Bibliography for HGH

- GH secretion falls by around 14% per decade of adult life (Toogood 2003)
- Avg. IGF-1 of known pituitary-damaged GH- deficient patients was 109 (Svensson)
- Normal IGF-I (µg/L) 196 ± 11.6; Acromegaly 800 ± 41[1], cured acromegaly 218 ± 20.7 Adult GH deficiency due to pituitary destruction 89.2 ± 12.2[2] (Marzullo)
- IGF-1 levels in persons with NO growth hormone production, diagnosed as growth hormone deficient, are identical to those of MANY "normal" adults: 80-110µg/L.
- Controls aged 41-60 had a mean IGF-1 of 220±1 S.D.=38. The 2 S.D. reference range found was ~144-296µg/L, the lab. Ref. range was 97-288. Colao
- One third of patients with GHD diagnosed by stimulated GH levels have IGF-I levels in the normal range (Molitch 2002)
- To convert IGF-1 from ng/ml to nmol/L multiply by 0.131
- GH stimulation testing is unreliable c/w IGF-1 levels (Hilczer 2006)
- "I think that we should be using the IGF-I level as a true integrated reflector of GH action at the low end of GH levels just as we do at the high end in patients with acromegaly." (Molitch, 2002)
- Pediatric Endocrinologists recommend abandoning GH stimulation tests in favor of IGF-1 levels (Federico)
- Sub-reference range IGF-1 is strongly predictive of abnormal insulin stimulation test , but a normal IGF-1 does not rule out GH deficiency in adults. (Bates)
- Depletion of certain micronutrients (*e.g.* magnesium, thiamine, vitamin D, and zinc) suppresses serum and tissue IGF-I levels (Clemmons, Ninh)
- Low testosterone and hypothyroidism suppress IGF-1 levels
- Elderly persons are still sensitive to GH, GH produces similar rises in IGF-1 compared to younger persons. (Arvat 1998). Implication: absent liver disease, low IGF-1 levels in older persons indicate reduced GH secretion under normal circumstances.
- GH replacement to attain IGF-1 of 202µg/L reduced cholesterol and LDL levels. (Florakis, 2000)
- Estradiol replacement in postmenopausal women increases GH secretion (Veldhuis 2008), similarly testosterone replacement increases GH secretion by the same mechanism in men (Veldhuis 2009).
- Glucocorticoids increase hepatic IGF-I and albumin synthesis, and decrease GH response to GHRH. (Borges 1999)
- Cushingoid features like abdominal obesity may be due to partial GH deficiency and ameliorated by optimizing GH levels with replacement (Stewart 2001)
- Much higher IGF-1 reference range in study of healthy subjects—mean for men 41-60yrs 224.6 with 1 standard deviation of 42.6. So -1SD=182, -2SD=139.4. Colao found in another study, using these ranges, that if IGF-1 was < mean-1.5SD, there was a 100% prediction of severe GHD! For men that means an IGF-1 < 160.7 means severe GHD. (Colao, 2008) Obviously lab reference ranges which include IGF-1 levels down to 100 and below are 2 SD based upon sick patients—the lab's own data on all patients tested.
- Lower IGF-1 within the reference ranges clearly correlated with hypertension and insulin resistance in middle aged adults, suggesting that the increase in these problems with age may be due to the partial GH deficiency caused by aging. (Colao, 2008)
- GH replacement improves serum DHEAS, probably by reducing cortisol levels, leading to higher ACTH production. (Isidori, 2003)

- Testosterone replacement even at low doses increases GH secretion and IGF-1 in older men (Muniyappa 2007)

Aberg ND, Brywe KG, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. ScientificWorldJournal. 2006 Jan 18;6:53-80.

Apart from regulating somatic growth and metabolic processes, accumulating ***evidence suggests that the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis is involved in the regulation of brain growth, development, and myelination****. In addition, both GH and IGF-I affect cognition and biochemistry in the adult brain. Some of the effects of GH are attributable to circulating IGF-I, while others may be due to IGF-I produced locally within the brain. Some of the shared effects in common to GH and IGF-I may also be explained by cross-talk between the GH and IGF-I transduction pathways, as indicated by recent data from other cell systems. Otherwise, it also seems that GH may act directly without involving IGF-I (either circulating or locally). Plasticity in the central nervous system (CNS) may be viewed as changes in the functional interplay between the major cell types, neurons, astrocytes, and oligodendrocytes. GH and IGF-I affect all three of these cell types in several ways. Apart from the neuroprotective effects of GH and IGF-I posited in different experimental models of CNS injury, IGF-I has been found to increase progenitor cell proliferation and new neurons, oligodendrocytes, and blood vessels in the dentate gyrus of the hippocampus. It appears that the MAPK signaling pathway is required for IGF-I-stimulated proliferation in vitro, whereas the PI3K/Akt or MAPK/Erk signaling pathway appears to mediate antiapoptotic effects. The increase of IGF-I on endothelial cell phenotype may explain the increase in cerebral arteriole density observed after GH treatment. The functional role of GH and IGF-I in the adult brain will be reviewed with reference to neurotransmitters, glucose metabolism, cerebral blood flow, gap junctional communication, dendritic arborization, exercise, enriched environment, depression, learning, memory, and aging.* ***Briefly, these findings suggest that IGF-I functions as a putative regenerative agent in the adult CNS. Hitherto less studied regarding in these aspects, GH may have similar effects, especially as it is the main regulator of IGF-I in vivo. Some of the positive cognitive features of GH treatment are likely attributable to the mechanisms reviewed here.***

Agha A; Walker D; Perry L; Drake WM; Chew SL; Jenkins PJ; Grossman AB; Monson JP Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. Clin Endocrinol (Oxf). 2007 Jan;66(1):72-7.

Background The effect of GH replacement on thyroid function in hypopituitary patients has hitherto been studied in small groups of children and adults with conflicting results. Objective We aimed to define the effect and clinical significance of adult GH replacement on thyroid status in a large cohort of GH-deficient patients. Patients and method We studied 243 patients with severe GH deficiency due to various hypothalamo-pituitary disorders. Before GH treatment, 159 patients had treated central hypothyroidism (treated group) while 84 patients were considered euthyroid (untreated group). GH dose was titrated over 3 months to achieve serum IGF-1 concentration in the upper half of the age-adjusted normal range. Serial measurements of serum T4, T3, TSH and quality of life were made at baseline and at 3 and 6 months after commencing GH replacement. ***Results In the untreated group, we observed a significant reduction in serum T4 concentration without a significant increase in serum T3 or TSH concentration; 30/84 patients (36%) became hypothyroid and needed initiation of T4 therapy.*** *Similar but lesser changes were seen in the treated group, 25 of whom (16%) required an increase in T4 dose. Patients who became hypothyroid after GH replacement had lower baseline serum T4 concentration, were more likely to have multiple pituitary hormone deficiencies and showed less improvement in quality of life compared with patients who remained euthyroid. Conclusion GH deficiency masks central hypothyroidism in a significant proportion of hypopituitary patients and this is exposed after GH replacement. We recommend that hypopituitary patients with GH deficiency and low normal serum T4 concentration should be considered for T4 replacement prior to commencement*

of GH in order to provide a robust baseline from which to judge the clinical effects of GH replacement.

Aimaretti G, Corneli G, Rovere S, Granata R, Baldelli R, Grottoli S, Ghigo E. Insulin-like growth factor I levels and the diagnosis of adult growth hormone deficiency. Horm Res. 2004;62 Suppl 1:26-33.

The current guidelines state that, within the appropriate clinical context, the diagnosis of adult growth hormone (GH) deficiency must be made biochemically using provocative tests. Measurement of insulin-like growth factor I (IGF-I) and binding protein 3 (IGFBP-3) levels cannot always distinguish between healthy and GH-deficient individuals. In particular, IGFBP-3 as a marker of GH status is clearly less sensitive than IGF-I and there is general agreement that its measurement does not provide useful diagnostic information. However, the diagnostic value of measuring IGF-I levels has been revisited recently. ***It has been confirmed that normal IGF-I levels do not rule out severe GH deficiency (GHD) in adults,*** *in whom the diagnosis has therefore to be based on the demonstration of severe impairment of the peak GH response to provocative tests.* ***It has also been emphasized that very low IGF-I levels in patients with high suspicion of GHD could be considered to be definite evidence for severe GHD.*** *This assumption particularly applies to patients with childhood-onset, severe GHD or with multiple hypopituitary deficiencies acquired in adulthood.* ***In addition, the use of IGF-I levels to monitor the efficacy and adequacy of recombinant human GH replacement remains widely accepted. (So why not use a low IGF-1 as definitive evidence of inadequate GH output in adults and treat with GH to raise the IGF-1—whether or not there is other evidence of pituitary insufficiency?—HHL)***

Albert SG, Haas MJ, Mooradian AD. The effects of recombinant human growth hormone (rhGH) supplementation on adipokines and C-reactive protein in obese subjects. Growth Horm IGF Res. 2006 Nov 20; [Epub ahead of print]

OBJECTIVE: Obese subjects have functional growth hormone deficiency (GHD). Recombinant human GH (rhGH) treatment of pituitary GHD improves serum levels of leptin, adiponectin and C-reactive protein (CRP). This study was undertaken to determine whether these rhGH-induced changes occur in obese subjects during rhGH supplementation. DESIGN: Randomized double-blind placebo-controlled trial of low-dose rhGH (200mug/day for the first month, then 400mug/day for men and 600mug/day for women thereafter) or placebo supplementation as an adjuvant to a standard weight loss program SUBJECTS: Forty healthy obese subjects, 28 premenopausal menstruating women (35+/-7 SD years) and 12 men (37+/-6years). MEASUREMENTS: Body weight, BMI, body composition (assessed by dual energy X-ray absorptiometry [DEXA]), and serum levels of glucose, insulin, IGF-I, IGFBP-3, insulin resistance index (homeostasis modal assessment [HOMA]), leptin, CRP and adiponectin were performed at baseline and at 6months. RESULTS: For similar entry BMI values, women when compared with men had higher percent body fat (BF) (43.5+/-4.6% vs. 29.8+/-4.0%, p<0.001), higher leptin levels (16.9+/-8.4mug/L vs. 4.2+/-3.0mug/L, p<0.001), and higher CRP levels (13.8+/-16.8mg/L vs. 2.4+/-3.2mg/L, p=0.04). Serum levels of leptin and CRP, but not adiponectin, correlated significantly with BF in both sexes. ***Recombinant human GH treatment increased levels of IGF-I Z-Score between baseline and 6months (from -0.7+/-0.9 SD to 0.1+/-1.1 SD, p=0.01) and modestly decreased BF (from 38.4+/-7.8% to 35.6+/-7.5%, p=0.046).*** *Despite increased IGF-I, there were no differences between rhGH and placebo with regard to changes in leptin, CRP, or adiponectin. CONCLUSION: It is concluded that in obesity, although rhGH treatment significantly increases IGF-I and modestly reduces body fat, the lack of significant changes in serum leptin, adiponectin or CRP levels suggests that rhGH treatment does not have a significant effect on these serum markers of adiposity.*

Arvat E, Ceda G, Ramunni J, Lanfranco F, Aimaretti G, Gianotti L, Broglio F, Ghigo E. The IGF-I response to very low rhGH doses is preserved in human ageing. Clin Endocrinol (Oxf). 1998 Dec;49(6):757-63.

