AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR GROWTH HORMONE USE IN GROWTH HORMONE-DEFICIENT ADULTS AND TRANSITION PATIENTS – 2009 UPDATE

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The American Association of Clinical Endocrinologists Medical Guidelines for Growth Hormone use in Growth Hormone Deficient Adults and Transition Patients – 2009 Update are systematically developed statements to assist health care providers in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

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Abbreviations

AACE = American Association of Clinical Endocrinologists; **AOGHD** = adult-onset growth hormone deficiency; **ARG** = arginine; **BEL** = best evidence level; **BMD** = bone mass density; **BMI** = body mass index; **COGHD** = childhood-onset growth hormone deficiency; **CPG** = clinical practice guidelines; **DEXA** = dual energy X-ray absorptiometry; **EL** = evidence levels; **FDA** = Food and Drug Administration; **GH** = growth hormone; **GHD** = growth hormone deficiency; **GHRH** = growth hormone releasing hormone; **IGF** = insulin-like growth factor; **IGFBP** = insulin-like growth factor binding protein; **ITT** = insulin tolerance test; **QOL** = quality of life; **SDS** = social desirability score

1. MISSION STATEMENT

For adults, proven benefits of recombinant human growth hormone (GH) replacement therapy have been demonstrated in those with GH deficiency (GHD) (**1 [EL 2], 2 [EL 2], 3 [EL 1], 4 [EL 2]**). This has resulted in its expanding use in clinical endocrine practice. GH has also been misused in recent years in certain factions of the sporting world because of its increased availability (**5 [EL 3], 6 [EL 3]**) and has been touted in the media as a formula for the "fountain of youth" for the elderly population (**7 [EL 4], 8 [EL 4]**). With recent advancements in our understanding of the benefits of GH replacement for GH-deficient patients and because of concerns about the unethical aspects of GH therapy for athletes and aging, the Board of Directors of the American Association of Clinical Endocrinologists (AACE) believes that an update to the previous AACE guidelines published in 2003 (**9 [EL 4]**) is warranted for practicing clinicians and the general public.

This report consists of recommendations for indications, diagnosis, and clinical use of GH in patients with biochemically proven GHD in transition years and in adulthood. However, it must be emphasized that physicians should use these guidelines concurrently with their best clinical judgment for each patient. These revised guidelines have also taken into consideration the use of GH in unapproved indications such as sports and aging, the safety issues of long-term GH replacement, recent changes in the clinical care of transition patients, recent unavailability of recombinant GH releasing hormone (GHRH) in the United States and its implications on the biochemical diagnostic testing of adult GHD, and recent data on glucose tolerance, mortality rates, pituitary tumor recurrence, cancer risk, and cardiovascular morbidity. They also expand the clinical context of the adult GHD syndrome to encompass patients with neurologic disorders which may affect the hypothalamus and pituitary gland such as previous traumatic brain injury or aneurysmal subarachnoid hemorrhage.

2. INTRODUCTION

GHD in adulthood associated with hypothalamic-pituitary dysfunction is now widely accepted as a distinct clinical syndrome, and is linked to a substantial number of metabolic abnormalities, many of which can be ameliorated with GH replacement therapy (**3 [EL 1]**). However, despite the growing body of evidence on the benefits of GH therapy (**1 [EL 2], 2 [EL 2], 3 [EL 1], 4 [EL 2]**), there is still considerable variability in the United States in the clinical practice of GH replacement for adults with GHD. This variability is multifactorial, partly due to the high cost of GH therapy (GH costs approximately $50 for 1 mg of GH, or $9,125 per year for a patient on an average GH dose of 0.5 mg/day), the need for daily injections, the lack of awareness regarding its indications, diagnosis, and long-term surveillance, and concerns about whether there are long-term risks involved. In addition, there is sometimes misunderstanding regarding the difference between true GHD (ie, lower GH secretion than normal for the appropriate age and sex) versus its unapproved use in nonmedical conditions such as sports and aging.

The availability of recombinant human GH from 1985 onward has given rise to many studies investigating the role of GH in adulthood, in particular the effects and safety of GH replacement in GH-deficient adults (**10 [EL 2], 11 [EL 3]**). In the United States, recombinant GH was approved by the Food and Drug Administration (FDA) in 1996 for use as replacement therapy in GH-deficient adults. Although treatment appears to be safe overall in the first decade of use in adults, certain parameters still necessitate long-term surveillance, such as whether GH replacement aimed at normalizing serum insulin-like growth factor (IGF)-I levels results in an increase in glucose intolerance, cancer, and hypothalamic/pituitary tumor recurrence (**12 [EL 1]**).

Despite widespread clinical experience, there is still a lack of consensus regarding the optimal approach to the dosing regimen. Early studies utilized GH doses based on body weight or body surface area derived from pediatric experience (**13 [EL 2], 14 [EL 2], 15 [EL 2]**). Although these studies reported beneficial effects of GH replacement, dose-related side effects such as arthralgia and peripheral edema were frequently observed. In light of these observations, many consensus statements have proposed that GH therapy should be started using low doses, and the dose adjusted to normalize serum IGF-I levels appropriate for age and sex (**16 [EL 1], 17 [EL 1], 18 [EL 1]**). Recent studies show that such individualized, stepwise, fixed-dose adjustments improved overall tolerability and efficacy (**19 [EL 1], 20 [EL 1]**).