

Second Editor's Comment: *HMGA2 encodes "High Mobility Group AT-Hook 2" and is sited on chromosome 12q14.3. It is expressed in undifferentiated mesenchyme. HMG proteins alter chromatin configuration and thereby gene expression. They do so by the binding of their "AT hook domains" to AT-rich DNA; this alters conformation of the double helix and permits transcription complexes to either promote or inhibit transcription of targeted genes. Microdeletions or mutations of HMGA2 have been associated with benign neoplasia (lipoma, salivary adenoma, uterine leiomyoma). Truncation of HMGA2 secondary to a pericentric inversion of chromosome 12 with breakpoints at 12p11.22-12q14.3 has been associated*

with a syndrome of somatic overgrowth, advanced bone and dental ages, multiple lipomas and a cerebellar tumor.² Truncations of mouse ortholog Hmga2 (Hmg1c) result in somatic overgrowth, lipomas, and increase in body fat.³ Homozygous deletion of mouse Hmga2 results in decrease in growth.⁴

Allen W. Root, MD

References

1. Growth Genet Horm. 2007;23:2.
2. Ligon AH, Moore SD, Parisi MA, et al. Am J Hum Genet. 2005;76:340-8.
3. Arlotta P, Tai AK, Manfioletti G, et al. J Biol Chem. 2000; 275:14394-400.
4. Zhou X, Benson KF, Ashar HR, Chada K. Nature. 1995;376:771-4.

Height and Health-related Quality of Life

Findings regarding associations between height and psychosocial variables are inconsistent. To address perceived methodological and design weaknesses in previous studies, Christensen and colleagues sought to clarify the nature of this relationship by analyzing data collected through a national health survey. Their primary aim was to assess the relationship between stature and health-related quality of life (HRQoL) in an adult general population sample in the UK. Secondly, they sought to evaluate potential moderating effects of social status, age, gender, and chronic conditions on the relationship between height and HRQoL.

This report is based on secondary analyses of the 2003 Health Survey for England (HSE03), conducted between January 2003 and March 2004, by the UK Department of Health. The HSE03 comprises a random general population sample for those living in private households in England (73% participation rate). Observations for 14,416 adults (>18 years of age) were included in the analyses. Height and weight were measured by a nurse; HRQoL was measured using the EQ-5D questionnaire (EuroQoL). The EQ-5D self-report consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 possible levels reflecting no health problems, moderate health problems, and extreme health problems. Using a specific British EQ-5D scoring algorithm which converts total scores to quality adjusted life years, the 5 dimensions were summarized into a single score. An individual who has no problems in any domain scores 1.0 and death equals 0.0.

Mean EQ-5D scores were lower in the shorter compared with taller subjects, as well as being lower than the overall population mean. Based on statistical criteria, the total sample was split into 3 standardized height (HSDS) subgroups: (1) HSDS ≤ -2.0 , n=606; (2) $-2.0 > \text{HSDS} \leq 0$, n=6580; and (3) HSDS > 0 , n=4760. In regression analyses adjusting for potential demographic confounds (age, gender, chronic illness, social class, and body weight), subgroup 1 had significantly lower

EQ-5D scores compared with subgroups 2 and 3, and subgroup 2 received lower scores than subgroup 3. Based on regression coefficients, an increase of 1 HSDS would be associated with a statistically significant increase in the EQ-5D score of 0.061 for subjects ≤ -2.0 HSDS, 0.010 for those between -2.0 and 0 HSDS, and 0.002 for those > 0 HSDS. The increase in EQ-5D score with increasing height in the > 0 HSDS, although statistically significant, was not considered of clinical significance. The main contributors to the reduced HRQoL in the shortest subgroup were problems with mobility, usual activities, and pain/discomfort. The authors concluded that increasing final height in children with short stature may be beneficial and could enhance HRQoL outcomes barring troublesome side effects and excessive cost of treatments.

Christensen TL, Djurhuus CB, Clayton P, Christiansen JS. An evaluation of the relationship between adult height and health-related quality of life in the general UK population. Clin Endocrinol (Oxf). 2007;67:407-12.

