Physiopathology, Diagnosis, and Treatment of GH Deficiency

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Abstract

Growth hormone deficiency (GHD) in adults arises due to decreased secretion of GH from the pituitary gland. Until two decades ago, GHD in adults was not accepted as a clinical syndrome, and it was supposed that GH has little physiologic effects after adolescence. However after the advent of recombinant GH, physiologic role of GH becomes clearer in the adult life, and the studies during the last two decades revealed GHD as a real disease associated with a plenty of clinical manifestations. GHD is one of the most common hormonal deficiencies in adults with hypopituitarism due to variety of causes. In the present chapter,

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acquired causes, pathophysiology, diagnosis, and treatment of GHD in adults will be discussed based on the recent advances in the literature.

Keywords
Growth hormone deficiency (GHD) · Growth hormone replacement therapy (GHRT) · Hypopituitarism · Recombinant GH (rhGH) · Traumatic brain injury (TBI) · Sheehan's syndrome · Pituitary · Hypothalamus

Introduction

Growth hormone deficiency (GHD) in adults arises as a result of decreased secretion of GH from the pituitary gland. Until two decades ago, GHD in adults was not accepted as a clinical syndrome, and it was assumed that GH has little physiologic effects after cessation of growth. After the advent of recombinant GH, the physiologic role of GH becomes clearer in the adult life. GH continues to be produced until older ages and is the most abundant hormone in the adult pituitary gland.

Epidemiology, Causes, and Pathophysiology of GHD in Adults

The pathophysiology of GHD is closely related to the causes of GHD. Therefore they are discussed under the same subtitle. Growth hormone deficiency (GHD) can develop due to a variety of conditions and may occur either as an isolated hormone deficiency or as multiple pituitary hormone deficiencies. GH deficiency is one of the most common hormonal deficiencies in hypopituitary adults. Moreover, GH is typically the first hormone to become clearly deficient in the majority of the different causes of hypopituitarism (Arafah 1986; Schneider et al. 2007a; Tanriverdi et al. 2015; Vance 1994).

Adults with GHD can be grouped into those who had GHD occurring in childhood (childhood-onset GHD, CO-GHD) and those who acquired GHD in adult life (adult-onset GHD, AO-GHD). In the KIMS database (Pfizer International Metabolic Database), which includes nearly 13,000 adults with GHD, nearly 25% of the patients were reported as having CO-GHD (Brabant et al. 2009). Congenital causes including some GH-gene-related mutations, congenital structural defects of the hypothalamo-pituitary region, and several acquired causes including perinatal insults are some of the causes of CO-GHD (Molitch et al. 2011). In this chapter the acquired causes of GHD in adults will be discussed.

Classical Causes

The most frequent classical causes of GHD in adults are pituitary adenomas and/or their treatment (Bates et al. 1996; Vance 1994). Vance et al. previously reported that the most common etiology of hypopituitarism was pituitary tumors and/or their

treatment. In that etiological classification, head trauma was accepted as an uncommon cause of hypopituitarism, and Sheehan's syndrome was not even listed, probably due to the fact that the data were largely derived from Western population studies (Vance 1994). To date, two population-based epidemiological studies have been published investigating the rates and causes of hypopituitarism (Fernandez-Rodriguez et al. 2013; Regal et al. 2001). Moreover three registry-based studies were published, and two of them specifically investigated the rates and causes of GHD in adults (Sassolas et al. 1999; Stochholm et al. 2006; Tanriverdi et al. 2014a).

In the population-based studies, the prevalence and incidence of hypopituitarism were reported to range 37–45 cases per 100,000 inhabitants and 2.1–4.2 cases per 100,000 per year, respectively (Fernandez-Rodriguez et al. 2013; Regal et al. 2001). In the first epidemiological study, the most common cause of hypopituitarism were pituitary tumors (nonsecretory adenomas were the most common) and/or their treatment, accounting for at least 60% of all cases. Non-tumoral causes were reported as 30% of all cases, and among them the idiopathic group (11% of all cases) and Sheehan's syndrome (6% of all cases; 2.6 per 100,000 women) were the first two leading etiologies. Additionally, 61% of all the patients had GHD (Regal et al. 2001). In the second epidemiological study at the same region, the most common cause of hypopituitarism was pituitary tumors (45.7%), and peri-pituitary tumors (craniopharyngioma, chordoma, meningioma) were seen in about 9% of the patients. Infiltrative diseases were reported in 5.3% of the patients, but Sheehan's syndrome was not reported, and traumatic brain injury (TBI) was reported as a rare cause of hypopituitarism in 1.4% of all patients (Fernandez-Rodriguez et al. 2013). In a recent registry study including 773 adult patients with hypopituitarism, the etiology of hypopituitarism was investigated in tertiary care institutions in Turkish population. In contrast to previous epidemiological studies, the most common etiology of hypopituitarism was non-tumoral causes (49.2%, including Sheehan's syndrome, idiopathic causes, empty sella, TBI, lymphocytic hypophysitis, apoplexia, subarachnoid hemorrhage, histiocytosis, acute meningitis). Pituitary tumors and/or treatment was found to cause hypopituitarism in 43.6% of all patients. However, when the causes were analyzed according to gender, the most common cause of hypopituitarism in males was pituitary tumors (nonsecretory pituitary adenomas were the most common, 20.9% among all patients); however one of the most common causes of hypopituitarism in females was Sheehan's syndrome (13.8% of all patients) (Tanriverdi et al. 2014a).

In the nationwide registry study conducted between 1980 and 1999 in Denmark, the incidence and causes of GHD were specifically investigated among 1823 patients with GHD. The average incidence rate of AO-GHD was reported as 3.3 per 100,000 per year. The most common causes of AO-GHD were as follows: pituitary adenomas and/or treatment (nonfunctioning adenomas were the leading cause), craniopharyngioma, peri-pituitary tumors, and apoplexy. Sheehan's syndrome, TBI, and meningitis/encephalitis were reported as very rare causes of GHD (less than 2% of all patients) (Stochholm et al. 2006). In a retrospective (data were collected during 1994–1995) registry study from France, 1652 adult patients with GHD were enrolled. The annual incidence of AO-GHD was reported as 1.2 per

100,000. The causes of GHD were not reported in detail, but the most common cause was pituitary tumors (78% of all patients), and non-tumoral pathologies were found in 8% of the patients (Sassolas et al. 1999). These two registry studies imply that by the year 2000, classical causes of GHD were predominant, such as pituitary and peri-pituitary tumors and/or their treatment. However, the studies published in the last decade clearly show that the etiological patterns of AO-GHD have slightly changed to non-tumoral causes, probably due to increasing awareness after the approval of GH replacement therapy in adults and/or due to accumulating data from different populations, which will be discussed in the next section.

