PRACTICE GUIDELINES

Canadian Consensus Guidelines for the Diagnosis and Management of Acromegaly

Shereen Ezzat, MD, FRCP(C), FACP1;
Omar Serri, MD, PhD, CSPQ2;
Constance L. Chik, MD, FRCP(C)3;
Michelle D. Johnson, MD, FRCP(C)4;
Hugues Beauregard, MD, FRCP(C)5;
Sorana Marcovitz, MD, FRCP(C)6;
B.L. Gregoire Nyomba, MD7;
Juan Rivera Ramirez, MD8;
Ehud Ur, MB, BS, MRCP9

1University of Toronto; Mount Sinai Hospital, Toronto, Ontario.
2University of Montreal; CHUM, Hôpital Notre-Dame, Montreal, Quebec.
3University of Alberta Heritage Medical Research Centre, Edmonton, Alberta.
4St. Paul's Hospital, Vancouver, British Columbia.
5McGill University; Montreal General Hospital, Montreal, Quebec.
6University of Manitoba; Health Sciences Centre, Winnipeg, Manitoba.
7Dalhousie University; Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

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Abstract

Acromegaly is a chronic condition associated with considerably increased morbidity and mortality if left unchecked. In December 2004, a national meeting was held to discuss the diversity in clinical practice across the country in diagnosing and treating patients with acromegaly, as well as to seek consensus on a number of management principles. The group reviewed recent guidelines and discussed issues of diagnosis, treatment, monitoring and treating comorbidities to seek a Canadian consensus on the management of this rare disorder.

Consensus was that diagnosis should include clinical and biochemical findings, but is hinged on establishing GH hypersecretion with IGF-I and OGTT testing. Treatment has traditionally included surgical resection or debulking, along with adjunctive medical therapy (primarily somatostatin analogues), if necessary, to normalize GH levels. The option of primary medical therapy in managing this condition has recently emerged and can be justified for non-surgical candidates or for those in whom surgery is not expected to be curative. Overall, improved screening practices and superior epidemiological data are required, since timely diagnosis and appropriate treatment are crucial for reducing the potentially debilitating effects of this chronic, progressive disease. The current evidence also supports the need for long-term follow-up of disease activity and comorbidities in diagnosed patients.

A national meeting was held to discuss the diversity in clinical practice across the country in diagnosing and treating patients with acromegaly, as well as to seek consensus on a number of management principles. After brief reviews of the most recent Canadian guidelines and the 2004 guidelines published by the American Association of Clinical Endocrinologists, the group was asked to specifically examine the issues of diagnosis, treatment, monitoring and treating comorbidities and seek a Canadian consensus on prac-
practice. This paper summarizes the working group’s findings and the points of consensus that were achieved.

**Introduction**

Acromegaly is a relatively rare disorder characterized by the hypersecretion of growth hormone (GH), usually the result of a pituitary somatotroph adenoma. GH stimulates production of insulin-like growth factor-I (IGF-I), the levels of which are also elevated in acromegaly. Its clinical presentation in advanced stages may include coarsened facial features, protruding jaw, widely spaced teeth, and large hands and feet. Patients may complain of headache and/or fatigue. Other manifestations may include unexplained hypertension, cardiovascular disease, diabetes mellitus, sleep apnea, hyperhidrosis, hypogonadism, carpal tunnel syndrome, and/or hypertrophic arthropathy. Symptoms of tumour growth may include headache, visual field defects, and/or cranial nerve entrapment.

Acromegaly is a chronic, progressive, potentially debilitating condition associated with significant morbidity and increased mortality. The mortality rate for uncontrolled disease activity is 2-4 times higher than that of the general population, principally because of the increased risk of cardiovascular disease. This increased mortality can be reversed if the elevated GH and IGF-I levels are successfully normalized. The increased morbidity is due to the metabolic effects of elevated GH and IGF-I, and to the mass effects of the pituitary adenoma. Depending on the comorbid condition, effects may also be partly reversible with normalization of hormone levels. For example, soft-tissue overgrowth can be at least partly diminished, but correcting bone enlargement may require surgical intervention.

