

# **Growth Hormone Replacement Therapy in Adults: Thirty Years of Personal Clinical Experience**

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## **Abstract**

The acute metabolic actions of purified human GH was first documented in adult hypopituitary patients more than 50 years ago, and placebo controlled long term GH trials in GH-deficient adults (GHDA) surfaced in 1989 with the availability of biosynthetic human GH. Untreated GHDA is associated with excess morbidity and mortality from cardiovascular disease and the phenotype includes fatigue, reduced aerobic exercise capacity, abdominal obesity, reduced lean body mass, osteopenia, and elevated levels of circulating cardiovascular biomarkers. Several of these features reverse and normalize with GH replacement. It remains controversial whether quality of life, assessed by questionnaires, improves. The known side effects are fluid retention and insulin resistance, which are reversible and dose-dependent. The dose requirement declines markedly with age and is higher in women. Continuation of GH replacement into adulthood in patients with childhood-onset disease is indicated, if the diagnosis is reconfirmed. GH treatment of frail elderly subjects without documented pituitary disease remains unwarranted. Observational data show that mortality in GH replaced patients is reduced compared to untreated patients. Even though this reduced mortality could be due to selection bias, GH replacement in GHDA has proven beneficial and safe.

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## Introduction

A growth-promoting activity of anterior pituitary extracts was discovered almost a hundred years ago by Evans and Long and growth hormone (GH) was isolated in 1944 and tested in human subjects by several groups (1). It became evident that species-specific differences existed and that only human and - to some extent - simian GH are active in man. The protein anabolic and lipid catabolic effects of GH were comprehensively tested by Maurice Raben and summarized in two seminal publications in 1962, which are recommendable readings owing to their clarity and prophetic strengths (2, 3). He was the first to hypothesize that GH replacement therapy in adults with hypopituitarism could be beneficial (3). Subsequently, GH extracted from human cadaveric pituitaries was used therapeutically to promote longitudinal growth in children with hypopituitarism and severe growth retardation, but the limited supply precluded the exploration of other indications. The use of pituitary human GH was halted in several countries in 1985 since it was associated with transmission of Creutzfeld-Jakob disease(4), which accelerated the approval of biosynthetic human GH, that first proved efficacious in GH-deficient children(5). This radically changed the scene by providing a potentially unlimited supply of pure and uncontaminated GH. In response to this, James Tanner, a leading expert in pediatric growth disorders and auxology, stated "We are now moving from an era in which there were too many patients chasing too little GH to an era in which there will be too much GH chasing too few patients."

One of the first potential indications to be pursued was GH replacement in adult patients with GH-deficiency (GHD) in two investigator-initiated trials (6, 7). This narrative review provides a personal account on the history of GH replacement in adults with a focus on the pivotal trials and the authors' own contributions.

## The pivotal trials

The first placebo-controlled trial was performed in Denmark as a collaboration between adult and pediatric endocrinologists and published in 1989 (6). The patients (n=22) all had childhood-onset GHD verified by at least two GH stimulation tests and had received GH replacement for a mean period of  $\approx 7$  years, which was

discontinued at least 6 months before study entry (mean duration of discontinuation  $\approx$  6 years). The diagnosis was reconfirmed prior to the study by a clonidine stimulation test, and the mean age at study start was  $\approx$  24 years. The study had a double-blind, placebo-controlled crossover design with 4 months treatment periods separated by a 4 months washout period and with the patients being studied at the end of each study period. The daily GH dose was 4 IU/m<sup>2</sup> body surface ( $\approx$ 1.1 mg/day). The major outcomes included body composition in terms of muscle and fat volume of the thigh region assessed by CT scan, isometric muscle strength, and aerobic exercise capacity assessed on a bicycle ergometer. In addition, glomerular filtration rate and renal plasma flow were measured isotopically. A significant increase in muscle volume ( $P < 0.01$ ) and a significant reduction in fat volume ( $P < 0.05$ ) was recorded together with a reduction in subscapular skinfold thickness ( $P < 0.01$ ). This was accompanied by a significant increase in exercise capacity ( $P < 0.05$ ) and an insignificant increase in muscle strength ( $P = 0.08$ ). Both GFR and RPF increased ( $P < 0.01$ ), which represented a normalization from subnormal levels. As expected, a treatment-induced increase in serum IGF-I levels ( $\mu\text{g/l}$ ) occurred [ $96 \pm 9$  (placebo) vs.  $224 \pm 28$  (GH),  $P < 0.001$ ].

Additional publications derived from the original trial revealed that GH replacement was associated with marked and concerted elevations (two to five fold) in the levels of serum osteocalcin and urinary excretion of deoxypyridinoline, indicative of increased bone remodeling (8, 9). Compelling evidence that GH promotes the extrathyroidal conversion of T4 to T3 was demonstrated for the first time in a placebo-controlled design (10). The patients also exhibited decreased sweating, which was reversed by GH (11). Finally, the original study was extended with an open phase of uninterrupted GH therapy, which documented continued improvement in body composition, exercise capacity, muscle strength, and forearm bone mineral content (12, 13).

