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Diagnosis and Management of Adult Growth Hormone Deficiency

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Introduction

For almost four decades, growth hormone (GH) has been used successfully to treat pituitary dwarfism but with treatment suspended after epiphyseal fusion. Body growth results from the stimulation by GH of a complex and integrated series of metabolic events, which are readily demonstrable in the adult after cessation of longitudinal growth. Virtually all body tissues examined to date contain receptors for GH. These observations suggest that GH has widespread effects and plays a general role in maintaining the metabolic process and the integrity of many tissues.

Raben first reported, nearly 40 yr ago, improved vigor and well-being in an adult woman with hypopituitarism treated with GH *(1)*. Treatment evaluation of GH in hypopituitary adults was largely ignored for the next 25 yr. A major reason for past neglect of treating adult hypopituitarism was the limited availability of pituitary-derived GH outside the pediatric setting. The availability of virtually unlimited supplies of human GH through recombinant technology has heralded an almost unprecedented level of research activities that have generated a wealth of information on GH, the consequences of GH deficiency in adults, and the benefits of replacement treatment. This article will review the diagnosis and management of these patients.

There is limited information on the epidemiology of hypopituitarism. A Swedish survey estimates the prevalence of hypopituitarism to be approx 175 cases per million *(2)*. The pathologies that result in hypopituitarism are similar to those that cause GH deficiency. Approximately 60–70% arise from pituitary tumors, 15–20% from craniopharyngiomas, 5% from other parasella tumors, 10% from idiopathic (congenital) tumors, with trauma, infiltrative, and inflammatory causes accounting for less than 5% *(3–5)*. The treatment of pituitary tumors is a significant cause of GH deficiency. Out of 165 patients with pituitary tumors evaluated before surgery, about 50% of patients already had evidence of GH deficiency *(6)*. After surgery, about 80% had evidence of GH deficiency. In patients who received post-operative radiotherapy, endocrine evaluation after 5 yr revealed that all patients were GH deficient *(6)*.

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Diagnosis of Adult GH Deficiency

One of the first indications of a possible deleterious effect of unsubstituted GH deficiency in hypopituitary adults came from a study in 1990, by Rosen and Bengtsson *(3)* who reported a twofold increase in mortality, mostly from cardiovascular disease. Increased mortality has since been confirmed in two recent studies *(7,8)*. These patients also suffer from significant morbidities characterized by a range of metabolic and functional abnormalities. Diagnosis of adult GH deficiency requires the awareness and recognition of the clinical phenotype followed by biochemical confirmation of hyposomatotropism.

Clinical Syndrome of Adult GH Deficiency

Adults with GH deficiency are not normal and have a recognizable clinical syndrome *(9),* which is detailed in **Table 1**. GH-deficient adults are more obese and display a disproportionate increase in central abdominal fat *(10)*. There is strong evidence linking obesity, and in particular abdominal obesity, to diabetes and cardiovascular disease *(11–14)*. GH-deficient adults harbor biochemical abnormalities that are strongly linked to the development of vascular disease, with increased concentrations of total and LDL cholesterol *(15,16)* and a higher prevalence of abnormal glucose tolerance *(17)*. There is increased plasminogen activator inhibitory activity and higher levels of fibrinogen *(18),* both markers of increased atherothrombotic propensity with fibrinogen also being a known risk factor for stroke and myocardial infarction *(19)*. These biochemical abnormalities may explain the finding of greater prevalence of atheromatous plaques in carotid and femoral vessels in these patients *(20)*.

GH-deficient adults have significant reduction in lean body and muscle mass, reduced muscle strength, and impaired physical fitness *(21–25)*. Bone mass is also reduced *(26,27),* and there is preliminary evidence of an increased rate of osteoporotic fractures *(28)*.

Cardiac function is impaired and characterized by reduced ventricular muscle mass, ejection fraction, and im-

Table 1
Syndrome of Adult GH Deficiency

Symptoms
Increased body fat
Reduced muscle bulk
Reduced strength and physical fitness
Reduced sweating
Impaired psychological well-being:
depressed mood
anxiety
reduced vitality and energy
increased social isolation
Signs
Overweight
Increased adiposity, especially abdominal
Poor muscular development
Reduced exercise performance
Thin, dry skin
Depressed affect
Investigations
Peak GH response to hypoglycaemia < 3 ng/mL (all patients)
Low IGF-I (60% of patients)
Hyperlipidemia: high LDL cholesterol, low HDL cholesterol
Elevated fasting insulin
Reduced bone mineral density

paired ventricular filling *(29–31)*. These findings, along with reduced lung size *(32)*, may contribute to decreased exercise capacity. There is impairment of sweating, which increases susceptibility to hyperthermia during exercise and may limit exercise performance *(33,34)*.