The estimated annual incidence, based on relatively old data, is 3-4 cases per million. This is probably an underestimate, but with no North American data, the true prevalence of the disease remains unclear. What is known is that, on average, those diagnosed with acromegaly have had the disease for nearly 10-15 years. As a result, the majority of patients are diagnosed at an advanced stage of their disease when their pituitary tumours are classified as macroadenomas (>10 mm in diameter). Improved screening and more accurate epidemiological data are needed to assess better the extent of the problem and improve diagnosis and treatment methods. Timely diagnosis and appropriate treatment are crucial to reducing the increased morbidity and mortality associated with this chronic, progressive disease.

With the publication of newer data and developments in available treatment modalities since the pub-

**TABLE 1A. Quality of evidence**

<table>
<thead>
<tr>
<th>Diagnostic studies</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>i) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard)</td>
</tr>
<tr>
<td></td>
<td>ii) Independent interpretation of the diagnostic standard (without knowledge of the test result)</td>
</tr>
<tr>
<td></td>
<td>iii) Selection of people suspected (but not known) to have the disorder</td>
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<tr>
<td></td>
<td>iv) Reproducible description of both the test and diagnostic standard</td>
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<td></td>
<td>v) At least 50 patients with and 50 patients without the disorder</td>
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<tr>
<td>Level 2</td>
<td>Meets 4 of the Level 1 criteria</td>
</tr>
<tr>
<td>Level 3</td>
<td>Meets 3 of the Level 1 criteria</td>
</tr>
<tr>
<td>Level 4</td>
<td>Meets 1 or 2 of the Level 1 criteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic studies</th>
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<tbody>
<tr>
<td>Level 1A</td>
<td>• Systematic overview or meta-analysis of high-quality randomized, controlled trials</td>
</tr>
<tr>
<td></td>
<td>• Appropriately designed randomized, controlled trial with adequate power to answer the question posed by the investigators</td>
</tr>
</tbody>
</table>

| Level 1B           | Nonrandomized clinical trial or cohort study with indisputable results |
| Level 2            | Randomized, controlled trial or systematic overview that does not meet Level 1 criteria |
| Level 3            | Nonrandomized clinical trial or cohort study |
| Level 4            | Other |
| Prognostic studies |  |
| Level 1            | a) Inception cohort of patients with the condition of interest, but free of the outcome of interest |
|                    | b) Reproducible inclusion/exclusion criteria |
|                    | c) Follow-up of at least 80% of subjects |
|                    | d) Statistical adjustment for extraneous prognostic factors (confounders) |
|                    | e) Reproducible description of outcome measures |
| Level 2            | Meets criterion a) above, plus 3 of the other 4 criteria |
| Level 3            | Meets criterion a) above, plus 2 of the other criteria |
| Level 4            | Meets criterion a) above, plus 1 of the other criteria |

**TABLE 1B. Grades of recommendations**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Grade A</td>
<td>The best evidence was at Level 1</td>
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<tr>
<td>Grade B</td>
<td>The best evidence was at Level 2</td>
</tr>
<tr>
<td>Grade C</td>
<td>The best evidence was at Level 3</td>
</tr>
<tr>
<td>Grade D</td>
<td>The best evidence was at Level 4 or consensus</td>
</tr>
</tbody>
</table>
TABLE 2. Differences from the 2000 Canadian guidelines\textsuperscript{2}

- Call for improved screening, more current North American epidemiological data.
- Definition of target populations for screening.
- Recommendation of IGF-I or OGTT (with GH) as screening test, depending on local availability and facilities.
- Recommendation of IGF-I and OGTT (with GH), plus clinical findings, for diagnosis.
- Two new treatment algorithms, including one devoted to medical therapy.
- Recommendation for decreased use of non-selective dopamine agonists; bromocriptine no longer recommended.
- Stronger recommendation for use of GH receptor antagonists (pegvisomant).
- Emerging support for primary medical therapy in patients who are not good surgical candidates or for whom surgery is not expected to be curative.
- Discussion of monitoring and treatment of related comorbidities.
- Recommendation to assess and stabilize comorbidities prior to treatment.