The second placebo-controlled trial was published 7 months later and differed in several respects (7). First, it mainly comprised patients with adult-onset GHD due to a pituitary tumor and its treatment. Second, it had a parallel design with a 6 months treatment period where each patient was examined before and after. The daily GH dose was  $\approx$  1.9 mg and the mean age of the patients was  $\approx$  39 years. The main outcomes were body composition assessed by conventional anthropometric measurements and total body potassium, and resting

energy expenditure using indirect calorimetry. Lean body mass (LBM) increased significantly and was accompanied by a significant reduction in fat mass. This was associated with an increase in REE also after correction for LBM. In addition, evidence of GH-induced insulin resistance, as judged by increased fasting levels of glucose and insulin, was reported. Beneficial effects of GH replacement on exercise capacity and hyperlipidemia were also reported from the original study. (14-16)

## **The syndrome of GH-deficiency in adults**

In a review of the literature in 1992, Cuneo et al. introduced 'syndrome' as a term to describe the emerging clinical picture of GH-deficiency in adults (GHDA) and the effects and side effects of GH replacement. (17) This concept was substantiated by studies from Sweden focusing on the phenotypical features of untreated GHDA (18-20) and new data regarding the impact of GH replacement (21-24). The syndrome overlaps with the metabolic syndrome as regards visceral obesity, hyperlipidemia, and atherosclerosis. Moreover, evidence of premature cardiovascular morbidity and mortality was reported in GH-untreated hypopituitary adults (25, 26). Echocardiographic studies documented a stimulatory effect of GH on diastolic volume, stroke volume, and myocardial contractility.(27) (28-30) It was also observed that untreated GHDA was accompanied by reduced total body water and extracellular fluid volume (18), which reverses by GH replacement (31, 32). Indeed, fluid retention was noted as a frequent and dose-dependent side effect of GH treatment in adults. The mechanism involves sodium retention, but it is uncertain if it is mediated by activation of the renin angiotensin aldosterone system (32, 33), suppression of atrial natriuretic peptide(34), or a direct renal effect of GH or IGF-I (35, 36). Of note, this increase in hydration accounts for a limited part of the GH-induced changes in body composition (36). Impaired thermoregulation in response to the ambient outside temperature (37) and during strenuous exercise (38, 39) were also documented and partly attributed to reduced sweating capacity (11).

Insulin resistance, which is a hallmark of the metabolic syndrome, is not part of the GHDA syndrome, rather the opposite. GH antagonizes the effects of insulin on glucose metabolism in both the liver and skeletal

muscle, which is causally linked to the lipolytic effects of GH (40). Indeed, increased insulin sensitivity and reactive hypoglycemia is characteristic of children and adolescents with GHD (41-43), whereas the opposite is true for active acromegaly (44). Treatment naïve with adult-onset GHD may, however, also exhibit insulin resistance (45), which likely represents the long-term consequences of obesity, reduced lean body mass (LBM) and physical inactivity. The direct insulin antagonistic effect of GH is rapidly reversible (46, 47), and in normal physiology it operates in the fasting state, where insulin activity is low (48, 49). However, daily subcutaneous GH injections in the evening is unable to fully imitate the endogenous GH pattern (50), wherefore GH replacement therapy invariably induces a certain degree of insulin resistance (49). Consequently, moderate elevations in the fasting levels of glucose and insulin are recorded in GHDA after GH replacement despite favorable changes in body composition (51).

The annual number of publications in the field of GHDA increased almost exponentially from two in 1989 to > 200 in 1999, which, in addition to corroborating the observations from the pivotal trials, added several original contributions (52). Dose-finding studies in different age groups were performed (53-55) and it was confirmed that adult patients are highly sensitive to GH in terms of serum IGF-I generation and side effects (56), and that male patients are more responsive to GH as compared to females (57, 58). These and other data translated into guidelines for the diagnosis and management of GHDA issued by the Growth Hormone Research Society, which had been established in 1993 (59). The indication for GH replacement in GHDA was approved by the European Union in 1994 alongside with several other countries. In the same year, KIMS, an international outcomes research database with longitudinal data about GH therapy in adults, was initiated by Pharmacia & Upjohn and continued by Pfizer until 2012 with the inclusion of more than 16000 patients from 31 countries (<https://medicaloutcomes.pfizer.com/kims>). This resource has generated numerous peer-reviewed publications, also recently (60), and similar surveillance programs have been initiated by other providers of biosynthetic GH. In addition to this, several meta-analyses of published data on adult GH replacement have been published on outcomes such as cardiovascular risk factors (51), muscle strength and exercise capacity (61, 62), bone mineral density (63, 64), body composition (65), cardiac function (66) (Figure 1). In short, the meta- analyses confirmed and substantiated both the beneficial effects of GH

replacement on body composition, bone mineral density, cardiac function and exercise capacity, as well as the side effects attributable to fluid retention and insulin resistance (51, 65) (Figure 2).

It remains an open question whether GH replacement therapy improves patient-reported outcomes such as quality of life (QoL) or cognitive function in the adult patient, since neither original studies nor meta-analyses provide unambiguous answers (65, 67-69). There is little doubt that QoL is reduced in the treatment naïve patients, but it has proven difficult to document significant positive GH effects in placebo-controlled trials, and improvements in open trials are prone to bias and regression towards the means. Most QoL studies have utilized generic or disease-specific questionnaires, which mainly record and depend on the respondents' remembrance and may fail to detect day-to-day experiences in real time; along the same line, it possible that improvements in remembered QoL cease to provide increased satisfaction, a phenomenon coined hedonic adaptation (70). In this regard, it is interesting that the most compelling – and beneficial – effects of adult GH replacement on QoL was recorded in a placebo-controlled crossover study, in which the spouse of the patient was asked to score the patient (71). Somewhat ironically, the National Institute for Health and Care Excellence (NICE) in the UK requires impaired pretreatment QoL in order to initiate adult GH replacement, and it also demands discontinuation of treatment in case of a lack of QoL improvement after 9 months treatment (72).

