can occur in patients with acromegaly in the absence of hypertension but is further aggravated by hypertension and glucose abnormalities [26]. In fact, the most important factor in the development of acromegalic cardiac hypertrophy is arterial hypertension [35]. Other cardiovascular effects that occur in patients with acromegaly include arrhythmias such as ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch block, and cardiac valve disease [36].

Treatment of acromegaly can slow cardiac disease progression and ultimately decrease cardiovascular morbidity and mortality [26]. Data from numerous studies show decreased left ventricular hypertrophy [30, 37–41], improvement in diastolic function [30, 37, 39–43], no change or improved systolic function [30, 37, 39–43], decreased heart rate [30, 38, 43], and decreased arrhythmias [41] following treatment with a somatostatin analogue. Table 4 highlights cardiac function endpoints from one study as an example of what might be achieved with disease control in patients with acromegaly [29].

Furthermore, in terms of impact on hypertension, acromegaly patients with controlled disease (defined as a normal IGF-1 concentration) have shown lower systolic (P = 0.04) and diastolic (P = 0.002) blood pressure values compared to those with uncontrolled disease [44].

Skeletal system complications

The most frequent complaint by patients with acromegaly is arthropathy [26]; up to 70% of patients with acromegaly have aural complications at diagnosis. It is currently unknown whether GH and IGF-1 control can reverse arthropathy in patients with acromegaly, however, improvement in signs and symptoms was demonstrated [45, 46]. Improvements observed with disease control include decreased carpal tunnel syndrome and a reduction in joint space thickness, as measured by articular cartilage thickness via ultrasound [26, 31, 47, 48] (Fig. 3) [31].

Vertebral fractures also appear to be decreased in patients with controlled compared to uncontrolled disease [32]. In this study, patients with controlled disease had a 33% fracture rate compared with an 80% fracture rate in patients with uncontrolled disease. In fact, patients with uncontrolled acromegaly experienced fractures even with normal bone mineral density, suggesting that normal bone mineral density is not protective against vertebral fractures in patients with uncontrolled disease. Patients with controlled disease had a 2.4-fold lower fracture rate compared with uncontrolled disease (P < 0.008).

Sleep apnea

Sleep apnea syndrome is defined as the presence of 5–10 sleep apnea episodes or hypopneas of at least 10 seconds duration/hour of nocturnal sleep [49]. Patients with acromegaly can have central, obstructive, or mixed sleep apnea, with obstructive sleep apnea being the most common form.

Results of some studies suggest an improvement in sleep apnea in patients achieving disease control [26, 28, 33]. In a small cross-sectional study, Davi et al. found that a higher proportion of patients with uncontrolled compared to controlled disease had obstructive sleep apnea (55 and 39%, respectively) [28]. Additionally, the average number of obstructive apnea events/hour was roughly 4 times higher among those with uncontrolled disease. Somatostatin analogue administration may be beneficial in some patients, particularly those with mixed or central sleep apnea [26].

Lipid metabolism

Achievement of disease control and treatment with somatostatin analogue therapy appears to have beneficial
effects on lipid metabolism, with studies reporting significant decreases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels and increases in high-density lipoprotein (HDL) associated with octreotide therapy [38, 50, 51]. Similar results are reported following treatment with lanreotide [52]. In a study designed to determine the effect of disease control on lipid metabolism, patients with controlled versus uncontrolled acromegaly had significantly lower triglycerides ($153.1 \pm 64.5$ vs. $223.4 \pm 107.4$ mg/dl; $P < 0.001$), very low-density lipoprotein (VLDL) cholesterol ($11\%$ decrease in LDL ($P = 0.01$), $31\%$ decrease in triglycerides ($P < 0.001$), $61\%$ decrease in VLDL ($P < 0.001$), $70\%$ decrease in Lp(a) ($P = 0.023$), $53\%$ decrease in HOMA-IR ($P = 0.032$).
Table 4  Improvement in cardiac function with disease control [29]