TABLE 3. Unexplained constellations of signs and symptoms

Unexplained constellation of common symptoms, including the following\textsuperscript{15}:

- Sweating
- Headaches
- Fatigue
- Arthralgias
- Visual field impairment
- Hypogonadism
- Decreased energy
- Muscular weakness
- Depression
- Decreased libido
- Paresthesiae
- Carpal tunnel syndrome

Unexplained constellation of common signs, including the following\textsuperscript{11}:

- Hypertension
- Sleep apnea
- Diabetes/impaired fasting glucose
- Peripheral neuropathy
- Osteoarthritis
- Carpal tunnel syndrome

Application of the previous Canadian guidelines document,\textsuperscript{3} the need for an updated consensus document on the diagnosis and treatment of acromegaly was identified. The levels of evidence and grading of recommendations are shown in Tables 1.

This consensus document builds on those previous Canadian guidelines\textsuperscript{3} (Table 2) and includes new treatment algorithms and updated treatment recommendations.

This document also presents a Canadian alternative to the recently published U.S. guidelines,\textsuperscript{2} taking into account local realities in its screening and diagnosis recommendations, providing treatment approaches based on the context and experience of Canadian experts (e.g., recommending addition or substitution of the dopamine agonist cabergoline prior to the use of a GH receptor antagonist), furnishing new treatment algorithms and pointing to Canadian guidelines for the monitoring and treatment of related comorbidities.

Screening and Diagnosis

Screening

Because acromegaly is slowly progressive, and because signs and symptoms are common and physical changes may initially be subtle, diagnosis has tended to occur late in the course of the disease.\textsuperscript{16} One study found the mean delay in diagnosis to be 9.2 yr.\textsuperscript{15} Such delays have serious repercussions. First, because acromegaly is such a disfiguring condition, by the time the diagnosis is made the patient’s physical appearance has often been altered irreversibly, and the metabolic and cardiovascular effects have taken a toll on the patient’s quality of life and potential survival. Second, diagnosing tumours when they have become macroadenomas reduces the chances for achieving strict control of the disease and increases the chances of damage to the remaining pituitary tissue with currently available therapies. These very important facts show the need for an increased awareness of the early manifestations of the disease among primary care providers, allowing for selective screening of individuals at risk.

Naturally indiscriminate screening of a large population would not be feasible or useful for what is still a relatively rare condition; carefully defining the population to be screened is essential in order to focus inquiry on those patients demonstrating evident signs and/or symptomatology. For this reason, it is recommended to screen a target population that may be at increased risk of harbouring the disease [Grade A, Level 1]. Such a population would include those with a constellation of the following apparently common but unexplained symptoms and signs, including the following: pituitary incidentaloma; recurrent colon polyps; sleep apnea; multiple skin tags; unexplained carpal tunnel syndrome; unexplained and persistent soft-tissue swelling, such as

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hand/foot soft-tissue swelling, jaw enlargement and/or dental malocclusion; unexplained oligomenorrhea or amenorrhea; unexplained hypertrophic osteoarthropathy; impaired glucose tolerance or diabetes mellitus particularly in the absence of a family history; and presenting in combination with any of the above. Constellations of such symptoms and signs are summarized in Table 3.

These features are particularly relevant in patients with acromegaly and should lead to consideration for screening.

Screening should be performed using a serum IGF-I level\(^1\) or a 75 g oral glucose tolerance test (OGTT) with GH levels, depending on local availability and facilities [Grade A, Level 1].

