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Management of Adult Growth Hormone Deficiency

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Growth hormone (GH) deficiency (GHD) in adults is characterized by perturbations in body composition, carbohydrate and lipid metabolism, bone mineral density, cardiovascular risk profile, and quality of life (QOL). Furthermore, it is likely, although unproven, that GHD contributes to the increase in cardiovascular morbidity and mortality that has repeatedly been observed in hypopituitary adults [1,2].

The availability of recombinant human GH from 1985 onward stimulated the investigation of the role of GH in adult life and in particular the effects of GH replacement in adults who have GHD. In the absence of any pilot data to indicate the most appropriate dose of GH, initial studies were performed using a dose based on weight or body surface area, derived from experience in the pediatric setting [3–5]. Although these studies provided evidence of the beneficial effects of GH replacement, they were also associated with a high incidence of side effects related to fluid retention, most commonly arthralgia and peripheral edema, which were demonstrated to be dose-related side effects of treatment.

This article summarizes current knowledge of managing GH replacement therapy in adults and mentions the experience of long-term treatment and safety.

Diagnosis of growth hormone deficiency in adults

The probability of the diagnosis of severe GHD in adults is high in patients who have gross hypothalamic-pituitary diseases and two or more other pituitary hormone deficiencies [6]. The tools for defining severe GHD in adults are well validated in patients who have well-defined hypothalamic-pituitary

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disease with and without other pituitary hormone deficiency [7]. The performance of the tests used to define GHD in adults have been less validated in patients who do not have major well-defined pituitary pathology, which is often the case in patients who have history of major head trauma without the presence of other pituitary hormone deficiency. A similar situation is the adolescent patient who has idiopathic isolated GHD diagnosed in childhood at the time of re-evaluation for continuing care and treatment into adulthood or the middle-aged or elderly patient who has symptoms and signs of severe GHD without any known hypothalamic-pituitary disease. Moreover, the performance of tests used to define GHD in adults has not been properly validated in obesity. The performance of the tests and the assay used to defined GHD is therefore of utmost importance [8].

GHD should be suspected in patients who have any form of hypothalamic-pituitary disease, patients who have any other pituitary hormone deficiency, patients who have received cranial irradiation or experienced severe head trauma, and young adults who have been diagnosed with GHD in childhood. Serum insulinlike growth factor (IGF)–I is GH dependent and useful in the screening and diagnostic procedure for GHD. IGF-I serum level is also affected by other factors, such as nutritional status and size of lean body mass [9], and with increasing age the overlap between those who have severe GHD and normative data becomes greater. Serum IGF-I concentration is a useful screening test, but a normal serum concentration does not rule out the presence of severe GHD at any age.

Various tests to stimulate GH secretion to determine a peak response have been used for diagnostic purposes in hypopituitarism and GHD. Among the validated tests, the insulin tolerance test (ITT), arginine-GH releasing hormone (Arg-GHRH), GHRH-GH releasing peptide (GHRP)–6, and GHRH-pyridostigmine are excellent, whereas clonidine and L-Dopa are inadequate [10]. The ITT has been used in the diagnosis of GHD since 1963 [11] and has in recent years been re-evaluated and found to have high sensitivity and specificity in all age groups [12]. The peak is reduced, however, in obesity [13] and may also be lower in women than in men [14], but this has not been considered in the cutoff levels. The ITT has been recommended as the test of choice in adults who have suspected GHD. The test is potentially hazardous, however, especially in patients who have heart disease and seizure disorders, but it has been found to be safe if performed in specialized units under adequate supervision [15].

The Arg-GHRH stimulation test benefits from the potentiating of both substances and a reproducible stimulation of the GH secretion is achieved [16]. The peak GH response to Arg-GHRH seems to be independent of age and sex but is reduced by obesity; therefore, BMI-related reference ranges have been established [17]. This test is safe and is associated with less discomfort than the ITT; it is therefore a good alternative for the ITT in most situations, except in patients who have a primary hypothalamic lesion. This phenomenon was clearly demonstrated in patients who had

received irradiation to the hypothalamic-pituitary area for a nonpituitary disorder who were defined to have severe GHD using the ITT and not by Arg-GHRH within 5 years after radiotherapy, whereas a consistency was obtained between the two tests thereafter [18]. The GHRH-GHRP-6 stimulation test has a peak GH response that is not influenced by age or body composition and as such is a promising test [19].