OBJECTIVES: The activity of the GH/IGF-I axis varies during life and is clearly reduced in the elderly. In fact, GH, IGF-I and IGFBP-3 levels in older people are clearly reduced and similar to those observed in patients with GH deficiency. The declining activity of the GH/IGF-I axis with advancing age may contribute to changes in body composition, structure, function and metabolism. In fact, treatment with pharmacological doses of rhGH restored plasma IGF-I levels, increased lean body mass and muscle strength while decreased adipose tissue mass in healthy elderly subjects. At present it is unclear whether peripheral GH sensitivity is preserved in aging. To clarify this point, we aimed to verify the effect of both single dose and short term treatment with very low rhGH doses on the IGF-I levels in normal elderly subjects. Normal young adults were studied as controls. DESIGN: We studied the IGF-I response to rhGH administration after single (20 micrograms/kg s.c.) or repeated administrations (5 micrograms/kg s.c. for 4 days) ***(0.375mg/d for 75kg person—HHL)*** *in two groups of young and elderly subjects. SUBJECTS: Twenty-seven healthy elderly (ES, 14 F and 13 M, age mean +/- SEM: 69.4 +/- 1.3 years, BMI: 23.9 +/- 0.5 kg/m2) and 21 young adult subjects (YS, 12 F and 9 M, 29.8 +/- 1.2 years, 23.8 +/- 0.5 kg/m2) were studied, divided into two groups. MEASUREMENTS: Group 1: blood samples for IGF-I and IGFBP-3 assay were drawn basally and 12 h after rhGH administration (20 micrograms/kg). Group 2: blood samples for IGF-I, IGFBP-3, glucose and insulin assays were drawn basally, 12 h after the first and the last rhGH administration (5 micrograms/kg). Free T3 (fT3), free T4 (fT4) and TSH levels were also assayed basally and after the last rhGH administration; oestradiol and testosterone levels were measured basally. RESULTS: Basal IGF-I levels were lower in ES (whole group) than in YS (whole group) (123.1 +/- 8.9 vs. 230.4 +/- 16.1 micrograms/l, P < 0.001) while IGFBP-3 levels in the two groups were similar (2.7 +/- 0.2 vs. 3.1 +/- 0.2 mg/l). No sex-related differences in IGF-I and IGFBP-3 levels were recorded in either group. Group 1: the single administration of 20 micrograms/kg rhGH induced a significant (P < 0.001) IGF-I rise both in YS (318.0 +/- 25.3 vs. 256.0 +/- 21.6 micrograms/l) and ES (187.2 +/- 16.8 vs. 100.4 +/- 9.5 micrograms/l). IGF-I levels after rhGH in ES persisted lower than those in YS (P < 0.001), but the percentage IGF-I increase after rhGH was higher (P < 0.001) in ES (91.6 +/- 12.9%) than in YS (23.9 +/- 5.0%) subjects. Both in YS and ES IGFBP-3 levels were significantly increased to the same extent by 20 micrograms/kg rhGH (3.0 +/- 0.2 vs. 2.3 +/- 0.2 mg/l; 2.9 +/- 0.2 vs. 2.6 +/- 0.2 mg/l, P < 0.001 vs. baseline). Group 2: basal glucose, insulin, fT3, fT4 and TSH levels in YS and ES were similar; testosterone levels in aged and young men were similar while oestradiol levels in aged women were lower (P < 0.01) than in the young ones. IGF-I levels were significantly increased 12 h after the first administration of 5 micrograms/kg rhGH both in ES (166.6 +/- 15.7 vs. 138.3 +/- 12.1 micrograms/l, P < 0.03) and YS (272.2 +/- 16.1 vs. 230.4 +/- 16.1 micrograms/l, P < 0.001). Twelve hours after the last rhGH administration IGF-I levels were further increased (P < 0.001) both in ES (208.7 +/- 21.1 micrograms/l) and YS (301.7 +/- 17.6 micrograms/l). IGF-I levels in ES persisted lower than those in YS at each time point (P < 0.001); however, the percentage IGF-I increase after rhGH in ES and YS was similar (after the first administration: 22.4 +/- 5.1 vs. 21.7 +/- 5.1%; after the last administration: 52.9 +/- 9.5 vs. 39.5 +/- 9.9%). No significant variation in IGFBP-3, glucose, insulin, fT3, fT4 or TSH levels was recorded in either ES or YS. CONCLUSIONS:* ***Our data demonstrate that IGF-I levels in aging are reduced but the peripheral sensitivity to rhGH is preserved. In fact, in aged subjects the percentage rhGH-induced IGF-I increase is similar or even higher.***

Arwert LI, Veltman DJ, Deijen JB, van Dam PS, Drent ML. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. Neuroendocrinology. 2006;83(1):12-9. Epub 2006 May 15.

Patients with childhood-onset growth hormone (GH) deficiency (GHD) show impairments in mood and cognitive functioning which may resolve following GH substitution. Brain functional magnetic resonance imaging (fMRI) during performance of a memory task was used to assess the cerebral activity of such patients. Thirteen childhood-onset GHD patients (mean age 27.3 +/- 6.9 years) were included in a double-blind, placebo-controlled study. The effects of 6 months of GH replacement or placebo therapy were studied using neuropsychological tests and fMRI. One patient was excluded from the study due to noncompliance with the protocol. Six months of GH substitution in these GHD

patients resulted in improved memory functioning, both for long-term and working memory. fMRI showed activations during the working memory task in prefrontal, parietal, motor, and occipital cortices, as well as in the right thalamus and anterior cingulate cortex. Decreased activation in the ventrolateral prefrontal cortex was observed after GH treatment as compared with placebo treatment, indicating decreased effort and more efficient recruitment of the neural system involved. ***It can be concluded that GH treatment for 6 months improved the long-term as well as the working memory in patients with GHD, and this was associated with decreased brain activation in the ventrolateral prefrontal cortex. GH substitution in GHD patients is beneficial for cognitive functioning, the effects of which can be visualized by means of neuroimaging.***

Baris D, Gridley G, Ron E, Weiderpass E, Mellemkjaer L, Ekbom A, Olsen JH, Baron JA, Fraumeni JF Jr. Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control. 2002 Jun;13(5):395-400.

OBJECTIVE: Several studies have suggested that patients with acromegaly have an increased risk of benign and malignant neoplasms, especially of the colon. To further investigate this relationship we evaluated cancer risk in population-based cohorts of acromegaly patients in Sweden and Denmark. METHODS: Nationwide registry-based cohorts of patients hospitalized for acromegaly (Denmark 1977-1993; Sweden 1965-1993) were linked to tumor registry data for up to 15-28 years of follow-up, respectively. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated to estimate cancer risk among 1634 patients with acromegaly. RESULTS: The patterns of cancer risk in Sweden and Denmark were similar. After excluding the first year of follow-up, 177 patients with acromegaly had a diagnosis of cancer compared with an expected number of 116.5 (SIR = 1.5. 95% CI = 1.3-1.8). Increased risks were found for digestive system cancers (SIR = 2.1, 95% CI = 1.62.7), notably of the small intestine (SIR = 6.0, 95% CI = 1.2-17.4), colon (SIR = 2.6, 95% CI = 1.6-3.8), and rectum (SIR = 2.5, 95% CI= 1.3-4.2). Risks were also elevated for cancers of the brain (SIR = 2.7, 95% CI= 1.2-5.0). thyroid (SIR = 3.7, 95% CI = 1.8-10.9), kidney (SIR = 3.2, 95% CI = 1.6-5.5), and bone (SIR= 13.8, 95% CI= 1.7-50.0). CONCLUSIONS: The increased risk for several cancer sites among acromegaly patients may be due to the elevated proliferative and anti-apoptotic activity associated with increased circulating levels of insulin-like growth factor-1 (IGF-1). Pituitary irradiation given to some patients may have contributed to the excess risks of brain tumors and thyroid cancer. Our findings indicate the need for close medical surveillance of patients with acromegaly, and further studies of the IGF-I system in the etiology of various cancers.

Bartke A; Brown-Borg, Life extension in the dwarf mouse Curr Top Dev Biol 2004;63:189-225.

Ames dwarf mice and Snell dwarf mice lack growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH), live much longer than their normal siblings, and exhibit many symptoms of delayed aging. "Laron dwarf mice," produced by targeted disruption of the GH receptor/GH-binding protein gene (GHR-KO mice), are GH resistant and also live much longer than normal animals from the same line. Isolated GH deficiency in "little" mice is similarly associated with increased life span, provided that obesity is prevented by reducing fat content in the diet. Long-lived dwarf mice share many phenotypic characteristics with genetically normal (wild-type) animals subjected to prolonged caloric restriction (CR) but are not CR mimetics. We propose that mechanisms linking GH deficiency and GH resistance with delayed aging include reduced hepatic synthesis of insulin-like growth factor 1 (IGF-1), reduced secretion of insulin, increased hepatic sensitivity to insulin actions, reduced plasma glucose, reduced generation of reactive oxygen species, improved antioxidant defenses, increased resistance to oxidative stress, and reduced oxidative damage. The possible role of hypothyroidism, reduced body temperature, reduced adult body size, delayed puberty, and reduced fecundity in producing the long-lived phenotype of dwarf mice remains to be evaluated. An important role of IGF-1 and insulin in the control of mammalian longevity is consistent with the well-documented actions of homologous signaling pathways in invertebrates.

Bates AS, Evans AJ, Jones P, Clayton RN. Assessment of GH status in adults with GH deficiency using serum growth hormone, serum insulin-like growth factor-I and urinary growth hormone excretion. Clin Endocrinol (Oxf). 1995 Apr;42(4):425-30.

OBJECTIVES: The benefits of treating adults with GH deficiency are now well recognized although the criteria for deciding which patients to treat are still not clear. At present the 'gold standard' is the insulin stress test (IST) which is unpleasant and potentially dangerous, particularly in patients with hypopituitarism. The aim of this study was to determine whether alternative methods of assessing GH status are reliable in predicting GH deficiency. SUBJECTS AND METHODS: Forty-four patients with unequivocal GH deficiency (peak IST < 2 mU/l) and 17 with partial deficiency (peak IST 2-10 mU/l) were studied. Each patient was assessed clinically with respect to the number of other pituitary axes affected and biochemically with an estimate of urinary GH excretion (uGH) and serum IGF-I. These markers were then related to GH status as defined by insulin stress testing. MEASUREMENTS: Insulin stress tests were performed using 0.1 units/kg i.v. and accepted with a blood glucose < 2 mmol/l. Serum GH and IGF-I were measured by radioimmunoassay whilst uGH was estimated by an immunoradiometric assay using commercially available reagents. uGH was estimated from the mean of two overnight urine collections which consisted of all urine passed from last voiding through to the first morning sample. RESULTS: The presence of unequivocal GH deficiency (peak IST < 2 mU/l) was predictable if 2 or more other pituitary axes were affected (90%). uGH declined significantly with the level of peak IST response (P < 0.001) and almost so with the number of other deficient hypothalamic-pituitary axes affected (P = 0.057). Thus, uGH accurately reflected GH status and showed good separation from normal controls in patients less than 40 years (specificity 79%) and between 40 and 60 years (specificity 67%). Above this age the method is less specific (36%). Patients excreted significantly less GH than controls in all three age groups (P < 0.01). ***Subnormal levels of IGF-I were strongly predictive of unequivocal GH deficiency (91% with subnormal IGF-I have a peak IST GH < 2 mU/l) although a normal value does not reliably exclude the diagnosis.*** *CONCLUSIONS: A diagnosis of adult GH deficiency can be reliably made without the need for an insulin stress test by using a combination of low urinary GH excretion, subnormal IGF-I levels and clinical assessment with regard to the number of other pituitary axes affected.*

Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenhein DS, Schoenfeld DA, Michel TH, Wittink H, Klibanski A. 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. Ann Intern Med 1996 Dec 1;125(11):932-4.