| Variable     | Untreated | Uncontrolled | Well controlled | Cured          |
|--------------|-----------|--------------|-----------------|----------------|
| IVSD (mm)    | 13.1 ± 1.6| 13.8 ± 1.1   | 9.6 ± 0.5              | 10.6 ± 1.3     |
| LVM (g)      | 250 ± 48  | 314 ± 57     | 201 ± 20              | 199 ± 43       |
| LVMi (g/m²)  | 126.0 ± 22.5| 153 ± 27.7 | 99.6 ± 9.5              | 100.3 ± 19.5   |
| FS (%)       | 30.9 ± 2.5| 29.9 ± 2.6   | 36.8 ± 1.7              | 37.4 ± 1.4     |
| LVEF (%)     | 57.8 ± 3.8| 59.7 ± 2.81  | 72.4 ± 2.6              | 73 ± 1.8       |

FS: fractional shortening, IVSD: inter-ventricular septum diameter, LVEF: left ventricular ejection fraction, LVM: left ventricular mass, LVMi: LVM index, LVM/body surface area

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|                  | untreated versus well controlled; | uncontrolled versus well controlled; | uncontrolled versus cured; | untreated versus cured |
|------------------|-----------------------------------|--------------------------------------|-----------------------------|------------------------|
|                  | P < 0.05                           | P < 0.05                             | P < 0.05                    | P < 0.5                |

Is HRQoL improved with controlled disease?

Four published studies compared HRQoL in patients with controlled and uncontrolled acromegaly using the AcroQoL instrument [53–56]. The AcroQoL is a disease-specific questionnaire designed to evaluate HRQoL in patients with acromegaly (Table 5) [57]. A significant difference between AcroQoL scores in controlled and uncontrolled patients was found only in the study by Trepp et al. [54]. This was the smallest of the four studies, enrolling only 33 patients with acromegaly; 21 patients (64%) were classified as being in remission (random GH value or a nadir GH value following an oral glucose tolerance test [OGTT] lipoprotein (VLDL) cholesterol (44.2 ± 14.3 vs. 112.8 ± 22.2 mg/dl; P < 0.001), and lipoprotein (a) (25.5 ± 15.8 vs. 85.1 ± 56.1 mg/dl; P = 0.023) and significantly higher HDL cholesterol (45.3 ± 14.0 vs. 44.6 ± 9.9 mg/dl; P < 0.001) concentrations [27].

Table 5  The AcroQoL questionnaire [57]

Scale 1: Physical

- My legs are weak
- I get depressed
- I have problems carrying out my usual activities
- The illness affects my performance at work or in my usual tasks
- My joints ache
- I am usually tired
- I feel like a sick person
- I feel weak

Scale 2–1: Psychological/appearance

- I feel ugly
- I look awful in photographs
- I look different in the mirror
- Some parts of my body (nose, feet, hands…) are too big
- I have problems doing things with my hands, for example, sewing or handling tools
- I snore at night
- It is hard for me to articulate words due to the size of my tongue

Scale 2–2: Psychological/personal relations

- I avoid going out very much with friends because of my appearance
- I try to avoid socializing
- I feel rejected by people because of my illness
- People stare at me because of my appearance
- I have problems with sexual relationships
- The physical changes produced by my illness govern my life
- I have little sexual appetite

Scales measured in frequency of occurrence (always, most of the time, sometimes, rarely, never) or degree of agreement (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree)

<1 μg/l and normal IGF-1 levels, six patients (18%) as having active disease, and the remaining six patients (18%) as having discordant results. Patients with active disease
had significantly lower total AcroQoL scores \( (P = 0.01) \) and lower scores on the physical \( (P = 0.021) \) and psychological scales \( (P = 0.023) \), and the personal relations subscale \( (P = 0.042) \) suggesting improved HRQoL with disease control.

Is there an economic benefit with disease control?

Two studies compared the economic burden of controlled and uncontrolled acromegaly \([58, 59]\). Both studies evaluated direct costs from the European perspective. No high-quality studies were identified in the United States that specifically assessed patient costs with controlled versus uncontrolled disease.