The diagnosis of severe GHD in adults has been considered to be a peak GH response to ITT of less than 3 μg/L [8,12]. Many of the studies documenting the beneficial effects of GH replacement therapy in adults have included subject with a peak GH response less than 5 μg/L, however. Other tests have their specific cutoff values for defining severe GHD ranging between 16.5 and 20.3 μg/L for Arg-GHRH, depending on BMI, and less than 10 μg/L for the GHRH-GHRP-6 stimulation test. The performance of the GH assay should also be considered in the interference with GH-binding proteins; the recombinant international reference preparation (IRP) 88/624 has been recommended for use in the GH assays [8]. Moreover, in patients who have a more limited degree of hypopituitarism, in particular those who have two or fewer pituitary hormone deficiencies, two independent stimulation test are recommended to diagnose severe GHD in adults [7,20].

Growth hormone replacement therapy

The aim of GH replacement is to achieve normalization of metabolic, functional, and psychologic consequences of adult hypopituitarism and severe GHD. Before commencement of GH replacement, it is necessary to ensure appropriate replacement of other pituitary hormone deficiencies, to determine the presence and severity of clinical features associated with the GHD, and to predict sensitivity to GH.

Appropriate evaluation of the hypothalamic-pituitary-adrenal axis is mandatory because there are indications that GH may attenuate the peripheral action of glucocorticoids by reducing the activity if the enzyme 11β hydroxysteroid dehydrogenase type 1 [21]. This enzyme preferably converts inactive cortisone to active cortisol, and commencing GH therapy may therefore push an individual who has incipient adrenal insufficiency into overt adrenal insufficiency. Moreover, administration of GH probably enhances the peripheral conversion of T4 to T3 and may thereby influence the thyroxin replacement therapy [22]. Finally, there are well-known interactions between sex steroids and GH action. It is well established that oral estrogen administration markedly reduces GH responsiveness [23] and there are also indications that testosterone potentiates the IGF-I response and the antinatriuretic action of GH [24]. A careful evaluation of other pituitary functions and an adequate replacement therapy, if needed, are therefore mandatory before initiating GH replacement therapy.

To monitor the clinical response to GH, it is necessary to determine the severity of the features associated with GHD in patients being considered

for replacement therapy. Baseline assessment should include measurement of body composition, bone mineral density (BMD) testing, glucose and lipid measurement, and assessment of psychologic well being. Baseline variables showing the greatest abnormalities can become important treatment targets for the individual patient. As a minimum, assessment of body composition should include measurement of height and weight, calculation of BMI, and measurement of waist and hip circumferences. Bio-impedance assessment (BIA) is a simple and relatively inexpensive technique that can be used in the clinic setting. Dual energy x-ray absorptiometry (DEXA) scanning performed at baseline can assess BMD and provide an estimate of lean body mass and total and regional fat distribution.

Dose selection

Knowledge of individual sensitivity to GH is helpful for deciding the initial dose of GH and the pace of dose titration in the individual patient. The first attempt to understand which patients develop side effects, and can therefore be considered more GH sensitive, was made by Holmes and Shalet [25]. They observed that in patients receiving a fixed dose of GH/kg body weight, side effects occurred more frequently in those who were older and more obese, and in whom the onset of GHD was during adult life. Furthermore, other studies demonstrated the effects of GH on body composition, lipid profile, and markers of bone turnover to be more marked in men [26–28]. In particular, women receiving oral estrogen replacement therapy were more resistant to GH in the serum IGF-I response [23]. There are also some indications that women receiving oral estrogen replacement therapy may be less prone to developing peripheral edema and other fluid-related side effects of GH treatment [29]. Other factors determining individual responsiveness to GH are not as obvious in the clinical setting and they include baseline adiposity and serum levels of GH-binding proteins [30]. The decision of final dose of GH and guiding during dose titration is therefore dependent on monitoring of clinical and biologic response markers [31,32]. An example of poor responsiveness is a young woman with childhood-onset disease and oral estrogen replacement therapy who is likely to need high doses of GH. She can be started with a dosage of 0.1 mg/d or higher and expected to need fast dose titration and in larger steps than a middle-aged man, who should commence treatment with 0.1 mg/d and will be dose-titrated in few and small steps toward an estimated target dosage of between 0.2 and 0.4 mg/d.