BACKGROUND: Patients with adult-onset growth hormone deficiency have reduced bone density and increased fat mass. Growth hormone at high doses may decrease body fat in these patients, but the effects of growth hormone at more physiologic doses on bone density and body composition have not been convincingly shown. OBJECTIVE: To determine whether long-term growth hormone therapy at a dose adjusted to maintain normal insulin-like growth factor 1 (IGF-1) levels has clinical effects in patients with adult-onset growth hormone deficiency. DESIGN: Randomized, placebo-controlled study. SETTING: Tertiary referral center. PATIENTS: 32 men with adult-onset growth hormone deficiency. INTERVENTION: Growth hormone (initial daily dose, 10 micrograms/kg of body weight) or placebo for 18 months. The growth hormone dose was reduced by 25% if IGF-1 levels were elevated. MEASUREMENTS: Body composition and bone mineral density of the lumbar spine, femoral neck, and proximal radius were measured by dual energy x-ray absorptiometry at 6-month intervals. Markers of bone turnover were also measured during the first 12 months of the study. RESULTS: Growth hormone therapy increased bone mineral density in the lumbar spine by a mean (+/- SD) of 5.1% +/- 4.1% and bone mineral density in the femoral neck by 2.4% +/- 3.5%. In the growth hormone group, significant increases were seen in the following markers of bone turnover: osteocalcin (4.4 +/- 3.6 mg/L to 7.2 +/- 4.6 mg/L) and urinary pyridinoline (39.0 +/- 19.8 nmol/mmol of creatinine to 55.7 +/- 25.5 nmol/mmol of creatinine) and deoxypyridinoline (8.4 +/- 7.1 nmol/mmol of creatinine to 14.9 +/- 9.4 nmol/mmol of creatinine). Percentage of body fat in the growth hormone group decreased (from 31.9% +/- 6.5% to 28.3% +/- 7.0%), and lean body mass increased (from 59.0

+/- 8.5 kg to 61.5 +/- 6.9 kg). These changes were significant compared with corresponding changes in the placebo group (P < 0.01 for all comparisons). CONCLUSIONS: Growth hormone administered to men with adult-onset growth hormone deficiency at a dose adjusted according to serum IGF-1 levels increases bone density and stimulates bone turnover, decreases body fat and increases lean mass, and is associated with a low incidence of side effects. PMID: 8967668 ***(Growth hormone administered to men with adult-onset growth-hormone deficiency at a dose adjusted to serum IGF-1 levels increases bone density and stimulates bone turnover, decreases body fat and increases lean mass, and is associated with a low incidence of side effects.—HHL)***

Baxter RC; Brown AS; Turtle JR, Radioimmunoassay for somatomedin C: comparison with radioreceptor assay in patients with growth-hormone disorders, hypothyroidism, and renal failure. Clin Chem 1982 Mar;28(3):488-95.

We raised an antiserum (Tr4) in rabbits against a basic somatomedin C-like peptide preparation. Using high-immunoreactivity somatomedin C tracer, we compared the performance of radioimmunoassays in which we used the Tr4 antiserum and a well-characterized somatomedin C antiserum distributed by the National Pituitary Agency (NPA) with that of the human placental-membrane somatomedin radioreceptor assay (RRA). In their cross reactivity toward various somatomedin-like and unrelated peptides, the two radioimmunoassay methods were almost identical, although NPA antiserum, with about fourfold higher titer than Tr4 antiserum, showed a slightly greater sensitivity for most peptides tested. Radioimmunoassay of acid-ethanol-extracted plasma samples from normal persons and acromegalic, hypopituitary, hypothyroid, and renal-failure patients revealed no analytical differences between the antisera (for 122 samples, r = 0.979 between methods). ***Somatomedin values for acromegalic and hypopituitary samples showed no overlap with normals. Values for hypothyroid and pre-dialysis renal-failure samples were significantly lower than normal.*** *By comparison, the RRA showed greater cross reactivity toward some somatomedin-like peptides and gave significantly lower values than radioimmunoassay for acromegalic and hypothyroid plasma extracts, and significantly higher value for hypopituitary and renal-failure samples. We conclude that the radioimmunoassay methods clearly are of greater diagnostic value than RRA for clinical somatomedin measurement.****(Low IGF-1 may be due to low thyroid hormone levels and may rebound when thyroid hormone levels are restored.—HHL)***

Bengtsson BA, Kippeschaar HPF, Abs R, Monson JP, FeldtRasmussen U, Wuster, Christian. Letters to the Editor. Growth hormone replacement therapy is not associated with any increase in mortality. J Clin Endocrin Metab 1999;84(11):4291-4292.

Bereket A, Lang CH, Wilson TA. Alterations in the growth hormone-insulin-like growth factor axis in insulin dependent diabetes mellitus. Horm Metab Res. 1999 Feb-Mar;31(2-3):172-81.

The growth hormone (GH)-insulin-like growth factor (IGF) axis and insulin are major anabolic effectors in promoting weight gain and linear growth. These two anabolic systems are interlinked at many levels, thus abnormalities in one of these systems effect the other causing disordered metabolic homeostasis. Insufficient portal insulinization in insulin dependent diabetes mellitus (IDDM) results in hepatic GH resistance and increased production of IGF-binding proteins-1 (IGFBP-1) and IGFBP-2. GH resistance is reflected by decreased hepatic IGF-I production. In addition, changes in other GH-dependent proteins are also observed in IDDM. Increased proteolysis of IGFBP-3 results in reduction of intact IGFBP-3. Serum ALS levels are also slightly diminished in untreated diabetic patients. Hepatic resistance to GH is, at least in part, caused by diminished GH receptors as reflected by diminished circulating GHBP levels. In addition, there is also evidence from experimental and human studies suggesting post-receptor defect(s) in GH action. As a result of these changes, circulating total and free IGF-I levels are decreased during insulinopenia. Lack of negative feed-back effect of IGF-I on GH secretion causes GH hypersecretion which increases hyperglycemia by decreasing sensitivity to insulin. GH hypersecretion in poorly controlled diabetic patients may play a role in the

pathogenesis of diabetic vascular complications. Most of these abnormalities in the GH-IGF axis in diabetes are reversed by effective insulinization of the patient. Addition of IGF-I treatment to insulin in adolescents with IDDM allows correction of GH hypersecretion, improves insulin sensitivity and glycemic control, and decreases insulin requirements. The effect of IGF-I treatment on diabetic complications has yet to be seen.

Biller BM, Sesmilo G, Baum HB, Hayden D, Schoenfeld D, Klibanski A. Withdrawal of long-term physiological growth hormone (GH) administration: differential effects on bone density and body composition in men with adult-onset GH deficiency. J Clin Endocrinol Metab. 2000 Mar;85(3):970-6.

Adults with acquired GH deficiency (GHD) have been shown to have osteopenia associated with a 3-fold increase in fracture risk and exhibit increased body fat and decreased lean mass. Replacement of GH results in decreased fat mass, increased lean mass, and increased bone mineral density (BMD). The possible differential effect of withdrawal of GH replacement on body composition compartments and regional bone mass is not known. We performed a randomized, single blind, placebo-controlled 36-month cross-over study of GH vs. placebo (PL) in adults with GHD and now report the effect of withdrawal of GH on percent body fat, lean mass, and bone density, as measured by dual energy x-ray absorptiometry. Forty men (median age, 51 yr; range, 24-64 yr) with pituitary disease and peak serum GH levels under 5 microg/L in response to two pharmacological stimuli were randomized to GH therapy (starting dose, 10 microg/kg x day, ***final dose 4 microg/kg x day)*** *vs. PL for 18 months. Replacement was provided in a physiological range by adjusting GH doses according to serum insulin-like growth factor I levels.* ***After discontinuation of GH, body fat increased significantly (mean +/- SEM, 3.18 +/- 0.44%; P = 0.0001) and returned to baseline. Lean mass decreased significantly (mean loss, 2133 +/- 539 g; P = 0.0016), but remained slightly higher (1276 +/- 502 g above baseline; P = 0.0258) than at study initiation. In contrast to the effect on body composition, BMD did not reverse toward pretreatment baseline after discontinuation of GH.*** *Bone density at the hip continued to rise during PL administration, showing a significant increase (0.0014 +/- 0.00042, g/cm2 x month; P = 0.005) between months 18-36. Every bone site except two (radial BMD and total bone mineral content), including those without a significant increase in BMD during the 18 months of GH administration, showed a net increase over the entire 36 months.* ***Therefore, there is a critical differential response of the duration of GH action on different body composition compartments. Physiological GH administration has a persistent effect on bone mass 18 months after discontinuation of GH.***

Black MM, Shuster s, Bottoms E. Skin Collagen and thickness in acromegaly and hypopituitarism. Clin Endocrinol (Oxf.) 1972;1:259-263.

Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St Clair C, Pabst KM, Harman SM. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA. 2003 Jul 23;290(4):462.

CONTEXT: Hormone administration to elderly individuals can increase lean body mass (LBM) and decrease fat, but interactive effects of growth hormone (GH) and sex steroids and their influence on strength and endurance are unknown. OBJECTIVE: To evaluate the effects of recombinant human GH and/or sex steroids on body composition, strength, endurance, and adverse outcomes in aged persons. DESIGN, SETTING, AND PARTICIPANTS: A 26-week randomized, double-blind, placebo-controlled parallel-group trial in healthy, ambulatory, community-dwelling US women (n = 57) and men (n = 74) aged 65 to 88 years recruited between June 1992 and July 1998. INTERVENTIONS: Participants were randomized to receive GH (starting dose, 30 micro g/kg, reduced to 20 micro g/kg, subcutaneously 3 times/wk) + sex steroids (women: transdermal estradiol, 100 micro g/d, plus oral medroxyprogesterone acetate, 10 mg/d, during the last 10 days of each 28-day cycle [HRT]; men: testosterone enanthate, biweekly intramuscular injections of 100 mg) (n = 35); GH + placebo sex

