

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



GH Replacement Therapy in GH-Deficient Adults

Luger A

J. Reproduktionsmed. Endokrinol 2006; 3 (6), 379-381

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



ENDO FERTI FORUM

ENDOKRINOLOGIE & FERTILITÄT
FÜR KLINIK & PRAXIS

20.-21. März 2026

Universitätsmedizin Mainz

Einladung zu unserer wissenschaftlichen Veranstaltung Endo-Ferti-Forum

Brücke(n) zwischen Unikliniken und Praxen an Rhein und Main(z)

– die aus dem bisherigen Format „Ferti Forum“ ab 2026 hervorgeht –



Freuen Sie sich auf spannende Vorträge und den lebendigen Austausch mit Kolleg:innen und Expert:innen aus Klinik und Praxis. Freitagabend laden wir Sie herzlich zu einem entspannten Empfang ein – eine perfekte Gelegenheit, Kontakte zu knüpfen und den Tag genussvoll ausklingen zu lassen.

Wissenschaftliche Leitung: Univ.-Professorin Annette Hasenburg, Dr. Susanne Theis, Universitätsmedizin Mainz, Sanitätsrat Dr. Werner Harlfinger, BVF Rheinland-Pfalz Dr. Rüdiger Gaase, BVF Hessen Dr. Klaus J. Doubek

Schirmherrschaften: Prof. Nicole Sänger, Uniklinik Bonn, Prof. Jan-Steffen Krüssel, Uniklinik Düsseldorf, Dr. Annette Bachmann, Uniklinik Frankfurt am Main, Prof. Christine Skala, Uniklinik Köln

Weitere Informationen
& Anmeldung unter



GH Replacement Therapy in GH-Deficient Adults

A. Luger

Growth hormone (GH) deficiency represents an indication for substitution therapy not only in children but also in adults. In the last twenty years, numerous studies have shown that GH deficiency in adults is characterized by a clearly defined syndrome which is associated with a double-increased mortality rate. GH deficiency in adults can be diagnosed only by dynamic tests. While the insulin tolerance test (ITT) has been the standard test in the past, the combined arginine-GH releasing hormone (GHRH) test has been used more often in the last years. It has the advantage to detect more readily GH deficiency in obese and elderly subjects. Severe GH deficiency is characterised by a maximal GH concentration of less than 3 ng/ml in the ITT, and less than 9 ng/ml in the arginine-GHRH test. Severe growth hormone deficiency represents a clear indication for GH substitution therapy which should be started in a dose of 0.15–0.30 mg/day. The GH dose should be adapted according to the age- and sex-specific reference ranges for insulin-like growth factor 1 (IGF-1). GH substitution therapy can reverse or at least ameliorate most of the symptoms of GH deficiency. Side effects such as muscle and joint aches as well as fluid retention can be observed sometimes at start of therapy. The incidence of diabetes mellitus and carcinomas is not increased by GH therapy. As is the case with other pituitary deficiencies, GH substitution therapy in adults with GH deficiency represents an established indication. *J Reproduktionsmed Endokrinol* 2006; 3 (6): 379–81.

Key words: growth hormone deficiency, growth hormone therapy, insulin tolerance test, body composition, cardiovascular risk profile, mortality

The syndrome of GH deficiency in adults was first described almost 20 years ago and is now a well-recognized entity and indication for GH substitution therapy in adults [1, 2]. Signs and symptoms of GH deficiency are shown in Table 1.

Rosen and Bengtsson reported increased mortality in GH-deficient adults mainly due to cardiovascular diseases [3]. These findings have been replicated by others [4, 5] and have stimulated research into the pathophysiological pathways that cause the twofold increased death rate in these patients. One of the most critical questions was whether or not GH-deficiency-related signs and symptoms could be reversed by adequate substitution therapy. Additional questions were:

- How should GH deficiency be diagnosed?
- Should all patients with documented GH deficiency be treated?
- Should substitution therapy in GH-deficient children be continued into adulthood?
- What is the right dose of GH and how should therapy be monitored?
- Could GH substitution therapy be associated with increased risk for recurrence of pituitary adenomas, diabetes or cancer?
- Are there diseases other than tumors (pituitary adenomas, craniopharyngeomas), irradiation and idiopathic GH deficiency that cause GH deficiency and if so, which patients should be screened?