## **The Transition Phase**

Normal puberty marks the transition from childhood to adulthood, and represents a period with marked physical changes including a pubertal growth spurt and the development of secondary sexual characteristics leading to attainment of adult reproductive capacity. Muscle and bone mass increase markedly during this period leading to the adult phenotype. These important physical changes depend in part on amplified GH secretion and action resulting in grossly elevated – even acromegalic - IGF-I levels in healthy subjects (73) (figure 3). Serum IGF-I levels remain elevated 2-5 years after peak height velocity, suggesting additional physiological actions of GH in this transition period on muscle and bone mass accrual. The transition phase

starts in late puberty when final adult height is attained ( $\approx$  mean age 15-17 years) and terminates in early adulthood when peak bone mass is reached (mean age  $\approx$  20-23 years).

Before 1985, GH replacement in childhood patients terminated as soon as a certain target height was achieved due to the scarce supply of pituitary GH, but the introduction of biosynthetic GH enabled continuation during the entire transition phase. The early adult GH replacement trials did not capture this important period, but a prospective study reported that discontinuation of GH replacement in childhood-onset patients at the time of transition induced unfavorable changes in lipid profile and body composition (74). Subsequently, a Danish double blind, placebo-controlled parallel study evaluated the effects of continuation vs. discontinuation of GH after cessation of linear growth (75, 76). This study revealed that GH discontinuation resulted in decreased IGF-I as well as increased body fat and insulin sensitivity in the placebo group. After resumption of GH, lean body mass and IGF-I increased. Likewise, increased muscle volume of the thigh, muscle/fat ratio and glucose oxidation rates increase following resumption of GH. Comparable results were reported in 2004 from an open study of 12 months continuation vs. discontinuation of GH replacement (77).

Guidelines as regards management of GHD patients during the transition are available and a few issues merit mention here (78). First, a large proportion of GHD children exhibit normal stimulated GH secretion when retested after completion of GH treatment. Therefore, GH status and the indication for continued GH replacement in adulthood must be evaluated on an individual basis, which requires retesting unless there is strong evidence of either organic panhypopituitarism or a genetic cause of GHD. Second, the pediatric mode of GH dosing according to body size (weight or body surface) translates into high daily doses to achieve the appropriate pubertal growth response and the normal high pubertal IGF-I levels. These high GH doses are usually continued in the transition period even when growth is decelerating due to sex steroid-induced epiphyseal closure. Third, the proper management of transition patients includes patient involvement and a close collaboration between pediatric and adult endocrinologists (78).



## **The Senescence**

Endogenous GH production and serum IGF-I levels decline with age (79) in parallel with senescent changes in body composition and physical performance (figure 3). Interestingly, in midlife adults, abdominal adiposity is the strongest and negative determinant of endogenous GH secretion (80). Such correlations have led to speculations about a causal link between reduced GH production and the physical frailties of aging, which has been coined ‘somatopause’ (81). This controversial concept is beyond the scope of our review, but a meta-analysis of GH treatment studies in elderly subjects without overt pituitary disease record only limited positive effects and a high prevalence of GH-related side effects (82).

Despite the age-associated decline GH secretion, elderly patients aged 60-80 years with panhypopituitarism due to well-defined pituitary pathology exhibit distinctly reduced GH and IGF-I levels as compared to age-matched controls (83). Moreover, GHDA patients in this age group seem to respond to GH replacement in the same manner as younger patients (84-86). However, the GH dose requirement in order not to exceed IGF-I levels above the upper normal range for age and to avoid side effects, declines with chronological age (fig. 3).

## **GH replacement and mortality**

Increased mortality in hypopituitary patients due to cardiovascular disease is well established and it has been difficult to resist the temptation to attribute this to unsubstituted GHD (26, 87). However, numerous underlying mechanisms may be equally - or more - likely, e.g. additional features of hypopituitarism including the underlying disease, treatment complications, and suboptimal substitution of additional pituitary deficiencies. It is also noteworthy, that mortality and cancer incidence are increased in acromegaly (88, 89), and that a strong inverse relation exists between activation of the IGF/insulin axis and longevity in many species (90, 91). Moreover, epidemiological human studies suggest an U shaped association between serum IGF-I levels and all-cause mortality in the general population (92). Most importantly, controlled studies of

GH replacement therapy with mortality as an endpoint do not exist and are very unlikely to appear in the future. An undisputable answer to the question whether GH replacement reduces mortality in GHD patients is therefore not available. However, observational studies in GHDA suggest that mortality is reduced in GH replaced patients as compared to GH-untreated patients (87, 93-95). A meta-analysis reported that the standardized mortality rate was 2.40 [95% CI: 1.46 – 3.34] in GH-untreated vs. 1.15 [95% CI: 1.05 – 1.24] in GH treated patients (87), and an even larger difference was reported recently by Stockholm et al. (93)

## Discussion

Adult subjects, including hypopituitary patients, were used to investigate the short-term metabolic effects of pituitary-derived human GH more than half a century ago, and it was speculated that GH replacement in GHDA could be beneficial (2, 3). This therapeutic option became feasible 25 years later with the introduction of biosynthetic GH, and a number of positive effects have been reported. Indeed, GH therapy in GHDA is probably the best-documented therapeutic indication in pituitary endocrinology in terms of placebo-controlled trials and observational studies. The change in body composition with reduced fat mass and increased lean body mass is the most robust effect. Most studies also record improvements in aerobic exercise capacity and cardiac function. As regards bone mass and strength, data from placebo-controlled trials for up to one year record increased bone turnover but unchanged or even reduced bone mass (96), whereas one study of 18 months observed a significant increase in BMD of both the lumbar spine and the femoral neck (97). An increase in BMD is also reported in several open trials of prolonged GH replacement therapy, and it is believed by most that GH replacement initially increases bone remodeling, which transiently reduces BMD, followed by a moderate but sustained increase at least in male patients (63). Whether this reduces the risk of osteoporotic fractures is uncertain, but observational studies suggest a reduced fracture risk (98). Whether Quality of life improves remains uncertain, since the results from placebo-controlled trials are ambiguous, and the results from open and observational studies are likely biased. The level of education is similar among GH treated adult patients as compared to the background

population, but a higher proportion of the patients are unemployed, retire earlier and are less likely to live with a partner (93, 99). These socioeconomic outcomes demonstrate that hypopituitarism remains a clinical challenge. Cancer risk is not increased with GH treatment, and mortality (100), if anything, is reduced (93, 94). The latter observation is reassuring even though it - to a large extent – is explained by selection bias (healthy user bias).