steroid (n = 30); sex steroid + placebo GH (n = 35); or placebo GH + placebo sex steroid (n = 31) in a 2 x 2 factorial design. MAIN OUTCOME MEASURES: Lean body mass, fat mass, muscle strength, maximum oxygen uptake (VO(2)max) during treadmill test, and adverse effects. RESULTS: In women, LBM increased by 0.4 kg with placebo, 1.2 kg with HRT (P =.09), 1.0 kg with GH (P =.001), and 2.1 kg with GH + HRT (P<.001). Fat mass decreased significantly in the GH and GH + HRT groups. In men, LBM increased by 0.1 kg with placebo, 1.4 kg with testosterone (P =.06), 3.1 kg with GH (P<.001), and 4.3 kg with GH + testosterone (P<.001). Fat mass decreased significantly with GH and GH + testosterone. Women's strength decreased in the placebo group and increased nonsignificantly with HRT (P =.09), GH (P =.29), and GH + HRT (P =.14). Men's strength also did not increase significantly except for a marginally significant increase of 13.5 kg with GH + testosterone (P =.05). Women's VO(2)max declined by 0.4 mL/min/kg in the placebo and HRT groups but increased with GH (P =.07) and GH + HRT (P =.06). Men's VO(2)max declined by 1.2 mL/min/kg with placebo and by 0.4 mL/min/kg with testosterone (P =.49) but increased with GH (P =.11) and with GH + testosterone (P<.001). Changes in strength (r = 0.355; P<.001) and in VO(2)max (r = 0.320; P =.002) were directly related to changes in LBM. Edema was significantly more common in women taking GH (39% vs 0%) and GH + HRT (38% vs 0%). Carpal tunnel symptoms were more common in men taking GH + testosterone (32% vs 0%) and arthralgias were more common in men taking GH (41% vs 0%). Diabetes or glucose intolerance occurred in 18 GH-treated men vs 7 not receiving GH (P =.006). CONCLUSIONS: In this study, GH with or without sex steroids in healthy, aged women and men increased LBM and decreased fat mass. Sex steroid + GH increased muscle strength marginally and VO(2)max in men, but women had no significant change in strength or cardiovascular endurance. Because adverse effects were frequent (importantly, diabetes and glucose intolerance), GH interventions in the elderly should be confined to controlled studies. (NOTE: A good example of a study done by **physicians who do not understand or practice hormone restoration**. The high indicence of side effects was due to excessive, non-physiological dosing. Their starting dose of 30mcg/kg 3x/week ((**7200mcg/week for 80kg human**) and maintenance GH dose of 20mcg/kg 3x/week (**4800mcg/week**) were both too high and given in large, infrequent doses. GH is secreted every night and should be given on a daily basis. The usual maintenance dose needed to achieve optimal IGF-1 levels in 80kg person is between **1400mcg/week** and **2800mcg/week maximum; 0.2mg to 0.4mg per day.** The testosterone dose was also too infrequent **and** too small by half. Studies show that testostosterone enanthate must be give @100mg IM each week to produce youthful testosterone levels in most men. Flawed studies like this are widely publicized as proof that hormone replacement is BUNK.

Blevins L Beneficial effects of growth hormone replacement in growth hormone-deficient adults *The Endocrinologist* 2002; 12:405-411 (Lippincott Williams and Wilkins)

Adverse effects of growth hormone replacement therapy are minor and are minimized by individualizing therapy based on clinical response. There is no increased incidence of tumor recurrence or development in pediatric patients undergoing long-term GH replacement or in acromegalic adults who have much higher levels of IGF-1 than with GH replacement. *The Growth Hormone Research Society has concluded that there are no data to suggest that IGF-1 modulates cancer risk in GH-treated patients.*

Bocchi EA, Massuda Z, Guilherme G, Carrara D, Bellotti G, Mecelin A, Rodriguez Sobrinho CR, Ramires JF. Growth hormone for optimization of refractory heart failure treatment. Arq Bras Cardiol 1999 Oct; 73(4):391-8.

Boguszewski CL, Meister LH, Zaninelli DC, Radominski RB. One year of GH replacement therapy with a fixed low-dose regimen improves body composition, bone mineral density and lipid profile of GH-deficient adults. Eur J Endocrinol. 2005 Jan;152(1):67-75.

OBJECTIVE: We have studied the effects on body composition and metabolism of a fixed low dose of growth hormone (GH), ***0.6 IU (0.2 mg)/day,*** *administered for 12 months to GH-deficient (GHD) adults. DESIGN AND METHODS: Prospective open-label study, using 18 GHD patients (11*

women, 7 men; aged 21-58 years). All investigations were performed at baseline and after 12 months. Body composition was determined by dual energy X-ray absorptiometry. RESULTS: Total body fat decreased (-1.74+/-2.87%) and lean body mass (LBM) increased (1.27+/-2.08 kg) after therapy (P < 0.05). ***Changes in truncal fat did not reach statistical signifi****cance, but a decrease varying from 0.72 to 2.78kg (1 to 8.7%) was observed in 13 (72%) patients. Bone mineral density (BMD) increased at lumbar spine, total femur and femoral neck (P < 0.05).* ***Levels of total and low-density lipoprotein (LDL)-cholesterol were lower after therapy (P < 0.05), and their changes were directly associated with values at baseline. Insulin levels increased and the insulin resistance index worsened at 12 months (P < 0.05).*** *Median IGF-I s.d. score was -4.30 (range, -11.03 to -0.11) at baseline and -1.73 (range, -9.80 to 2.26) at 12 months. Normal age-adjusted IGF-I levels were obtained with therapy in 5 of 11 patients who had low IGF-I levels at baseline. Changes in IGF-I levels were not correlated with any biological end point, except changes in LBM (r = 0.53, P = 0.02). Side effects were mild and disappeared spontaneously. CONCLUSIONS: One-year of a fixed low-dose GH regimen in GHD adults resulted in a significant reduction in body fat, total cholesterol and LDL-cholesterol, and a significant increase in LBM and BMD at lumbar spine and femur, regardless of normalization of IGF-I levels. This regimen led to an elevation of insulin levels and a worsening of the insulin resistance index.* ***(The insulin levels increased due to increased lipolysis—a good thing—but blood sugar did not increase. Does the insulin elevation mean that the dose was too high, or do beneficial levels of GH simply exacerbate the normal tendency to higher insulin levels with age? Is the higher insulin level in this context a bad thing at all?—HHL)***

Bohdanowicz-Pawlak A, Szymczak J, Bladowska J, Bednarek-Tupikowska G, Bidzinska B, Milewicz A. Risk factors of cardiovascular disease in GH-deficient adults with hypopituitarism: a preliminary report. Med Sci Monit. 2006 Feb;12(2):CR75-80.

BACKGROUND: We estimated the influence of GH deficiency (GHD) in adults on chosen risk factors of cardiovascular disease and bone density. MATERIAL/METHODS: Fifty-four adults (mean age: 50.4 years) with hypopituitarism were studied. We measured blood pressure, body mass index, waist-to-hip ratio, total body fat, and bone mineral density and the serum levels of lipids, glucose, insulin, pituitary hormones, estradiol, testosterone, and thyroxine, and the excretion of free cortisol in 24-h urine. GHD was confirmed with the insulin intravenous test (IIT) with a GH response to IIT of <3 microg/ml. The control group consisted of 73 healthy adults. RESULTS: Increased levels of LDL-cholesterol and triglycerides and decreased levels of HDL-cholesterol in the GHD group were observed. Fasting serum glucose and insulin levels were significantly higher in the GHD group than in controls. Significant differences in the QUICKI and FIRI indexes were observed. Twenty-three percent of the hypopituitary patients were hypertensive and 65% were obese. The percentage of total body fat was significantly higher in the studied group than in controls. Thirty-seven percent of the GHD patients were osteoporotic and 23% were osteopenic. CONCLUSIONS: An atherogenic lipid profile, insulin resistance, obesity, and increased body and trunk fat in GHD adults may cause the higher risk of cardiovascular disease in these patients. ***GHD adults should receive human recombinant GH along with conventional replacement therapy. This may be a useful method in protecting against early onset of atherosclerosis, metabolic disturbances, and osteoporosis, especially in young patients.***

Borges MH, Pinto AC, DiNinno FB, Camacho-Hübner C, Grossman A, Kater CE, Lengyel AM. IGF-I levels rise and GH responses to GHRH decrease during long-term prednisone treatment in man. J Endocrinol Invest. 1999 Jan;22(1):12-7.

Glucocorticoid excess is associated with a blunted GH response to GHRH. IGF-I levels in hypercortisolism are controversial and have been reported as low, normal or high. The aim of this study was to evaluate longitudinally time-dependent changes in the GH response to GHRH, IGF-I, IGFBP-3 and albumin values in patients during corticotherapy. Six patients received GHRH before and after one week and one month of prednisone administration (20-60 mg/d, orally). IGF-I, IGFBP-3 and albumin were determined in each test, at time 0. Ten normal controls were also

evaluated in one occasion. There were no differences in basal GH values, GH response to GHRH, IGF-I and IGFBP-3 levels between controls and patients before starting corticotherapy. Albumin (g/l; mean+/-SE) values were lower in patients before treatment (31+/-4) than in controls (43+/-1). After one week of prednisone administration there was a significant decrease in peak GH (microg/l) levels (before: 18.8+/-7.4; 1 week: 5.0+/-1.3), which was maintained after one month (8.1+/-3.5). ***IGF-I (microg/l) levels increased significantly, from 145+/-23 to 205+/-52 after one week of therapy, reaching levels of 262+/-32 after one month.*** *IGFBP-3 (mg/l) values did not increase significantly (before: 2.1+/-0.2; 1 week: 2.5+/-0.3; 1 month: 2.8+/-0.2). Albumin levels showed a significant rise both after one week (36+/-4) and one month (42+/-3) of corticotherapy. In summary, we observed a marked decrease in the GH response to GHRH after one week and one month of prednisone administration associated with an increase in circulating IGF-I and albumin values. The physiological implications of these findings are still uncertain.* ***It is possible that glucocorticoids increase hepatic IGF-I and albumin synthesis, although other mechanisms may have a role.***

Burger AG, Monson JP, Colao AM, Klibanski A. Cardiovascular risk in patients with growth hormone deficiency: effects of growth hormone substitution. Endocr Pract. 2006 Nov-Dec;12(6):682-9.

OBJECTIVE: To review the literature on the increased cardiovascular risk in patients with growth hormone (GH) deficiency and the positive effects of GH replacement. METHODS: We analyze the factors that contribute to cardiovascular risk in GH deficiency, including body composition and lipid profile, and summarize GH treatment strategies and results described in the literature. RESULTS: The prominent clinical finding in patients with GH deficiency is the increased abdominal fat, even in patients with normal weight. Cardiac ejection volume tends to be decreased, and arterial distensibility is diminished. The lipid status is also worsened, accompanied by increased inflammatory markers, such as highly sensitive C-reactive protein. Typically, GH treatment reduces visceral fat and increases muscle mass, changes that diminish cardiovascular risk. Because of direct effects as well as increased hemodynamic performance and increased blood volume, cardiac performance is improved. ***With GH therapy, total cholesterol and low-density lipoprotein levels decrease by 10% to 20%, and inflammatory markers such as C-reactive protein decline.*** *Carbohydrate metabolism during moderate to long-term treatment is minimally affected, although obese patients with GH deficiency on rare occasion may have hyperglycemia or even diabetes. CONCLUSION: The relevance of the beneficial effects of GH on the cardiovascular system is strongly suggested but not fully proved. The results in a large cohort of GH-treated patients (the KIMS or Pharmacia and Upjohn International Metabolic Surveillance database) demonstrated no difference in cardiovascular risk in comparison with that in a control population after a mean of 3 years of treatment.*

Caidahl K, Eden S, Bengtsson BA. Cardiovascular and renal effects of growth hormone. Clin Endocrinol (Oxf). 1994 Mar;40(3):393-400.