Based on the KIMS pharmaco-epidemiological database, Abs. et al. analyzed the demographic and clinical characteristics of 1034 adult patients with GHD. The first three common etiologies of GHD were reported as pituitary tumors and/or their treatment (53.9%), craniopharyngioma (12.3%), and idiopathic causes (10.2%). Moreover, cranial tumors far from the pituitary and their treatment by surgery or cranial irradiation caused GHD in 7% of the patients (Abs et al. 1999). In one of the recent reanalysis of the KIMS database investigating the etiologies of GHD in 13,167 adult patients, the three most common causes of GHD were pituitary adenomas (44%), idiopathic causes (16%), and craniopharyngioma (11%) (Brabant et al. 2009). In the KIMS database, during 10 years' time, although pituitary adenomas were still the most common cause of adult GHD, the rate of tumoral causes was substantially decreased, and non-tumoral causes including idiopathic causes increased (Abs et al. 1999; Brabant et al. 2009). However it is important to mention that the diagnostic criteria for the idiopathic GHD were not standardized and stringent in these database studies. Therefore the reported relatively high frequency of idiopathic causes is controversial. Detailed history, including head trauma and contact sports and central nervous system infections, and stringent diagnostic criteria (section "Who to Test") are warranted for precise diagnosis of idiopathic GHD (Melmed 2013; Molitch et al. 2011). Based on the current data, substantial amount of the adult patients with the diagnosis of idiopathic GHD might have overlooked TBI history (section "Nonclassical Causes").

The pathophysiology of hypopituitarism due to pituitary adenomas is mainly associated with size of the tumor. Microadenomas (<1 cm) very rarely cause hypopituitarism. Rates of hypopituitarism (particularly GH is the most common pituitary hormone deficit) increase with tumor size; pituitary dysfunction was present in all patients with tumors >4 cm in diameter (Nomikos et al. 2004). Nearly 50% of patients with macroadenomas evaluated before surgery already had GHD; after surgery about 80% of the patients had GHD. Moreover, it was found that GHD developed after 5 years in 100% of the patients who had received radiotherapy after surgery (Littley et al. 1989). Macroadenomas cause pituitary hormone deficiencies by compressing the portal vessels in the pituitary stalk, either directly due to an expanding tumor mass or indirectly by increasing intrasellar pressure (Arafah et al. 2000). The risk of hypopituitarism due to pituitary surgery depends on the size of the original adenoma, the degree of infiltration, and the experience of the surgeon. However patients undergoing transsphenoidal surgery less likely develop pituitary hormone deficiencies than transcranial surgical approach. Pituitary functions may

also recover after pituitary surgery. Since, surgical debulking of an adenoma may reduce pressure on the portal vessels and normal pituitary tissue (Arafah et al. 2000). The possible mechanisms by which cranial irradiation causes hypopituitarism are not fully understood. It is thought that ionizing radiation causes direct neuronal damage and consequent degeneration (Darzy 2013). Moreover somatotropes are the most sensitive pituitary cells to radiation damage and the only cells affected by radiation doses lower than 20 Gy (Littley et al. 1989). Therefore most of the acquired classical causes of GHD lead to attenuated GH synthesis and secretion via several mechanisms including somatotroph impingement, compression, inflammation, or vascular insult (Melmed 2013). The acquired causes of GHD in adults are summarized in Table 1. The common classical causes of GHD are as follows: pituitary adenomas and/or their treatment including surgery or cranial irradiation, idiopathic causes, craniopharyngioma, cranial tumors far from the pituitary, and their treatment including surgery or cranial irradiation. The rare classical causes of GHD are as follows: peri-pituitary tumors (meningiomas, gliomas, metastases) and/or their treatment, lymphocytic hypophysitis, empty sella, apoplexia, and infiltrative/granulomatous diseases (Langerhans cell histiocytosis, sarcoidosis, tuberculosis, hemochromatosis).

Table 1 Acquired causes of adult-onset GH deficiency

Pituitary adenomas and/or their treatment[a]
Brain injury[a]
Traumatic brain injury
Sports-related head trauma (including chronic repetitive head trauma)
Subarachnoid hemorrhage
Blast injury
Sheehan's syndrome (postpartum pituitary necrosis)[b]
Peri-pituitary tumors
Craniopharyngiomas, meningiomas, gliomas, chordomas, metastases, etc.
Cranial tumors far from the pituitary and their treatment (surgery or cranial irradiation)
Infarction
Apoplexia
Infections
Acute viral or bacterial meningitis/meningoencephalitis, abscess, fungal infections
Autoimmune disorders
Lymphocytic hypophysitis
Infiltrative/granulomatous diseases
Tuberculosis, histiocytosis, sarcoidosis, hemochromatosis, etc.
Empty sella
Idiopathic causes

[a]Although pituitary adenomas are the most common classical cause of GHD, an increasing number of recent studies and estimated prevalence have revealed that brain injury might outnumber pituitary adenomas in causing GHD

[b]Sheehan's syndrome is still an important problem in developing and underdeveloped countries and not a very rare cause of GHD, as previously known

Nonclassical Causes

Under the title of nonclassical causes of GHD, some of the discussed causes (such as sports-related head trauma and blast injury) which appeared in the current literature are novel; however, some of the other discussed causes (such as TBI, Sheehan's syndrome, subarachnoid hemorrhage, and acute viral or bacterial meningitis/meningoencephalitis) were known previously but accepted as very rare causes of GHD in adults.

