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Canadian endocrinologists' views on growth hormone replacement therapy in adult survivors of pediatric brain tumors following achievement of final height

Most endocrinologists surveyed in a recent study support using individual patient assessments to consider potential benefits of growth hormone replacement therapy versus the expense and risks.

ABSTRACT

Background: **The majority of survivors of pediatric brain tumors treated with radiation therapy will develop growth hormone deficiency as a result of their treatment or underlying disease that will continue after they achieve their final height and enter adulthood. However, the reinstitution of growth hormone replacement therapy (GHRT) following achievement of final height remains controversial because of the lack of conclusive clinical evidence for benefits, the expense, and the risks of treatment. A study was undertaken to determine the views of Canadian endocrinologists on GHRT to treat growth hormone deficiency in survivors of pediatric brain tumors following achievement of final height, and to establish whether these views were in accord with Canadian provincial pharmaceutical policy regarding coverage for GHRT.**

Methods: **An online questionnaire was distributed to 120 endocrinologists with expertise in endocrine complications following treatment for childhood cancer. The study population was identified using the membership lists of the Canadian Society of Endocrinology and Metabolism and the Canadian Pediatric Endocrine Group. The survey was completed in late June 2013.**

Results: **A total of 44 respondents (37%) completed the survey. The overwhelming majority (91%) believe GHRT benefits survivors of pediatric brain tumors after achievement of final height, while almost half (46%) described side effects associated with discontinuing GHRT. The extent of both benefits and side effects was considered to depend on the individual patient and the severity of growth hormone deficiency. Most respondents (71%) believe that GHRT for adults who have survived pediatric brain tumors should be eligible for provincial drug plan coverage, and commonly described difficulty in obtaining coverage for GHRT under current provincial policies. The majority of respondents (88%) were in favor of a national policy for coverage.**

Conclusions: **Most Canadian endocrinologists surveyed support using individual patient assessments to consider the manifestations of growth hormone deficiency and the potential benefits versus the expenses and risks. Because of the difficulty in obtaining GHRT and the lack of coverage under current Canadian provincial drug plans, most also support a national approach to funding GHRT, believing it would substantially benefit survivors of pediatric brain tumors.**

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Background

Growth hormone deficiency (GHD) is frequently observed in survivors of pediatric brain tumors who were treated with high-dose cranial radiation therapy (more than 36 Gy). Almost 100% of patients treated with high-dose radiation to the hypothalamic-pituitary region will be diagnosed with GHD[1-3] and require growth hormone replacement therapy (GHRT). It is common practice to discontinue GHRT after the achievement of final height, and to subsequently determine whether GHRT should be reinstituted using adult GHD diagnostic criteria.[4]

Survivors of pediatric brain tumors treated with cranial radiation therapy, especially those who develop multiple pituitary hormone deficiencies, have a high risk of lifelong GHD.[5-8]

Endocrinology consensus guidelines state that GHRT is not indicated solely for the purposes of achieving final height, but to ensure full somatic development.[9] Furthermore, these guidelines recommend that GHRT should not be discontinued in patients who present with persistent GHD after they achieve their final height.[9] Current treatment guidelines recommend 0.2 mg/day of growth hormone for young adult men with GHD and 0.3 mg/day for young women.[9] Dosage should be adjusted based on clinical and biochemical response.[9]

It is estimated that 1 year of GHRT for a young adult with GHD would cost between $5000 and $6000. However, there is conflicting evidence regarding the benefits of GHRT, and whether the benefits of GHRT justify the expense and outweigh the risks of treatment remains controversial.[10-13]

Given that the majority of survivors of pediatric brain tumors treated with cranial radiation therapy will continue to be severely GH-deficient in adulthood, it is imperative to evaluate the need for continuation of GHRT after achievement of final height.[14] We undertook a study to determine the views of Canadian endocrinologists regarding GHRT to treat GHD during adulthood in survivors of pediatric brain tumors following achievement of final height, and to establish whether Canadian provincial pharmaceutical policies regarding coverage of GHRT to treat adult GHD reflect the views of Canadian endocrinologists.

Methods

We began our study by obtaining approval from the Research Ethics Board of the BC Cancer Agency. We then developed a questionnaire to collect demographic information and obtain Canadian endocrinologists' views (see the **Figure**). The questionnaire included questions about whether GHRT was beneficial in survivors of pediatric brain tumors with GHD after the achievement of final height, and whether there were side effects associated with discontinuing GHRT. We also developed questions to determine the current state of coverage for GHRT in the province of practice for each endocrinologist and to determine whether endocrinologists support national drug plan coverage for GHRT, rather than the current provincial coverage.