OBJECTIVE: With the advent of recombinant human GH (rhGH), it has become possible in controlled clinical studies to explore the effects of GH replacement in adults with GH deficiency. The objective of this study was to determine cardiovascular and renal effects of GH replacement in adults with GH deficiency. PATIENTS: We studied ten patients (one woman and nine men), mean age 47 years, with GH deficiency. DESIGN: The patients were given s.c. rhGH (Humatrope, Eli Lilly) 0.5 U/kg/week or placebo in a 6-month double blind cross-over study. Cardiac and renal function was measured before drug administration (baseline), before cross-over (i.e. after 6 months), and before termination of drug administration (after another 6 months). Analysis of variance was used to compare measurements during GH replacement with baseline and placebo measurements. One patient was excluded because of atrial fibrillation. MEASUREMENTS: Main outcome measures were glomerular filtration rate and Doppler-echocardiographic estimates of cardiac function and structure. Computerized exercise electrocardiogram, spirometry, and blood samples for analyses of plasma hormones were also obtained. RESULTS: Left ventricular function

was maintained during GH replacement. However, left ventricular mass increased from 211 to 249 g (P < 0.05) mainly due to increased left ventricular dimension since wall thicknesses did not increase. The left atrium increased from 38 to 41 mm (P < 0.05), possibly because stroke volume increased from 92 to 118 ml (P < 0.0001) and cardiac output increased from 5.29 to 7.58 l/min (P < 0.05). Total peripheral resistance decreased from 18.9 to 12.4 mmHg min/l (P < 0.05), and diastolic blood pressure from 79 to 72 mmHg (P < 0.05). Heart rate at rest increased from 58 to 70 beats/min. Systolic blood pressure at rest was unchanged, as was systolic blood pressure during dynamic exercise. GH replacement did not cause ST-abnormalities. Serum creatinine decreased from 91.4 to 85.3 mumol/l (P < 0.05) and glomerular filtration rate increased from 89.6 to 99.8 ml/min (P < 0.01). CONCLUSIONS: ***Thus, GH replacement has favourable cardiovascular and renal effects including increase of stroke volume and glomerular filtration rate with reduction of peripheral resistance.***

Caufriez A, Golstein J, Tadjerouni A, Bosson D, Cantraine F, Robyn C, Copinschi G. Modulation of immunoreactive somatomedin-C levels by sex steroids. Acta Endocrinol (Copenh). 1986 Jun;112(2):284-9.

Among 28 menstruating women tested once randomly during the cycle, somatomedin-C (Sm-C) values were lower in the 10 women in normal follicular phase than in the 10 women in normal luteal phase or the 8 women with hyperandrogenism. Among these 28 subjects, Sm-C showed a positive correlation with testosterone and a positive correlation of borderline significance with oestradiol. ***A positive correlation was also evidenced between Sm-C and in progesterone among the 20 women of this group who were not hyperandrogenic.*** *In 5 other normal women investigated daily throughout an entire menstrual cycle, Sm-C concentrations were higher during days +4 to +9 of this cycle (luteal phase) than during days -3 to -8 (follicular phase). In another group of 21 healthy women, Sm-C values were increased during medroxyprogesterone acetate (150 mg trimestrially) treatment. In 7 normal men, Sm-C decreased during ethinyl-oestradiol (1 mg daily for 5 days) administration. These findings suggest that circulating Sm-C levels are modulated by variations of sex steroids which occur during the menstrual cycle as well as by pharmacological doses of oestrogens and progestagens. PMID: 2943106*

Caufriez A, Leproult R, L'hermite-Balériaux M, Moreno-Reyes R, Copinschi G. A potential role for endogenous progesterone in modulation of growth hormone, prolactin and thyrotropin secretion during normal menstrual cycle. Clin Endocrinol (Oxf). 2009 Oct;71(4):535-42.

Summary Objective: Previous studies investigating the fluctuations of endocrine secretion across the menstrual cycle yielded inconsistent results. Our objective was to evaluate during the menstrual cycle the potential role of endogenous oestradiol and progesterone in the regulation of hormones primarily controlled by the circadian clock and/or the sleep-wake cycle. Subjects and design: Ten normally cycling young lean women were investigated once during follicular, once during luteal phase. Sleep was polygraphically recorded, blood samples were obtained at 20-min intervals for 24 hours. Results: Sleep variables and diurnal melatonin and cortisol profiles (hormones primarily controlled by the circadian clock) were similar in both conditions. The TSH evening rise (a circadian marker) was similar in both conditions, but the sleep-related nocturnal TSH decrease occurred earlier during the luteal phase (P = 0.03) and tended to correlate positively with progesterone levels (r(s) = -0.64, P < 0.06). Daytime GH secretion and afternoon/evening PRL secretion (hormones primarily controlled by the sleep-wake homeostasis) were increased in the luteal phase compared to the follicular phase (GH: P = 0.04; PRL: P = 0.01). ***The increase in 24-h GH secretion was associated with higher progesterone levels*** *(r(s) = 0.78, P = 0.02). In luteal phase, the evening PRL rise was associated with higher progesterone (r(s) = 0.70, P = 0.04) and oestradiol (r(s) = 0.72, P = 0.03) levels. Conclusion: The present data indicate that in normally cycling young women, daytime GH and PRL secretions are increased in luteal phase. These data also suggest that endogenous progesterone could play a modulation role on pituitary hormones*

secretion, stimulating GH and PRL release and enhancing the inhibitory action of sleep on TSH secretion.

Carroll, PV Littlewood R, Weissberger AJ, Bogalho P, McGauley G, Sonksen PH, Russell-Jones DL. The effects of two doses of replacement growth hormone on the biochemical, body composition, and psychological profiles of growth hormone-deficient adults. Eur J Endocrinol 1997 Aug;137(2):146-53.

This study examined the effects of growth hormone (GH) replacement on the insulin-like growth factor-I (IGF-I), body composition and psychological profiles of GH-deficient adults. We assessed whether two doses of GH produced different effects on these variables and whether patients who, at the end of the study chose to remain on long-term GH replacement responded differently to those who chose to abandon therapy. Forty-two adults (aged 42.9 +/- 1.9 years (mean +/- S.E.M.)) with documented GH deficiency entered two studies (24 in study 1, 18 in study 2). Biochemical, body composition and psychological profiles were assessed at baseline, and after 6 months and 1 year. Psychological assessments were performed using well-established, independent, validated 'Quality of Life' questionnaires (Nottingham Health Profile (NHP) and the Psychological General Well-Being Schedule (PGWB)). The study protocols differed only in the doses of growth hormone (0.024 mg/kg per day and 0.012 mg/kg per day respectively). ***(for 70kg person: 1.7 and 0.8 mg/day—both high doses-HHL)*** *Comparison between studies and between patients eventually continuing and abandoning GH therapy was performed. GH replacement was associated with significant changes in IGF-I levels (P < 0.001), body composition (P < 0.01) and self-perceived well-being (NHP, P < 0.01; PGWB, P < 0.01). The higher dose of GH produced a greater IGF-I response than the lower dosage (44.6 +/- 7.3 vs 26.2 +/- 3.6 nmol/l, P < 0.05), but no better psychological response (NHP, P = 0.22; PGWB, P = 0.23). Those deciding to continue replacement therapy did not respond differently to those choosing to abandon therapy with respect to IGF-I (P = 0.72), body composition (P = 0.38) and psychological assessment (NHP, P = 0.29; PGWB, P = 0.24). GH replacement in GH-deficient adults was associated with significant improvements in self-perceived well-being as well as changes in body composition and other variables. This improvement was similar at two different doses of replacement GH. Those patients electing to continue on long-term replacement did not achieve a demonstrably different psychological, body composition or biochemical benefit to those patients deciding to discontinue replacement.*

Ceda GP, Dall'Aglio E, Maggio M, Lauretani F, Bandinelli S, Falzoi C, Grimaldi W, Ceresini G, Corradi F, Ferrucci L, Valenti G, Hoffman AR. Clinical implications of the reduced activity of the GH-IGF-I axis in older men. J Endocrinol Invest. 2005;28(11 Suppl Proceedings):96-100.

During the last decade, a significant body of evidence has accumulated, indicating that IGF-I might play a role in several pathological conditions commonly seen during aging, such as atherosclerosis and cardiovascular disease (CVD), cognitive decline, dementia, sarcopenia and frailty. A vascular protective role for IGF-I has been suggested because of its ability to stimulate nitric oxide production from endothelial and vascular smooth muscle cells. In cross sectional studies, low IGF-I levels have been associated with unfavorable CVD risk factors profile, such as atherosclerosis, abnormal lipoprotein levels and hypertension, while in prospective studies, lower IGF-I levels predict future development of ischemic heart disease. The fall in IGF-I levels with aging correlates with cognitive decline and it has been suggested that IGF-I plays a role in the development of dementia. ***IGF-I is highly expressed within the brain and is essential for normal brain development. IGF-I has anti-apoptotic and neuroprotective effects and promotes projection neuron growth, dendritic arborization and synaptogenesis. Collectively, these data are consistent with a causal link between the age-related decline in GH and IGF-I levels and cognitive deficits in older persons.*** *Finally, there is evidence of a relationship between declining GH and IGF-I levels and age-related changes in body composition and physical function. However, few studies have documented a precise role of IGF-I in the development of sarcopenia, frailty and poor mobility. We*

have recently documented that serum IGF-I is significantly associated with measures of muscle strength and physical performance in men and to a lesser extent in women. ***In conclusion, IGF-I is a pleiotropic hormone that in older persons may positively affect the cardiovascular system, the central nervous system and physical function.***

Cenci MC, Conceição FL, Soares DV, Spina LD, Brasil RR, Lobo PM, Michmacher E, Vaisman M. Impact of 5 years of growth hormone replacement therapy on cardiovascular risk factors in growth hormone-deficient adults. Metabolism. 2008 Jan;57(1):121-9.

The benefits of long-term effects of growth hormone (GH) substitution on carbohydrate and lipid metabolism in GH-deficient (GHD) adults are still controversial. The purpose of this study was to evaluate the effects of 5 years of GH substitution on body composition, glucose and lipid metabolism, and carotid artery intima-media thickness (IMT) in GHD adults. Fourteen patients were clinically assessed every 3 months for 5 years. Serum insulin-like growth factor 1 levels, lipid profile, oral glucose tolerance test, and ultrasonography of the carotid arteries were performed at baseline, 6 months, and every year during replacement. Visceral fat was measured by computed tomographic scan at baseline and at 6, 12, 24, and 60 months. The waist circumference was reduced after 6 months but increased during the next months toward baseline values. Visceral fat decreased during the study. Fasting glucose and insulin levels did not change, as well as the homeostasis model assessment of insulin resistance index. Despite an initial increase in frequency of abnormal glucose tolerance, mean 2-hour oral glucose tolerance test glucose levels decreased during the last 2 years. There was an increase in apolipoprotein A-1 levels during the treatment. Apolipoprotein B levels were reduced after 6 months and remained stable thereafter. A reduction in carotid artery IMT was observed during replacement. ***We concluded that 5 years of GH replacement therapy promoted positive effects on visceral fat, lipid profile, and carotid artery IMT in GHD adults. Long-term therapy improves insulin sensitivity through a reduction in visceral fat, and continuing monitoring is mandatory in terms of glucose metabolism.***

Chihara K, Kato Y, Kohno H, Takano K, Tanaka T, Teramoto A, Shimatsu A. Safety and efficacy of growth hormone (GH) during extended treatment of adult Japanese patients with GH deficiency (GHD). Growth Horm IGF Res. 2008 Aug;18(4):307-17.