Initial dose monitoring

There is a significant overlap of serum IGF-I levels between normal and GHD individuals, with up to half of all individuals who have confirmed GHD having IGF-I levels in the low-normal age-dependent range. This overlap reflects the multiple influences on IGF-I other than age, including

genetic factors, nutritional status, and sex steroids [33]. The dose titration and monitoring of subjects who have normal baseline serum IGF-I levels usually allows a small dose of GH, whereas patients who have below-normal serum levels of IGF-I at baseline can tolerate larger doses before IGF-I exceeds the upper limit of normal. In the latter case, dose titration toward clinically meaningful endpoints is easier. By using serum IGF-I as a dose titration monitor, therefore, those who have the lowest serum IGF-I at baseline most likely receive the highest maintenance dose of GH [34].

Serum IGF-I is still the most useful biologic marker for dose titration of GH in adults. It is a more sensitive serum marker than other well-known GH-dependent markers, such as serum IGF binding protein (IGFBP)–3 and acid-labile subunit (ALS), which respond less markedly to the same dose of GH [35]. In a comparative study, serum IGF-I, IGFBP3, and ALS concentrations in GHD adults were measured before and after commencement of three different doses of GH [35]. Compared with IGF-I, a higher dose of GH was necessary to increase IGFBP3 and ALS into their respective normal ranges, and throughout the study IGFBP3 and ALS proved less sensitive to the effects of GH than IGF-I. In another dose titration study, measurement of serum IGFBP3 and ALS was of no additional value over measurement of serum IGF-I as a marker for monitoring dose titration [32].

The serum IGF-I response to GH administration mainly reflects the hepatic effect of GH, because more than 70% of the circulating IGF-I is produced in the liver [36]. The overall effect of GH depends both on GH and IGF-I and it is likely that many of the anabolic and metabolic effects of GH are primarily mediated through IGF-I [37].

Another important consideration is that the relationship between serum IGF-I response during GH treatment and other treatment effects, such as metabolic endpoints and body composition, is poor [27,38]. The serum IGF-I response and the achieved serum IGF-I levels therefore cannot be used as a surrogate marker for other efficacy variables. Although serum IGF-I can no longer be assumed to reflect the effect of GH in all tissues, it remains a useful and important marker to detect over-replacement with GH. Recent studies have demonstrated that serum levels of IGF-I in the upper normal range in normal subjects are predictive of increased risk for breast, colon, and prostate cancer. Although these findings should not be extrapolated to physiologic GH replacement in adults who have GHD, it is considered prudent to maintain serum IGF-I levels in the normal range during GH replacement therapy [39].

Because IGF-I only reflects one aspect of efficacy of GH replacement, other simple measures to monitor GH dose titration have been evaluated, such as changes in extracellular water (ECW) measured by BIA [40] and normalization of other compartments of the body composition, such as body fat and body cell mass [31]. The effect of GH to increase ECW through its antinatriuretic action occurs within 3 to 5 days of starting GH

replacement [41]. Because increased ECW is one of the measurements that changes most consistently during GH treatment, it may be a more useful endpoint for monitoring GH replacement than other aspects of body composition. This concept was first explored by using BIA, a marker of tissue hydration [40]. Electrical impedance was increased in GHD subjects, indicating reduced body hydration, and exhibited a dose-dependent decrease during GH replacement. The dose that normalized tissue hydration was similar to the dose that normalized serum IGF-I in most of the study subjects [35].

Growth hormone dose titration

The observation that a GH dose that is inadequate in one subject can lead to side effects of overdosage in another has prompted the development of methods of individual dose titration. In this paradigm, the dose of GH is titrated against both clinical features of GHD and evidence of overtreatment, determined by serum IGF-I and clinical evidence of side effects, in particular symptoms and signs related to fluid retention. In a study of an individualized dose regimen of GH replacement in which the dose of GH was titrated against serum IGF-I, body composition and clinical response comparison was made with a conventional weight-based regimen [31]. Following 1 year of GH replacement, a mean dosage of 0.45 mg/d was obtained during individualized dose titration and a mean dosage of 0.55 mg/d was obtained during the weight-based regimen after some dose adjustments because of side effects. Although the efficacy of GH treatment was similar in the two groups, side effects occurred in 30% of cases during individualized dose titration compared with 70% in the weight-based group (Fig. 1). Also, within the group receiving dose titration those with the lowest starting dose of GH experienced the fewest side effects of treatment. The interpretation is therefore to commence treatment with a low daily dose of GH independent of body weight and thereafter dose-titrate toward adequate clinical effects and normalization of serum IGF-I.