Side effects in terms of fluid retention and impaired insulin sensitivity are recognized, but they are dose-dependent, rapidly reversible, and probably of limited concern. Nevertheless, caution and vigilance are mandated to avoid overtreatment not least of the elderly patient. The daily GH dose requirement to avoid supernormal IGF-I levels and side effects may become as low as 0.1 mg in male patients aged  $\geq 70$  years (personal observation), which is more than 10 fold lower than the doses used in the early adult trials. This raises the question whether lifelong treatment is justified? In this regard, it should be recalled that although serum IGF-I is strictly GH-dependent, its performance as a biomarker of GH treatment is far from perfect (101). The need for better biomarkers of GH treatment is accentuated by the recent introduction of long acting GH preparations, since these compounds in contrast to daily subcutaneous GH therapy result in fluctuating serum IGF-I levels (102).

In conclusion, the first anecdotal report in 1962 of GH replacement in a patient with adult hypopituitarism concluded that ‘observations will be needed in more cases to indicate whether the favorable effect was more than coincidental’ (3). In 2018, it is safe to state that observations from numerous trials confirm the beneficial effects and justify this treatment modality.

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## References

1. BECK JC, MCGARRY EE, DYRENFURTH I, VENNING EH. Metabolic Effects of Human and Monkey Growth Hormone in Man. *Science*. 1957;125(3253):884-5.
2. Raben MS. Growth Hormone. *New England Journal of Medicine*. 1962;266(1):31-5.
3. Raben MS. Growth Hormone. *New England Journal of Medicine*. 1962;266(2):82-6.
4. Beardsley T. FDA ban on pituitary product. *Nature*. 1985;315(6018):358-9.
5. Kaplan SL, Underwood LE, August GP, Bell JJ, Blethen SL, Blizzard RM, et al. Clinical studies with recombinant-DNA-derived methionyl human growth hormone in growth hormone deficient children. *Lancet (London, England)*. 1986;1(8483):697-700.
6. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, et al. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet (London, England)*. 1989;1(8649):1221-5.
7. Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *The New England journal of medicine*. 1989;321(26):1797-803.
8. Johansen JS, Pedersen SA, Jorgensen JO, Riis BJ, Christiansen C, Christiansen JS, et al. Effects of growth hormone (GH) on plasma bone Gla protein in GH-deficient adults. *J Clin Endocrinol Metab*. 1990;70(4):916-9.
9. Schlemmer A, Johansen JS, Pedersen SA, Jorgensen JO, Hassager C, Christiansen C. The effect of growth hormone (GH) therapy on urinary pyridinoline cross-links in GH-deficient adults. *Clin Endocrinol (Oxf)*. 1991;35(6):471-6.
10. Jorgensen JO, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE, Christiansen JS. Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. *J Clin Endocrinol Metab*. 1989;69(6):1127-32.
11. Pedersen SA, Welling K, Michaelsen KF, Jorgensen JO, Christiansen JS, Skakkebaek NE. Reduced sweating in adults with growth hormone deficiency. *Lancet (London, England)*. 1989;2(8664):681-2.
12. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Moller J, Muller J, et al. Long-term growth hormone treatment in growth hormone deficient adults. *Acta endocrinologica*. 1991;125(5):449-53.
13. Juul A, Pedersen SA, Sorensen S, Winkler K, Jorgensen JO, Christiansen JS, et al. Growth hormone (GH) treatment increases serum insulin-like growth factor binding protein-3, bone isoenzyme alkaline phosphatase and forearm bone mineral content in young adults with GH deficiency of childhood onset. *Eur J Endocrinol*. 1994;131(1):41-9.
14. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. *Journal of applied physiology (Bethesda, Md : 1985)*. 1991;70(2):695-700.
15. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *Journal of applied physiology (Bethesda, Md : 1985)*. 1991;70(2):688-94.
16. Cuneo RC, Salomon F, Watts GF, Hesp R, Sonksen PH. Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. *Metabolism: clinical and experimental*. 1993;42(12):1519-23.
17. Cuneo RC, Salomon F, McGauley GA, Sonksen PH. The growth hormone deficiency syndrome in adults. *Clin Endocrinol (Oxf)*. 1992;37(5):387-97.
18. Rosen T, Bosaeus I, Tolli J, Lindstedt G, Bengtsson BA. Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1993;38(1):63-71.