OBJECTIVES: To assess the effects of a growth hormone (GH) replacement therapy using a GH dose regimen based on serum insulin-like growth factor (IGF-I) concentrations in Japanese adults with GH deficiency (GHD). DESIGN: In this multicentre, uncontrolled, open-label study, Japanese adults with GHD who had received either GH replacement therapy (GH-GH group, n=35) or placebo (Placebo-GH group, n=36) in a previous randomised, double-blind, placebo-controlled trial were treated with GH replacement therapy for 48 weeks. GH treatment was started at a dose of 0.003 mg/kg/day administered by subcutaneous injection for the first 8 weeks, after which the dose was adjusted to maintain patients' serum IGF-I levels within the reference range adjusted for age and gender. Body composition, serum lipids, serum IGF-I and IGF binding protein-3 (IGFBP-3) levels were measured throughout study. Symptom and quality of life scores were also determined. RESULTS: Lean body mass (LBM) was increased compared with baseline (the end of the preceding double-blind trial) at 24 and 48 weeks, with a mean (+/-SD) increase of 1.3% (+/-4.2%) at week 48 in the GH-GH group (an increase of 6.6% [+/-6.0%] from the start of the preceding double-blind trial) and a larger increase of 4.7% (+/-5.9%) in the Placebo-GH group. Body fat mass (BFM) increased slightly from baseline in the GH-GH group with a mean increase of 2.9+/-10.6% at week 48 (a decrease from the start of the preceding double-blind trial at 48 weeks of 7.8% [+/-15.0%]) but decreased by 6.5% (+/-11.7%) at week 48 in the Placebo-GH group. Serum lipids were unchanged or slightly increased from baseline in the GH-GH group but patients' lipid profiles improved in the Placebo-GH group. In patients who received placebo during the double-blind study, individualised GH therapy in this open-label study increased mean LBM at 48 weeks by 6.2+/-6.8% in patients with CO GHD and by 3.0+/-4.4% in patients with AO GHD. Changes in mean LBM and mean BFM at week 48 were +4.1+/-4.5% and -2.4+/-10.5%, respectively, in

females and +5.0+/-6.7% and -8.9+/-11.8%, respectively, in males. In patients who received GH treatment during the double-blind study, overall changes in LBM, BFM and IGF-I SD score after 24 weeks and 48 weeks were small, with no significant differences between subgroups. While the overall incidence of adverse events was broadly similar in the GH-GH and Placebo-GH groups (97% and 89%, respectively), the incidence of treatment-related events was higher in the GH-GH group (83% vs 42% in the Placebo-GH group). Most adverse events in both treatment groups were of mild or moderate severity and not clinically significant. The incidences of oedema and cases of high IGF-I during the IGF-I level-adjusted treatment regimen were lower than those during the preceding fixed dose titration. CONCLUSION: ***Long-term GH replacement therapy was well tolerated in Japanese adults with GHD. GH treatment maintained the improvements in body composition and lipid profiles in the patients previously treated in the double-blind study (GH-GH group) and improved these parameters in previously untreated patients (Placebo-GH group). Individualised GH administration based on IGF-I levels was well-tolerated and effective.*** *PMID: 18282776*

Cianfarani S, Tondinelli T, Spadoni GL, Scire G, Boemi S, Boscherini B. Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? Clin Endocrinol (Oxf). 2002 Aug;57(2):161-7.

OBJECTIVE: The diagnosis of GH insufficiency (GHI) in childhood is not straightforward. Our aim was to test the sensitivity and specificity of height velocity (HV), IGF-I, IGFBP-3 and GH stimulation tests alone or in combination in the diagnosis of GHI. DESIGN: A retrospective review of patients with GHI and idiopathic short stature (ISS) diagnosed in our centre and followed up to the completion of linear growth. PATIENTS: Thirty-three GHI children and 56 children with ISS were evaluated. GHI diagnosis was based on fulfilment of anthropometric, endocrine and neuroradiological criteria: stature < or = -2 z-score, delayed bone age (at least 1 year), GH peak response to at least two different provocative tests < 10 micro g/l (20 mU/l), brain MRI positive for hypothalamus-pituitary abnormalities, catch-up growth during the first year of GH replacement therapy > or = 75th centile, peak GH response to a third provocative test after growth completion < 10 micro g/l (20 mU/l). Children with anthropometry resembling that of GHI but with peak GH responses > 10 micro g/l (20 mU/l) were diagnosed as ISS. MEASUREMENTS: All subjects underwent standard anthropometry. GH secretory status was assessed by clonidine, arginine and GHRH plus arginine stimulation tests. IGF-I and IGFBP-3 circulating levels were measured by immunoradiometric assay (IRMA). The following cut-off values were chosen to discriminate between GHI and nonGHI short children: HV < 25th centile over the 6-12 months prior to the initiation of GH therapy, peak GH responses < 10 or < 7 micro g/l (< 20 or < 14 mU/l) and IGF-I and IGFBP-3-values < -1.9 z-score. Sensitivity (true positive ratio) and specificity (true negative ratio) were evaluated. RESULTS: Taking 10 micro g/l (20 mU/l) as the cut-off value, sensitivity was 100% and specificity 57% for GH provocative tests, whereas taking 7 as the cut-off value, sensitivity was 66% and specificity rose to 78%. Sensitivity was 73% for IGF-I and 30% for IGFBP-3 measurement, whilst specificity was 95% for IGF-I and 98% for IGFBP-3 evaluation. HV assessment revealed a sensitivity of 82% and a specificity of 43%. ***When HV and IGF-I evaluations were used in combination, sensitivity reached 95% and specificity 96%. When both HV and IGF-I are normal (26% of our subjects) GHI may be ruled out, whereas when both the indices are subnormal (23%) GHI is so highly likely that the child may undergo only one GH provocative test and brain MRI and, thereafter, may begin GH therapy without any further test.*** *In case of discrepancy, when IGF-I is normal and HV < 25th centile (44% of children), due to the relatively low sensitivity of IGF-I assessment and low specificity of HV, the patient should undergo GH tests and brain MRI. Finally, in the rare case of HV > 25th centile and subnormal IGF-I-values (7%), due to the high specificity of IGF-I measurement, the child should undergo one provocative test and brain MRI for the high suspicion of GHI. CONCLUSIONS:* ***Our results suggest that a simple assessment of HV and basal IGF-I may exclude or, in association with only one stimulation test, confirm the diagnosis of GH insufficiency in more than half of patients with short stature.***

Cittadini A, Grossman JD, Napoli R, et al. Growth hormone attenuates early left ventricular remodeling and improves cardiac function in rats with large myocardial infarction. J Am Coll Cardiol 1997;29:1109-16.

Colao A, Di Somma C, Filippella M, Rota F, Pivonello R, Orio F, Vitale G, Lombardi G. Insulin-like growth factor-1 deficiency determines increased intima-media thickness at common carotid arteries in adult patients with growth hormone deficiency. Clin Endocrinol (Oxf). 2004 Sep;61(3):360-6.

OBJECTIVE: To investigate the role of IGF-1 on intima-media thickness (IMT) at common carotid arteries by Doppler ultrasonography. SUBJECTS: Thirty-nine patients (17 women, 22 men, aged 25-70 years) with severe GH deficiency (GHD), 19 with normal and 20 with low IGF-1 levels, and 39 sex-, age- and body mass index (BMI)-matched healthy controls. RESULTS: Patients with GHD showed abnormalities in lipid profile, and increased fibrinogen levels, mean IMT (0.88 +/- 0.26 vs. 0.69 +/- 0.14 mm, P < 0.001), and systolic and diastolic peak velocity (P < 0.001) compared to controls. Eight patients (18%) and one control (2.1%, P = 0.04) had well-defined plaques. In controls, but not in patients with GHD, mean carotid IMT was correlated with age (r = 0.78, P < 0.001). ***In both controls (r = -0.82; P < 0.0001) and patients with GHD (r = -0.84, P < 0.0001), serum IGF-1 levels were inversely correlated with mean IMT at common carotid arteries.*** *At the stepwise multiple regression, the variables most significantly related to IMT in GH-deficient patients were total cholesterol levels (t = 5.2, P < 0.001), followed by disease duration (t = 2.4, P = 0.02), while* ***in controls the variables most significantly related to IMT were IGF-1 levels (t = -9.9, P < 0.001), followed by low density lipoprotein (LDL)-cholesterol levels*** *(t = -2.3, P = 0.02). Compared to patients with normal IGF-1 levels, those with* ***low IGF-1 levels had lower high density lipoprotein (HDL)-cholesterol levels (1.0 +/- 0.2 vs. 1.3 +/- 0.2 mmol/l, P = 0.0002), and higher glucose (54.3 +/- 6.1 vs. 48.9 +/- 5.9 mmol/l, P = 0.008), insulin (25.2 +/- 6.8 vs. 18.8 +/- 6.0 mUl/l, P = 0.004), total cholesterol (7.1 +/- 1.1 vs. 4.9 +/- 0.6 mmol/l, P < 0.0001), total/HDL-cholesterol ratio (7.2 +/- 1.8 vs. 3.9 +/- 0.7, P < 0.0001), fibrinogen levels (319.8 +/- 56.9 vs. 241.8 +/- 53.0 mg/dl, P < 0.0001) and mean IMT at common carotid arteries (1.05 +/- 0.25 vs. 0.69 +/- 0.07 mm, P < 0.0001).*** *Atherosclerotic plaques were found only in GH-deficient patients with low IGF-1 levels. CONCLUSIONS:* ***GH-deficient patients have alterations in lipid profile with an increase in the total/HDL-cholesterol ratio, which is an index of increased cardiovascular risk, but only patients with IGF-1 deficiency have increased IMT.***

Colao A, Di Somma C, Cascella T, Pivonello R, Vitale G, Grasso LF, Lombardi G, Savastano S. Relationships between serum IGF1 levels, blood pressure, and glucose tolerance: an observational, exploratory study in 404 subjects. Eur J Endocrinol. 2008 Oct;159(4):389-97.

BACKGROUND: In the general population, low IGF1 has been associated with higher prevalence of cardiovascular disease and mortality. OBJECTIVE: To investigate the relationships between IGF1 levels, blood pressure (BP), and glucose tolerance (GT). SUBJECTS: Four-hundred and four subjects (200 men aged 18-80 years). Exclusion criteria: personal history of pituitary or cardiovascular diseases; previous or current treatments with drugs interfering with BP, GT, or lipids, corticosteroids (>2 weeks), estrogens, or testosterone (>12 weeks); smoking of >15 cigarettes/day and alcohol abuse (>3 glasses of wine/day). RESULTS: Two hundred and ninety-six had normal BP (73.3%), 86 had mild (21.3%), and 22 had severe (5.4%) hypertension; 322 had normal GT (NGT (79.7%)), 53 had impaired glucose tolerance (IGT (13.1%)), 29 had diabetes mellitus (7.2%). ***Normotensive subjects had significantly higher IGF1 levels (0.11+/-0.94 SDS) than those with mild (-0.62+/-1.16 SDS, P<0.0001) or severe (-1.01+/-1.07 SDS, P<0.0001) hypertension. IGF1 SDS (t=-3.41, P=0.001) independently predicted systolic and diastolic BP (t=-2.77, P=0.006) values.*** *NGT subjects had significantly higher IGF1 levels (0.13+/-0.90 SDS) than those with IGT (-0.86+/-1.14 SDS, P<0.0001) or diabetes mellitus (-1.31+/-1.13 SDS, P<0.0001). IGF1 SDS independently predicted fasting glucose (t=-3.49, P=0.0005) and homeostatic model assessment (HOMA)-R (t=-2.15, P=0.033) but not insulin (t=-1.92, P=0.055) and HOMA-beta (t=-0.19, P=0.85). CONCLUSION:* ***IGF1 levels in***

the low normal range are associated with hypertension and diabetes in subjects without pituitary and cardiovascular diseases. *PMID: 18603571*

Colao A, Di Somma C, Savastano S, Rota F, Savanelli MC, Aimaretti G, Lombardi G. A reappraisal of diagnosing GH deficiency in adults: role of gender, age, waist circumference, and body mass index. J Clin Endocrinol Metab. 2009 Nov;94(11):4414-22.