Studies of psychological function have also revealed significant abnormalities as assessed by measures of quality of life *(35,36)*. GH-deficient adults were found to have lower energy scores and dysfunctional emotional reaction *(35,36)*. There was lower self-perception of quality of life with patients reporting reduced health, control, vitality, and more anxiety. A Dutch survey of social integration reported that GH-deficient adults had lower social status *(37)*. These patients were on a lower professional scale, had lower income, were often without partners, and living at home with their parents.

Thus, adults who lack GH have a recognizable syndrome of metabolic derangement, abnormal body composition, reduced physical fitness, and impaired psychological well-being and social integration.

Diagnostic Tests of Adult GH Deficiency

While the features of GH deficiency are recognizable, they are not particularly distinct as they mimic the body composition and biochemical changes of the aging process *(38)*. GH secretion falls progressively, with aging which is associated with a progressive increase in adiposity, which itself reduces GH secretion *(39,40)*. Thus, clinical suspicion must be confirmed by accurate biochemical diagnosis to ensure that GH-deficient patients are accurately identified and treated.

There are three widely accepted approaches for assessing GH secretory status. These are measuring (1) the peak GH response to a provocative test, (2) spontaneous GH secretion, and (3) serum concentrations of GH-regulated proteins such as IGF-I and IGF binding protein-3 (IGFBP-3). The merits of each have been carefully investigated.

Provocative Tests

The diagnosis of adult GH deficiency is established by provocative testing of GH secretion. Patients must be on adequate and stable hormone replacement for other hormonal deficits prior to testing. A number of provocative tests are available and include insulin tolerance test (ITT), arginine, glucagon, clonidine, GHRH alone or in combination with arginine, or pyridostigmine. However, the GH releasing potency differ between these agents with the ITT being a better stimulator of GH release than arginine, glucagon, or clonidine *(41)* (**Fig. 1**). These observations indicate that the diagnostic threshold values of normality vary between tests and cannot be extrapolated from one test to another *(42)*.

The Growth Hormone Research Society has recommended the ITT as the diagnostic test of choice *(43)*. It is superior to measuring integrated 24 h GH concentration or IGF-I *(44)* (**Fig. 2**). Provided that adequate hypoglycemia (less than 2.2 mmol/L or 40 mg/dL) is achieved, the ITT distinguishes GH deficiency from the reduced GH secretion that accompanies normal aging and obesity. The ITT should be performed in experienced endocrine units under supervision. The test is contraindicated in patients with electrocardiographic evidence or history of ischemic heart disease and in patients with seizure disorders. Given these precautions, the insulin tolerance test is safe with a risk of adverse event of less than 1 in 450 *(45)*. Normal subjects respond to insulin-induced hypoglycemia with a peak GH concentration of greater than 5 μg/L *(45)*. Severe GH deficiency is defined by a peak GH response to hypoglycemia of less than 3 μg/L *(43)*. These cut-off values were defined in GH assays employing polyclonal competitive radioimmunoassays. However, GH immunoassay results vary between different methods and, therefore, the cut-off value may need to be adjusted appropriately.

For patients in whom the ITT is contraindicated, alternative provocative tests of GH secretion must be used with appropriate cut-offs because of their varying ability to stimulate GH release. At present, the combined administration of arginine and GH-releasing hormone (GHRH) is the most promising alternative *(46)*, being of equal reliability to the ITT *(47)*. Other alternatives include arginine alone or glucagon. These tests have less well-established diagnostic value compared to the ITT. Other stimulatory