In a subsequent study, the GH replacement dose was titrated against serum IGF-I, aiming for levels in the upper half of the age-related reference range, and results were compared with retrospective data from subjects treated with a weight-based regimen (Fig. 2). Median maintenance dosages in this study were 0.27 mg/d in men and 0.4 mg/d in women, significantly lower than maintenance dosages of 0.5 mg/d used in the weight-based regimen. An important observation was the longer duration of dose titration in the women if initial dose and dose titration steps were the same in men and women (see Fig. 2). There was no difference in the degree of improvement of QOL observed in the different regimens. Taken together, these two studies provide important indications that using an individualized dose titration allows similar average beneficial effects with fewer side effects and a lower maintenance GH dose than using a weight-based regimen. Some

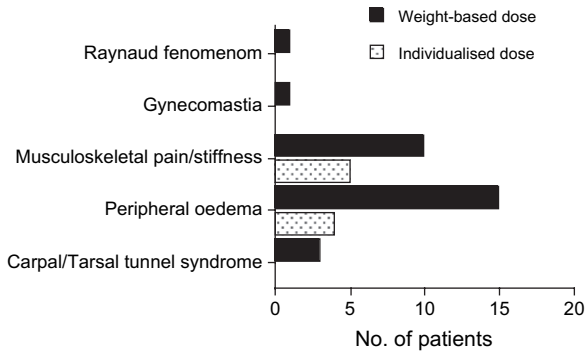

Fig. 1. Side effects in 60 adults receiving 6 months of GH replacement therapy. Thirty patients received a weight-based dosage regimen with 12 μg/kg/d and 30 patients received an individually titrated dosage regimen. (*Adapted from* Johannsson G, Rosén T, Bengtsson B-Å. Individualized dose titration of growth hormone (GH) during GH replacement in hypopituitary adults. Clin Endocrinol [Oxf] 1997;47:575; with permission.)

variations on the initial dose and pace and steps during dose titration should be considered based on the estimated final dose that can be anticipated from published data on individual sensitivity [26,30,42,43]. An older patient may need a lower initial dose of GH with slow dose titration (0.05–0.1 mg at a time), whereas a young woman can be commenced on a larger dose (0.1–0.3 mg) with faster dose titration in larger steps.

Another important observation from postmarketing surveillance studies reveals that subjects initially treated with a high dose of GH are more likely to remain on a high dose in the long term and frequently exhibit supraphysiologic serum levels of IGF-I [44]. Presently there are no data available to

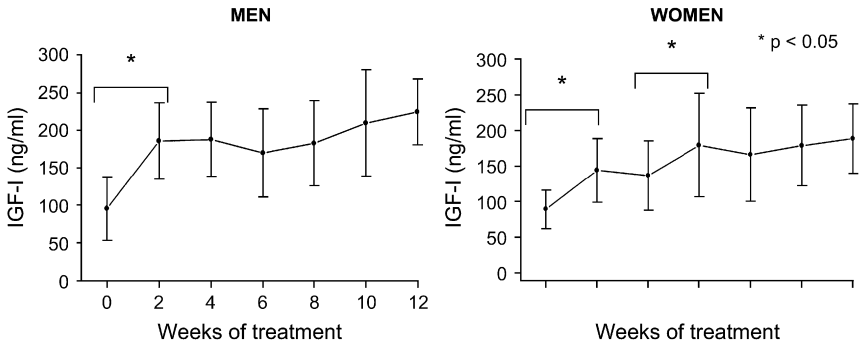

Fig. 2. Serum levels of IGF-I versus weeks of treatment during dose titration in men and women. Serum IGF-I increased significantly between 0 and 2 weeks in males and remained stable thereafter. In contrast, serum IGF-I increased between 0 and 2 weeks and 4 and 6 weeks in females. (*From* Drake WM, Coyte D, Camacho-Hübner C, et al. Opimizing growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab 1998;83:3915; with permission.)

demonstrated harmful effects of slightly high serum levels of IGF-I during GH replacement in adults. An indication, however, comes from a small open study on subjects who received GH replacement early, when high weight-based doses were used for years, demonstrating that their left ventricular mass increased to levels greater than those to be expected from normative values [45].

