Turk J Endocrinol Metab 2019;23:181-186

Growth Hormone Deficiency in the Transition Period

Çocukluktan Erişkinliğe Geçiş Döneminde Büyüme Hormonu Eksikliği

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Abstract

The importance of continuing growth hormone therapy in the transition and adulthood periods must be studied in adolescents with growth hormone deficiency with childhood onset. Continuation of growth hormone therapy during the transition period in patients with permanent growth hormone deficiency is recommended as the therapy has positive effects on adult body composition and regional body fat distribution as well as its promotion of an increase in bone mineral content. The chance of having permanent growth hormone deficiency is higher in patients with a mass lesion involving the pituitary area, multiple pituitary hormone deficiency, isolated growth hormone deficiency associated with an identified mutation (i.e., growth hormone 1 *(GH1)* gene, growth hormone releasing hormone receptor *(GHRHR)* gene, sex determining region Y(SRY)-box 3 *(SOX3*) gene), midline defects, and congenital structural hypothalamo-pituitary disorders, such as an ectopic posterior pituitary; thus, such patients do not require retesting. The patients with idiopathic isolated growth hormone deficiency are recommended to undergo retesting. The most appropriate time for a retest is the age when the child achieves 98-99% of the adult height. The insulin tolerance test is preferred during the transition period and a threshold level of <5 ng/mL is recommended as the diagnostic criterion for complete growth hormone deficiency. Growth hormone doses higher than those used in adults (e.g., 70 mcg/kg/day) should be used until linear growth has been achieved. Decreased quality of life is another criterion for the initiation of therapy. This review addresses the definition of growth hormone deficiency and indications and usage of growth hormone therapy during the transition period.

Keywords: Growth hormone deficiency; transition period; retesting

Özet

Çocukluk döneminde büyüme hormonu eksikliği (BHE) başlayan ve büyüme hormonu tedavisi kullanan ergenlerin, geçiş ve erişkin dönemde büyüme hormonu tedavisine devam etmesinin önemi araştırılmalıdır. Büyüme hormonu tedavisinin erişkin vücut kompozisyonu ve bölgesel yağ dağılımı üzerine pozitif etkisi ve kemik mineral yoğunluğunda artış sağlaması nedeniyle kalıcı büyüme hormonu eksikliği olan olgularda geçiş döneminde büyüme hormonu tedavisine devam edilmesi önerilmektedir. Hipofizer bölgeyi ilgilendiren kitle lezyonu, çoğul hipofizer hormon eksiklikleri, tanımlanmış bir mutasyonla ilişkilendirilen izole büyüme hormonu eksikliği (örn. büyüme hormonu 1 *(BH-1)* geni, büyüme hormonu salgılatıcı hormon reseptör *(BHRHR)* geni, Y kromozomu üzerindeki cinsiyet farklılaşmasını kontrol eden bölge (SRY)-box 3 *(SOX3)* geni), orta hat kusurları ve ektopik posterior hipofiz gibi konjenital yapısal hipotalamo-hipofizer bozuklukları olan olgularda kalıcı büyüme hormonu eksikliği olasılığı çok yüksek olduğundan, tekrar testlerinin yapılmasına gerek yoktur. İdiyopatik izole büyüme hormonu eksikliği olanlara tekrar testlerinin yapılması önerilmektedir. Test tekrarı için en uygun zaman çocuğun boyunun erişkin boyun %98-99'una ulaştığı yaştır. Geçiş döneminde insülin tolerans testi tercih edilmektedir ve eşik değerin <5 ng/mL olması tam büyüme hormonu eksikliği eksikliği için tanı kriteri olarak önerilmektedir. Lineer büyüme tamamlanıncaya kadar erişkinlerde kullanılan dozlardan daha yüksek dozlarda (örneğin; 70 mcg/kg/gün) büyüme hormonu kullanılması gerekmektedir. Yaşam kalitesinde azalma, tedaviye başlamak için kullanılan başka bir kriterdir. Bu çalışmada, büyüme hormonu eksikliğinin tanımı ve büyüme hormonu tedavisinin geçiş döneminde kullanılma endikasyonları üzerinde durulması amaçlanmıştır.