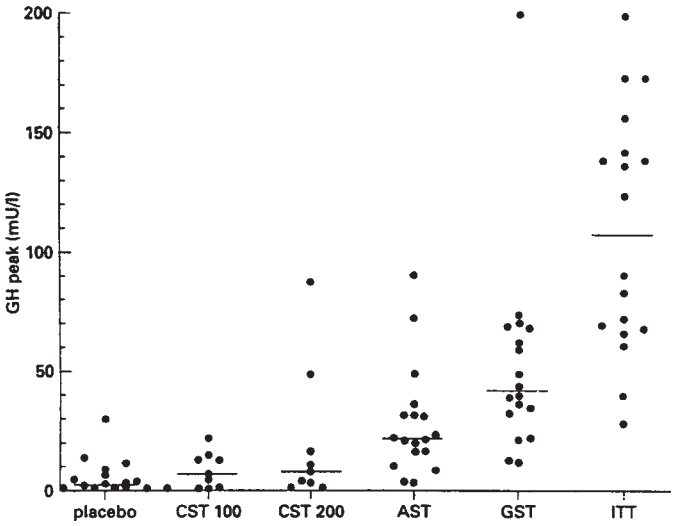

Fig. 1. Peak GH response to placebo, oral clonidine 100 μg (CST 100) and 200 μg (CST 200), arginine (AST), glucagon (GST) and to the insulin tolerance test (ITT) in 18 normal male adults. Reproduced from Rahim, et al. *(41).*

tests including the use of GH secretagogues may prove to be useful but require further validation.

Spontaneous Secretion

This is most commonly estimated by measuring GH from frequent samples obtained over a 24-h period. Integrated GH measurements obtained in this way do not readily discriminate GH-deficient patients from normal subjects even with the use of highly sensitive assays *(48,49).* Together with its labor-intensive nature, this procedure is more suitable as a research tool and cannot be recommended as a practical or reliable diagnostic test for GH deficiency *(44)* (Fig. 2).

Biochemical Markers of GH Action

Biochemical markers of GH action include IGF-I, IGF-binding protein-3 (IGFBP-3) and the acid labile subunit of the IGF-I-binding protein complex. Of the three biochemical markers, the merit of IGF-I has been the most intensively studied. Serum IGF-I concentrations are only useful when age-adjusted normal ranges are used. While IGF-I levels are reduced in adult GH deficiency, a normal concentration does not exclude the diagnosis *(44)* (Fig. 2). A subnormal IGF-I level in an adult patient with coexisting pituitary hormone deficits is strongly suggestive of GH deficiency, particularly in the absence of conditions known to reduce IGF-I levels, such as malnutrition, liver disease, poorly controlled diabetes mellitus, and hypothyroidism. A review of recently published data involving a total of 340 patients show that IGF-I concentration is subnormal in about 60% of adults with proven GH deficiency *(42).* The separation of IGF-I values between GH deficient and normal subjects is greatest in the young. As IGF-I levels decline in normal subjects with aging, IGF-I becomes less reliable as a biochemical marker of GH deficiency in patients over 50 yr old when the values merge with those of normal subjects *(46).* Measurement of IGFBP-3 or the acid labile subunit does not offer any advantage over IGF-I.

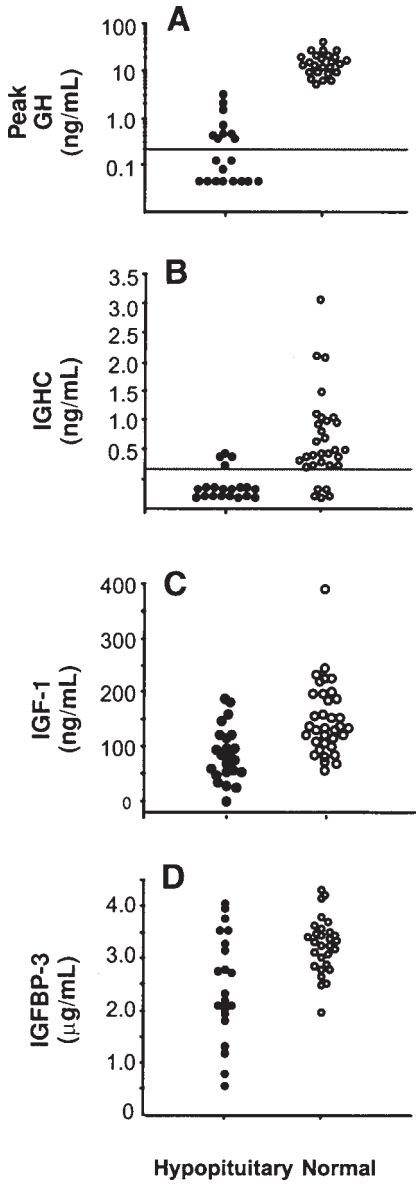

Fig. 2. Comparison of peak GH concentration obtained during an insulin tolerance test (A), integrated GH concentration (IGHC) obtained from blood withdrawal every 20 min for 24 hours (B), IGF-I (C) and IGFBP-3 concentrations (D) in patients with organic hypopituitarism and age- and sex-matched normal subjects. The horizontal line denotes the limit of reading. Reproduced from Hoffman, et al. *(44).*