Table 1. Signs and symptoms of GH deficiency in adults

- Increased body fat mass (predominantly visceral fat)
- Reduced muscle mass
- Reduced bone mineral density
- Increased cardiovascular risk profile
- Decreased quality of life
- Increased need of health care resources

Received: May 11, 2006; accepted after revision: September 29, 2006
From the Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Austria
Correspondence: Prof. Anton Luger, M.D., Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, A-1090 Vienna, Währinger Gürtel 18–20; e-mail: anton.luger@meduniwien.ac.at

Diagnosis of GH Deficiency

Only subjects with evidence of hypothalamic pituitary disease or persons who have received cranial irradiation or patients with childhood onset of GH deficiency should be considered for evaluation for GH deficiency [6]. Due to the numerous factors influencing basal GH and insulin-like growth factor 1 (IGF-1) concentrations (body mass index, stress, age, sex, drugs, diseases) neither parameter is suited for diagnosing GH deficiency. In adults, this should be accomplished by dynamic tests and patients should be receiving stable and adequate hormone replacement for other hormonal deficits before testing [6].

The most common stimulation test used to detect GH deficiency in adults is the insulin tolerance test (ITT) which, however, is contraindicated in subjects with known cardiovascular diseases and epilepsy [6]. Since the former are expected to be widely used in GH-deficient patients, the combined arginine-GHRH or arginine-GH-releasing peptide-6 (GHRP-6) tests have become more popular over the past years despite their higher costs [7, 8]. As an additional advantage, they can more readily detect obese and elderly subjects as GH-deficient than other tests. In the Port Stevens Conference for the diagnosis and treatment of adults with GH deficiency, a cut-off level for severe GH deficiency was set at 3 ng/ml in the insulin tolerance test [6]. The cut-off level for the arginine-GHRH test was set at 9 ng/ml. In a large study of 322 patients with organic hypothalamic-pituitary disease, different cut-off levels according to the individual body mass index (BMI) were described for the arginine-GHRH test [9]: 11.5 ng/ml for normal-weight subjects ($\text{BMI} \leq 25 \text{ kg/m}^2$), 8 ng/ml in overweight subjects ($\text{BMI} 25\text{--}30 \text{ kg/m}^2$) and 4.2 ng/ml in obese subjects ($\text{BMI} > 30 \text{ kg/m}^2$). Biller et al also reported a GH cut-off point of 4.2 ng/ml in obese patients [8]. In the absence of a morphological cause for GH deficiency, i. e. in idiopathic cases, the diagnosis of GH deficiency should be confirmed by a second stimulation test.

Severe GH deficiency is now considered as an indication for GH substitution therapy. It should be mentioned, however, that an intermediate category of partial GH deficiency has been identified (arbitrarily defined as patients with a GH peak $> 3 \text{ ng/ml}$ but $< 7 \text{ ng/ml}$ in the ITT

and > 9 ng/ml but < 16.5 ng/ml in the arginine-GHRH test, respectively) which exhibits most signs and symptoms of GH deficiency although in a less pronounced manner than in severe GH deficiency [10]. At present, it is not clear whether these patients should also receive GH replacement therapy and no data exist on the efficacy and safety of such a therapy. In children with GH deficiency, therapy should be stopped after attainment of final height around the age of 18 for at least 3 months and at least one stimulation test should document the persistence of GHD [11] before substitution therapy is continued into adulthood.

Therapy

Once the diagnosis has been established GH substitution therapy should start with a low dose of 0.15–0.30 mg/day as higher doses have been associated with an increased incidence of side effects [6, 12]. Doses should be adjusted according to sex- and age-adjusted IGF-1 reference ranges. Female patients apparently need higher GH doses which might be due, at least in part, to the antagonistic action of oral estrogens at the liver resulting in lower IGF-1 concentrations [13]. In GH-deficient patients receiving additional substitution therapies, IGF-1 concentrations should be checked whenever the dose of these therapies is modified. GH substitution therapy is a life-long therapy and should be monitored at least in yearly intervals as soon as a stable condition has been achieved.