Traumatic Brain Injury (TBI) and Sports-Related Head Trauma

Traumatic brain injury (TBI) is a worldwide public health problem which affects mainly the young or middle-aged adult population. Although it is commonly stated in textbooks as one of the rare causes of hypopituitarism, after the year 2000, substantial amount of studies showed that head trauma-mediated hypopituitarism could actually be more frequent. In a meta-analysis including 1015 adult TBI patients, from 10 cross-sectional and 4 12-month prospective studies, the pooled prevalence of anterior hypopituitarism was reported as 27.5% (95% CI, 22.8- 28.9). The pooled prevalences of hypopituitarism in mild, moderate, and severe TBI (severity is classified according to Glasgow Coma Scale) were estimated as 16.8%, 10.9%, and 35.3%, respectively. These data clearly demonstrated that although the risk of developing hypopituitarism is highest in severe TBI, the risk is substantially high in mild TBI and is even comparable with moderate TBI. In addition, the most common pituitary hormone deficiency after TBI was GHD, and isolated GHD was found to be more frequent than multiple hormone deficiencies (Schneider et al. 2007b). The reported variations in the frequency of GHD after TBI are in part caused by the heterogeneity of the dynamic endocrine tests and/or diagnostic criteria for GHD (Kokshoorn et al. 2010). Moreover, the variations in inclusion criteria for mild, moderate, and severe TBI patients and genetic background in different populations could be other reasons for the different prevalences of GHD reported in studies (Tanriverdi et al. 2008a, 2015; Tanriverdi and Kelestimur 2015).

Reanalysis of hypopituitarism in the chronic phase after TBI was performed in a recent systematic review including 1203 adult patients. Prospective studies performed 3 and 5 years after TBI were also included (Tanriverdi et al. 2008b, 2013) in this analysis. By using conservative criteria, the overall rate of persistent GHD after TBI was 12%, which was significantly more common than in the normal population (Tanriverdi et al. 2015). The incidence of head trauma is nearly 40-fold higher than that of pituitary adenomas, and at least 10–15% of these TBI patients have GHD. Therefore these findings suggest that TBI-induced hypopituitarism could be one of the most common causes of adult GHD (Schneider et al. 2007a) (Table 1). However future epidemiological studies are warranted to confirm this estimated rate. Nevertheless, the main problem found in this field is that the clinicians who treat TBI patients have very little awareness of the risk of GHD after TBI, and most of these patients were not referred to an endocrinologist.

Sports, including contact/combative sports (boxing, kickboxing, soccer, football, ice hockey, rugby, etc.), are common around the world, especially among the younger generation. Sports-related head trauma (including mainly sports-related chronic repetitive head trauma) is an important public health problem that is associated with increased risk of TBI. In a previous study, 21% of all TBIs, which equate to an incidence rate of 170 per 100,000, were identified as resulting from a sports-related activity (Theadom et al. 2014). The International Kickboxing Federation estimated that about one million participants around the world are involved in kickboxing. Like boxing, kickboxing is characterized by chronic repetitive head trauma, and the head is one of the most frequently injured organs (Zazryn et al. 2003). Although the relationship between boxing and kickboxing TBI has been known for a long time, pituitary functions have not been routinely investigated until recently. Current data clearly showed that nearly 10–20% of active boxers or kickboxer and nearly 40% of retired athletes have GHD, and most of them have isolated GHD (Kelestimur 2005; Tanriverdi et al. 2007, 2008c). Recently, the risk of TBI-induced hypopituitarism in football players has been investigated in a cohort of retired US professional football players. GH deficiency (19.1%) was reported as the most common pituitary dysfunctions after repetitive sports-related head trauma in football players (Kelly et al. 2014). These abovementioned studies clearly demonstrated that sports-related TBI is a novel cause of GHD in adults. Although pituitary dysfunction has been shown in sports-related head trauma, large-scale screening studies are warranted to understand the real burden of GHD among active and retired athletes.

The exact pathophysiology of pituitary dysfunction after TBI and sports-related head trauma is not well understood, but multiple pathological mechanisms have been proposed, including compression of the pituitary gland and hypothalamic nuclei or interruption of the long hypophyseal portal vessels by edema; direct mechanical trauma to the pituitary gland, stalk, and/or hypothalamus; increased intracranial pressure; hemorrhage; skull fracture; any cause of ischemic/hypoxic insult; genetic predisposition (Apo E polymorphisms); persistent neuroinflammation; and autoimmunity caused by antipituitary and/or antihypothalamus antibodies (Dusick et al. 2012; Tanriverdi et al. 2015).

Blast Injury

Blast TBI from explosive devices is mainly seen in soldiers. However, unfortunately, due to increased war injuries all over the world, many civilians are also exposed to blast injury. Recently, the relationship between blast injury (blast TBI) and pituitary dysfunction was investigated in two studies including small number of soldiers. The first study included 26 male soldiers whose blast exposure was at least 1 year prior to the evaluation. In 42% of the participants with blast injury, deficiencies in one or more pituitary axis were reported. The most common pituitary hormone deficits were GH and FSH/LH deficiencies (Wilkinson et al. 2012). The second study included 19 male soldiers who had blast TBI and 39 male controls that had non-blast TBI. The authors demonstrated that 32% of the soldiers had anterior pituitary dysfunction (10.5% had

GHD), which was significantly more frequent than in the non-blast TBI group (Baxter et al. 2013). These two studies imply that blast injury may cause hypopituitarism at least 12 months after the event. The literature data in this area are too premature to accept blast injury as a frequent cause of GHD, but it is a new cause of GHD.

Sheehan's Syndrome

Sheehan's syndrome was first described by HL Sheehan and classically refers to postpartum pituitary dysfunction due to pituitary necrosis occurring after severe hypotension and shock secondary to massive bleeding during delivery (Kelestimur 2003; Sheehan 1937). In the developed regions and countries of the world, Sheehan's syndrome was reported to be a very rare cause of hypopituitarism due to the advent of modern obstetric care (Rosen and Bengtsson 1990; Sheehan 1965; Toogood et al. 1995). However, in the KIMS pharmaco-epidemiological database, 1034 GH-deficient patients, mainly from different parts of European countries, were analyzed, and Sheehan's syndrome was found as the sixth most common cause of GHD (3.1% of all patients) (Abs et al. 1999). In a recent population-based retrospective study from Iceland, the prevalence of Sheehan's syndrome (5.1 per 100,000 women) was found to be higher than expected (Kristjansdottir et al. 2011). This prevalence is clearly higher than in two previous epidemiological studies from Spain (Fernandez-Rodriguez et al. 2013; Regal et al. 2001). These recent findings suggest that in Western countries, Sheehan's syndrome seems to be not a very rare etiology of hypopituitarism and GHD as previously thought, probably due to increased migration from underdeveloped countries or to less improved obstetric care in the rural parts of the developed countries.