Diagnostic Consideration

GH deficiency should be defined biochemically within an appropriate clinical context. The GH Research Society has recommended that biochemical testing for GH deficiency be considered in patients with a high probability of

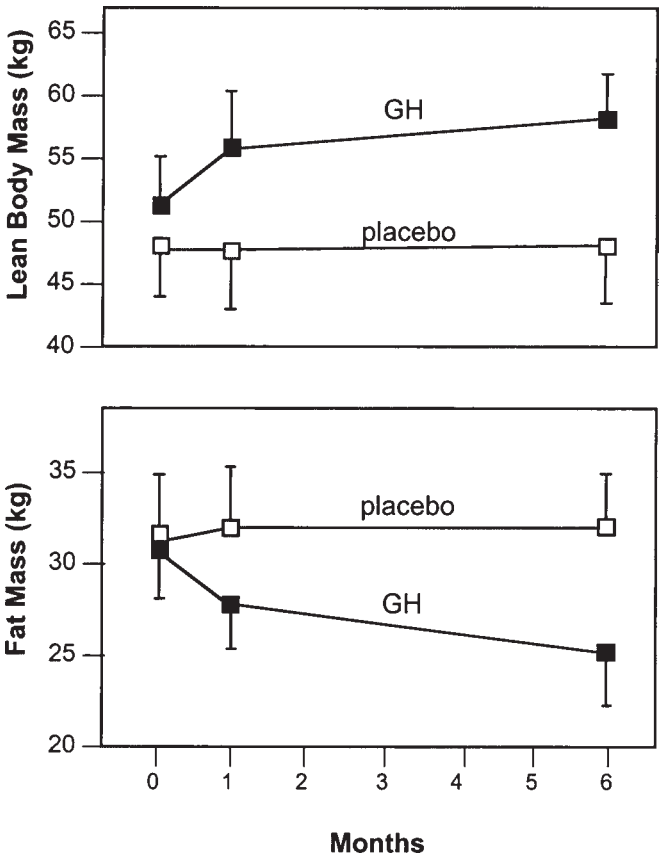

Fig. 3. Body composition in GH-deficient adults during treatment with either GH or placebo for 6 mo. (A) fat mass and (B) lean body mass. Reproduced from Salomon, et al. *(10).*

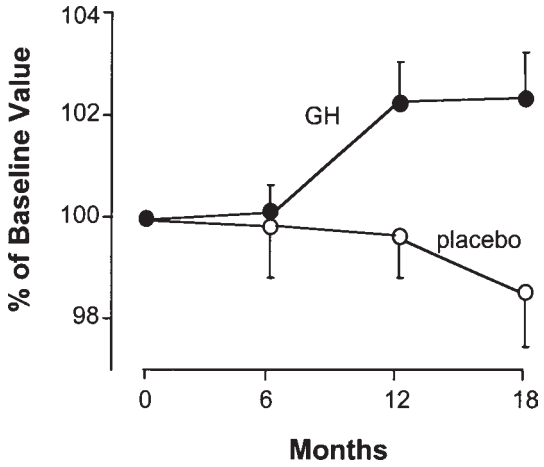

Fig. 4. Bone mineral density of the lumbar spine in GH-deficient adults during treatment with either GH or placebo for 18 mo. Reproduced from Baum, et al. *(59).*

hypothalamus-pituitary disease and manifesting clinical features of the syndrome *(43).* This includes patients with a past history of organic hypothalamic-pituitary dysfunction, cranial irradiation, or known childhood onset of GH deficiency. In patients with organic hypothalamic-pituitary disease, the prevalence of GH deficiency is strongly linked to the number of pituitary hormone deficits, ranging from approx 45% with no deficit, to virtually 100% if 3–4 pituitary hormone deficiencies are present *(50).* Patients with childhood-onset GH deficiency should be retested as adults before committing them to long-term GH replacement. About one-quarter of patients demonstrate normal GH responses when retested in adulthood using the same stimulation test *(51).*

Management of Adult GH Deficiency

Effects of GH Replacement

The beneficial effects of GH replacement in hypopituitary adults were first reported in 1989 *(10,52).* Since then, numerous studies have confirmed these initial observations *(53)* (**Table 2**). The most consistent effect of GH replacement is on body composition *(5,10,52–55).* In all reported studies, GH treatment causes an increase in lean body mass and in skeletal muscle size as assessed from cross-sectional thigh muscle area. There is a corresponding reduction in body fat with the most prominent and abundant reduction occurring in visceral fat *(54,55).* These changes are sustained beyond 12 mo of treatment *(56,57)* (**Fig. 3**).