Effects on Body Composition and Cardiovascular Risk Profile

Numerous studies have shown unequivocally that GH therapy restores body composition: lean body mass is increased and body fat mass is decreased whereas body weight remains more or less stable [2, 14–16]. These effects are sustained over treatment periods of 10 years [17]. In addition, an increase in bone mineral density has been demonstrated in many studies [15, 18, 19]. It should be mentioned, however, that in the first year, especially after six months, bone mineral density can decrease substantially and a gain in bone mineral density is observed usually only in the second year of treatment and continues into the third and fourth year.

Beneficial effects on the cardiovascular risk profile – lipid and blood glucose concentrations as well as blood pressure – have also been demonstrated in many studies in patients receiving GH replacement therapy [15, 16, 20, 21]. Furthermore, echocardiographic studies have revealed at least partial correction of GH-deficiency-related dysfunction (reduced left ventricular mass, decreased ejection fraction, abnormal left ventricular filling) [22]. In addition, reduction of increased intima-media thickening in carotid and femoral arteries following institution of GH replacement therapy and normalization of vascular reactivity have been reported in GH-treated GH-deficient adults [22, 23]. It remains to be proven that GH therapy not only exerts beneficial effects on surrogate parameters but also increases life expectancy in GH-deficient adults. The evidence currently available, however, suggests that this goal will be achieved. Finally, the reduced quality of life in GH-deficient adults can also be restored by GH replacement therapy [24–26].

Table 2. Diagnosis of GH deficiency

	Stimulation test	Cut-off
Severe GH deficiency	Insulin tolerance test	< 3 ng/ml
Partial GH deficiency	Insulin tolerance test	3–7 ng/ml
Normal	Insulin tolerance test	> 16.5 ng/ml
Severe GH deficiency	Arginine-GHRH test	< 9 ng/ml (for differential cut-off points according to BMI see text)

Pharmacoeconomical studies have also demonstrated that the use of health care facilities (number of doctor visits, number of days spent in hospitals, number of days of sick leave) is reduced after introduction of GH replacement therapy [26]. Thus, strong evidence has accumulated over the past 20 years that GH deficiency should be considered as a severe threat to health and well-being and therefore be treated by adequate substitution therapy.

Side Effects

Muscle and joint aches as well as fluid retention are observed mainly at the beginning of therapy. In most circumstances, these symptoms can be ameliorated by dose reduction and disappear despite continuation of therapy. Because of the increased incidence of colo-rectal cancer in patients with acromegaly and the numerous epidemiological reports on the increased risk for the most common carcinomas (breast, colon, prostate, lung) in subjects with GH/IGF-1 concentrations in the upper normal range [27] special attention has been attributed to the incidence of carcinomas in patients on GH replacement therapy as well as to the recurrence of pituitary tumors. Until present, however, such a correlation has not been found [28]. The available data suggest that GH replacement therapy in GH-deficient adults is safe.

New Indications

Over the past years, evidence has accumulated that a considerable proportion of patients exhibit insufficiency of one or more anterior pituitary functions following traumatic brain injury [29, 30]. As in other situations, GH secretion is one of the most commonly affected pituitary functions. Thus, testing the anterior pituitary function should be considered in these patients, especially if signs or symptoms of GH deficiency are suspected. However, since pituitary dysfunction might be transient, a definite diagnosis of GH deficiency should not be made earlier than 6–12 months after injury. Subarachnoid hemorrhage and primary hyperparathyroidism might also induce GH deficiency [31, 32].

Based on the observation that GH declines with age and that many symptoms of aging are reminiscent of GH deficiency, an estimated 25,000–30,000 persons receive, or rather self-administer, GH as an anti-aging therapy in the USA [33]. However, no data are available that GH – especially what dose of GH – is effective and safe in elderly persons when it is used in pharmacological doses that result in IGF-1 plasma concentrations above the sex- and age-adjusted reference range. Thus, GH should not be used as an anti-aging drug until long-term studies have proven its effectiveness and safety.