First Editor's Comment: *HRQoL should (1) represent a multidimensional construct, including several core dimensions (eg, physical functioning and symptoms, psychological and emotional state, and social functioning), (2) be patient, rather than physician, centered, and (3) reflect subjective evaluations of daily functioning and psychological well-being.¹ The use of patient reported outcomes, such as HRQoL measures, are encouraged and may soon be mandated by the FDA for the evaluation and approval of new drugs and medical interventions.² Rigorous standards for the development and psychometric evaluation of HRQoL measures have been promoted by the World Health Organization. It is therefore a positive development to see research published examining the relationship between measured height and subjective reports of QoL. In the FDA's review of growth hormone (GH) treatment for the indication of idiopathic short stature (ISS), HRQoL was not utilized as an endpoint in the approval process.^{3, 4}*

Christensen and colleagues acknowledged that

inferring a causal relationship between height and HRQoL is not possible because of the single point, cross-sectional design of this survey. This limitation notwithstanding, they stated that their study “conclusively show(s) a significant correlation between adult height and HRQoL, which may indicate that improving final height in children with growth disorders who are receiving GH treatment should result in positive HRQoL outcomes, even if studies to date do not always show a benefit in childhood or adolescence.” However, the use of a single method (the EQ-5D) makes such a statement (even as speculation) premature. Further, no controlled study, to date, has demonstrated a psychological benefit of increased growth velocity/height through the use of GH treatment.

A curious aspect of this study’s findings concerns the pattern of scores for individual EQ-5D dimensions. Based on the authors’ review of earlier studies suggesting that short stature exerts a psychosocial stress associated with poorer intellectual, psychosocial, and psychiatric function, it is surprising that the main contributors to reduced HRQoL in the shortest subgroup were problems with mobility, usual activities, and pain/discomfort. It is not obvious why shorter participants would more likely experience problems with walking or be confined to bed (as defined by the instrument), or experience more pain or discomfort unless, however, the short stature was accompanied by other features which compromised function—in which case, it is likely that the features accompanying the short stature, rather than the short stature itself, account for the compromised function.

Finally, the investigators pointed out the associations between height and HRQoL in adulthood are nonlinear; ie, it was only among the shortest survey participants (ie, <-2.0 HSDS) that meaningful improvements in HRQoL with increased height was predicted. Provided we accept correlational findings as evidence of causation, one implication of this is that GH-induced increases in adult height beyond -2.0 HSDS would not yield personal benefit. This finding therefore provides empirical support for the ethical argument of terminating GH treatment at the point at which the individual achieves an adult height within the lower portions of the normative range.⁵

In this context, it is noteworthy that this article is not accompanied by a disclosure statement indicating conflict; the first 2 authors’ affiliation is listed as Global Development, Novo Nordisk A/S.

David E. Sandberg, PhD

Second Editor’s Comment: Projects which have tried to assess the effect of height on QoL, either in childhood or adult life, have been bedeviled by underpowered studies, the fallibility of questionnaires as a technique of QoL assessment, and the apparent extraordinary ability of children to adapt to their physical and environmental circumstances. The analysis of the data of Christensen et al showed a significant correlation between adult short stature and HRQoL. Height had a 6-fold greater correlation with HRQoL in the short adult population (ie, height <-2 SD) compared to the taller population subgroup. Very short subjects (height <-3 SD) were particularly affected and had very low QoL. It is likely that this study will be quoted in order to justify treatment of short children with GH. It should be appreciated that an improvement of adult height from -2.0 to -1.0 SD during GH therapy did not change the HRQoL to a large extent. Nevertheless when GH therapy offers the opportunity to make a large difference in adult height, for example in GH deficiency, adult HRQoL is likely to improve significantly.

Martin O. Savage, MD

References

1. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996. 49-56.
2. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Food and Drug Administration.
3. Sandberg DE. Atrium: The Report of the Northwestern Medical Humanities and Bioethics Program. 2006;3:13-5.
4. Food and Drug Administration, Center for Drug Evaluation and Research. Endocrinologic and Metabolic Drugs Advisory Committee Meeting, June 10, 2003.
5. Allen DB. Pediatrics. 2006;118:343-8.

Effects of Gluten-free Diet in Atypical Celiac Disease

Celiac disease frequently presents growth impairments as evidenced by an inflammatory enteropathy from T-cell hypersensitivity to certain cereal antigens; catch-up growth may be induced by initiation of a gluten-free diet. Street et al sought to study children longitudinally over their first year on the diet. Children with atypical celiac disease (patients with typical gastrointestinal symptoms as well as in an atypical fashion) were followed; outcome measures included changes and correlations in growth parameters, insulin-like growth factor (IGF) axis members, and the proinflammatory

cytokines implicated in celiac disease pathophysiology, interleukin (IL)-6 and tumor necrosis factor (TNF)- α .

Twenty children (9 male), aged 4.2 to 14.2 (mean 9.6) years at diagnosis of atypical celiac disease, were followed; 17 completed the one-year evaluations and 3 were lost to follow-up. Of note, all had atypical celiac disease and presented with recurrent abdominal pain, anemia, nausea, occasional vomiting, and fatigue, or were screened due to family history. None had diarrhea or malnutrition, 11 children were prepubertal at diagnosis, and during the year’s follow-up, 2 boys progressed from