Is GH Replacement for Adult GH Deficiency Safe?

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Since the description of adult GH deficiency (AGHD) as a distinct disorder associated with pituitary failure, as well as the availability of recombinant human GH, endocrinologists have been treating these patients with replacement GH at doses ranging from 0.15 to 0.3 mg/d, and higher in younger women (1). AGHD may be acquired during adulthood because of pituitary and/or hypothalamic secretory compromise or pathologic damage. Furthermore, childhood-onset GH deficiency of structural and genetic origin persists during adulthood. Because the primary phenotype of GH sufficiency is linear growth, diagnosis of the disorder during adulthood after closure of the bone epiphyses is challenging. Clinical features of AGHD include central obesity, loss of lean body mass, osteoporosis, lipid disorders, cardiovascular dysfunction, decreased quality of life, and psychologic disorders. Because these features are commonly encountered in the general population in GH-replete adults, and AGHD is so rare, the diagnosis of AGHD requires rigorous demonstration of hypothalamic and/or pituitary damage as visualized by magnetic resonance imaging, as well as evidence for compromised pituitary GH reserve as reflected by results of provocative stimulation testing with or without reduced IGF-1 levels. Given the limitations of GH assay performance, the pulsatility of GH secretion, as well as GH suppression after food, in the face of elevated body mass index as well as during normal aging, more than 1 test may be required (2). Adult GH replacement administered appropriately at physiologic doses to patients with rigorously proven pituitary dysfunction may improve lean body mass, reverse central obesity and associated metabolic dysfunction, improve or arrest osteoporosis, enhance quality of life (3), and possibly reverse adverse mortality rates (4).

Extensive surveillance studies have reported on GH side effects including salt and fluid retention, edema, carpal tunnel syndrome, hyperglycemia, arthralgias, myalgias, paresthesias, atrial fibrillation, headache, and sleep apnea, in addition to signs and symptoms from unmasking thyroid and/or adrenal dysfunction (2).

In an elegant analysis, interrogation of the KIMS registry comprising 15,809 patients with AGHD (relatively equal sex distribution, with 94% Caucasian patients) treated for up to 18.3 years (83,128 patient-years) was used to assess long-term safety of GH replacement therapy (5).

This study is characterized by drawbacks inherent to surveillance programs, including a lack of monitored controls, GH dose fluctuations and injection compliance during the long duration of the study, and varying degrees of documentation of underlying pituitary dysfunction and replacement of other hormones. Notwithstanding these important caveats in interpretation of the results, registries such as KIMS provide useful observational information helpful to endocrinologists in treating these patients. In surveying AGHD patients receiving GH and followed for a mean of 5.3 years, Johannsson et al put to rest some of the inconsistent and conflicting results in the literature derived from earlier smaller studies with less rigorous statistical validation. Authors were faced with several challenges to apply appropriate analysis methodology for ascertaining true GH-related new-onset safety signals. These constraints include the heterogenous nature of specific AGHD etiology, inherent clinical features of non-GH-related hypopituitarism, and variable treatments of the observed cohort. Consistent with prior epidemiologic studies, they report that 60% of patients with AGHD had an underlying pituitary or hypothalamic tumor, and almost 70% of patients had 2 or more additional pituitary deficits with variable associated hormone replacement requirements. Importantly, in the absence of a control cohort, the presence of comorbidities associated with AGHD including hypertension, diabetes, and arthritis, further challenged identification of true GH-related side effects.

GH-related adverse events as reported by treating physicians were observed in 18.8% of patients, mainly associated with fluid retention, and were more likely related to IGF-1 levels and more prominent within the first year of treatment. Overall, crude rates of GH-related adverse events were significantly associated with patients > 45 years of age, those harboring a pituitary or hypothalamic tumor, as well as those with AGHD acquired during adulthood, rather than childhood-onset AGHD. Adjusted adverse event rates were not proportional to GH dose, although dose changes between study points were not clearly discernable, and GH doses may well have been titrated downward because of adverse events during the course of the surveillance. Lipid and glucose metabolism were not appreciably changed, and myocardial infarction (0.5%) and stroke (0.8%) were not significantly increased over expected rates.

Cancer incidence rates have been associated with higher IGF-1 levels and local GH receptor activation suppresses colon epithelial p53 tumor suppressor expression (6). GH also coregulates cancer-related signaling pathways (7). It is
therefore important that rigorous evidence-based assurances can be given physicians and patients that physiologic replacement GH doses do not induce new tumorigenesis. Notably, in this study, this concern has again been alleviated similarly to previous smaller studies because new malignancy onset was not increased compared with the general population after adjusting for age, sex, treatment duration, and GHD etiology (standardized incidence ratio, 0.92; 95% CI, 0.83-1.01). This finding is likely the most significant and reassuring conclusion derived from this study and will favorably affect clinical practice and alleviate apprehension.

Of particular concern in AGHD management is the potential effect of GH replacement on reinitiating or accelerating pituitary adenoma growth (8). Reassuringly, pituitary adenoma recurrence rates in KIMS (2.7%) were not different from the expected natural history for growth of these lesions. Overall, mortality during the observation (3.8%) was attributed mainly to neoplasms, cardiovascular disorders, infections, and stroke, supporting findings of prior reports.

Notwithstanding the limitations of an observational study of 5.3 years mean duration, with only 19% of patients followed for > 10 years, the reported new findings are reassuring that the approved practice of carefully titrated physiologic GH replacement doses for well-defined AGHD are indeed safe and tolerable in patients with proven pituitary dysfunction. It would, however, be irresponsible to derive reinforcement for the inappropriate and illegal use of GH in pituitary-replete individuals or in aging, or to enhance athletic performance from results of this carefully analyzed cohort surveillance. In their well-designed and comprehensive analysis, Johansson et al bolster the clinical relevance of current guidelines for safe and effective GH replacement for AGHD.

Disclosures
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Data Availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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