References:

- Salomon F, Sonksen PH. Physiological role of growth hormone in adult life. *Acta Paediatr Scand* 1987; 377: 158–63.
- Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen, T, Skakkebaek NE, Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1989; 1: 1221–5.
- Rosen T, Bengtsson BÅ. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990; 336: 285–8.
- Bülow B, Hagmar L, Mikoczy Z, Norström CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf)* 1997; 46: 75–81.
- Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001; 357: 425–31.
- Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metabol* 1998; 83: 379–81.
- Popovic V, Pekic S, Doknic M, Micic D, Damjanovic S, Zarkovic M, Aimaretti G, Corneli G, Ghigo E, Dieguez C, Casanueva FF. The effectiveness of arginine + GHRH test compared with GHRH + GHRP-6 test in diagnosing growth hormone deficiency in adults. *Clin Endocrinol (Oxf)* 2003; 59: 251–7.
- Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, Stavrou S, Kleinberg DL, Chipman JJ, Hartman ML. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metabol* 2002; 87: 2067–79.
- Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, Croce CG, Grottoli S, Maccario M, Colao A, Lombardi G, Ghigo E, Camanni F, Aimaretti G. The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. *Eur J Endocrinol* 2005; 153: 257–64.
- Murray RD, Adams JE, Shalet SM. Adults with partial growth hormone deficiency have an adverse body composition. *J Clin Endocrinol Metabol* 2004; 89: 1586–91.
- Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. European Society of Paediatric Endocrinology. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. *Eur J Endocrinol* 2005; 152: 165–70.
- Kehely A, Bates PC, Frewer P, Birkett M, Blum WF, Mamessier P, Ezzat S, Ho KK, Lombard G, Luger A, Marek J, Russel-Jones D, Sönksen P, Attanasio AF, on behalf of the GDED Study Group. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. *J Clin Endocrinol Metabol* 2002; 87: 1974–9.
- Mah PM, Webster J, Jönsson P, Feldt-Rasmussen U, Koltowska-Häggström, Ross RJM. Estrogen replacement in women of fertile years with hypopituitarism. *J Clin Endocrinol Metabol* 2005; 90: 5964–9.
- Salomon F, Cuneo RC, Hesp R, Sönksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* 1989; 321: 1797–803.
- Binnerts A, Swart GR, Wilson JH, Hoogerbrugge N, Pols HA, Birkenhager JC, Lamberts JMW. The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. *Clin Endocrinol (Oxf)* 1992; 37: 79–87.
- Rosenfalck AM, Maghsoudi S, Fisker S, Jørgensen JO, Christiansen JS, Hilsted J, Vølund AA, Madsbad S. The effect of 30 months of low-dose replacement therapy with recombinant human growth hormone (rhGH) on insulin and C-peptide kinetics, insulin secretion, insulin sensitivity, glucose effectiveness, and body composition in GH-deficient adults. *J Clin Endocrinol Metabol* 2000; 85: 4173–81.
- Gibney J, Wallace JD, Spinks T, Schnorr L, Ranicar A, Cuneo RC, Lockhart S, Burnand KG, Salomon F, Sönksen PH, Russel-Jones D. The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. *J Clin Endocrinol Metabol* 1999; 84: 2596–602.
- Kotzmann H, Riedl M, Bernecker P, Clodi M, Kainberger F, Kaiser A, Woloszczuk W, Luger A. Effect of long-term growth-hormone substitution therapy on bone mineral density and parameters of bone metabolism in adult patients with growth hormone deficiency. *Calcified Tissue Int* 1998; 62: 40–6.
- Bex M, Abs R, Maiter D, Beckers A, Lamberigts G, Bouillon R. The effects of growth hormone replacement therapy on bone metabolism in adult-onset growth hormone deficiency: a 2-year open randomized controlled multicenter trial. *J Bone Miner Res* 2002; 17: 1081–94.
- Al-Shoumer KA, Gray R, Anyaoku V, Hughes C, Beshyah S, Richmond W, Johnston DG. Effects of four years' treatment with biosynthetic human growth hormone (GH) on glucose homeostasis, insulin secretion and lipid metabolism in GH-deficient adults. *Clin Endocrinol (Oxf)* 1998; 48: 795–802.
- Colao A, di Somma C, Pivonello R, Cuocolo A, Spinelli L, Bonaduce D, Salvatore M, Lombardi G. The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study. *J Clin Endocrinol Metabol* 2002; 87: 1088–93.
- Colao A, Marzullo, Di Somma C, Lombardi G. Growth hormone and the heart. *Clin Endocrinol (Oxf)* 2001; 54: 137–54.
- Pfeifer M, Verhovec R, Zizek B, Prezelj J, Poredos P, Clayton RN. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metabol* 1999; 84: 453–7.
- McGauley GA, Cuneo RC, Salomon F, Sönksen PH. Psychological well-being before and after growth hormone deficiency. *Horm Res* 1990; 33: 52–4.
- Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Haag E, Karlsson FA. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. *J Clin Endocrinol Metabol* 1995; 80: 3585–90.
- Hernberg-Ståhl E, Luger A, Abs R, Bengtsson BÅ, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP, the KIMS International Board on behalf of the KIMS Study Group. Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency. *J Clin Endocrinol Metabol* 2001; 86: 5277–81.
- Cohen P, Clemmons DR, Rosenfeld RG. Does the GH-IGF axis play a role in cancer pathogenesis? *Growth Horm IGF Res* 2000; 10: 297–305.
- Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? *Clin Endocrinol* 2006; 64: 115–21.
- Leal-Cerro A, Flores JM, Rincon M, Murillo F, Pujol M, Garcia-Pesquera F, Dieguez C, Casanueva FF. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term severe traumatic brain injury. *Clin Endocrinol* 2005; 62: 525–32.
- Schneider HJ, Schneider M, Saller B, Petersenn S, Uhr M, Husemann B, von Rosen F, Stalla GK. Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. *Eur J Endocrinol* 2006; 154: 259–65.
- Kreitschmann-Andermahr I, Hoff C, Saller B, Niggemeier S, Pruemper S, Hütter BO, Rohde V, Gressner A, Matern S, Gilsbach JM. Prevalence of pituitary deficiency in patients after aneurismal subarachnoid hemorrhage. *J Clin Endocrinol Metabol* 2004; 89: 4986–92.
- Cecconi E, Gasperi M, Bogazzi F, Grasso L, Genovesi M, Marcocci C, Pinchera A, Procopio M, Bartelena L, Martino E. Improvement of growth hormone deficiency in patients with primary hyperparathyroidism after parathyroidectomy: results of a prospective study. *J Clin Endocrinol Metabol* 2004; 89: 1213–6.
- Perls TH, Reisman NR, Olshansky SJ. Provision or distribution of growth hormone for "antiaging". Clinical and legal issues. *J Am Med Assoc* 2005; 294: 2086–90.