**Diagnosis**

A definitive diagnosis of acromegaly is ideally based on both biochemical and clinical findings. When there are sufficient clinical grounds to suspect a patient has acromegaly, laboratory testing should be performed to confirm elevation of growth hormone and establish a diagnosis. Both the IGF-I and the OGTT are preferred for the purposes of diagnosis: the IGF-I usually as an initial screening test, and the 2-hour OGTT for confirmation.

It should be noted that both IGF-I and OGTT can be used for screening and/or diagnosis, but each has its own limitations that must be taken into account when selecting a test. Nevertheless, testing for acromegaly must also be applicable and practical in the community, and a 2-hour specialized OGTT for growth hormone may not always be available in outreach centres, for example.

In situations in which there is discordance between clinical suspicions and biochemical findings, patients should be referred to an endocrine centre of excellence for further investigation [Grade D, consensus].

**Clinical findings**

Clinical suspicion of acromegaly should be raised when patients present with any of the signs and symptoms mentioned in Screening, above, but especially when they present with a combination of two or more of these findings: soft-tissue swelling, such as hand/foot soft-tissue swelling or enlargement; unexplained carpal tunnel syndrome or other nerve-entrapment syndromes; jaw enlargement and/or dental malocclusion; visual field defects; unexplained and atypical headaches; scalp and forehead skin folding or increase in hat size; nasal polyps; obstructive sleep apnea; unexplained oligomenorrhea or amenorrhea; galactorrhea; unexplained hypertrophic osteoarthropathy; new impaired glucose tolerance or diabetes as described above; and arterial hypertension [Grade A, Level 1].

**Testing**

**IGF-I**

The serum IGF-I test is simple to administer but, given the wide variations in results across laboratories and the lack of standardization of this test across Canada, the results may not always be solely reliable. Standardization of this test is needed, establishing normal age ranges with large cohorts. Until this is the case, the IGF-I test is useful as a screening tool and for diagnosis in conjunction with the 2-hour OGTT [Grade A, Level 1].

**OGTT**

All patients suspected of having acromegaly should undergo a 2-hour OGTT to monitor for growth hormone [Grade A, Level 1]. While IGF-I is simple to administer and can provide evidence of integrated growth hormone secretion, an OGTT is important because it can provide parametric measurement of growth hormone levels over time. It is a relatively simple test to administer, but it may be difficult to perform in outreach centres where there is less experience with this specialized procedure. The OGTT for growth hormone should be conducted for only 2 hours, because of the natural rise in growth hormone that normally occurs following the 2-hour interval.

The 2-hour OGTT test can be performed even in patients with overt diabetes,\(^1\) if it is conducted in a controlled environment in a medical facility; however, physicians may need to be sensitive to patient concerns in these circumstances and explain the reasons behind the test to allay any fears.

A normal GH response during an OGTT is to have at least one value less than 1 µg/L during the 2-hour test. An OGTT in which GH levels consistently remain above 1 µg/L throughout the test, in conjunction with the clinical picture and the results of IGF-I testing, is used to confirm a diagnosis of acromegaly.

**Other testing**

Other testing in conjunction with IGF-I and OGTT for diagnosis may include the following [Grade D, consensus]:

- Growth hormone-releasing hormone (GHRH) measurement for detection of an ectopic source of acromegaly, if this is suspected when no pituitary lesions are visualized despite elevated GH/IGF-I levels.
- Assessment of anterior pituitary function for all patients as a baseline: cortisol, prolactin, thyroid hormones (free thyroxine and thyroid-stimulating hormone), testosterone. Estrogen is not necessary if menses are intact.
- Determination of metabolic status (e.g., calcium, lipid profile, glucose tolerance), depending on the patient’s clinical presentation.

**Imaging**

Magnetic resonance imaging (MRI) is the preferred imaging modality for diagnosis; computed tomography (CT) may be used if MRI is not available or if it cannot be performed (e.g., in a patient with a pacemaker) [Grade D, consensus].