19. Rosen T, Eden S, Larson G, Wilhelmsen L, Bengtsson BA. Cardiovascular risk factors in adult patients with growth hormone deficiency. *Acta endocrinologica*. 1993;129(3):195-200.
20. Rosen T, Hansson T, Granhed H, Szucs J, Bengtsson BA. Reduced bone mineral content in adult patients with growth hormone deficiency. *Acta endocrinologica*. 1993;129(3):201-6.
21. Jorgensen JO, Thuesen L, Muller J, Ovesen P, Skakkebaek NE, Christiansen JS. Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. *Eur J Endocrinol*. 1994;130(3):224-8.
22. Bengtsson BA, Eden S, Lonn L, Kvist H, Stokland A, Lindstedt G, et al. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab*. 1993;76(2):309-17.
23. Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, et al. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clin Endocrinol (Oxf)*. 1992;36(1):45-52.
24. Jorgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C, Christiansen JS. Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clin Endocrinol (Oxf)*. 1996;45(6):681-8.
25. Markussis V, Beshyah SA, Fisher C, Sharp P, Nicolaides AN, Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet (London, England)*. 1992;340(8829):1188-92.
26. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet (London, England)*. 1990;336(8710):285-8.
27. Beshyah SA, Shahi M, Skinner E, Sharp P, Foale R, Johnston DG. Cardiovascular effects of growth hormone replacement therapy in hypopituitary adults. *Eur J Endocrinol*. 1994;130(5):451-8.
28. Thuesen L, Christiansen JS, Sorensen KE, Jorgensen JO, Orskov H, Henningsen P. Increased myocardial contractility following growth hormone administration in normal man. An echocardiographic study. *Danish medical bulletin*. 1988;35(2):193-6.
29. Thuesen L, Jorgensen JO, Muller JR, Kristensen BO, Skakkebaek NE, Vahl N, et al. Short and long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults. *Clin Endocrinol (Oxf)*. 1994;41(5):615-20.
30. Cuneo RC, Salomon F, Wilmschurst P, Byrne C, Wiles CM, Hesp R, et al. Cardiovascular effects of growth hormone treatment in growth-hormone-deficient adults: stimulation of the renin-aldosterone system. *Clinical science (London, England : 1979)*. 1991;81(5):587-92.
31. Moller J, Frandsen E, Fisker S, Jorgensen JO, Christiansen JS. Decreased plasma and extracellular volume in growth hormone deficient adults and the acute and prolonged effects of GH administration: a controlled experimental study. *Clin Endocrinol (Oxf)*. 1996;44(5):533-9.
32. Moller J, Jorgensen JO, Frandsen E, Laursen T, Christiansen JS. Body fluids, circadian blood pressure and plasma renin during growth hormone administration: a placebo-controlled study with two growth hormone doses in healthy adults. *Scandinavian journal of clinical and laboratory investigation*. 1995;55(8):663-9.
33. Moller J, Moller N, Frandsen E, Wolthers T, Jorgensen JO, Christiansen JS. Blockade of the renin-angiotensin-aldosterone system prevents growth hormone-induced fluid retention in humans. *The American journal of physiology*. 1997;272(5 Pt 1):E803-8.
34. Moller J, Jorgensen JO, Moller N, Hansen KW, Pedersen EB, Christiansen JS. Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. *J Clin Endocrinol Metab*. 1991;72(4):768-72.
35. Kamenicky P, Mazziotti G, Lombes M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. *Endocr Rev*. 2014;35(2):234-81.
36. de Boer H, Blok GJ, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocr Rev*. 1995;16(1):63-86.

37. Juul A, Skakkebaek NE. Growth hormone deficiency and hyperthermia. *Lancet* (London, England). 1991;338(8771):887.
38. Juul A, Behrenscheer A, Tims T, Nielsen B, Halkjaer-Kristensen J, Skakkebaek NE. Impaired thermoregulation in adults with growth hormone deficiency during heat exposure and exercise. *Clin Endocrinol (Oxf)*. 1993;38(3):237-44.
39. Juul A, Hjortskov N, Jepsen LT, Nielsen B, Halkjaer-Kristensen J, Vahl N, et al. Growth hormone deficiency and hyperthermia during exercise: a controlled study of sixteen GH-deficient patients. *J Clin Endocrinol Metab*. 1995;80(11):3335-40.
40. Nielsen S, Moller N, Christiansen JS, Jorgensen JO. Pharmacological antilipolysis restores insulin sensitivity during growth hormone exposure. *Diabetes*. 2001;50(10):2301-8.
41. Press M, Notarfrancesco A, Genel M. Risk of hypoglycaemia with alternate-day growth hormone injections. *Lancet* (London, England). 1987;1(8540):1002-4.
42. Jorgensen JO, Flyvbjerg A, Lauritzen T, Alberti KG, Orskov H, Christiansen JS. Dose-response studies with biosynthetic human growth hormone (GH) in GH-deficient patients. *J Clin Endocrinol Metab*. 1988;67(1):36-40.
43. Jorgensen JO, Moller J, Alberti KG, Schmitz O, Christiansen JS, Orskov H, et al. Marked effects of sustained low growth hormone (GH) levels on day-to-day fuel metabolism: studies in GH-deficient patients and healthy untreated subjects. *J Clin Endocrinol Metab*. 1993;77(6):1589-96.
44. Moller N, Schmitz O, Joergensen JO, Astrup J, Bak JF, Christensen SE, et al. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. *J Clin Endocrinol Metab*. 1992;74(5):1012-9.
45. Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA. Growth hormone-deficient adults are insulin-resistant. *Metabolism: clinical and experimental*. 1995;44(9):1126-9.
46. Zierler KL, Rabinowitz D. ROLES OF INSULIN AND GROWTH HORMONE, BASED ON STUDIES OF FOREARM METABOLISM IN MAN. *Medicine*. 1963;42:385-402.
47. Krusenstjerna-Hafstrom T, Clasen BF, Moller N, Jessen N, Pedersen SB, Christiansen JS, et al. Growth hormone (GH)-induced insulin resistance is rapidly reversible: an experimental study in GH-deficient adults. *J Clin Endocrinol Metab*. 2011;96(8):2548-57.
48. Rabinowitz D, Zierler KL. A METABOLIC REGULATING DEVICE BASED ON THE ACTIONS OF HUMAN GROWTH HORMONE AND OF INSULIN, SINGLY AND TOGETHER, ON THE HUMAN FOREARM. *Nature*. 1963;199:913-5.
49. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev*. 2009;30(2):152-77.
50. Jorgensen JO. Human growth hormone replacement therapy: pharmacological and clinical aspects. *Endocr Rev*. 1991;12(3):189-207.
51. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. *J Clin Endocrinol Metab*. 2004;89(5):2192-9.
52. Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab*. 1998;83(2):382-95.
53. Moller J, Jorgensen JO, Lauersen T, Frystyk J, Naeraa RW, Orskov H, et al. Growth hormone dose regimens in adult GH deficiency: effects on biochemical growth markers and metabolic parameters. *Clin Endocrinol (Oxf)*. 1993;39(4):403-8.
54. de Boer H, Blok GJ, Popp-Snijders C, Stuurman L, Baxter RC, van der Veen E. Monitoring of growth hormone replacement therapy in adults, based on measurement of serum markers. *The Journal of Clinical Endocrinology & Metabolism*. 1996;81(4):1371-7.
55. Johannsson G, Rosen T, Bengtsson BA. Individualized dose titration of growth hormone (GH) during GH replacement in hypopituitary adults. *Clin Endocrinol (Oxf)*. 1997;47(5):571-81.