Anahtar kelimeler: Büyüme hormonu eksikliği; geçiş dönemi; retest (tekrar testi)

Introduction

The effects of growth hormone deficiency (GHD) may substantially vary depending on the stage of life of the individual. Children and adolescents are most vulnerable to the effects of GHD and the most significant effects of growth hormone (GH) during this period are witnessed in linear growth. GH

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Received: 15/03/2019 **Received in revised form:** 07/05/2019 **Accepted:** 19/06/2019 **Available online:** 03/07/2019

DOI: 10.25179/tjem.2019-65793

therapy in childhood aims to promote growth to achieve the maximum height appropriate for the target height and within the normal height ranges of the population. The use of GH replacement therapy in doses sufficient to promote growth in childhood is thus preferred. Only a small proportion of patients followed up with a diagnosis of GHD in childhood and who undergo GH therapy require continuing GH therapy in adulthood. In childhood, patients having both complete and incomplete GHD are considered candidates for GH replacement, whereas only adult patients with severe and complete GHD are treated. Besides growth promotion, GH therapy in adulthood also promotes lipolysis, muscle mass, and bone mineralization, reducing the risk of cardiovascular disease, taking advantage of other metabolic effects such as increasing exercise tolerance and increasing quality of life. Low-dose GH therapy is required for this purpose in adulthood.

Growth is complete by the age of 16.5-17 years in boys and 14.5-15 years in girls, while increases in muscle mass, muscle strength, and bone mineralization continue until the mid-20s. This is referred to as the transition period when growth has been completed but adult bone and muscle mass have not yet been reached. This period continues from puberty to 6-7 years after reaching the adult height, corresponding to an average age of 15-25 years (1,2). The transition period also marks physical and psychosocial changes that start in late puberty and end after reaching full maturity. This review addresses the definition of GHD and indications and usage of GH therapy during this transition period.

Indications for the Continuation of GH Therapy into Adulthood in Cases that are Followed up with the Diagnosis of GHD in Childhood

The importance of continuing growth hormone (GH) therapy in the transition and adulthood periods must be studied in adolescents with GH deficiency (GHD) with childhood onset. In permanent GHD, GH therapy is used in the transition period after adult height has been reached (Figure 1) (3-5). Continuation of GH therapy during the transition period in patients with permanent GHD is recommended because of the therapy has positive effects on adult body composition and regional body fat distribution as well as the promotion of an increase in bone mineral content.

Continuation of GH therapy into adulthood is not recommended in patients undergoing GH therapy for indications other than GHD (i.e., Turner syndrome, Noonan syndrome, Prader Willi syndrome, chronic renal failure, idiopathic short stature, children with low birth weight). However, GH therapy is continued in adulthood in patients with Prader-Willi syndrome because of the sustained positive effects of GH therapy on body composition (1,6,7).

Reassessment with Retests for GHD in the Transition Period

Patients requiring retesting

Various datasets have demonstrated that the secretion of GH returns to normal when retests are performed in adulthood after the cessation of GH replacement therapy in 25-75% of children diagnosed with idiopathic isolated GHD in childhood (8). The patients diagnosed with partial GHD in previous dynamic tests (peak GH, 5-10 ng/mL) are more likely to have a normal GH response in retests (9). The patients with idiopathic isolated GHD are recommended to undergo retests for a reassessment of GHD during the transition period. GH response was normal in retests for GHD in the later periods of life in approximately 50% of patients who received central nervous system (CNS) irradiation for various reasons in childhood, and who were followed up with a diagnosis of GHD; these patients are recommended to undergo retests in the transition period (10). Although GHD is not detected during the transition period, irradiation-induced injury to the hypothalamus and pituitary gland may progress over the following 5-10 years after completion of radiotherapy, and the patients must, therefore, be reassessed with retests in adulthood.

Previous studies have suggested that an insulin-like growth factor 1 (IGF-1) level of ≤-2 standard deviation (SD) after cessation of GH treatment should be considered sufficient evidence for permanent GHD in patients with a high probability of having