OBJECTIVE: The objective of the study was to reevaluate the diagnostic accuracy of GH peak after GHRH plus arginine test (GHRH+ARG) according to patients' age, body mass index (BMI), and waist circumference to diagnose GH deficiency (GHD). OUTCOME MEASURES: GH peak after GHRH+ARG and IGF-I levels reported as sd score. SUBJECTS: Subjects included 408 controls (218 women, 190 men, aged 15-80 yr) and 374 patients with hypopituitarism (167 women, 207 men, aged 16-83 yr). RESULTS: ***In the (elderly) healthy subjects 15-25 yr old (young), 26-65 yr old (adults) and older than 65 yr, GH cutoffs were 15.6, 11.7, and 8.5 microg/liter,*** *11.8, 8.1, and 5.5 microg/liter, and 9.2, 6.1, and 4.0 microg/liter, respectively, in the lean, overweight, and obese subjects. Waist circumference was the best predictor of GH peak (t = -7.6, P < 0.0001) followed by BMI (t = -6.7, P < 0.0001) and age (t = -5.7, P < 0.0001). Based on the old (<9.1 microg/liter) and new GH cutoff, 286 (76.5%) and 276 (73.8%) of 374 hypopituitary patients had severe GHD. The receiving-operator characteristic analysis showed GH cutoffs in line with the third percentile or slightly higher results so that the prevalence of GHD increased to 90.1%. CONCLUSIONS:* ***The results of the current study show that waist circumference and BMI are the strongest predictors of GH peak after GHRH+ARG followed by age.*** *However, the old cutoff value of 9.0 microg/liter was in line with the new cutoffs in 95% of patients. PMID: 19773395*

Conti E, Carrozza C, Capoluongo E, Volpe M, Crea F, Zuppi C, Andreotti F. Insulin-like growth factor-1 as a vascular protective factor. Circulation. 2004 Oct 12;110(15):2260-5.

Conclusions: Until recently, IGF-1 was considered a mediator of vascular disease. ***Increasing evidence indicates, instead, that IGF-1 protects against endothelial dysfunction, atherosclerotic plaque development, the metabolic syndrome, clinical instability, and ischemic myocardial damage.*** *Some of these effects are related to the induction, by IGF-1, of constitutive NO production. Experimental and clinical data suggest that signaling from ischemic tissues causes changes in IGF-1's regulatory system, including compensatory increases in PAPP-A, presumably aimed at expanding tissue IGF-1 concentrations. Measurement of circulating IGF-1 may add valuable information to the current assessment of cardiovascular risk. Individuals with traditional cardiovascular risk factors but normal or elevated IGF-1 may be protected, at least in part, against disease. With reduced IGF-1 levels, instead, vascular risk factors may fully exert their detrimental effects, through unopposed endothelial dysfunction, endothelial apoptosis, and development of unstable plaques.* ***Those with markedly reduced IGF-1 might develop disease even in the absence of traditional risk factors. It is worth noting that healthy centenarians have high serum IGF-1 concentrations.***

Coschigano KT; Clemmons D; Bellush LL; Kopchick JJ Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. Endocrinology 2000 Jul;141(7):2608-13.

GH has many biological roles, including promotion of growth. Most, if not all, of its roles are achieved through interaction with its receptor. We chose to study the effects of loss of GH signaling on growth and aging in a mouse model for Laron Syndrome (LS) in which the GHR/BP gene has been disrupted. We observed that mice homozygous for the disruption (-/-) were significantly smaller than normal wild-type (+/+) mice as well as mice heterozygous for the disruption, even at 1.5 yr of age. IGF-I levels were also significantly lower in the -/- mice and remained low as the mice aged. IGFBP-3 levels were severely reduced in the -/- mice, whereas IGFBP-1, -2, and -4 levels remained unchanged. Finally, the -/- mice lived significantly longer than +/+ and +/- mice. The latter result contradicts the anti-aging GH data and suggests the need for further analysis of GH and aging.

Cowell CT, Wuster C. The effects of growth hormone deficiency and growth hormone replacement therapy on bone. A meeting report. Horm Res 2000;54 Suppl 1:68-74.

Christ ER, Carroll PV Russell-Jones DL, Sonksen PH. The consequences of growth hormone deficiency in adulthood, and the effects of growth hormone replacement. Schweiz Med Wochenschr 1997 Aug 30;127(35):1440-9.

The availability of recombinant human growth hormone (GH) has resulted in investigation of the role of GH in adulthood and the effects of GH replacement in the GH-deficient adult. These studies have led to the recognition of a specific syndrome of GH-deficiency, characterized by symptoms, signs and investigative findings. Adults with long-standing growth hormone deficiency are often overweight, have altered body composition, with reduced lean body mass (LBM), increased fat mass (FM), reduced total body water and reduced bone mass. In addition, there is reduced physical and cardiac performance, altered substrate metabolism and an abnormal lipid profile predisposing to the development of cardiovascular disease. Adults with GH deficiency report reduced psychological well-being and quality of life. These changes may contribute to the morbidity and premature mortality observed in hypopituitary adults on conventional replacement therapy. GH treatment restores LBM, reduces FM, increases total body water and increases bone mass. Following GH therapy, increases are recorded in exercise capacity and protein synthesis, and "favourable" alterations occur in plasma lipids. In addition, psychological well-being and quality of life improve with replacement therapy. GH is well tolerated; adverse effects are largely related to fluid retention and respond to dose adjustment. It is likely that GH replacement will become standard therapy for the hypopituitary adult in the near future. The benefits of GH replacement in the GH-deficient adult have been unequivocally demonstrated in studies lasting up to 3 years. The results of longer term studies are awaited to determine whether these benefits are sustained over a lifetime.

Cummings MH, Christ E, Umpleby AM, Albany E, Wierzbicki A, Lumb PJ, Sonksen PH, Russell-Jones DL. Abnormalities of very low density lipoprotein apolipoprotein B-100 metabolism contribute to the dyslipidaemia of adult growth hormone deficiency. J Clin Endocrinol Metab 1997 Jun;82(6):2010-3.

Davies JS, Obuobie K, Smith J, Rees DA, Furlong A, Davies N, Evans LM, Scanlon MF. A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. Clin Endocrinol (Oxf). 2000 Mar;52(3):295-303.

OBJECTIVES: Adult GH deficiency (GHD) is associated with profound alterations in body composition, lipid profiles and quality of life which frequently improve after GH therapy. However, the beneficial effects of treatment are not derived by all and consequently some scepticism persists with regard to the use of GH therapy in adults. We assessed whether a 3-month therapeutic assessment with GH therapy could be used to determine which GHD adults should be treated over the longer term. We also assessed the continued prescription of GH by general practitioners (GPs) following the initial therapeutic assessment. DESIGN: A three month open therapeutic trial of GH in GHD adults. Patients were treated with GH at an initial dose of 0.01 iU/kg/d, increased after 1 month to 0.015 iU/kg/d for males ***(0.375mg/d for 75kg male-HHL)*** *and 0.02 iU/kg/d for females. After completion of the three months the continued prescription of GH by the GPs was assessed. PATIENTS: All adult GHD patients were considered for GH therapy. Thirty-nine GHD adults wanted GH therapy (group 1) and their baseline characteristics such as age, duration of GHD, and IGF-1 concentration were compared with 24 subjects who declined to receive GH (group 2). MEASUREMENTS: Measurements of body composition using bioelectrical impedance analysis, lipids and quality of life measured using a dedicated questionnaire were made before and after GH therapy. The response of the general practitioners to continued GH therapy after the initial therapeutic assessment was also noted. RESULTS: Compared with subjects who declined GH therapy (group 2), subjects of group 1 were younger (46.4 +/- 14.4 vs. 54.2 +/- 15.7 years, P < 0.05) and had lower peak GH responses to provocative testing (1.4 +/- 2.1 vs. 2.9 +/- 2.7 mU/l, P <*

0.001), though there were no differences between IGF-1 concentration (11.7 +/- 6.2 vs. 14. 2 +/- 7.9 nmol/l). ***Following three months of GH therapy, there were significant improvements in all measured parameters including increased free fat mass (50.2 vs. 52.4 kg, P < 0.005) and total body water (37 vs. 38.7 l, P < 0.005), reduced fat mass (31.6 vs. 29.8 kg, P < 0.005), reduced AGHDA score (7 vs. 4, P < 0.001) and reduced cholesterol (6.3 vs. 5.8 mmol/l, P < 0.001), LDL (4 vs. 3.33 mmol/l, P < 0.001) and cholesterol/HDL ratio (5.57 vs. 4.67, P < 0.001). IGF-1 concentrations were significantly increased following treatment (12 vs. 32.4 nmol/l)(91.8 vs. 248ng/ml-HHL).*** *Six subjects decided to discontinue GH therapy, 2 before the end of the study due to potential drug-related side-effects and 4 subjects derived no benefit from treatment. Despite the demonstrable benefits of treatment for the remaining 33 GHD adults, 6 GPs refused to continue to prescribe GH therapy for reasons of lack of familiarity with the drug or advice from their health authority. CONCLUSION: Patients who wanted GH therapy were usually younger and more severely GHD than counterparts who elect not to be treated. However, a therapeutic trial of GH therapy is required to distinguish those subjects who derive benefit from treatment. We have shown that three months of low dose GH therapy is a sufficient period to elicit significant beneficial responses in quality of life, body composition parameters and lipids for the majority of patients and appears to be a sufficient period for patients to decide whether they want longer term therapy. The initial therapeutic trial also provides the objective evidence for the general practitioners to decide upon the continued prescription of therapy. Despite the positive evidence provided by this study, a small minority of general practitioners still refuse to prescribe GH therapy.*

Degerblad M, Elgindy N, Hall K, Sjoberg HE, Thoren M. Potent effect of recombinant growth hormone on bone mineral density and body composition in adults with panhypopituitarism. Acta Endocrinol (Copenh). 1992 May;126(5):387-93.

Six patients (21-50 years) with growth hormone deficiency and panhypopituitarism were given recombinant growth hormone, somatotropin, 0.04-0.1 U.kg.body wt-1.day-1(2.5U/d minimum--high dose-HHL), for 12 months. All patients reported improved well-being with increased working capacity. Bone mineral density, as measured by single photon absorptiometry at two sites on the forearm, showed increased values in 5/6 patients after 12 months when measured at the most distal site (predominantly trabecular bone) and in 4/6 at the more proximal site (predominantly cortical bone). Five patients continued therapy for an additional year and after 18 months a significant increase in bone mineral density was seen at both the distal and proximal sites. The mean annual increase in bone mineral density was 12.0 +/- 0.6 (SEM)% and 3.8 +/- 1.3% at the distal and proximal sites, respectively. In a growth hormone deficient control group without growth hormone therapy, the corresponding values were -2.4 +/- 0.6% and -1.9 +/- 0.4%, respectively. Lean body mass, estimated anthropometrically, increased significantly after 12 months and total body potassium, measured by whole body counting technique, increased in 4/6 patients. During growth hormone treatment, the IGF-1 values were above the mean values for age and 50% of the values were above the mean +2 SD. B-glucose, P-insulin, serum IGF-2, procollagen-III peptide and phosphate increased and urea, creatinine and IGF-binding protein-1 decreased during treatment. ***The beneficial effects of growth hormone substitution, especially on bone mineral density, indicate that growth hormone substitution should be considered in all patients with hypopituitarism and growth hormone deficiency, irrespective of age. (The 64,000 question: Who is deficient? Isn't everybody with IGF-1 levels less than 200ng/ml?-HHL)***

Donahue AN, Aschner M, Lash LH, Syversen T, Sonntag WE. Growth hormone administration to aged animals reduces disulfide glutathione levels in hippocampus. Mech Ageing Dev. 2006 Jan;127(1):57-63. Epub 2005 Oct 21.