**Treatment**

**Surgical Therapy**

Surgery should be considered as the first-line therapy in all patients with microadenomas and in those with non-invasive macroadenomas (Figure 1) [Grade A, Level 1]. In this group, there is a reasonable (60-80%) chance of remission with surgery alone.\(^7,9,10\) Even when complete resection is not possible, surgical decrease of tumour burden may relieve mass effects, such as vision loss, and possibly lead to more effective use of medical/radiation therapy.\(^17,18\) In cases of invasive macroadenomas, surgery alone is unlikely to normalize GH/IGF-I. Surgery is not recommended where the lesion cannot be identified with certainty. The only major contraindication for surgical treatment is poor medical condition (e.g., poor cardiac and pulmonary function); however, even in these cases patients' overall condition may be improved by medical pre-treatment, making them better future surgical candidates [Grade A, Level 1].\(^7,19\)

The goal of surgery for acromegaly is the normalization of GH and IGF-I levels, leading to alleviation of comorbidities and reduction in symptoms of mass effect (e.g., headache, vision problems).\(^2\) The risks are the general risks of surgery and anesthesia, as well as possible postoperative pituitary insufficiency.\(^20\) Perioperative glucocorticoids are required for patients who have abnormal preoperative morning cortisol levels (<450 nmol/L) or abnormal ACTH test.\(^20\) To minimize risks, surgical resection should be performed in centres with experience in pituitary surgery, and by a multidisciplinary team with extensive experience in this area.\(^21,22\)

In general, surgical prognosis is better for smaller tumours.\(^7,9,20,26-28\) For this reason, improved screening and diagnosis are essential for ensuring that tumours are identified and treated promptly, before reaching the stage of compressive or invasive macroadenomas.

**Medical Therapy**

Developments in medical therapy since the publication of the 2000 Canadian guidelines\(^5\) have included the increased availability of GH receptor antagonists.
(pegvisomant) and better data to support their use, as well as further data to support the decreased use of dopamine agonists.

Candidates for primary medical therapy include those with macroadenomas unlikely to be cured by surgery, and those in poor medical condition, for whom surgery is unlikely to give good response or improved outcome [Grade D, consensus]. Secondary medical therapy should be considered for those in whom surgery has failed (persistently elevated IGF-I levels and non-suppression of GH <1 µg/L during an OGTT) (Figure 2) [Grade A, Level 1].

Somatostatin analogues should be used as first-line medical therapy [Grade A, Level 1]. First-line or second-line therapy with a dopamine agonist (i.e., cabergoline) can be considered in co-prolactin-secreting adenomas and in patients with mildly to moderately elevated IGF-I levels (25-50% above upper limits of normal) [Grade C, Level 3]. A switch to a GH receptor antagonist (i.e., pegvisomant) can be considered in patients in whom other medical therapies have failed [Grade A, Level 1]; however, patients on pegvisomant therapy require special monitoring of the size of the pituitary lesion with MRI. If pegvisomant fails to normalize IGF-I levels or is contraindicated because of proximity of tumour to adjacent structures, radiotherapy should be considered (see Radiation Therapy, below).

Somatostatin analogues
The first-generation SSAs (e.g., octreotide) have a short half-life, requiring multiple daily subcutaneous injections. They have been shown to reduce GH and IGF-I in 50-70% of patients.29-31 These agents result in maximal GH suppression in 2 hours, and the effect lasts approximately 6 hours.

Second-generation SSAs (octreotide LAR, lanreotide) have a longer duration of action (once-monthly intramuscular injection) and have clinical benefits similar to the short-acting formulations.32 Patient compliance can also be enhanced because of ease of administration and the more sustained effects of the long-acting formulation. The major barriers to their use are expense23 and the fact that SSA treatment requires administration and monitoring by a healthcare team.

Because of their rapid response and clearing, it may be helpful to use short-acting SSAs to assess potential response and any possible adverse effects before initiating treatment with long-acting SSAs.