Almost 100% of patients treated with high-dose radiation to the hypothalamic-pituitary region will be diagnosed with GHD

The survey was designed to be voluntary and anonymous, and the questionnaire was distributed using the online tool FluidSurveys (http://fluidsurveys.com) to 120 members of the Canadian Society of Endocrinology and Metabolism (CSEM) and the Canadian Pediatric Endocrine Group (CPEG) who were identified as having expertise in treating endocrine complications in survivors of pediatric brain

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Please answer the questions below.

1. **What province or territory do you practise medicine in currently?**
   - ☐ Ontario
   - ☐ Quebec
   - ☐ British Columbia
   - ☐ Alberta
   - ☐ Manitoba
   - ☐ Saskatchewan
   - ☐ Nova Scotia
   - ☐ New Brunswick
   - ☐ Newfoundland and Labrador
   - ☐ Prince Edward Island
   - ☐ Northwest Territories
   - ☐ Yukon
   - ☐ Nunavut

2. **How long have you been in practice?**
   - ☐ Less than 5 years
   - ☐ 5–10 years
   - ☐ 10–20 years
   - ☐ Over 20 years

3. **Is your practice predominantly:**
   - ☐ Adult patients
   - ☐ Pediatric patients
   - ☐ A mixture of both pediatric and adult patients

4. **Do you believe that GHRT is beneficial in adult survivors of PBTs with GHD after achievement of final height?**
   - ☐ Yes
   - ☐ No

   Please could you specify why below:

   _____

5. **Do survivors of PBTs generally suffer from significant side effects when GHRT is discontinued after achievement of final height?**
   - ☐ Yes
   - ☐ No

   Please could you specify why below:

   _____

6. **What are the conditions under which a patient is considered to have GHD as an adult in your province/territory?**

   _____

   _____

7. **Are all adult survivors of PBTs with childhood-onset GHD eligible for GHRT coverage through a government-funded drug program in the province you practise in?**
   - ☐ Yes
   - ☐ No

   Please could you specify why below:

   _____

8. **Can coverage for GHRT be granted under special circumstances (e.g., through Special Authority) in the province that you practise in?**
   - ☐ Yes
   - ☐ No

   Please could you specify why below:

   _____

9. **If the cost of GHRT is not covered, do you believe that it should be covered by the government for the treatment of GHD in adult survivors of PBTs?**
   - ☐ Yes
   - ☐ No

   Please could you specify why below:

   _____

10. **Would you support the introduction of a Canadian national GHRT funding policy for adult survivors of PBTs?**
    - ☐ Yes
    - ☐ No

    Please could you specify why below:

    _____

Figure. Questionnaire distributed to endocrinologists surveyed.

tumors. The survey was completed in late June 2013. Responses were analyzed using descriptive statistics and content analysis.

Results

A total of 44 respondents (37%) completed the survey, including roughly similar numbers of endocrinologists with an adult patient population (50%) and with a pediatric patient population (45%) (see **Table 1**). The vast majority of respondents (82%) have been in practice for more than 10 years. Furthermore, the majority of respondents practise in Ontario, Quebec, or British Columbia.

Respondents reported they generally assess GHD in adults by discontinuing GHRT after the achievement of final height and using provocative testing (e.g., insulin tolerance test), measuring serum insulin-like growth factor 1 (IGF-1) to determine whether thresholds are reached for a diagnosis of adult GHD, or both.

Benefits of GHRT

The overwhelming majority of survey respondents (91%) believe GHRT benefits adult survivors of pediatric brain tumors (see **Table 2**). The main benefits described by respondents include improvements in patient quality of life, energy, body composition, lipid profile, bone-mineral composition, body habitus, and metabolic parameters, as well as decreased cardiovascular risk and prevention of metabolic syndrome. The respon-

dents frequently commented that the benefits were dependent on the individual and on the severity of GHD. A minority of respondents (9%) indicated they did not feel that GHRT was beneficial based on a lack of conclusive clinical evidence.

Almost half of respondents (46%) indicated that survivors of pediatric brain tumors suffer from side effects when GHRT is discontinued after achievement of final height, and that these effects vary depending on the patient's history and perception of well-being. Respondents described symptomatic patients who are often severely GH-deficient, with abnormal body composition, decreased energy, exercise intolerance, depressed or flattened mood, and reduced quality of life.

Coverage of GHRT costs

Respondents indicated that when seeking coverage of GHRT costs for a patient, the treating endocrinologist must submit all relevant medical information to a provincial expert advisory committee for evaluation. This includes a letter describing the consequences for the patient of withdrawing GHRT, improvements while on GHRT, and results from clinical tests documenting GHD. Respondents commonly reported that they were unsuccessful in obtaining coverage for drug costs through current provincial plans for adult survivors of pediatric brain tumors with GHD following achievement of final height.