Initial studies evaluating changes in bone mineral density (BMD) over 6–12 mo of treatment gave conflicting results. However more recent studies reporting long-term data show progressive increases in BMD beyond 12–18 mo of treatment *(58–60)* (**Fig. 4**). The gain is more marked in those patients with low BMD before commencing GH treatment.

Several studies have investigated whether the increase in lean body and muscle mass during GH treatment is accompanied by an improvement in muscle strength. Some studies have reported significant improvements in quadriceps or hip muscle strength after 6 mo of treatment *(57,61).* The strongest data have recently been provided by Johannsson, et al. who reported normalization of isometric quadriceps force and torque after 2 yr of treatment *(62).*

Many studies have also reported improvements in exercise capacity and performance and an increase in maximal oxygen uptake *(21,57,63,64).* GH treatment exerts a range of positive effects on cardiac function. The studies show significant increases in stroke volume, cardiac output, left ventricular wall mass, and left ventricular end diastolic function *(21,65–67).*

GH replacement induces significant positive effects on lipoprotein metabolism. Most studies report a decrease in total cholesterol *(10,54,68–70).* Less consistently reported are effects on increasing HDL cholesterol and reducing LDL cholesterol and ApoB *(54,69,70).* The favourable effects on lipoprotein profile are more evident after treatment for longer than one year.

Table 2
Summary of the Clinical Consequences of GH Deficiency in Adults and the Impact of GH Replacement Treatment

	GH deficiency	GH replacement
Metabolism		
Lipolysis	decreased	restored
Protein anabolism	decreased	restored
Glucose tolerance	impaired	restored
Total cholesterol	increased	decreased
LDL	increased	decreased
HDL	decreased	increased
Body composition		
Body fat	increased	restored
Abdominal fat	increased	restored
Lean body mass	decreased	restored
Muscle bulk	decreased	restored
Function		
Muscle strength	decreased	restored
Exercise capacity	decreased	restored
Quality of life	impaired	improved

Studies assessing GH effects on psychological function have also reported improvements in psychological well-being and in quality of life *(55).* Improvement in well-being may take up to 6 mo *(71).* In a study involving a partner questionnaire, spouses observed significant improvements in several aspects of their partners' mood and behavior with active treatment *(72).*

A recent study has reported significant differences in clinical and biochemical presentation and responses to GH therapy between patients with childhood-onset and those with adult-onset GH deficiency *(5).* Patients with adult-onset GH deficiency demonstrated greater improvement in quality of life measures and in lipid profiles, but lesser changes in body composition. The data suggest the existence of two entities, developmental and metabolic, and the different functions of GH at different periods of life.

The collective data provide unequivocal evidence that GH replacement normalizes body composition, improves physical fitness and muscle strength, increases bone mass, and improves psychological function. A more detailed and comprehensive review of the effects of GH replacement in adults with GH deficiency from The Growth Hormone Research Society has recently been published *(53).*

Therapeutic Issues

Dosage

GH dosage employed in several early trials of replacement was somewhat excessive as supranormal levels of IGF-I and a high prevalence of side effects were encountered in a significant percentage of patients during treatment. The dosage regimens in many of these trials were weight-based. A weight and fixed-dose regimen may not be appropriate since it commits obese patients to a larger dose. This is not compatible with the known physiological reduction in GH secretion with adiposity, nor does it allow for reduced GH secretion with aging *(39).* However, more recent trials employing a dosage regimen designed to maintain IGF-I levels in the normal range have encountered virtually no untoward effects *(59).* It is clear that GH replacement dosage needs to be individualized as is the case for other types of hormone replacement therapy.

The Growth Hormone Research Society has recommended that the replacement dosage not be weight-based. Patients are to be commenced on a low dose (0.15–0.3 mg/d; 0.45–0.9 IU/d) and thn gradually increased in accordance with clinical and biochemical responses *(43).* The maintenance dosage may vary considerably and is influenced by gender and age, but rarely exceeds 1 mg/d (3 IU/d). Women appear to require higher doses than men *(73)*, while the elderly require lower doses. A recent study of dose optimization designed to achieve normal IGF-I levels reported the average daily maintenance dose to be 1.2 IU in women and 0.8 IU in men *(74).* GH should be administered subcutaneously each day in the evening.