The World Health Organization estimated that nearly 100,000 women died yearly due to Sheehan's syndrome and approximately more than three million women were suffering from Sheehan's syndrome. In India, in the Kashmir region, Sheehan's syndrome frequency was reported as 3.1% among the female population, and two-thirds of women were still giving birth at home (Zargar et al. 2005). In a retrospective study from the Philippines, the data of 143 patients with hypopituitarism at a tertiary care institution were analyzed. Sheehan's syndrome was reported in 8% of all patients, which is the third most frequent etiology of hypopituitarism, suggesting a higher occurrence of Sheehan's syndrome than in the Western population (Elumir- Mamba et al. 2010). In a recent registry study, 773 adult patients with hypopituitarism who were admitted to tertiary care institutions in a Turkish population were included. The frequency of Sheehan's syndrome among all patients was found as 13.8%, which is the second most common cause of hypopituitarism. Only 17% of the patients with Sheehan's syndrome were less than 40 years old, implying the tendency of decreasing frequency over time probably due to the decrease in home deliveries and the improvement of obstetric care in Turkey (Tanriverdi et al. 2014a). It was previously demonstrated that patients with Sheehan's syndrome have more severe pituitary hormone deficiencies than in the patients with hypopituitarism due to other causes, and almost all patients have severe GHD (Kelestimur et al. 2005; Tanriverdi et al. 2005).

Therefore, current literature data imply that Sheehan's syndrome is a nonclassical cause of GHD in developed countries, but due to the reemergence of Sheehan's

syndrome in the Western world, it is not a rare cause of GHD, as previously thought. However, in underdeveloped and developing countries, Sheehan's syndrome still seems to be one of the leading causes of GHD.

The certain pathophysiology of GHD in Sheehan's syndrome is not clearly understood. It is well-known that the pituitary gland is physiologically enlarged during pregnancy which makes it vulnerable to ischemia. The basic process is infarction secondary to arrest of blood flow to the anterior lobe of the pituitary gland, and it may be due to massive postpartum uterine hemorrhage, vasospasm, thrombosis, or vascular compression. The size of the sella may play a role in the pathogenesis of Sheehan's syndrome. A relatively small sella size, hypercoagulation, genetic factors, and pituitary autoimmunity were also suggested as risk factors for the development of Sheehan's syndrome (Diri et al. 2016; Kelestimur 2003; Kovacs 2003).

Other Nonclassical Causes of GHD

Several studies after the year 2000 have demonstrated that aneurysmal subarachnoid hemorrhage (Karaca et al. 2013; Kelly et al. 2000; Kronvall et al. 2015) and acute viral or bacterial meningitis/meningoencephalitis (Schaefer et al. 2008; Tanriverdi et al. 2012; Tsiakalos et al. 2010) may cause substantial frequency of GHD which is in contrast to previous knowledge.

Unlike TBI and Sheehan's syndrome, the current literature data are not consistent or sufficient to draw a clear conclusion regarding the real frequencies of GHD in these disorders. However, based on the current findings, it is tempting to speculate that subarachnoid hemorrhage and acute viral or bacterial meningitis/meningoencephalitis are nonclassical etiologies of AO-GHD which cause higher frequencies of hypopituitarism than previously known.

Based on the classical literature knowledge and current data, the acquired causes of GHD in adults are listed in Table 1.

Diagnosis of GHD in Adults

Clinical Features of GHD in Adults

GHD in adults results in a clinical syndrome characterized by symptoms and signs summarized in Table 2. Adults with GHD manifest a range of body compositional, physical, and psychological abnormalities. The functions of several organ systems are directly altered by the loss of or decreased effects of GH.

GHD in adults manifest decreased lean body mass and increased body fat mass, particularly in the visceral compartment. Therefore these patients are mainly overweight or obese and display a disproportionate increase in abdominal fat. Body composition abnormalities are mainly due to the loss of lipolytic and anabolic actions of GH. Together these alterations contribute to the development of metabolic syndrome (Attanasio et al. 2010; Carroll et al. 1998; Hoffman et al. 1995; Moller and Jorgensen 2009).

Table 2 Symptoms and signs of adult GHD

Increased body fat mass (patients are overweight mainly with abdominal adiposity)
Reduced muscle bulk (decreased lean body mass)
Reduced strength and exercise performance
Reduced sweating (thin and dry skin)
Psychological problems and decreased quality of life (depression, anxiety, fatigue, impaired sleep, increased social isolation, memory problems, and impaired cognitive functions)

Exercise capacity is reduced in patients with GHD, and patients show significant impairment in physical performance and muscle strength. Exercise performance could be dependent on several factors including neuromuscular and cardiorespiratory functions. Furthermore, a mild reduction in body sodium levels and water volume has been described in adult patients with GHD. This decrease in tissue hydration could partially be responsible for reduced lean body mass measurements and reduced exercise performance (Amato et al. 1993; Cuneo et al. 1992). GH and/or IGF-I has an important role in skin physiology, and GHD deficiency in adults causes structural and functional changes in the skin and its appendages. The eccrine sweat glands are hypoplastic causing decreased sweat secretion rate, and skin thickness is decreased (Lange et al. 2001; Tanriverdi et al. 2014b).

Impaired quality of life (QoL) and decreased psychological well-being are well-established clinical features in adult patients with GHD. Decreased energy and vitality, depressed mood, increased anxiety, social isolation, impaired cognitive functions, and deficits in memory and concentration are commonly reported in these patients (Golgeli et al. 2004; McGauley et al. 1990). Additionally decreased in sleep quality and impaired sleep physiology may also contribute to the decreased QoL (Ismailogullari et al. 2009; Tanriverdi et al. 2014b).

GHD in adults is difficult to diagnose based on clinical features because the signs and symptoms of GHD are nonspecific. Therefore cause-specific history (Table 1) becomes more important for clinical suspicion and selecting patients for diagnostic testing.

Who to Test?