SSAs have been shown to relieve acromegaly-related symptoms, such as headaches, sweating and arthralgias, in about 75% of patients. Some studies have shown reduction in tumour size, but in a smaller group of patients (30-50%),34-37 which may make SSAs a good option as secondary therapy following partial response to surgery.

The normalization of GH and IGF-I levels with SSA therapy has also been associated with improvement in left-ventricular cardiac function,38 since persistent high GH has been associated with higher blood pressure and impaired cardiac performance. Octreotide treatment has been associated with decreased prostate size and volume39 and with favourable response in sleep apnea with the long-acting formulation.40

Adverse effects associated with all SSAs include abdominal cramps and diarrhea, but these tend to be temporary. SSAs have also been associated with increased incidence of gallbladder sludge and stones, but this is generally not of major clinical significance. Monitoring of blood glucose is also required to exclude the development of diabetes or glucose intolerance during SSA therapy.

SSAs should be considered as primary therapy for those who refuse surgery or who are poor surgical candidates. Some nonrandomized data have shown that SSAs are effective in the long term in reducing GH and IGF-I in patients who have not had pituitary surgery,29 but the effects of SSAs on long-term acromegaly-related complications and mortality remain to be demonstrated.

Dopamine agonists
Dopamine agonists are now recommended less highly than they were in the previous Canadian guidelines, because they have been shown to be less effective than SSAs or GH-receptor antagonists. Drug-related adverse events associated with this class include GI discomfort and orthostatic hypotension.

Bromocriptine is generally not recommended for medical therapy of acromegaly.2 Cabergoline, a more selective dopamine 2 receptor agonist, may have greater benefit than the other non-selective dopamine agonists in the treatment of this condition. It has been shown to lower IGF-I to <300 µg/L in approximately 35% of patients41,42 (normal ranges: <300 µg/L), and 114-492 µg/L). It may be considered as a first-line treatment in selected cases of co-secreting growth hormone and prolactin adenomas with mild to moderate elevations of IGF-I (25-50% above upper limits of normal). It may also be useful in combination with SSAs in patients in whom SSAs lead to only partial control of the disease.43
GH receptor antagonists
This relatively new class of drugs blocks GH action directly by competing with natural GH for binding with the GH receptor, leading to reduced synthesis of IGF-I.

Pegvisomant is the only agent in this class currently available. Administered daily (10-20 mg sc), it has been shown to reduce and even normalize circulating IGF-I in >90% of patients.44,45 Nonetheless, its long-term effects on tumour growth and comorbidities remain to be established.

Pegvisomant is recommended for those in whom surgery, SSAs and dopaminergic agents have failed.

Radiation Therapy
Radiotherapy should be used following resection of as much of the adenoma as possible and should be viewed as a treatment of last resort, after all other options - surgical and medical - have been shown to be ineffective [Grade A, Level 1]. That is, if pegvisomant and all other medical therapies fail to normalize IGF-I levels following pituitary surgery, radiotherapy should be considered (stereotactic with gamma knife, if possible).

Conventional fractionated radiation may take 10-20 years to reach full effectiveness. In one study, it reduced serum GH to <5 μg/L in 77% of patients (15-year follow-up)46; other studies have shown a reduction to <2.5 μg/L in 25% of patients (5-year follow-up)47 and reduction of IGF-I to normal in 5% after 6.8 yr.48

More recently, stereotactic radiotherapy has been used, including gamma knife radiosurgery. There is some suggestion that stereotactic radiotherapy may lead to earlier biochemical remission49,51 than conventional radiotherapy. In one study, mean time to remission for gamma knife surgery was 1.4 yr, versus 7.1 yr for conventional radiotherapy49; another study demonstrated a mean time to remission of 14 mo with gamma knife surgery.50 It has been shown to lower IGF-I to normal in a number of studies.41,42,49 However, stereotactic methods should be used only when the distance between the tumour and the optic chiasm is >5 mm, because of the potential for vision damage.