Interactions

GH may influence the metabolism of many substances including hormones and medications. GH stimulates the activity of the hepatic cytochrome P450 system which is a major pathway of the oxidative metabolism of several drugs including anticonvulsants and theophylline. It is likely that dosage adjustments may be necessary in patients commencing GH treatment. Cortisol is also metabolized by the hepatic cytochrome P450 system. There is biochemical evidence that GH increases the metabolic disposition of cortisol and may increase the risk of adrenal insufficiency *(75)* which has been reported in some studies *(54).* While a causal relationship remains unproven, GH-deficient patients on GH therapy should be strongly advised to increase the dosage of glucocorticoids when ill, as is generally recommended.

GH stimulates the peripheral conversion of T4 to T3. This effect may be frequently seen as a fall in circulating T4 levels particularly in patients on thyroid hormone replacement for hypopituitarism *(76).* If T3 is not monitored during GH replacement, a fall in T4 may be misinterpreted as inadequate substitution and may lead to unnecessary increase in the dosage of thyroid hormone replacement.

Estrogen has significant effects on the metabolic and endocrine functions of the liver which are dependent on the route of administration. When compared to the transdermal route, oral estrogen reduces IGF-I and fat oxidation, effects which are opposite those of GH *(77).* The possibility that oral estrogens may antagonize GH action is supported by the observation that women are less responsive than men to GH *(73).* GH-deficient women who are also hypogonadal should receive estrogen by a nonoral route during GH replacement.

Safety

The principle of hormone replacement therapy predicates that hormone replacement restores the untreated, morbid, hormone-deficient state to normal. Side effects may be encountered as a consequence of inappropriate dosage or the failure of the mode of hormone replacement to induce a pharmacokinetic profile that mimics normal physiology. The same issues apply to GH replacement therapy. The experience from several large multicenter clinical trials indicates that GH treatment is safe and well-tolerated *(54,56,78).*

The most common side effects arise from the antinatriuretic action of GH which causes fluid retention *(79,80).* These manifest as dependent edema, parasthesia, and carpal tunnel syndrome, and occur with greater frequency in older patients *(54,56,78).* However, these symptoms are mild, dose-related, and resolve in the majority of patients either spontaneously or with dosage reduction *(81).*

Although GH antagonizes insulin action, the risk of developing hyperglycemia is very low. Only two cases of reversible diabetes were reported from two European multicenter trials with a combined total of 400 patients *(56,78).* Insulin sensitivity improves and may normalize after some months of treatment *(82).* This paradoxical effect arises from the reduction in central abdominal fat which ameliorates insulin resistance.

Because GH promotes the growth of tissues, concern has been expressed that GH therapy may increase the risk of pituitary tumor recurrence or the development of neoplasia. Analysis of the extensive pediatric experience shows no convincing evidence for a causal link between GH treatment and tumor recurrence or the development of neoplasia including leukaemia *(83).* It has recently been reported that mean IGF-I levels are higher in patients with prostate and breast cancers than in controls *(84,85).* One interpretation of these observations is that elevating IGF-I, which occurs with GH treatment, may increase the risk of developing prostate and breast cancers. If this is true, patients with acromegaly who have sustained elevated IGF-I levels should have a higher incidence of these malignancies. There are conflicting reports about whether cancer incidence is increased in this disease, but many have lacked statistical power. The biggest study to date involving over 1000 acromegalic patients found overall cancer incidence rates to be lower than in the general population. There was no significant increase in site-specific cancer rates including breast cancer *(86).* These data in acromegaly provide the persuasive evidence against a causal association between IGF-I and malignancy. Current recommendations for cancer prevention and early detection should be practiced in the hypopituitary adult treated with GH. It should be emphasized that the issues should be viewed in the context of restoring a GH-deficient state to normal. Nevertheless, it is important for future studies to establish whether the incidence of cancer or tumor recurrence in GH-replaced hypopituitary patients is different from untreated patients.

Conclusion

Hypopituitary patients on conventional replacement therapy have impaired health characterized by abnormalities of substrate metabolism, body composition, physical performance and psychological function. GH deficiency in patients with organic pituitary disease can be accurately diagnosed by the ITT. GH replacement is safe, well-tolerated, and restores health. Side effects are minor and minimized by individualizing dosage requirements. Because GH is expensive, its use should be restricted to those with proven GH deficiency. Based on global evidence of safety and efficacy, adults with GH deficiency should be placed on GH therapy, a principle consistent with the tenet of hormone replacement in the practice of endocrinology.

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