To select appropriate candidates for GH replacement therapy (GHRT), the principles of the evaluation of patients for diagnostic testing are as follows (Ho 2007; Molitch et al. 2011):

1. The adult patients with structural hypothalamic/pituitary disease (surgery or irradiation in these areas), history of TBI, or evidence of other pituitary hormone deficiencies should be considered for testing for acquired GHD.
   Because TBI is an important cause of hypopituitarism and at least 10–15% of patients have GHD, it is tempting to suggest that the first approach should be testing all patients with a history of head trauma. However, this strategy is not

cost-effective and would result in unnecessary health resource consumption for a community. Those patients (regardless of the severity of TBI) who need hospitalization for at least 24 h and who need ICU monitoring, in particular, should be screened for GHD during the acute phase and prospectively (yearly at least 5 years after TBI). Those with a history of complicated mild TBI, moderate TBI, and severe TBI at any time after the event are good candidates for biochemical testing for GHD. But mild TBI patients who are discharged from emergency units and/or who have no loss of consciousness or who have posttraumatic amnesia of less than 30 min are not recommended for GHD testing (Tanriverdi et al. 2015).

2. Patients with CO-GHD should be retested as adults after achievement of adult height (except cases with specific proven mutations, congenital lesions causing multiple hormone deficiencies, irreversible structural hypothalamic-pituitary lesions/damage).
3. To enhance the diagnostic precision of the idiopathic acquired GHD in adults, stringent criteria are necessary. Exhaustive history for an overlooked organic cause of GHD such as head trauma, meningitis, contact sports, etc. is warranted (Melmed 2013). In the absence of suggestive clinical circumstances, there is a significant false-positive error rate in response to a single dynamic test. Therefore two GH stimulation tests are recommended for the diagnosis of idiopathic GHD in adults.
4. Serum insulin-like growth factor-1 (IGF-I) concentrations are useful only when age-adjusted normal ranges are used. Normal IGF-I levels does not exclude the diagnosis of GHD but makes dynamic tests mandatory. There is considerable overlap in serum IGF-I levels between individuals with and without GHD. However, a low age-matched IGF-I levels, in the absence of liver disease, poorly controlled diabetes, malnutrition, and oral estrogen therapy, are strong evidence for GHD and may be useful in identifying patients who may benefit from GH replacement therapy (GHRT) and therefore require dynamic testing for GHD.

Additionally adult patients with three or more other pituitary hormone deficiencies with an IGF-I level below age-matched reference range have a likelihood of GHD more than 95% (Diri et al. 2015; Hartman et al. 2002). Therefore in these patients, performing GH stimulation test for the diagnosis of GHD is not necessary or could be performed optional (Molitch et al. 2011).

In summary, owing to false-positive rates of current diagnostic dynamic tests, diagnostic testing for GHD should be considered in patients with high pretest probability of hypothalamic-pituitary disorders who fulfill the abovementioned criteria. In all these cases, an intention to treat needs to be presented before testing.

Dynamic Tests and Diagnostic Criteria

GH is secreted episodically; therefore measurement of a low basal or random plasma GH level is not diagnostic, and as mentioned above measurement of IGF-I level is of limited utility in diagnosing GHD. So, for the diagnosis of adult GHD, the GH-IGF-I

axis should be evaluated by dynamic tests (stimulation tests), unless all other pituitary axes are deficient and age-matched IGF-1 is low (Molitch et al. 2011; Schneider et al. 2007a). Except idiopathic GHD, one stimulation test is sufficient for the diagnosis of GHD in patients who are selected according to appropriate criteria (section "Who to Test?"). Moreover patients have to be adequately replaced with other deficient hormones before any GH stimulation test is performed.

For the diagnosis of adult GHD, the insulin tolerance test (ITT) and GHRH + arginine tests are now considered as the tests of choice with similar accuracy (Molitch et al. 2011; Schneider et al. 2007a).

The ITT explores the integrity of the hypothalamic-pituitary function and is considered the gold standard for the evaluation of GH axis (Schneider et al. 2007a); however, it cannot be performed in patients with severe cardiovascular morbidity and epileptic seizures. For the ITT, peak GH response levels lower than 3 mcg/l indicate severe GH deficiency in adults (if hypoglycemia is adequately reached) (Molitch et al. 2011; Schneider et al. 2007a). For patients in the transition phase between puberty and early adulthood, cutoff levels of 6.1 (Maghnie et al. 2005) or 5 μg/l (Clayton et al. 2005) have been suggested.

The GH-releasing hormone plus arginine test (GHRH + ARG, 1 mcg/kg GHRH i.v. as a bolus plus 30 g arginine as an infusion over 30 min) is easy to perform, is well tolerated, and has been shown to reliably detect severe GH deficiency in a lean adult population when a cutoff of 9 mcg/l is used (Aimaretti et al. 1998; Ghigo et al. 1996). However, the GH response to GHRH + ARG, and to all known GH provocative stimuli, significantly declines with increasing body mass index in adults (Bonert et al. 2004; Qu et al. 2005); thus, the use of a non-BMI-related cutoff in obese subjects causes a high percentage of false-positive results (Schneider et al. 2006). Therefore appropriate BMI-adjusted cutoff levels for diagnosing GHD are proposed as follows: 11 mcg/l for those with a BMI less than 25 kg/m^2, 8 mcg /l for those with a BMI of 25–30 kg/m^2, and 4 mcg/l for those with a BMI higher than 30 kg/m^2 (Biller et al. 2002; Corneli et al. 2005).

Another potent and validated provocative test is the GHRH+ GH-releasing peptide-6 test (Kelestimur et al. 2006; Popovic et al. 2000). It has a BMI-dependent cutoff (10 and 5 mcg /l for lean and obese with BMI $>$ 35 kg/m^2, respectively) and possesses great accuracy in distinguishing normal subjects from patients with GH deficiency (Kelestimur et al. 2006; Popovic et al. 2000).

As mentioned above, the GHRH + arginine test is a good and reliable alternative if ITT is contraindicated. However, in the recent Endocrine Society guidelines, the glucagon stimulation test (GST) is accepted as a good alternative test for the diagnosis of GH deficiency when GHRH is unavailable or there is contraindication for ITT (Molitch et al. 2011). The GST (1 mg glucagon im [1.5 mg for patients $>$90 kg], GH measurements every 30 min until 240 min after administration) has been proposed as an alternative diagnostic because it is able to differentiate between GH-deficient and healthy subjects with an acceptable sensitivity and specificity if a peak GH of 3 μg/l is considered (Gomez et al. 2002; Molitch et al. 2011). However, like the other tests, it is age- and BMI-dependent (Gomez et al. 2002; Molitch et al. 2011), and it is more time-consuming than other stimulation tests (Gomez et al.