Evidence is accumulating that the optimum approach to GH replacement is to commence treatment at a low dose and then titrate upward depending on the response of GH-dependent variables, avoiding serum IGF-I levels greater than the upper limit of age-adjusted normative values. Evidence from several studies suggests that variables most sensitive to change are those that are the most abnormal at baseline. A baseline evaluation is therefore helpful to determine which endpoint is most important for each individual patient to follow.

Quality of life and well-being

The beneficial effect of GH replacement on psychologic well-being and QOL in adults who have GHD is an important endpoint for replacement therapy. Many of the patients being considered for GH treatment have high expectations for improved well-being; this aspect of treatment should therefore be monitored clinically or by using standardized questionnaires, or preferably both.

To date, no studies have specifically used QOL as an endpoint against which to titrate GH. In a study that only included GHD patients who had a subjectively low QOL on clinical interview [46], GH was replaced using a dose-titration regimen, aiming to increase IGF-I into the upper half of the normal range. As expected, QOL was seen to improve using two different questionnaires, but the improvement was most marked in those in whom QOL was most abnormal at baseline. This finding also included patients who had childhood-onset GHD who have as a group normal baseline QOL and do not on average respond to treatment [43]. The findings of that study support the strategy to quantify the degree of psychologic impairment at baseline and use it in the monitoring of treatment.

A study of long-term effects on QOL found that improvements that occur shortly after the initiation of GH therapy are sustained in the longer term [47]. Moreover, it seems that some aspects of QOL continue to improve during long-term therapy. Another aspect to consider during monitoring of treatment is that almost one third of the patients who experienced beneficial effects of GH therapy stated that such effects had become noticeable only after GH had been administered for at least 6 months [47]. This finding has clear implications for clinical practice: once the decision has been made to initiate GH therapy, the therapy should be continued for an adequate period of time before judgments are made regarding its efficacy in improving QOL and psychologic well-being. The onset of the effects of GH

may be further delayed in some patients who receive individual dose titration after starting with a low dose of GH.

Glucose and lipid metabolism

Using several techniques, it has been demonstrated that insulin sensitivity is reduced in adults who have GHD [48]. Insulin sensitivity is further reduced following short-term GH replacement but returns later to baseline values; no further change in insulin sensitivity has been seen in observational studies lasting up to 7 years using the hyperinsulinemic glucose clamp for assessment [49]. In an open 5-year study comprising more than 100 patients, glycosylated hemoglobin and serum triglyceride levels tended to decrease after more than 3 years of treatment [50]. This long-term neutral or slightly beneficial effect probably reflects a balance between the counterregulatory effect of GH and the indirect insulin sensitizing effect of the other metabolic effects of treatment, such as reduced visceral fat. A large postmarketing surveillance study did not demonstrate an increase in the incidence of diabetes during GH replacement more than what is expected in the background population [51].

GH also exerts complex effects on plasma lipids. The net effect of these changes during GH replacement is consistent reduction in total and LDL cholesterol and apoprotein B, and in some studies increases in HDL cholesterol concentration [52]. Like the improvements in body composition and QOL, the most marked improvements occur in individuals in whom the most abnormal baseline values exist.

Plasma lipids should be measured before treatment is commenced as an overall assessment of cardiovascular risk profile, and should be monitored on a regular basis, particularly in patients who have baseline abnormalities or other cardiovascular risk factors. Assessment of glucose metabolism can be performed by using the oral glucose tolerance test, performed in selected patients who have other strong risk factors for diabetes, or more simply by measuring fasting levels of glucose to monitor long-term trends.