The majority of respondents indicated that there is a need for the government to establish definitive and transparent eligibility criteria for coverage. Respondents indicated that an evaluation based on an individual therapeutic trial of GHRT with clear objective and subjective measures would be the best approach to considering drug cost coverage. However, a

Table 1. Characteristics of 44 respondents to survey about growth hormone replacement therapy.

Characteristic		% of respondents
Number of years in practice	Less than 5 years	2
	5–10 years	16
	10–20 years	52
	Over 20 years	30
Patient population of practice	Adult	50
	Pediatric	45
	Mix of adult and pediatric	5
Province of current practice*	British Columbia	18
	Alberta	11
	Saskatchewan	5
	Manitoba	2
	Ontario	34
	Quebec	20
	Nova Scotia	9

*Percentages do not total 100 due to rounding.

Table 2. Percentage of "yes" responses to survey questions about growth hormone replacement therapy in survivors of pediatric brain tumors.

Question	% "yes" responses
Do you believe that GHRT is beneficial in adult survivors of PBTs with GHD after achievement of final height?	91
Do survivors of PBTs generally suffer from side effects when GHRT is discontinued after achievement of final height?	46
Are all adult survivors of PBTs with childhood-onset GHD eligible for GHRT coverage through a government-funded drug program in the province you practise in?	21
Can coverage for GHRT be granted under special circumstances (e.g., through Special Authority) in the province that you practise in?	59
If the cost of GHRT is not covered, do you believe that it should be covered by the government for the treatment of GHD in adult survivors of PBTs?	71
Would you support the introduction of a Canadian national GHRT funding policy for adult survivors of PBTs?	88

GHRT = growth hormone replacement therapy
PBTs = pediatric brain tumors
GHD = growth hormone deficiency

minority of respondents commented that universal public coverage for GHRT cannot be justified, given fiscal constraints in health care, the high cost of GHRT, and the lack of conclusive clinical evidence for the benefits of GHRT.

Respondents agreed that a national policy would increase transparency and consistency, promote equity, and be a model for public coverage of expensive therapies required by vulnerable populations. Respondents were in favor of an evidence-based national policy that advocates for a trial of therapy and has criteria that are sufficiently stringent to select the patients most likely to benefit.

Limitations of study

This study had some limitations. The majority of respondents were from Canada's three largest provinces (Ontario, Quebec, and British Columbia), meaning that the results obtained may not represent all of Canada. Furthermore, there were no respondents from the lower-population provinces of New Brunswick, Newfoundland and Labrador, and Prince Edward Island. This limitation was addressed to some degree by incorporating data from Nova Scotia respondents who had treated patients from New Brunswick and Prince Edward Island and provided information on coverage in those provinces.

Conclusions

Studies have shown that many of the adverse effects resulting from adult GHD can be reversed by GHRT.[15] GHRT has been associated with improvements in body composition, metabolic and cardiovascular function, muscle strength, bone-mineral density, and quality of life.[16,17] Growth hormone deficiency is very common and often severe in survivors of pediatric brain tumors following achievement of final height.[14,18] Although discontinuation of GHRT in severely GH-deficient patients has been found to have negative effects on metabolic parameters and body composition, in addition to increased risk of cardiovascular events,[11,17] a study by Murray and colleagues found only minor improvements in body composition, lipid profile, and bone-mineral density in GH-deficient survivors of childhood cancer following 12 to 18 months of GHRT.[19] Not surprisingly, controversy still remains regarding the magnitude of improvements with GHRT and whether these improvements can justify the expense and risks for all patients. Some guidelines and researchers say GHRT is justified, but only after determining the likelihood of substantial benefit by assessing the patient for manifestations of GHD prior to initiating GHRT and re-evaluating following a trial of GHRT.[4,17]

Thresholds decrease significantly for diagnosis of GHD from childhood (less than 10 μg/L) to adulthood (less than 3 μg/L), according to diagnostic criteria for provocative testing that are used to warrant GHRT.[9,20] The adult threshold for severe GHD and accepted criterion for GHRT of less than 3 μg/L does not take into consideration GH responses after provocative testing for most adolescents in late puberty who have reached final height, which will often exceed 5 μg/L. In fact, endocrinology consensus guidelines recommend that the criterion in patients who are in transition from adolescence to adulthood should be less than 5 μg/L.[4,9,20] Thus, the accepted threshold for response to provocative testing for adults can mean that endocrinologists encounter significant difficulty in obtaining coverage for patients who have achieved their final height but are still in need of GHRT.

Across Canada, provinces cover the cost of GHRT during childhood to promote achievement of final height.[21] Coverage following achievement of final height, regardless of pre-existing GHD and previous underlying disease, requires review from the province's expert advisory committee. Due to limitations in adult diagnostic criteria as well as lack of concrete supporting clinical evidence, endocrinologists encounter difficulties in obtaining coverage for their patients. In addition, the responsibility for coverage of outpatient medications falls on the provincial government, and as a result there are provincial disparities leading to inequitable access.[22] In fact, studies have found a significant number of Canadians lack access to medications and experience undue financial hardship because of disparities in pharmaceutical policy across Canada.[22-26] Implementation of a national policy would remove such disparities and promote equity.