Table 3 Dynamic tests for the diagnosis of adult GHD

Stimulation test	GH diagnostic cutoff value	Advantages	Disadvantages
Insulin tolerance test (ITT)	3 mcg/l	Gold standard test; simultaneous assessment of ACTH reserve	Contraindicated in ischemic heart disease and history of seizures; due to risk adverse effects, continuous presence of physician is required
GHRH plus arginine (GHRH + ARG)	BMI <25 kg/m^2: 11 mcg/l BMI 25–30 kg/m^2: 8 mcg/l BMI >30 kg/m^2: 4 mcg/l	Low risk of adverse effects; good accuracy; test of choice if ITT is contraindicated	GHRH is not commercially available in most countries
GHRH plus GHRP-6	10 mcg/l (5 mcg/l if BMI >35 kg/m^2)	Good accuracy and tolerability	GHRH is not commercially available in most countries
Glucagon stimulation test (GST)	1 mcg/l[a], 3 mcg/l[b]	Low risk of severe adverse effects; recommended if ITT is contraindicated and GHRH is unavailable; good accuracy by using appropriate cutoff levels	Adverse effects (nausea, vomiting, headache, and rarely late hypoglycemia), more time-consuming than other stimulation tests

GHRH growth hormone-releasing hormone, *GHRP* GH-releasing peptide, *BMI* body mass index
[a]Diri et al. 2015; Hamrahian et al. 2016
[b]Molitch et al. 2011

2002; Molitch et al. 2011). Recent studies clearly demonstrated that GST with cutoff level 3 μg/l has considerable false-positive rates. Therefore peak GH cutoff point decreased to 1 μg/l with a significantly high diagnostic accuracy (Diri et al. 2015; Hamrahian et al. 2016). By using appropriate cutoff values, the reliability and efficacy of GST and ITT could be similar (Simsek et al. 2014).

The recommended stimulation tests for the diagnosis of adult GHD and the diagnostic cutoff values are summarized in Table 3.

Treatment of GHD in Adults

Effects of GHD and GHRT

The effects of GHD and GH replacement therapy (GHRT) are summarized in Table 4. It is important to mention that GH-deficient adult patients with isolated GHD and multiple pituitary hormone deficiencies have similar clinical presentation and respond equally well to GHRT (Abs et al. 2005; Klose et al. 2009).

Table 4 Summary of the effects of adult GHD and the response to GHRT

Untreated GHD	Effects of GHRT	Comments
Adverse effects on body composition and exercise capacity	**Reversal of adverse changes**	
↓ LBM and muscle bulk	↑ LBM and muscle bulk	
↑ Body fat mass and WHR	↓ Body fat mass (mainly visceral) and WHR	GHRT has sustained effects (10 years) on lean body mass and muscle strength but not on body fat
↓ Exercise performance and skeletal muscle strength	↑ Exercise performance and skeletal muscle strength	
Increased CVS risk factors and premature atherosclerosis	**Improvement of CVS risk factors**	
↑ Total and LDL-C	↓ Total and LDL-C	
↓ HDL-C	↑ HDL-C	Although estimated risks of cardiovascular events or cardiovascular mortality decreased after GHRT, there is no study demonstrating the increased longevity due to GHRT
↑ Pro-inflammatory markers (CRP and IL-6)	↓ Pro-inflammatory markers	
↑ Carotid IMT and arterial stiffness	↓ Carotid IMT and arterial stiffness	
↓ LV mass and diameter, ↓ EF (mainly in CO-GHD)	Myocardial changes commonly improve	
Increased risk of osteoporosis	**Reversal of adverse changes**	
↓ BMD ↑Fracture rate	↑BMD ↓Fracture rate	In short-term GHRT, the BMD generally does not increase; however after 18–24 months of the treatment, the bone effects are seen
Impaired QoL and decreased psychological well-being	**Sustained long-term improvement in affected QoL areas**	Ideally assessed with specifically designed standardized questionnaire such as the AGHDA

Abbreviations: *GHD* growth hormone deficiency, *GHRT* growth hormone replacement therapy, *BMD* bone mineral density, *CVS* cardiovascular, *QoL* quality of life, *AGHDA* assessment of GHD in adults, *LBM* lean body mass, *WHR* waist-to-hip ratio, *IMT* intima-media thickness

Body Composition Parameters and Exercise Capacity

GHD in adults is characterized by decreased lean body mass and muscle bulk and increased body fat mass (increased waist-to-hip ratio). These changes are independent from the etiology of the GHD (Attanasio et al. 2010; Carroll et al. 1998; Kelestimur et al. 2005; Moller and Jorgensen 2009; Tanriverdi et al. 2005). Moreover exercise capacity and muscle strength are reduced in adult patients with GHD, and patients show significant impairment in physical performance (Amato et al. 1993; Cuneo et al. 1992; Johannsson et al. 1997). GHRT induces important changes in body composition. Most of the studies clearly demonstrated significant reduction in body fat and increase in lean body mass. The greatest reduction in body

fat occurs in visceral and abdominal fat. Long-term, 10 years duration, studies showed that GHRT has sustained effects on lean body mass but not on body fat (Gotherstrom et al. 2009; Hoffman et al. 2004). The changes in body composition generally occurred without a significant change in body weight.

Untreated GHD in adults has reduced exercise performance and isometric muscle strength. GHRT has beneficial effects on muscle strength and exercise performance. The increase in exercise capacity is in parallel with an increase in maximal oxygen uptake, and the oxygen consumption increased progressively over a 5-year period of GHRT (Cenci et al. 2009). In a long-term study, GHRT increased muscle strength (isometric knee flexor and hand grip strength) gradually over the first 5 years and thereafter protects against the age-decline and normalize muscle strength over a 10-year period (Gotherstrom et al. 2009). Therefore GHRT of adults with GHD offers substantial clinical benefits in exercise capacity and body composition (Molitch et al. 2011).