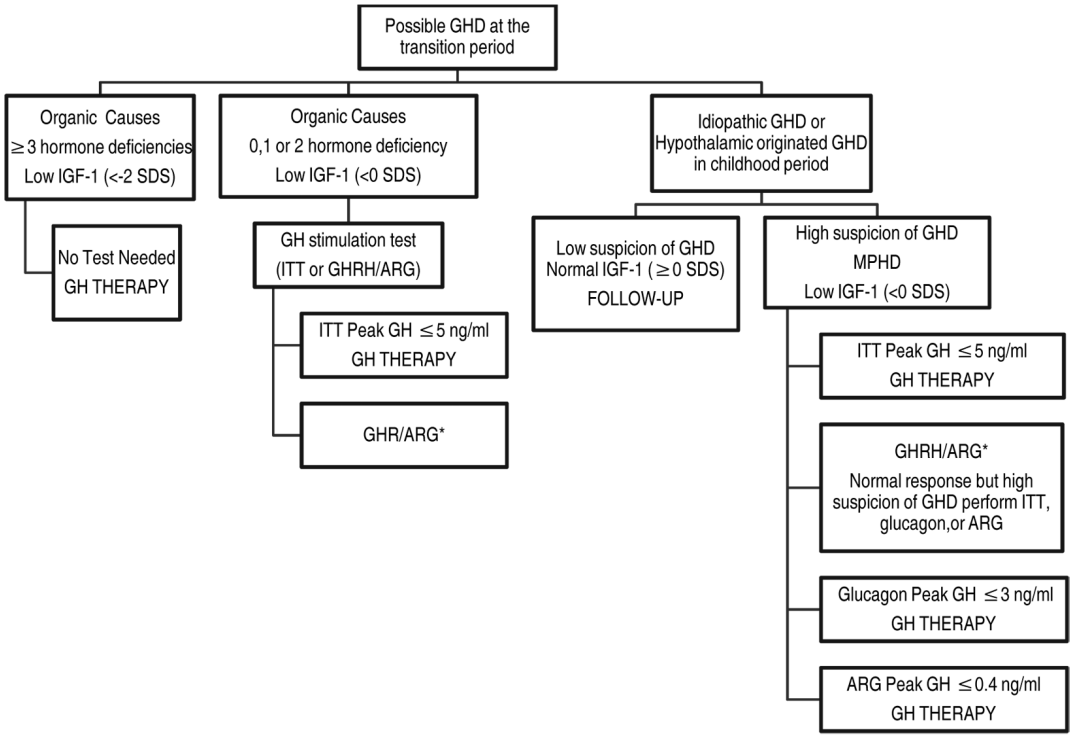

Figure 1: The principles for evaluating patients with possible growth hormone deficiency in the transition period (4)
* GH THERAPY BMI <25 kg/m² and peak GH >11 ng/mL, BMI 25-30 kg/m² and peak GH <8 ng/mL, BMI >30 kg/m² and peak GH <4 ng/mL.

GHD (1). If IGF-1 is >-2 SD, the patient should undergo a GH stimulation retest, and the diagnosis of GHD is confirmed if there is a low GH response to the test. In patients less likely to have GHD in retests, an IGF-1 measurement is recommended in conjunction with a GH stimulation retest. Normal IGF-1 levels do not rule out the possibility of GHD, and patients with suspected GHD and normal IGF-1 levels should be further investigated with a stimulation test.

Patients who do not require retesting

The chance of having permanent GHD is higher in patients with a mass lesion involving the pituitary area (craniopharyngioma, etc.) and multiple pituitary hormone deficiency (MPHD) secondary to pituitary surgery, patients with transcription factor mutations (i.e., POU1F1, PROP1, HESX1, LHX3, and LHX4) determined with molecular genetic studies that result in MPHD, or patients with isolated GHD associated with an identified mutation (i.e., GH1, GHRHR, SOX3), patients with midline defects or pituitary stalk agenesis, and patients with congenital structural hypothalamo-pituitary disorders, such as an ectopic posterior pituitary; thus, such patients do not require retesting. The chance of having permanent GHD is high in patients with MPHD, regardless of any association with a structural pituitary disorder (11). The probability of GHD continuing in adulthood is 96% in patients with a deficiency of three pituitary hormones, and 99% in patients with a deficiency of four pituitary hormones (12). These patients, therefore, do not require retesting.

Although patients with isolated GHD require retests and those with MPHD do not require retests because of the high expectation of permanent deficiency, there are also reports on patients with isolated GHD in childhood but who meet the criteria for severe GHD when a retest is performed in adulthood, as well as patients with MPHD who have normal GH reserves when a retest is performed (13).

Timing of retesting

The diagnosis of GHD should be reassessed and GH secretion should be retested in young adults that were followed up in childhood with a diagnosis of GHD. The most appropriate time for a retest is the age when the child achieves 98%-99% of the adult height (bone age in females is 14-15 girls and 16-17 years in boys) and growth rate under GH replacement therapy is ≤2-2.5 cm/year. This transition period is the most common timing for a retest. In individuals in whom a retest is deemed necessary, GH therapy must be interrupted for some period before performing a stimulation test. For retests, there is no clear definition of the shortest interval free from GH therapy without affecting the test results. Consensus reports (14) and clinical practice guidelines recommend a 1-3-month interval between the discontinuation of GH therapy and a retest (15). The shortest interval defined in the literature is 8-15 days (16), although a one-month interval is often recommended.

GH stimulation tests that can be performed as a retest and the threshold levels for these tests

GH stimulation tests with pharmacological agents such as arginine, clonidine, glucagon, and levodopa are commonly used in childhood. The insulin tolerance test (ITT) (17) is not widely preferred as it can cause hypoglycemia in childhood, but it is preferred in adults and during the transition period and is considered the most reliable and gold standard test for diagnosing GHD. A threshold level of <5.1 ng/mL for peak GH shows 95% sensitivity and 92% specificity, whereas a threshold level of <3.3 ng/mL shows specificity up to 95%. The "GH releasing hormone" (GHRH) plus arginine test has higher sensitivity, but may show a false-positive normal GH response in cases with GHD of hypothalamic origin, as GHRH directly stimulates the pituitary gland (18). A threshold level of <4.1 ng/mL for peak GH level in a GHRH plus arginine test yields 95% sensitivity and 92% specificity, whereas a threshold level of <1.5 ng/mL yields 95% specificity. GH stimulation tests using glucagon can be performed in conditions where ITT is contraindicated due to the risk of hypoglycemia, such as in cases with coronary artery disease, cerebrovascular event, epilepsy, and transcranial surgery.