The majority of Canadian endocrinologists surveyed for this study believe that the need for GHRT in adult survivors of pediatric brain tumors should be assessed on an individual basis. In addition, this study found that many of the endocrinologists surveyed would like a national approach to drug coverage because of difficulties they encounter when seeking coverage for childhood cancer survivors who could benefit from GHRT.

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Competing interests

None declared.

References

1. Littley MD, Shalet SM, Beardwell CG, et al. Radiation-induced hypopituitarism is dose-dependent. Clinical Endocrinol (Oxf) 1989;31:363-373.
2. Brennan BM, Rahim A, Mackie EM, et al. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. Clin Endocrinol (Oxf) 1998;48:777-783.
3. Turner CD, Rey-Casserly C, Liptak CC, et al. Late effects of therapy for pediatric brain tumor survivors. J Child Neurol 2009;24:1455-1463.
4. Clayton PE, Cuneo RC, Juul A, et al. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol 2005;152:165-170.
5. Tauber M, Moulin P, Pienkowski C, et al. Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. J Clin Endocrinol Metab 1997;82:352-356.
6. Nicolson A, Toogood AA, Rahim A, et al. The prevalence of severe growth hormone deficiency in adults who received growth hormone replacement in childhood. Clin Endocrinol (Oxf) 1996;44:311-316.
7. Stanhope R. Transition from paediatric to adult endocrinology: Hypopituitarism. Growth Horm IGF Res 2004;14:85-88.
8. Darzy KH, Shalet SM. Pathophysiology of radiation-induced growth hormone deficiency: Efficacy and safety of GH replacement. Growth Horm IGF Res 2006;16:30-40.
9. Ho KK. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: A statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol 2007;157:695-700.
10. Mauras N, Pescovitz OH, Allada V, et al. Limited efficacy of growth hormone (GH) during transition of GH-deficient patients from adolescence to adulthood: A phase III multicenter, double-blind, randomized two-year trial. J Clin Endocrinol Metab 2005;90:3946-3955.
11. Johannsson G, Albertsson-Wikland K, Bengtsson BA. Discontinuation of growth hormone (GH) treatment: Metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. J Clin Endocrinol Metab 1999;84:4516-4524.
12. Carroll PV, Drake WM, Maher KT, et al. Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. J Clin Endocrinol Metab 2004;89:3890-3895.
13. Ter Maaten JC. Should we start and continue growth hormone (GH) replacement therapy in adults with GH deficiency? Ann Med 2000;32:452-461.
14. Gleeson HK, Gattamaneni H, Smethurst L, et al. Reassessment of growth hormone status is required at final height in children treated with growth hormone replacement after radiation therapy. J Clin Endocrinol Metab 2004;89:662-666.
15. Carroll PV, Christ ER, Bengtsson BA, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: A review. J Clin Endocrinol Metab 1998;83:382-395.
16. Thomas JD, Monson JP. Adult GH deficiency throughout lifetime. Eur J Endocrinol 2009;161:S97-S106.
17. Alexopoulou O, Abs R, Maiter D. Treatment of adult growth hormone deficiency: Who, why and how? A review. Acta Clin Belg 2010;65:13-22.
18. Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. Endocr Relat Cancer 2004;11:589-602.
19. Murray RD, Darzy KH, Gleeson HK, et al. GH-deficient survivors of childhood cancer: GH replacement during adult life. J Clin Endocrinol Metab 2002;87:129-135.
20. Israel E, Attie KM, Bengtsson BA, et al. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: Summary statement of the GH Research Society. J Clin Endocrinol Metab 2000;85:3990-3993.
21. Ungar WJ, Witkos M. Public drug plan coverage for children across Canada: A portrait of too many colours. Healthc Policy 2005;1:100.
22. Daw JR, Morgan SG. Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010. Health Policy 2012;104:19-26.
23. Coombes ME, Morgan SG, Barer ML, et al. Who's the fairest of them all? Which provincial pharmacare model would best protect Canadians against catastrophic drug costs? Healthc Q 2004;7:13-19.
24. Demers V, Melo M, Jackevicius C, et al. Comparison of provincial prescription drug plans and the impact on patients' annual drug expenditures. CMAJ 2008;178:405-409.
25. Law MR, Cheng L, Dhalla IA, et al. The effect of cost on adherence to prescription medications in Canada. CMAJ 2012;184:297-302.
26. Romanow R. Building on values: The future of health care in Canada–final report. Commission on the Future of Health Care in Canada. Ottawa, ON: Health Canada; 2002. BCMJ