56. Cuneo RC, Judd S, Wallace JD, Perry-Keene D, Burger H, Lim-Tio S, et al. The Australian Multicenter Trial of Growth Hormone (GH) Treatment in GH-Deficient Adults. *J Clin Endocrinol Metab.* 1998;83(1):107-16.
57. Johannsson G, Bjarnason R, Bramnert M, Carlsson LM, Degerblad M, Manhem P, et al. The individual responsiveness to growth hormone (GH) treatment in GH-deficient adults is dependent on the level of GH-binding protein, body mass index, age, and gender. *J Clin Endocrinol Metab.* 1996;81(4):1575-81.
58. Burman P, Johannsson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *J Clin Endocrinol Metab.* 1997;82(2):550-5.
59. 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 Metab.* 1998;83(2):379-81.
60. Krzyzanowska-Mittermayer K, Mattsson AF, Maiter D, Feldt-Rasmussen U, Camacho-Hubner C, Luger A, et al. New Neoplasm During GH Replacement in Adults With Pituitary Deficiency Following Malignancy: A KIMS Analysis. *J Clin Endocrinol Metab.* 2018;103(2):523-31.
61. Rubeck KZ, Bertelsen S, Vestergaard P, Jorgensen JO. Impact of GH substitution on exercise capacity and muscle strength in GH-deficient adults: a meta-analysis of blinded, placebo-controlled trials. *Clin Endocrinol (Oxf).* 2009;71(6):860-6.
62. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *J Clin Endocrinol Metab.* 2008;93(11):4413-7.
63. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):852-60.
64. Xue P, Wang Y, Yang J, Li Y. Effects of growth hormone replacement therapy on bone mineral density in growth hormone deficient adults: a meta-analysis. *International journal of endocrinology.* 2013;2013:216107.
65. Hazem A, Elamin MB, Bancos I, Malaga G, Prutsky G, Domecq JP, et al. Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. *Eur J Endocrinol.* 2012;166(1):13-20.
66. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation.* 2003;108(21):2648-52.
67. Deijen JB, Arwert LI, Witlox J, Drent ML. Differential effect sizes of growth hormone replacement on Quality of Life, well-being and health status in growth hormone deficient patients: a meta-analysis. *Health and quality of life outcomes.* 2005;3:63.
68. Arwert LI, Deijen JB, Witlox J, Drent ML. The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: a meta-analysis. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society.* 2005;15(1):47-54.
69. Falletti MG, Maruff P, Burman P, Harris A. The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature. *Psychoneuroendocrinology.* 2006;31(6):681-91.
70. Kahneman D, Krueger AB, Schkade DA, Schwarz N, Stone AA. A Survey Method for Characterizing Daily Life Experience: The Day Reconstruction Method. *Science.* 2004;306(5702):1776-80.
71. Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E, et al. 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 Metab.* 1995;80(12):3585-90.
72. .

73. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab.* 1994;78(3):744-52.
74. Johannsson G, Albertsson-Wikland K, Bengtsson BA. Discontinuation of growth hormone (GH) treatment: metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. *J Clin Endocrinol Metab.* 1999;84(12):4516-24.
75. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab.* 2000;85(5):1874-81.
76. Norrelund H, Vahl N, Juul A, Moller N, Alberti KG, Skakkebaek NE, et al. Continuation of growth hormone (GH) therapy in GH-deficient patients during transition from childhood to adulthood: impact on insulin sensitivity and substrate metabolism. *J Clin Endocrinol Metab.* 2000;85(5):1912-7.
77. Carroll PV, Drake WM, Maher KT, Metcalfe K, Shaw NJ, Dunger DB, et al. Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. *J Clin Endocrinol Metab.* 2004;89(8):3890-5.
78. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. *European Journal of Endocrinology.* 2005;152(2):165-70.
79. Veldhuis JD, Roelfsema F, Keenan DM, Pincus S. Gender, age, body mass index, and IGF-I individually and jointly determine distinct GH dynamics: analyses in one hundred healthy adults. *J Clin Endocrinol Metab.* 2011;96(1):115-21.
80. Vahl N, Jorgensen JO, Skjaerbaek C, Veldhuis JD, Orskov H, Christiansen JS. Abdominal adiposity rather than age and sex predicts mass and regularity of GH secretion in healthy adults. *The American journal of physiology.* 1997;272(6 Pt 1):E1108-16.
81. Toogood AA. The somatopause: an indication for growth hormone therapy? *Treatments in endocrinology.* 2004;3(4):201-9.
82. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Annals of internal medicine.* 2007;146(2):104-15.
83. Toogood AA, O'Neill PA, Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. *J Clin Endocrinol Metab.* 1996;81(2):460-5.
84. Toogood AA, Shalet SM. Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease: a dose-finding study. *J Clin Endocrinol Metab.* 1999;84(1):131-6.
85. Fernholm R, Bramnert M, Hagg E, Hilding A, Baylink DJ, Mohan S, et al. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. *J Clin Endocrinol Metab.* 2000;85(11):4104-12.
86. Franco C, Johannsson G, Bengtsson B-Ak, Svensson J. Baseline Characteristics and Effects of Growth Hormone Therapy over Two Years in Younger and Elderly Adults with Adult Onset GH Deficiency. *The Journal of Clinical Endocrinology & Metabolism.* 2006;91(11):4408-14.
87. Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess Mortality Associated With Hypopituitarism in Adults: A Meta-Analysis of Observational Studies. *The Journal of Clinical Endocrinology & Metabolism.* 2015;100(4):1405-11.
88. Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C, et al. Cancer Incidence in Patients with Acromegaly: A cohort study and meta-analysis of the literature. *J Clin Endocrinol Metab.* 2018.
89. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol.* 2008;159(2):89-95.