Long-term monitoring and safety

The beneficial effects of GH replacement on body composition, lipid profile, and psychologic well-being that are early response variables are sustained in small studies of up to 10 years' duration [53]. Endpoints and efficacy variables that have only been detected in controlled and open longitudinal studies after more prolonged duration of treatment are changes in bone mineral content (BMC) and BMD. More than 12 to 18 months of treatment have been needed to detect a progressive increase in these endpoints in both childhood-onset [54,55] and adult-onset patients [27,56]. The magnitude of increase of BMC in lumbar spine is approximately 9%, with women responding less than men [50,56] (Fig. 3). The increase in the

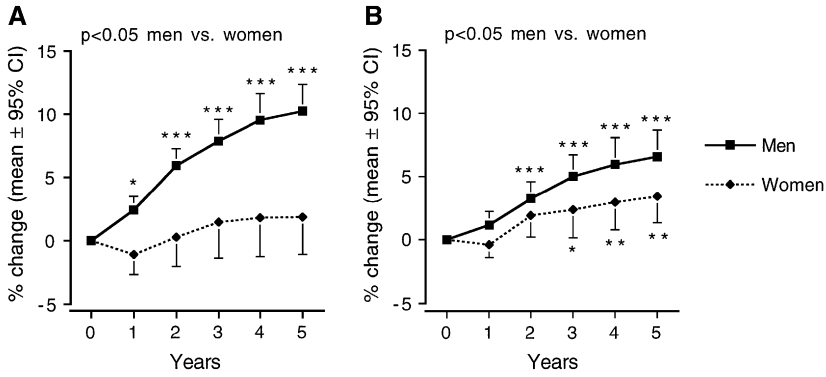

Fig. 3. Lumbar spine BMC (*A*) and BMD (*B*) in men and women during 5 years of GH replacement in 118 patients who had adult-onset GHD. The vertical bars indicate the 95% CI for the mean values shown. Between-group P values are based on an analysis of the percent change from baseline, whereas within-group P values in men and women are based on an analysis of the absolute values. *, P < .05; **, P < .01; ***, P < .001 versus baseline. (*From* Gotherstrom G, Svensson J, Koranyi J, et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. J Clin Endocrinol Metab 2001;86(10):4663; with permission.)

amount of bone induces an increase in BMC and bone area resulting in less marked effect on BMD [57]. This reduced effect is because of increased endosteal and periosteal bone formation in cortical bone with less marked effect on trabecular bone as shown in histomorphometric data from men who had childhood onset disease who were treated with GH for 5 years [54]. BMD is normalized in most patients [50].

The effect on muscle strength and muscle function is delayed for 12 to 18 months of treatment [27], except in one study demonstrating increased muscle strength in one muscle group after 6 months of treatment [58]. With a treatment duration of 2 to 5 years in a large group of patients mean muscle strength is normalized [59] (Fig. 4).

Although there is no evidence to date that GH increases the risk for diabetes mellitus in adults [51], data suggest that it may do so in children. Reported data from an international surveillance study including more than 20,000 subjects indicated that GH treatment was associated with a sixfold increase in new cases of type 2 diabetes [60]. Although long-term data in adults are encouraging, ongoing monitoring of glucose metabolism in patients receiving long-term GH replacement is recommended [39].

No study has directly demonstrated reduced vascular morbidity and mortality in response to long-term GH replacement in adults. One of the most useful surrogate markers for atherosclerosis is intima-media thickness (IMT). IMT is increased in adults who have GHD and some short-term studies have demonstrated that GH replacement reduces IMT [61,62]. Moreover, recent preliminary data suggest that mortality during long-term