The most serious potential complication of radiotherapy is loss of normal pituitary function. Conventional radiotherapy has the highest rates of post-therapeutic hypopituitarism, associated with up to 100% of patients,52 while gamma knife radiosurgery has been associated with lower rates of hypopituitarism (28%).49 Other potential complications include radiation necrosis, loss of vision and development of a secondary malignant lesion. As well, because pituitary irradiation may impair fertility, the pros and cons of this therapeutic approach should be discussed in detail with young adults before beginning treatment.

Monitoring and Treating Comorbidities
Because of GH hypersecretion and its related metabolic effects, acromegaly is generally associated with a number of disease-related symptoms and comorbidities (Table 4).

Patients with acromegaly should be assessed for comorbidities upon diagnosis and receive regular follow-up to monitor for any change.

Monitoring
Patients with acromegaly should be assessed every 6 months for IGF/GH control, using the IGF-I and yearly using the 2-hour OGTT [Grade D, consensus]. Patients should also be monitored regularly for disease-related symptoms (to assess the success of treatment), and for evidence of comorbidities, as required [Grade D, consensus].

Depending on the patient's existing comorbidities and risk factors, monitoring should also include standard

<table>
<thead>
<tr>
<th>TABLE 4. Symptoms and comorbidities to assess and monitor</th>
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<tbody>
<tr>
<td>Disease-related symptoms</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Hyperhidrosis</td>
</tr>
<tr>
<td>Metabolic comorbidities</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
</tr>
<tr>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td>Cardiovascular comorbidities</td>
</tr>
<tr>
<td>• Cardiovascular disease</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Skeletal/dental comorbidities</td>
</tr>
<tr>
<td>• Arthritis</td>
</tr>
<tr>
<td>• Carpal tunnel syndrome</td>
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<tr>
<td>• Jaw malocclusion</td>
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<tr>
<td>• Osteoporosis</td>
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<tr>
<td>• Sleep apnea</td>
</tr>
<tr>
<td>Respiratory comorbidities</td>
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<tr>
<td>Gastrointestinal comorbidities</td>
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<tr>
<td>• Colon polyps</td>
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<tr>
<td>Genitourinary comorbidities</td>
</tr>
<tr>
<td>• Prostate enlargement</td>
</tr>
<tr>
<td>• Urinary stones</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>• Hypopituitarism</td>
</tr>
<tr>
<td>• Goitre/nodular thyroid</td>
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testing for metabolic abnormalities (e.g., lipid testing), cardiovascular risk factors (e.g., echocardiography), musculoskeletal abnormalities (e.g., bone mineral density scanning), respiratory problems (e.g., sleep apnea assessment), gastrointestinal disorders (e.g., colonoscopy) and genitourinary abnormalities (e.g., prostate examinations, kidney scans) [Grade D, consensus].

Monitoring for hypopituitarism after surgery and/or radiotherapy should include metabolic monitoring and imaging (MRI, not CT), especially for patients taking pegvisomant [Grade D, consensus].

**Treating Comorbidities**

Monitoring and treating the comorbidities associated with acromegaly are essential for improving the quality of life of patients and probably reducing the increased mortality associated with this disease. This means modification of risk factors; early diagnosis; and careful management of comorbidities.

**Cardiovascular Disease**

Patients with acromegaly and cardiovascular disease or cardiovascular risk factors will benefit from normalization of GH and IGF-I. Research has shown that left-ventricular size and function may improve when GH levels are returned to normal. Diabetes, glucose intolerance and hypertension may also be improved with normalization of IGF-I levels.

Patients with left-ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease and ischemic heart disease should be treated using standard therapies [Grade A, level 1]. Standard dietary methods may be used to manage diabetes mellitus, hypertension and hyperlipidemia [Grade A, level 1]. Treatment targets for cardiovascular comorbidities may be found in the most recent relevant Canadian guidelines.