Didoni et al. performed a cost-of-illness study assessing health resource consumption due to acromegaly and associated comorbidities \([58]\). This retrospective study evaluated approximately 7 years of data obtained from 142 patients treated at two hospitals in northern Italy in the Italian Healthcare Service. Direct costs analyzed included those for hospitalizations, diagnostic and laboratory tests, specialist visits, and drugs. Ninety-one patients had controlled disease (GH following an OGTT < 1 µg/l and IGF-1 normal for age) and 43 patients had uncontrolled disease (GH following an OGTT > 1 µg/l and/or an increased IGF-1 for age). Total annual costs were approximately 1.6 times higher in patients with uncontrolled disease (GH following an OGTT > 1 µg/l and/or an increased IGF-1 for age). Total annual costs were €12,533 compared to controlled disease (€7,968). Drug costs accounted for most of the cost differences between the controlled and uncontrolled patients. Drug costs were 1.74 times higher in patients with uncontrolled versus controlled disease. Although the rate of overall comorbidities was similar between the controlled and uncontrolled groups, the rate of diabetes was 17% higher and hypertension 44% higher in the uncontrolled than controlled group. The economic value of reducing rates of diabetes and hypertension could be substantial, as this study suggests 60% higher costs related to these two comorbidities in patients with uncontrolled acromegaly.

Luque-Ramírez et al. determined costs for 11 acromegaly patients with invasive pituitary adenomas \([59]\). Data were analyzed for 4 years following diagnosis. Costs were determined using data from the Centre for Health Economics and Social Policy Studies and the Official College of Pharmacists in Spain (year not specified). All patients underwent transsphenoidal pituitary surgery; 10 patients also required medical therapy (somatostatin analogue \( n = 6 \); bromocriptine \( n = 3 \); somatostatin analogue plus bromocriptine \( n = 1 \)); six patients also required fractionated radiotherapy. A total of five patients had controlled disease (GH < 2 µg/l and an IGF-1 level normal for age) and six patients had uncontrolled disease (five patients had a GH > 2 µg/l but normal IGF-I and one patient had a GH < 2 µg/l but an elevated IGF-I level). The mean annual global cost/patient was €7,570. Interestingly, in this study annual global treatment costs were higher in patients with controlled disease (€9,874) versus uncontrolled disease (€7,072). However, three patients with uncontrolled disease received only bromocriptine, a lower cost therapy than somatostatin analogues. Analysis of somatostatin analogue therapy costs found higher treatment costs in patients with uncontrolled compared to controlled disease. Not surprisingly, annual treatment costs were lowest for the patient cured with surgery alone (€1,343).

Discussion

Disease burden is defined as the impact of a health problem measured by financial cost, mortality, morbidity, or other indicators \([60]\). The objective of this assessment was to determine acromegaly disease burden as measured by clinical, HRQoL, and economic outcomes. Results from this critical literature review show that the clinical burden of controlled and uncontrolled acromegaly is fairly well defined in terms of mortality. In comparison, the burden of controlled and uncontrolled acromegaly in terms of morbidity, HRQoL, and direct and indirect costs is less defined. Few studies assessed the impact of disease control on direct medical care costs and HRQoL. No studies assessed the impact of disease control on indirect costs such as work productivity/employment.

A review of data from registry studies shows that the majority of patients with acromegaly do not achieve disease control \([7–9]\). Results from this review document the benefits of controlled compared with uncontrolled disease. Mortality, morbidity, and costs are all decreased in patients with controlled compared to uncontrolled disease. The effect of controlled disease on HRQoL is less clear. Results from one study suggest improved HRQoL in patients with controlled compared to uncontrolled disease \([54]\). Several possibilities may explain why an association between HRQoL and disease control is not evident. First, the AcroQoL tool may not be sufficiently sensitive to detect differences in HRQoL between controlled and uncontrolled patients. Second, patients with acromegaly continue to have cosmetic and orthopedic deformities because of the lag time encountered to diagnosis, and in many cases these are not reversed with treatment. The effect of these deformities on HRQoL is not known. Finally, the influence of comorbidities on HRQoL measures is not known. Unfortunately, the rarity of this disorder makes evaluating the influence of comorbidities difficult.
Conceptualizing an outcomes tool for acromegaly

When presented with an acromegaly diagnosis, patients typically have numerous questions concerning how this disease will impact the rest of their life. Healthcare providers are in need of a tool to aid them in addressing these questions. This tool needs to incorporate data on clinical outcomes such as morbidity and mortality, HRQoL outcomes, and economic outcomes including direct and indirect costs. This tool would benefit patients, healthcare providers and policy makers evaluating treatment options for this patient population. Major gaps in the existing literature surrounding health outcomes analyses in acromegaly include lack of integration of the impact that comorbidities have on mortality, costs, HRQoL, and individual patient productivity both before and after diagnosis in situations of suboptimal disease control.