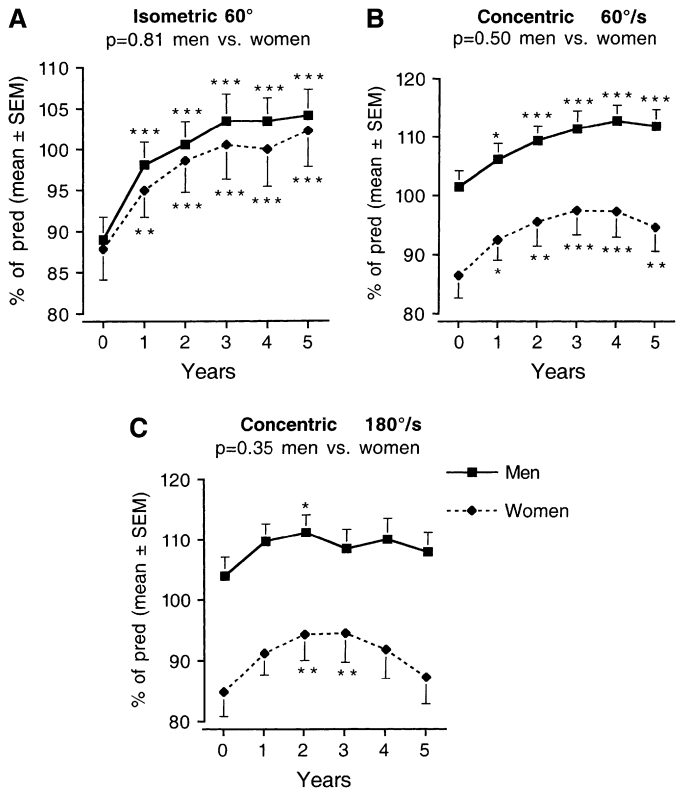

Fig. 4. Observed/predicted value ratios for isometric 60 degrees (*A*), concentric 60 degrees/s (*B*), and concentric 180 degrees/s (*C*) knee flexor strength in men and women during 5 years of GH replacement in 109 patients who had GHD of adult onset. The vertical bars indicate the SE for the mean values shown. Between-group P values are based on an analysis of the percentage change from baseline, whereas within-group P values in men and women are based on an analysis of the absolute values. *, $P < .05$; **, $P < .01$; ***, $P < .001$ versus baseline. (*From* Svensson J, Stibrant Sunnerhagen K, Johannsson G. Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. J Clin Endocrinol Metab 2003;88(5):2066; with permission.)

GH replacement in adults is similar to the mortality in the background population [63]. Although the data are reassuring they are preliminary and with a patient population heavily burdened by cardiovascular risk factors and increased premature vascular mortality, cardiovascular risk factors, such as lipids, blood pressure, smoking, and glucose metabolism, should be monitored and effectively treated in accordance with available guidelines.

Neoplasia

The mitogenic and growth-promoting effects of GH and IGF-I and their impact on neoplasia provide a theoretic basis by which GH treatment could

increase cancer risk and promote tumor growth. When assessing cancer rates, it must be taken into consideration that subjects who have hypopituitarism secondary to genetic or tumor-related causes might have an inherently higher risk for neoplasia compared with normal subjects, and furthermore, that some treatment modalities, including radiotherapy, might also increase the risk for secondary neoplasia. Two retrospective studies have supported such notions. These studies found increased rate of and mortality from neoplasia in patients who had pituitary adenomas, suggesting an association that may be inherent or attributable to increased surveillance of this patient population [64,65].

Three recent prospective studies have demonstrated that serum IGF-I levels within the upper normal range are predictive of cancer. In a meta-analysis of hormonal predictors of prostate cancer, it was found that men who had either serum testosterone or IGF-I levels in the upper quartile of the population had an approximately twofold higher risk for developing prostate cancer [66]. In other prospective trials among premenopausal women there was a 4.5-fold relative risk for breast cancer in the highest quartile of serum IGF-I compared with the lowest quartile [67]. Similar results were also found for colorectal cancer in men [68]. These studies have also demonstrated an inverse association between risk for cancer and serum IGFBP-3 concentration (ie, the highest risk is among subjects who have high serum IGF-I and low serum IGFBP-3 levels). The significance of these studies, both for the hypopituitary and the general population, is unknown. In the context of GH replacement it provides a clear rationale for maintaining IGF-I within the age-matched normal range.

For several other reasons, long-term monitoring of subjects receiving GH replacement remains essential. Monitoring is necessary to detect changes in GH dose requirements. There is some evidence that sensitivity to GH increases during long-term GH replacement [69] and GH replacement doses are lower in the elderly; any change in requirement is likely to be a reduction. Additionally, changes in replacement of other hormones, in particular commencement or discontinuation of oral estrogen, may alter GH requirement [23]. The consensus is that clinical screening for neoplasia should be based on general recommendations for adults and that current data do not support a more extensive screening program for patients who have hypopituitarism and GH replacement [39].

Neuroimaging surveillance

Another important aspect to consider during long-term monitoring and surveillance of GH replacement is the risk for regrowth or recurrence of the hypothalamic-pituitary or brain tumor responsible for most of the hypopituitarism seen in patients who have adult-onset disease. The progression-free survival in patients who have pituitary tumor has been reported as between 12% and 69% after surgery, and between 72% and 92% following

surgery and radiotherapy [70]. These data are from the time before GH became part of the replacement therapy of hypopituitarism.