Cardiovascular Risk Factors and Mortality

Most of the cardiovascular risk of GHD in adults appears to be related to dyslipidemia, inflammation, and impaired myocardial function.

GH affects lipoprotein metabolism, and increased total and LDL cholesterol, decreased HDL cholesterol, and increased triglyceride levels were reported in adults with GHD (Cuneo et al. 1998; Rosen et al. 1993; Sesmilo et al. 2000; Tanriverdi et al. 2005). GHRT was shown to decrease total cholesterol levels significantly. Most, but not all, studies have shown decreases in LDL cholesterol and increases in HDL cholesterol after institution of GHRT. It seems that GHRT has little effect on triglyceride levels (Maison et al. 2004; Sesmilo et al. 2000). It was recently demonstrated that the favorable effects of GHRT in improving dyslipidemia maintained for 2 years (Abs et al. 2006). Additionally pro-inflammatory markers including CRP and IL-6 are elevated in GHD, and administration of GHRT significantly decreases the inflammatory markers which are related with cardiovascular risk (Bollerslev et al. 2006; Sesmilo et al. 2000).

Epidemiological data revealed that increases in carotid intima-media thickness (IMT) may predict the development of symptomatic coronary artery disease nearly 8 years after the initial measurement (Hodis et al. 1998). Increased carotid IMT and arterial stiffness have been documented in adults with GHD. Several short- and long-term studies showed that GHRT reduces carotid IMT and improves flow-mediated dilatation (Borson-Chazot et al. 1999; Gibney et al. 1999). Moreover myocardial function may also be significantly impaired in adult patients with GHD. Some echocardiography studies revealed a reduced left ventricular (LV) mass and intraventricular septal thickness and decreased LV diameter in adult patients with GHD. But these myocardial changes and decreased ejection fraction are more prominent in childhood-onset GHD (Colao et al. 2001; Sartorio et al. 1997). Analysis of several treatment studies has demonstrated that most consistent increases after GHRT were LV mass, longitudinal myocardial velocities, stroke volumes, and LV end-diastolic volumes (Maison and Chanson 2003; Ozdogru et al. 2007).

Hypopituitarism is associated with significantly increased mortality when compared with age- and gender-matched populations. Although GHD is not the only independent predictor, it has a significant contribution to the increased mortality in adult patients with hypopituitarism (Rosen and Bengtsson 1990; Sherlock et al. 2010). The most important causes of premature mortality in adult patients with GHD are cerebrovascular and cardiovascular diseases. In KIMS database it has been demonstrated that in 10 years, estimated risks of cardiovascular events or cardiovascular mortality calculated from different score algorithms are significantly increased in adult patients with GHD. Moreover after 4 years of GHRT, these estimated cardiovascular risks were returned to baseline level in these patients (Schneider et al. 2011). However to date it has not yet been shown that GHRT significantly improves the mortality and increases longevity. But two recent meta-analyses clearly demonstrated that short- and long-term GHRT does not increase cardiovascular mortality (Deodati et al. 2014; Stochholm and Johannsson 2015).

In summary GHRT in adults significantly improves several cardiovascular surrogate outcomes including lipid profile, inflammatory cardiovascular biomarkers, carotid IMT, and some aspects of myocardial function.

Bone Mineral Density

Several studies have shown that in adult patients with GHD, bone mineral density (BMD) is decreased ranging from osteopenia to osteoporosis (Holmes et al. 1994; Tanriverdi et al. 2005). Moreover osteoporotic fracture rate was also increased due to GHD (Wuster et al. 2001). Nearly 35% of CO-GHD patients and 20% of AO-GHD patients have osteoporosis (T scores less than −2.5 SD), and the age of onset of GHD significantly affects the severity of the bone mass loss (Lissett and Shalet 2000). GHRT has an overall anabolic effect on bone tissue, but its effects are biphasic. After the short-term GHRT (before 12 months of treatment), the BMD generally does not increase and may even show a decrease (Biller et al. 2000). However after 18–24 months of GHRT, most studies have shown significant increase in BMD, mainly with greater effects at vertebral sites (Biller et al. 2000; Shalet et al. 2003). Data regarding the effects of GHRT on fracture rates are limited. In one study GHRT has shown to be decreasing the rate of radiological vertebral fractures (Mazziotti et al. 2006).

Quality of Life

Impaired quality of life (QoL) and decreased psychological well-being are common in adults with GHD, but QoL evaluations in GHD patients have shown high degree variability. QoL is usually assessed via self-administered questionnaires and ideally assessed with specifically designed standardized questionnaire such as the AGHDA (Assessment of GHD in Adults) (Koltowska-Haggstrom et al. 2009). Significant impairment of QoL was more frequently observed in adults with AO-GHD than in those with CO-GHD (Attanasio et al. 1997). Several studies have demonstrated that

GHRT improves QoL in most of the patients and this improvement sustained for long term (Koltowska-Haggstrom et al. 2009; Murray et al. 1999).

Treatment Strategies of GHD and Monitoring

Evidence supporting beneficial effects of recombinant GH (rhGH) in adults with GHD led to the extensive approval of GHRT especially in patients with severe GHD. In adults initially weight-based dosing regimen was used, leading to supraphysiological doses and increased incidence of adverse effects (mainly fluid retention). It therefore is recommended in recent years that GH-dosing regimens should be individualized rather than weight-based, and starting low dose (0.2–0.3 mg/day between the age 30 and 60 years) and titration according to clinical response, side effects, and IGF-I levels is essential (Cook et al. 2009; Ho 2007; Molitch et al. 2011). GH secretion is higher in younger individuals than in older ones and in women than in men. Estrogen inhibits GH action in the liver, and in women usually more GH is required to achieve the same IGF-I response (Birzniece et al. 2009). Therefore while rhGH dosing, age, gender, and estrogen status need to be taken into consideration. 0.4–0.5 mg/day and 0.1–0.2 mg/day starting doses are recommended in younger age (<30 years) and in older age (>60 years) and patients with diabetes, respectively (Cook et al. 2009).