Figure 4 outlines a conceptual model for assessing relevant health economic outcomes in acromegaly. For example, the economic impact of reducing comorbidities with strict biochemical control could be considered (e.g., cardiac/hypertension, diabetes). One approach, in the absence of acromegaly-specific data, would be to assess the average treatment cost for each comorbidity from published medical literature. For example, the cost of a vertebral fracture is estimated at more than $3,800 in the first year [61], the annual/patient cost of cardiovascular disease is more than $6,300/year [62], the cost of sleep apnea is more than $2,200 [63], and the cost of arthropathy is more than $3,100 annually [64]. These patients are at risk of multiple comorbidities with suboptimal control, thus, the additive economic impact of reduced comorbidities may be significant. In addition, shortening the latency period between onset of disease, diagnosis, and treatment will likely reduce the burden of high-cost complications that may not be fully reversible such as diabetes, hypertension, and facial deformity. There is a clear need to develop a full assessment of the economic burden of acromegaly, as well as the comparative effectiveness of available treatment options using both economic modeling and retrospective

Fig. 4 Conceptual model of the value of disease control in acromegaly
data analysis. This could be achieved by analyzing claims data or undertaking extensive chart reviews.

Conclusions

Although the benefits of acromegaly disease control are well-known, there are many unanswered questions about the benefits of controlled compared with uncontrolled disease regarding the dimensions of morbidities, HRQoL, and costs. Benefits of controlled disease, defined as a GH < 2.5 µg/l and a normal age-adjusted IGF-1 level, must clearly be defined. The availability of a tool to aid healthcare providers, policy makers, and patients in determining the effects of disease control on clinical, HRQoL, and economic outcomes is needed. Future studies need to evaluate clinical outcomes and also HRQoL and economic outcomes achieved with controlled disease. Incorporation of these data into a tool, which healthcare providers and policy makers could use to evaluate treatment options and determine the most effective treatment plans would be invaluable for patients.