Mitteilungen aus der Redaktion

Besuchen Sie unsere Rubrik

☒ Medizintechnik-Produkte



Neues CRT-D Implantat
Intica 7 HF-T QP von Biotronik



Artis pheno
Siemens Healthcare Diagnostics GmbH



Philips Azurion:
Innovative Bildgebungslösung

Aspirator 3
Labotect GmbH



InControl 1050
Labotect GmbH

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☒ Bestellung e-Journal-Abo

Haftungsausschluss

Die in unseren Webseiten publizierten Informationen richten sich **ausschließlich an geprüfte und autorisierte medizinische Berufsgruppen** und entbinden nicht von der ärztlichen Sorgfaltspflicht sowie von einer ausführlichen Patientenaufklärung über therapeutische Optionen und deren Wirkungen bzw. Nebenwirkungen. Die entsprechenden Angaben werden von den Autoren mit der größten Sorgfalt recherchiert und zusammengestellt. Die angegebenen Dosierungen sind im Einzelfall anhand der Fachinformationen zu überprüfen. Weder die Autoren, noch die tragenden Gesellschaften noch der Verlag übernehmen irgendwelche Haftungsansprüche.

Bitte beachten Sie auch diese Seiten:

[Impressum](#)

[Disclaimers & Copyright](#)

[Datenschutzerklärung](#)