After starting GHRT patients should be monitored at 1- to 2-month intervals during dose titration, and dose increments are suggested as 0.1–0.2 mg/day based on IGF-I levels, clinical response, and side effects. Target for IGF-I level is the upper half of the age-adjusted reference range. After maintenance doses have been achieved, monitoring is generally recommended at 6-month intervals. Clinical evaluation (blood pressure, weight, waist circumference, BMI, etc.) and assessment for side effects along with IGF-I level measurements should be performed during semiannual monitoring. Fasting glucose and fasting lipid profile annually and after any GH dose increase. But if the patient is diabetic or susceptible to glucose intolerance, fasting glucose and HbA1c monitoring could be more frequent. Optimally QoL measures need to be assessed at baseline and then at least annually. If the initial bone DEXA scan is abnormal, repeat evaluations are recommended at 1.5- to 2-year intervals (Cook et al. 2009; Molitch et al. 2011).

Some studies have shown that GHRT causes a decrease of serum tree T4 levels. Additionally GHRT has also been found to cause lowering effect on serum cortisol levels due to reversal of the increased conversion of cortisone to cortisol during GHD (Giavoli et al. 2004; Porretti et al. 2002). Thus, thyroid and adrenal functions need to be monitored, and if the patients are on thyroid and/or steroid replacement therapy, drug doses should be adjusted during GHRT.

The optimal duration of GHRT is unclear. If benefits are achieved, continuation of the treatment is recommended. In the literature 10–15 years of safety and benefits of the GHRT in adults have been demonstrated (Appelman-Dijkstra et al. 2013; Elbornsson et al. 2013). On the other hand, if there are no obvious or objective benefits of the treatment after at least 1 year, discontinuing may be appropriate.

Side Effects and Long-Term Safety of GHRT

The most common side effects, occurring in approximately 5–18% of patients, are related to fluid retention and paresthesia, peripheral edema, joint stiffness, myalgia, and arthralgia. Carpal tunnel syndrome occurs almost 2% due to GHRT (Holmes and Shalet 1995). Most of these adverse effects are transient and improve with dose reduction.

Retinopathy and benign intracranial hypertension are extremely rare complications of GHRT and reported as case reports in adults (Koller et al. 1998; Malozowski et al. 1993). However presence of benign intracranial hypertension and proliferative retinopathy are accepted as contraindications of GHRT (Table 5). Pregnancy is not a contraindication for GHRT, but treatment should be discontinued in the second trimester, as GH is produced by the placenta (Ho 2007; Karaca et al. 2010).

Because GH and IGF-I stimulate the growth of tissues, there has been concern that GHRT may increase the risk of pituitary adenoma recurrence or development of neoplasia. Analysis of extensive pediatric experience demonstrated that GHRT is not linked to the development of malignancy or tumor recurrence (Bell et al. 2010; Darendeliler et al. 2006). Moreover GHRT does not increase tumor recurrence, malignancy rates, and malignancy-related mortality in adult patients (Burman et al. 2013; van Bunderen et al. 2014). Although there are substantial numbers of studies showing that GHRT is not linked to increased cancer risk or tumor recurrence, it is recommended that GHRT should not be used in patients with active malignancy (Table 5) (Molitch et al. 2011).

The overall effect of GHRT on insulin resistance is controversial. GHRT decreases fat mass and increasing IGF-I improves insulin sensitivity. But, GH also

Table 5 Recommendations for adult GHRT and monitoring

Starting dose
0.2–0.3 mg/day between the age 30 and 60 years
0.4–0.5 mg/day in younger age (<30 years)
0.1–0.2 mg/day in older age (>60 years) and in patients with diabetes
Dose titration
Patient should be monitored at 1- to 2-month intervals during dose titration, and dose increments are suggested as 0.1–0.2 mg/day based on IGF-I levels, clinical response, and side effects
Goal and monitorization
Target for IGF-I level is the upper half of the age-adjusted reference range
After maintenance doses are achieved, monitoring is generally recommended at 6-month intervals
If the patients are on thyroid and/or steroid replacement therapy, drug doses should be adjusted during GHRT
Women may require more rhGH doses than men, and dose requirements are greater with oral than with transdermal estrogen therapy in women
If there are no obvious or objective benefits of the treatment after at least 1 year, discontinuing GHRT may be appropriate
Contraindications
Presence of active malignancy, benign intracranial hypertension, and proliferative retinopathy

directly antagonizes insulin action in the liver and other tissues (Clemmons 2004). A meta-analysis of placebo-controlled studies revealed that GHRT was associated with a slight increase in both fasting insulin levels and fasting glucose (Maison et al. 2004). Therefore GHRT is not contraindicated in patients with diabetes mellitus, but lower starting rhGH doses (Table 5) and adjustment of antidiabetic medications are required (Molitch et al. 2011).

In a position statement published recently, it was concluded that GH currently has a good safety record when used for approved indications and at recommended doses, but continued surveillance of the GHD patients exposed to rhGH treatment is required to address the long-term safety (Allen et al. 2016).

Summary

It has been previously demonstrated that GH is one of the most frequent hormonal deficiencies in adult patients with hypopituitarism. The most common classical causes of AO-GHD are pituitary adenomas and/or their treatment. However, during the last decade, an increasing number of studies from different parts of the world have revealed that non-tumoral causes of hypopituitarism such as traumatic brain injury and Sheehan's syndrome are more common than previously known.

GHD in adults is difficult to diagnose based on clinical features because the signs and symptoms of GHD are nonspecific. Therefore cause-specific history becomes more important for clinical suspicion and selecting patients for diagnostic testing. The adult patients with structural hypothalamic/pituitary disease (surgery or irradiation in these areas), history of TBI, or evidence of other pituitary hormone deficiencies should be considered for testing for acquired GHD. For the diagnosis of adult GHD, the insulin tolerance test and GHRH + arginine tests are now considered as the tests of choice with similar accuracy. However, the glucagon stimulation test is accepted as a good alternative test for the diagnosis of GH deficiency when GHRH is unavailable or there is contraindication for insulin tolerance test.

GHD in adults is associated with impaired body composition and exercise capacity, increased cardiovascular risk factors and premature atherosclerosis, increased risk of osteoporosis, impaired QoL, and decreased psychological well-being. Short- and long-term studies clearly demonstrated that after physiological dose of GHRT, most of these adverse changes are normalized in adult patients with GHD. rhGH currently has a good safety record when used for approved indications and at recommended doses.

Cross-References

► Neuroendocrine Control of Carbohydrate Metabolism
► Neuroendocrinology of Bone Metabolism

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