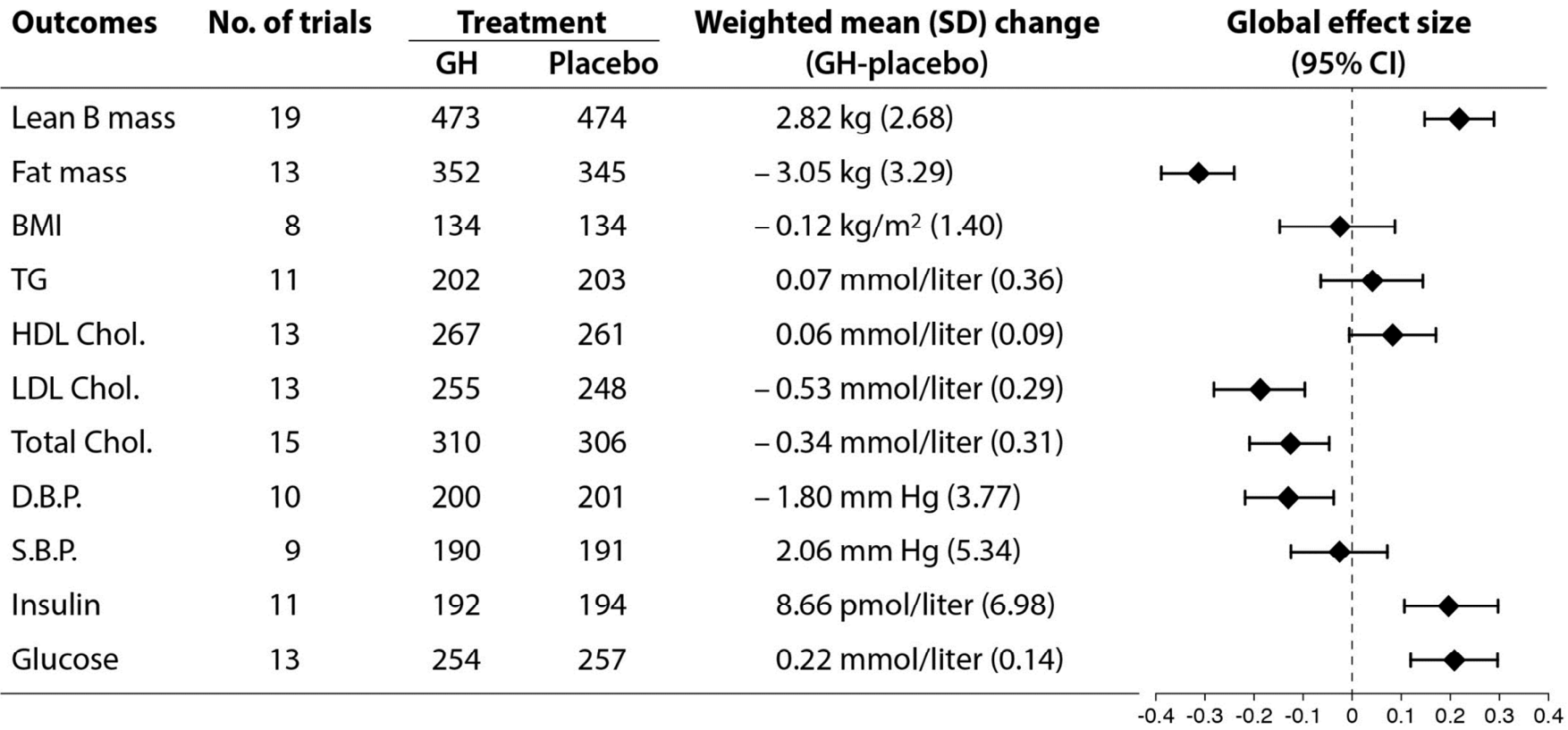
90. Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. *Cell*. 2015;161(1):106-18.
91. Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nature reviews Endocrinology*. 2013;9(6):366-76.
92. Burgers AM, Biermasz NR, Schoones JW, Pereira AM, Renehan AG, Zwahlen M, et al. Meta-analysis and dose-response meta-regression: circulating insulin-like growth factor I (IGF-I) and mortality. *J Clin Endocrinol Metab*. 2011;96(9):2912-20.
93. Stochholm K, Berglund A, Juul S, Gravholt CH, Christiansen JS. Socioeconomic factors do not but GH treatment does affect mortality in adult-onset growth hormone deficiency. *J Clin Endocrinol Metab*. 2014;99(11):4141-8.
94. Olsson DS, Trimpou P, Hallen T, Bryngelsson IL, Andersson E, Skoglund T, et al. Life expectancy in patients with pituitary adenoma receiving growth hormone replacement. *Eur J Endocrinol*. 2017;176(1):67-75.
95. Berglund A, Gravholt CH, Olsen MS, Christiansen JS, Stochholm K. Growth hormone replacement does not increase mortality in patients with childhood-onset growth hormone deficiency. *Clin Endocrinol (Oxf)*. 2015;83(5):677-83.
96. Hansen TB, Brixen K, Vahl N, Jorgensen JO, Christiansen JS, Mosekilde L, et al. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: a double blind, randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 1996;81(9):3352-9.
97. Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim DS, Schoenfeld DA, et al. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Annals of internal medicine*. 1996;125(11):883-90.
98. Mo D, Fleseriu M, Qi R, Jia N, Child CJ, Bouillon R, et al. Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: a prospective observational cohort study. *The lancet Diabetes & endocrinology*. 2015;3(5):331-8.
99. Holmer H, Svensson J, Rylander L, Johannsson G, Rosen T, Bengtsson BA, et al. Psychosocial health and levels of employment in 851 hypopituitary Swedish patients on long-term GH therapy. *Psychoneuroendocrinology*. 2013;38(6):842-52.
100. Stochholm K, Johannsson G. Reviewing the safety of GH replacement therapy in adults. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*. 2015;25(4):149-57.
101. Johannsson G, Bidlingmaier M, Biller BMK, Boguszewski M, Casanueva FF, Chanson P, et al. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocrine connections*. 2018;7(3):R126-r34.
102. Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, Casanueva FF, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *European Journal of Endocrinology*. 2016;174(6):C1-C8.