Severe (complete) GHD in adults is defined as peak GH response of <3 ng/mL in response to an ITT, and this threshold is considered a criterion for GH replacement therapy in adults (19). This threshold, however, is considered low for the transition period. The best GH response to a GH stimulation test in normal children is achieved in late adolescence, when GH levels are >5 ng/mL. Thus, a threshold level of <5 ng/mL in patients undergoing ITT is recommended as the diagnostic criterion for complete GHD in the transition period (19,20). A study on adolescents going through the transition period showed that a threshold level of 6.1 ng/mL for peak GH response in ITT yielded 100% specificity and 96% sensitivity (21). The threshold level recommended for the glucagon test in adulthood is 3 ng/mL, whereas the threshold levels in a GHRH plus arginine test, after the body mass index (BMI) is considered, are as follows: BMI <25 kg/m^2, <11 ng/mL; BMI 25-30 kg/m^2, <8 ng/mL; and BMI >30 kg/m^2, <4 ng/mL. Tests other than ITT have not been validated in the transition period, and no evaluations that considered BMI in the transition period have been made. GH stimulation tests with clonidine or L-dopa alone are not recommended in adolescence and during the transition period (22). The threshold levels for GH stimulations tests used in the transition period are given in Table 1.

Appropriate Dose of GH Therapy and Follow-up of Patients in the Transition Period

GH doses higher than those used in adults should be used during the transition period until linear growth has been achieved (when the annual growth rate is <2-2.5 cm). The use of 70 mcg/kg/day pubertal dose mimics the physiological conditions and increases linear growth, as insufficient growth was observed in some adolescents treated with standard GH doses (40 mcg/kg/day in prepubertal period). However, it is not known whether the GH dose should be increased and what dose should be used in adoles-

Table 1. The threshold levels for GH stimulations tests used in the transition period.

GH stimulation tests	Threshold level (ng/mL)		
Insulin tolerance test (ITT)	≤5		
GHRH plus arginine test	<11 (BMI <25 kg/m^2)	<8 (BMI 25-30 kg/m^2)	<4 (BMI >30 kg/m^2)
Glucagon	≤3		
Arginine	≤0.4		

cence. The patient should be switched to adult doses when the continuation of GH therapy is planned after linear growth has been completed. The initial GH dose in adults is 200-300 mcg/day, although women, in general, require higher doses than men (600-900 mcg/day). Women taking oral estrogen particularly require higher doses.

Therapy should be initiated with adult doses in adolescents in the transition period, and the dose should be titrated 1-2 months after initiating GH therapy at an adult dose to maintain an IGF-1 level in the upper half of normal ranges defined for age and gender (23). One or two clinical control visits per year can be arranged after achieving a dose that does not cause side effects. Thorough medical history must be obtained, and IGF-1, fasting glucose, HbA1c, and lipid profile must be tested at each control visit to evaluate the patient for possible side effects. A baseline evaluation of body composition and bone mineral density via dual-energy x-ray absorptiometry screening is recommended, as GH therapy affects body composition and regional body fat distribution. If any disturbance is detected in a baseline evaluation, the screening must be repeated 18 months later to evaluate the response to therapy (23,24).

Decreased quality of life is another criterion for the initiation of GH therapy in adults with GHD, and the quality of life must be evaluated in patients suffering from somatic and psychological complaints. This criterion is evaluated using a self-administered questionnaire containing questions that inquire health status, economic status, and social factors, although the disease-specific quality of life questionnaires are also available, which are validated tools widely used in current practice (24-26).

Conclusion

Continuation of GH therapy during the transition period in patients with permanent GHD is recommended because the therapy has positive effects on the adult body composition, but the continuation of GH therapy in adulthood is not recommended in patients undergoing GH therapy for indications other than GHD. The chance of having permanent GHD is higher in patients with a mass lesion involving the pituitary area, MPHD, isolated GHD associated with an identified mutation (i.e., GH1, GHRHR, SOX3), midline defects, and congenital structural hypothalamo-pituitary disorders, such as an ectopic posterior pituitary. Therefore, such patients do not require retesting, while patients with idiopathic isolated GHD are recommended to undergo retesting.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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