Growth Hormone Deficiency and other Indications for Growth Hormone Therapy – Adult

Prohibited substances: Human Growth Hormone

1. Medical Condition

Growth hormone deficiency (GHD) and other indications for growth hormone therapy in adults.

2. Diagnosis

a. Medical History

GHD is a result of dysfunction of the hypothalamic-pituitary axis either at the hypothalamic or pituitary levels. Adults who have GHD include individuals who have been diagnosed with GHD as a child and those who have acquired GHD as an adult due to hypothalamic-pituitary disease. Adult-onset GHD is an uncommon disorder. The symptoms are subtle and common place, including fatigue, poor exercise capacity, abdominal obesity and impaired psychosocial function. There is no pathognomonic feature. [1-4]

For the individual who has been diagnosed with GHD as a child, the transition period can be defined as beginning in late puberty, the time when near adult height has been attained, and ending with full adult maturation (6-7 years after achievement of adult height). During this period ongoing growth hormone therapy may be necessary to attain somatic maturation, normal intermediary metabolism and appropriate quality of life.

Adults who develop GHD *de novo* include individuals with hypothalamic-pituitary disease, e.g., pituitary tumors, subarachnoid hemorrhage, surgery or irradiation in these cranial areas or traumatic brain injury. Such individuals may have other pituitary hormone deficiencies. In general, the diagnosis of GHD should be determined by an endocrinologist with expertise in pituitary disorders.

b. Diagnostic criteria

The diagnosis of GHD requires an appropriate/plausible clinical setting and is confirmed through biochemical testing. Evaluation for GHD should be performed in patients with a history of hypothalamic-pituitary disease (e.g., pituitary tumors), after cranial irradiation, after significant traumatic brain injury (TBI) and in some individuals who have been treated for GHD as a child. MRI of the brain with specific attention to the hypothalamus and pituitary should be considered when assessing new GHD for hypothalamus or pituitary structural abnormalities in adults or in transition patients.

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1. The diagnosis of GHD is confirmed by undertaking one of the following validated GH stimulation tests[1-4]:
   i. Insulin Tolerance Test (< 3 ng/mL)
   ii. Macimorelin Test (threshold (< 2.8 ng/mL)
   iii. Glucagon Stimulation Test (< 3 ng/mL)

   IGF-1 levels have a high specificity, but low sensitivity (30-40% with GHD have IGF-1 in the age-matched normal range).

   Patients with the following disorders do not require a GH stimulation test[1-4]

   a) More than three additional pituitary hormone deficits and a low IGF-I level (strong evidence for hypopituitarism);
   b) Transcription factor mutation known to result in pituitary maldevelopment and hypopituitarism (e.g., *POUIF1* (Pit-1), *PROP-1*, *LHX-3*, *LHX-4*);
   c) Mutations in genes known to result in isolated GHD (e.g. *GH-1* or *GHRH-R*).

2. Re-evaluation for the adolescent/adult who is transitioning, having been treated for childhood GHD, is mandatory because some forms of childhood GHD may recover. For emerging adults who were diagnosed with GHD as children/adolescents, an IGF-1 level should be measured after 2-4 weeks off hGH therapy. However, in certain conditions a GH stimulation test is not required because GHD is almost certain on clinical or genetic grounds (see above). For the insulin tolerance test, the threshold for diagnosis is a peak GH < 6 ng/mL (6). The diagnostic thresholds for the Macimorelin and the Glucagon Stimulation test have not been determined.

When evaluating individuals with traumatic brain injury, **the timing of the evaluation is critical.** The evaluation should be undertaken no sooner than 12 months after injury.

c. Other relevant medical information

a) GH and IGF-1 results must be expressed in mass units;
b) Below normal range IGF-1 concentration is insufficient evidence for GHD. GH stimulation testing must be performed unless there is conclusive other evidence of hypothalamic-pituitary dysfunction (such as an organic lesion and hypopituitarism with more than 3 additional pituitary hormones being deficient or the presence of the genetic disorders listed above);
c) Therapeutic use exemption (TUE) for the treatment of adult GHD should be granted for only those who have conclusive evidence of GHD;
d) Subjects should be investigated for other pituitary hormone deficits and these should be adequately replaced before biochemical evaluation for GHD is performed.

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3. Treatment

a. Name of prohibited substance[1]

Human growth hormone, (e.g., Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Valtropin, TevTropin) and long acting hGH analogs (e.g., Somapacitan, lonapegsomatropin, somatrogon, efpegsomatropin)

b. Route of administration

Subcutaneous injections

c. Dosage and frequency

i. Women: 0.3 mg/day (may need higher dosage if taking oral estrogens)
ii. Men: 0.2mg/day

These are starting doses. Adjust dose depending upon clinical assessment, adverse effects and IGF-1 levels maintained at 0 to +1 SD unless previous history of malignancy.

d. Recommended duration of treatment

i. Adult onset GHD requires lifelong treatment;
ii. Childhood onset GHD requires re-evaluation within the transition period.

4. Non-prohibited alternative treatments

No alternative for human growth hormone substitution.

5. Consequences to health if treatment is withheld

The following consequences to health for individuals with untreated GHD include:

a) Decreased quality of life;
b) Decreased lean mass;
c) Decreased bone mineral density;
d) Increased fat mass;
e) Increase in cardiovascular risk factors.

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6. Treatment monitoring

Treatment should be periodically monitored using the following:

a) IGF-1 levels (ensuring that they are in the age-stratified normal range);
b) Blood glucose and Hemoglobin A1c;
c) Cardiovascular risk markers;
d) Bone density;
e) Quality of life (QoL) by use of GHD specific questionnaires, e.g., QoL-AGHDA.

7. TUE duration

a) Ten years if genetic, congenital or hypothalamic-pituitary structural abnormality (lifelong use);
b) Two years if due to brain trauma or irradiation.

The results of regular monitoring should be submitted annually for review.

8. Appropriate cautionary matters

Due to the significant risk for abuse of growth hormone for performance enhancement, these requirements must be strictly followed. The diagnosis should be confirmed by an endocrinologist with expertise in hypothalamic-pituitary disorders.

Given the potential controversy associated with the approval of a TUE for Growth Hormone, the opinion of an independent endocrinologist with expertise in hypothalamic-pituitary disorders is strongly suggested.

Also, the TUE reviewers working on behalf of the national anti-doping agencies (NADOs) and international federations (IFs) should be endocrinologists with expertise in hypothalamic-pituitary disorders.

Most patients with GHD self-administer GH. Although self-administration may seemingly present difficulty with monitoring, a logbook of growth hormone prescriptions and administration should be maintained by the athlete. The administration logbook may be subject to review at any time including for the annual review. Quantities of growth hormone administered to the athlete must be strictly controlled and limited by prescription.

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