**Legends to figures.**

**Figure 1.** Results of meta-analysis of GH effects on cardiovascular risk factors from Maison et al. (51). (Copyright © 2004, Oxford University Press). Abbreviations: Lean B mass, Lean body mass; TG, triglycerides; Chol., cholesterol; D.B.P., diastolic blood pressure; S.B.P., systolic blood pressure; ns, nonsignificant.

**Figure 2.** Serum IGF-I levels as a function of chronological age in 3851 healthy subjects of both sexes. The grey area indicates the duration of the transition phase. Modified from Juul et al.

**Figure 3.** Daily GH dose (mg) in GH-deficient adults employed to ensure a serum IGF-I level within the upper normal range for age as a function of chronological age. The figures are based on the authors own experience and data from the literature (42, 52, 53, 83, 85). In addition to age, the GH dose also depends on gender.



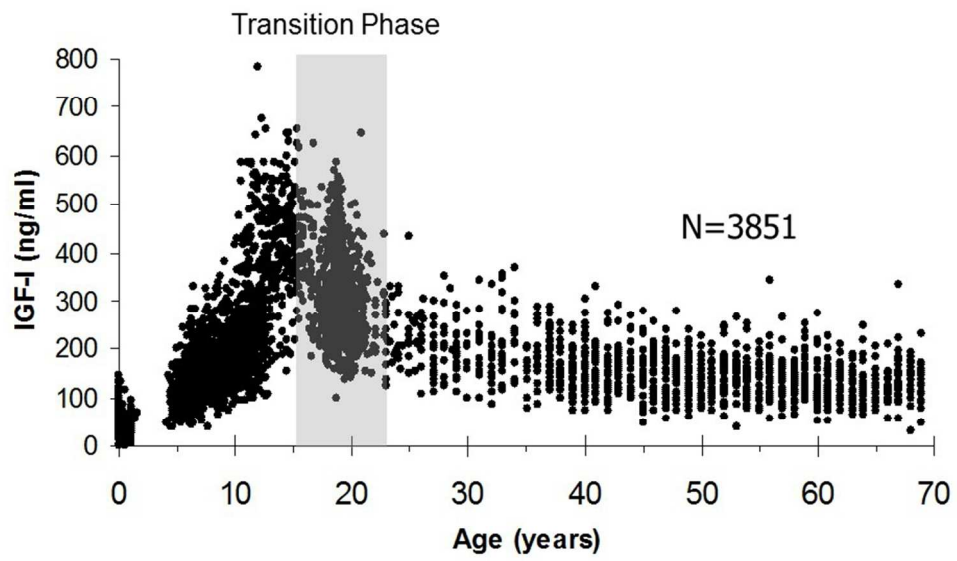


Figure 2

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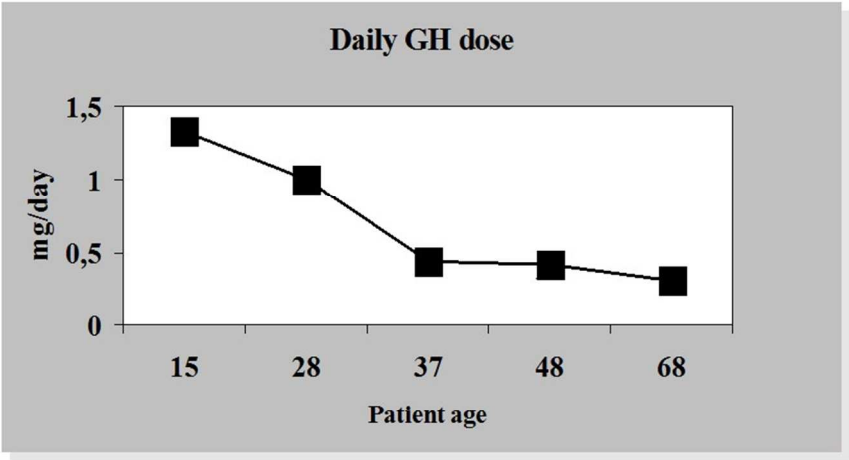


Figure 3  
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