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References

1. Melmed S (2006) Medical progress: acromegaly. N Engl J Med 355:2558–2573
2. Holdaway IM, Rajasoorya C (1999) Epidemiology of acromegaly. Pituitary 2:29–41
3. Reddy R, Hope S, Wass J (2010) Acromegaly. BMJ 341:c4189
4. Nachtigall L, Delgado A, Swearingen B, Lee H, Zerikly R, Klibanski A (2008) Changing patterns in diagnosis and therapy of acromegaly over two decades. J Clin Endocrinol Metab 93:2035–2041
5. Oranje MR, Fram NR, Herman-Bonert V, Melmed S (2000) Pituitary tumor registry: a novel clinical resource. J Clin Endocrinol Metab 85:168–174
6. Biermasz NR, Roelfsema F, Pereira AM, Romijn JA (2009) Cost-effectiveness of lanreotide autogel in treatment algorithms of acromegaly. Expert Rev Pharmacoecon Outcomes Res 9:223–234
7. Petersenn S, Buchfelder M, Reinecke M, Strasburger CM, Hohlohm R, Quabbe HJ, Plockinger U (2008) Results of surgical and somatostatin analog therapies and their combination in acromegaly: a retrospective analysis of the German acromegaly register. J Clin Endocrinol Metab 195:525–532
8. Bex M, Abs R, T’Sjoen G, Moschi C, Velkeniers B, Maemans K, Maiter D (2007) AcoBel: the Belgian registry on acromegaly: a survey of the ‘real-life’ outcome in 418 acromegalic subjects. J Clin Endocrinol Metab 157:399–409
9. Mestrion A, Webb SM, Astorga R, Benito P, Catala M, Gazzambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, De PP, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora I, Albarada M, Gilabert M (2004) Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish acromegaly registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol Metab 151:439–446
10. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Lawes E, Schlechte J, Vance ML, Ho K, Giustina A (2009) Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94:1509–1517
11. Feelders RA, Hofland LJ, van Aken MO, Nijgers SJ, Lamberts SW, de Herder WW, van der Lely A-J (2009) Medical therapy of acromegaly: efficacy and safety of somatostatin analogues. Drugs 69:2207–2226
12. Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B (2002) Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol 57:713–717
13. Minniti G, Gilbert DC, Brada M (2009) Modern techniques for pituitary radiotherapy. Rev Endocr Metab Disord 10:135–144
14. Beauregard C, Truong U, Hardy J, Serri O (2003) Long-term outcome and mortality after transspHENoidal adenectomy for acromegaly. J Clin Endocrinol Metab 58:86–91
15. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS (2004) Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 89:1613–1617
16. Trepp R, Stettler C, Zwahlen M, Seiler P, Diem P, Christ ER (2005) Treatment outcomes and mortality of 94 patients with acromegaly. Acta Neurochir 147:243–251
17. Kauppinen-Makelin R, Sane T, Reunanen A, Valimaki MJ, Niisanen L, Markkanen H, Lohytniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J, Voutilainen E (2005) A nationwide survey of mortality in acromegaly. J Clin Endocrinol Metab 90:4081–4086
18. Aboch S, Tyrell JB, Lamborn KR, Hannegan LT, Applebury CW, Wilson CB (1998) Transepithelial microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. J Clin Endocrinol Metab 83:3411–3418
19. Biermasz NR, Dekker FW, Pereira AM, Van Thiel SW, Schutte PJ, Van DH, Romijn JA, Roelfsema F (2004) Determinants of survival in treated acromegaly in a single center: predictive value of serum insulin-like growth factor I measurements. J Clin Endocrinol Metab 89:2789–2796
20. Holdaway IM (2007) Excess mortality in acromegaly. Horm Res 68(Suppl 5):165–172
21. Swearingen B, Barker FG, Katsnelson L, Biller BL, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT (1998) Long-term mortality after transspenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83:3419–3426
22. Shimatsu A, Yokogoshi Y, Saito S, Shimizu N, Irie M (1998) Long-term survival and cardiovascular complications in patients with acromegaly and pituitary gigantism. J Endocrinol Invest 21(Suppl 8):55–57
23. Holdaway IM, Bolland MJ, Gamble GD (2008) A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol Metab 159:93–98
24. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP (2008) Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 93:61–67
25. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, Hawkins MM, Bates AS, Stewart PM (2009) ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. J Clin Endocrinol Metab 94:4216–4223
26. Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25:102–152
diseases, injuries, and risk factors in 1990 and projected to 2020. 
Harvard University Press, Cambridge

61. Tosteson AN, Burge RT, Marshall DA, Lindsay R (2008) Ther-
apies for treatment of osteoporosis in US women: cost-effec-
tiveness and budget impact considerations. Am J Manag Care 14:605–615

62. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson 
TB, Flegal K, Ford E, Furie K, Go A, Greenland K, Haase N, 
Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, 
Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, 
Nichol G, O’Donnell C, Roger V, Rosamond W, Sacco R, Sorlie 
P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, 
Wong N, Wylie-Rosett J, Hong Y (2009) Heart disease and stroke 
statistics–2009 update: a report from the American heart associ-
ation statistics committee and stroke statistics subcommittee. 
Circulation 119:480–486

63. Kapur V, Blough DK, Sandblom RE, Hert R, de Maine JB, 
Sullivan SD, Psaty BM (1999) The medical cost of undiagnosed 
sleep apnea. Sleep 22:749–755

64. Ray GT, Collin F, Lieu T, Fireman B, Colby CJ, Quesenberry CP, 
Van den Eeden SK, Selby JV (2000) The cost of health condi-
tions in a health maintenance organization. Med Care Res Rev 
57:92–109