**Skeletal/Dental Comorbidities**

Skeletal and/or dental comorbidities benefit most from early diagnosis and normalization of GH levels, since the bone enlargement associated with acromegaly, unlike the soft-tissue overgrowth, is not easily reversed with normalization of hormone levels [Grade D, consensus]. Corrective surgery may be required to treat bone enlargement, but this should not be scheduled until after normalization/stabilization of hormone levels.

Hypercalcaemia/hypercalciuria may occur with high levels of GH, and diminish with successful treatment.

Arthropy and carpal tunnel syndrome may be due in part to soft-tissue overgrowth and may be relieved somewhat when excess GH secretion is normalized, but degenerative arthritis is irreversible and should be treated appropriately.

Patients with acromegaly should be screened for osteoporosis. If osteoporosis is present and is not corrected by hormone stabilization, consider antiresorptive therapy [Grade D, consensus].

**Respiratory Disorders**

Because patients with acromegaly have a high prevalence of obstructive pulmonary disease, putting them at a higher-than-normal risk for pulmonary infection and its associated mortality, they should be vaccinated for influenza and pneumococcal pneumonia and be recommended for a smoking cessation program, if necessary [Grade D, consensus].

Normalization of GH hypersecretion may improve symptoms of sleep apnea; nevertheless, sleep studies should be performed to determine the source of the sleep apnea (central or obstructive) and determine a course of treatment [Grade D, consensus].

**Gastrointestinal Disorders**

Acromegaly is associated with an increased risk of pre-cancer colon polyps, but any demonstrated increased prevalence of colon cancer remains controversial. However, there is an increased risk of death in those who do develop colon cancer. Screening and early detection may improve survival, and monitoring for and removal of precancerous polyps will prevent development into cancer. Colonoscopies are recommended particularly in newly diagnosed patients, those over the age of 50, those with persistently active disease or those with previously identified polyps.

**Genitourinary Disorders**

Patients with acromegaly are at increased risk for prostate enlargement, and for urinary stones. Standard monitoring and treatment should be applied [Grade D, consensus].

**Hypopituitarism**

The risk of developing hypopituitarism depends on how acromegaly is treated. Hypopituitarism resulting from the compressive effects of a tumour may actually be relieved by surgical decompression, but new hypopituitarism may occur as a result of surgery or radiotherapy. Pituitary function should be assessed in
the immediate post-treatment period. Early postoperative assessment depends on daily clinical assessment of the patient. A morning plasma cortisol >450 nM reflects normal hypothalamic-pituitary adrenal axis function, and levels less than 100 nM are suggestive of ACTH deficiency. Those with values <450 nM should be retested using the insulin tolerance test as early as 7-10 days after surgery or, if more convenient, 4-6 weeks postoperatively [Grade D, consensus]. Adrenal, thyroid and gonadal axes should be assessed 6-12 weeks post-surgery [Grade D, consensus]. Monitoring of pituitary function after radiotherapy should be lifelong, as hypopituitarism may develop decades following treatment [Grade D, consensus].

Conclusion
Acromegaly is a chronic condition associated with increased morbidity and mortality if left unchecked. Diagnosis should include clinical and biochemical findings, but is hinged on establishing GH hyperssecretion with IGF-I and OGGT testing. Treatment has traditionally included surgical resection or debulking, along with adjunctive medical therapy (primarily somatostatin analogues), if necessary, to normalize GH levels. The option of primary medical therapy in managing this condition has recently emerged and can be justified for non-surgical candidates or for those in whom surgery is not expected to be curative. Overall, improved screening practices and superior epidemiological data are required, since timely diagnosis and appropriate treatment are crucial for reducing the potentially debilitating effects of this chronic, progressive disease. The current evidence also supports the need for long-term follow-up of disease activity and comorbidities in diagnosed patients.

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References

Address correspondence to:
Shereen Ezzat, MD, FRCP(C), FACP, Mount Sinai Hospital, 437-600 University Ave., Toronto ON, M5G 1X5; e-mail: sezzat@mtsinai.on.ca

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