In a prospective study of 100 patients who had pituitary and peripituitary tumors receiving GH replacement therapy only one case of slight intracellular enlargement was noted after 1 to 4 years of follow-up [71]. Ninety-one percent of the patients had received external radiotherapy. Another retrospective study of patients who had craniopharyngioma compared 32 patients who received GH replacement for a mean period of 6.3 years with 53 patients who had not received GH who had similar tumor and treatment characteristics and follow-up period [72]. During the period of observation, 4 patients treated with GH and 22 not receiving GH developed tumor recurrence. Finally a prospective study of 60 childhood brain tumor survivors receiving adult GH replacement therapy detected only one incurable ependymoma and one residual meningioma that progressed in size over a mean period of 6.7 years [73]. Secondary neoplasia was detected both before and after commencing GH treatment. The results from these studies do not indicate that GH replacement increases tumor recurrence or tumor regrowth, but the studies are small and the follow-up periods are limited. Vigilance and long-term surveillance are therefore indicated in patients previously treated for tumors, in particular those who have increased risk for a secondary tumor, as was the case in childhood brain tumor survivors.

Specific conditions, including pregnancy

The labeled contraindication to GH treatment in adults is uncontrolled malignancy. Relative contraindications are proliferative diabetic retinopathy and benign intracranial hypertension. Patients who have hypopituitarism and diabetes mellitus can be treated, but initial dose should be low and dose titration slow, with close monitoring of glucose metabolism. In patients who have type I diabetes the response in serum IGF-I is markedly attenuated because of reduced availability of insulin to the liver [74]. Normalization of serum IGF-I cannot always be obtained, therefore, and dose titration and monitoring should be guided by other measures.

During pregnancy, the pulsatile release of pituitary GH is progressively suppressed and replaced by a continuous secretion of placental GH into the maternal circulation [75]. After delivery, there is a gradual normalization of the pituitary GH secretion [76]. Placental GH is a major regulator of maternal serum IGF-I levels during pregnancy [77]. GH does not cross the placenta and therefore its effects on the fetus are probably indirect and mediated by maternal IGF-I production and by actions on substrate supply to the fetus [78]. Normal pregnancies have been reported in GH-deficient women [79].

Currently, because of the lack of safety data, GH therapy is not licensed for use during pregnancy. If one takes into account the normal GH physiology during pregnancy, it would be advisable and justifiable to maintain

the replacement therapy in women who have GHD, at least until the time enough placental production of GH is achieved. In an attempt to reproduce the gestational GH physiology, eight GH-deficient women during 12 distinct pregnancies received their ordinary pregestational GH dose during the first 3 months of gestation, and the dose was gradually tapered off during the subsequent 3 months [80]. This treatment strategy was demonstrated to be safe to the mother and the fetus. No important adverse events or major obstetric complications were observed. Moreover, no women complained of excess fatigue during the first 3 months of gestation, as was the experience in some cases when GH replacement was discontinued when pregnancy was confirmed [80].

Summary

GH replacement therapy in adults, as documented in published work with correct diagnosis of severe GHD, using dose titration and monitoring of treatment by serum IGF-I and clinical efficacy, is a safe therapy. In patients who have hypothalamic-pituitary tumor as underlying cause of hypopituitarism neuroimaging is recommended before commencement of GH replacement and thereafter according to ordinary surveillance routines. Although the long-term experience is limited in patients who have remnant tumor, all present data indicate that the treatment is safe in such patients. Before GH replacement is started, baseline assessment of clinical features of GHD, optimal route, and dose of other hormone replacement therapy should be ensured and the patient's sensitivity to GH should be estimated. This evaluation should then guide the decision of the starting dose of GH and the pace of dose titration along with what clinical variables are most useful to monitor. Serum IGF-I should be monitored and used as a safety variable, avoiding being greater than the upper limit of age-related normative values. Long-term clinical efficacy and safety data are growing fast. Although all data support the safety and efficacy of GH replacement in adults, continued monitoring during long-term treatment should include safety assessments with respect to this powerful metabolic hormone.

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