Systemic growth hormone (GH) and insulin-like growth factor-1 (IGF-1), potent anabolic hormones, decrease with age. ***In humans and animal models, administration of growth hormone or IGF-1 to aged subjects improves learning and memory, suggesting that the age-related decline in cognitive performance results, in part, from peripheral GH/IGF-1 deficiency.*** *However, the cellular mechanisms by which GH/IGF-1 effect cognitive function are unknown. We propose that*

the effects of these hormones may be mediated by increasing cellular redox potential resulting in reduced oxidative stress. Because the most abundant endogenous antioxidant is glutathione (GSH), we assessed GSH and disulfide glutathione (GSSH) levels in hippocampus and frontal cortex of young (4-month-old) and aged (30-month-old) male Fisher 344xBrown Norway rats treated with porcine growth hormone (200microg/animal, twice/daily) or vehicle. We report that hippocampal levels of GSSG increase with age (0.54+/-0.08 to 1.55+/-0.24nmolGSSG/mgprotein, p<0.05) and growth hormone treatment ameliorates both the age-related rise in GSSG (1.55+/-0.24 to 0.87+/-0.24nmolGSSG/mgprotein, p<0.05) and the decline in GSH/GSSG ratios. Analysis of GSSG reductase activity in aged animals indicated no effect of either age or growth hormone treatment (p=0.81). Although similar age-related increases in GSSG and decreases in GSH/GSSG ratios were evident in frontal cortex, growth hormone had no effect. Subsequently, we assessed whether the effects of age and growth hormone treatment result from modulating trace metal accumulation. Thirteen metals were analyzed in hippocampus and frontal cortex by inductive coupled plasma mass spectrometry. Aluminum, copper, iron, manganese and zinc levels increased with age (p<0.05 each) but growth hormone replacement had no effect on metal accumulation. ***Our results indicate that growth hormone replacement attenuates the age-related increase in oxidative stress in hippocampus without effects on glutathione reductase or trace metal accumulation. We conclude that the age-related decline in circulating growth hormone and IGF-1 contribute to increased oxidative stress in hippocampus with age.***

Elgzyri T, Castenfors J, Hagg E, Backman C, Thoren M, Bramnert M. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. Clin Endocrinol (Oxf). 2004 Jul;61(1):113-22.

OBJECTIVES: To assess effects of GH replacement therapy on cardiac structure and function, exercise capacity as well as serum lipids in elderly patients with GH deficiency (GHD). PATIENTS AND METHODS: Thirty-one patients (six females, 25 males), aged 60-79 years (mean 68 years) with GHD on stable cortisone and thyroxine substitution were studied. All men with gonadotropin deficiency had testosterone and one woman had oestrogen replacement. They were randomized in a double-blind manner to GH or placebo treatment for 6 months, followed by another 12 months GH (Humatrope, Eli Lilly & Co, Uppsala, Sweden). GH dose was 0.017 mg/kg/week for 1 month and then 0.033 mg/kg/week divided into daily subcutaneous injections at bedtime. Echocardiography, exercise capacity tests and serum lipid measurements were performed at 0, 6, 12 and 18 months. RESULTS: During the 6-month placebo-controlled period there were no significant changes in the placebo group, but in the GH-treated group there was a significant increase in IGF-I to normal levels for age, with median IGF-I from 6.9 to 18.5 nmol/l, ***increase in resting heart rate and maximal working capacity.*** *During the open GH study, IGF-I increased from 8.7 to 19.2 nmol/l at 6 months and 18.8 nmol/l at 12 months (P </= 0.001). At 6 months, in the open GH study group, a minor decrease in aortic outflow tract integral (VTI) from 21.8 to 20.7 cm (P = 0.031) and an increase in heart rate at rest from 63 to 67 bpm (P = 0.017), heart rate at maximum exercise from 138 to 144 bpm (P = 0.005) and maximum load at exercise from 142 to 151 Watts (P = 0.014) were seen. These changes were temporary and returned at 12 months with no significant difference from baseline values.* ***Left ventricular dimensions and blood pressure showed no significant changes.*** *At 6 months, in the open GH study group, there was a significant decrease in serum low-density lipoprotein (LDL) cholesterol from 3.7 to 3.4 mmol/l (P = 0.006), a decrease in LDL/HDL ratio from 3.4 to 3.1 (P = 0.036) and a decrease in serum total cholesterol from 5.6 to 5.3 mmol/l (P = 0.036).* ***At 12 months, serum lipids showed same changes with a significant decrease in serum LDL cholesterol (P = 0.0008), in LDL/HDL ratio (P = 0.0005) and in serum total cholesterol (P = 0.049).*** *Serum HDL cholesterol showed no significant change at 6 months, at 12 months a significant increase was seen from 1.2 to 1.4 mmol/l (P = 0.007). There were no significant changes in serum triglycerides. CONCLUSIONS: GH substitution to elderly patients with GHD caused only a transient increase in heart rate. At the end of the 12 months there were no significant changes on cardiac noninvasive structural and functional parameters. Maximal working capacity transiently*

improved. Thus, the therapy was safe without negative effects on cardiac structural and functional noninvasive parameters. Lipid profiles improved with reduction of serum LDL cholesterol accompanied by significant improvement of LDL/HDL ratio and serum HDL cholesterol after 12 months treatment.

Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Sacca L. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med 1996 Mar 28;334(13):809-14.

Federico G, Street ME, Maghnie M, Caruso-Nicoletti M, Loche S, Bertelloni S, Cianfarani S; Study Group on Physiopathology of growth processes; Council of ISPED. Assessment of serum IGF-I concentrations in the diagnosis of isolated childhood-onset GH deficiency: a proposal of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). J Endocrinol Invest. 2006 Sep;29(8):732-7.

The diagnosis of GH deficiency (GHD) is based on the measurement of peak GH responses to pharmacological stimuli. Pharmacological stimuli, however, lack precision, accuracy, are not reproducible, are invasive, non-physiological and some may even be hazardous. Furthermore, different GH commercial assays used to measure GH in serum yield results that may differ considerably. In contrast to GH, IGF-I can be measured on a single, randomly-obtained blood sample. A review of the available data indicates that IGF-I measurement in the diagnosis of childhood-onset isolated GHD has a specificity of up to 100%, with a sensitivity ranging from about 70 to 90%. We suggest an algorithm in which circulating levels of IGF-I together with the evaluation of auxological data, such as growth rate and growth, may be used to assess the likelihood of GHD in pre-pubertal children. ***(Notice that pediatric endocrinologists are abandoning the unreliable stimulation tests that are still being touted as necessary to diagnose GH deficiency in adults! Why not use the IGF-1 in adults also?—HHL)***

Florakis D, Hung V, Kaltsas G, Coyte D, Jenkins PJ, Chew SL, Grossman AB, Besser GM, Monson JP. Sustained reduction in circulating cholesterol in adult hypopituitary patients given low dose titrated growth hormone replacement therapy: a two year study. Clin Endocrinol (Oxf). 2000 Oct;53(4):453-9.

OBJECTIVE: To study the effects of short (6 months) and longer-term (up to 24 months) growth hormone (GH) replacement therapy using a dose titration regimen, on lipid and glucose metabolism in GH-deficient, hypopituitary adults. DESIGN: On-going open study of GH treatment up to 24 months. Measurements were performed at baseline and at 6, 12, 18 months and 2 years during therapy (data shown at 6 months and 2 years only). Using a dose titration regimen the median GH dose used to achieve and maintain IGF-I levels above the median, but below the upper limit of the age-related reference range (median IGF-I 202.5 microg/l, range 76-397 microg/l), was 1.2 IU daily (range 0.4-3 IU) [0.8 IU/day, males; 1.6 IU/day, females]. PATIENTS: Ninety GH-deficient hypopituitary adults (54 female, median age 48 years, range 19-79 years) entered the study and 24 (14 female, median age 45 years, range 32-79 years) have concluded the 2 year period of assessment. MEASUREMENTS: Body mass index (BMI), waist and hip circumference ratio (WHR), fasting lipids, glucose and glycated haemoglobin (HbA1c) levels were measured at 6 month intervals during GH therapy. RESULTS: Using the dose titration regimen, compared to pretreatment values, total and low density lipoprotein (LDL)-cholesterol levels were significantly lower at 6 months (mean +/- SEM, 5.61+/-0.1 vs. 5.25+/-0.1, and 3.85+/-0.19 vs. 3.43+/-0.26, respectively, P<0.05), and were maintained throughout the study. Male patients had significantly lower pretreatment total and LDL cholesterol levels than females (mean +/- SEM, 5.33+/-0.16 mmol/l vs. 5.7+/-0.12 mmol/l and 3.8+/-0.23 mmol/l vs. 3.92+/-0.29 mmol/l, respectively, P< 0.05). A decrease in total cholesterol was confined to patients with pretreatment total cholesterol levels above 5.8 mmol/l; patients with the highest pretreatment cholesterol levels (> 6.4 mmol/l) obtained the greatest cholesterol reduction (mean +/- SEM, 7.13 +/- 0.14 mmol/l vs. 5.76+/-0.31 mmol/l,

P<0.05). ***A cholesterol-lowering effect of GH therapy was evident in patients who had elevated pre-GH total cholesterol levels even if they were already receiving and continuing lipid lowering medication (mean +/- SEM, 5.62+/-0.22 vs. 5.03+/-0.285, P<0.05).*** *A modest increment in high density lipoprotein (HDL)-cholesterol was evident at 18 months but there was no significant change in triglycerides at any time point. Fasting plasma glucose increased significantly at 6 months but remained within the reference range. Glycated haemoglobin increased significantly at 6 months and was maintained throughout the study; one patient developed frank diabetes mellitus while receiving treatment. There was a weak but significant correlation between the increment in glycated haemoglobin and pretreatment BMI (r = + 0.215, P<0.05). CONCLUSION: The effect of GH on lowering total and low density lipoprotein-cholesterol is more prominent in patients with higher pretreatment cholesterol levels and is evident even in patients receiving other lipid-lowering medication. A modest increment in mean fasting glucose (within the reference range) and mean glycated haemoglobin persisted throughout the study. One patient developed diabetes mellitus. A GH replacement regimen using low dose and careful titration to avoid elevated IGF-I levels and adverse effects is associated with sustained beneficial effects on circulating lipids.*

Genth-Zotz S, Zotz R, Geil S, Voigtlander T, Meyer J, Darius H. Recombinant growth hormone therapy in patients with ischemic cardiomyopathy. Circulation 1999;99:18-21.

Gibney J, Wallace JD, et al The effects of 10 years of Recombinant human growth hormone (GH) in adult GH-deficient patients.

Compared to a group of 11 matched GH-deficient controls during the treatment period, GH-treated group's lean body mass increased, LDL decreased, carotid intimal thickness decreased and psychological well-being improved.

Gilchrist FJ, Murray RD, Shalet SM. The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. Clin Endocrinol (Oxf). 2002 Sep;57(3):363-70.

BACKGROUND: Quality of life (QoL) is reduced in GH-deficient adults compared with the normal population. Further support for the role of GH in the maintenance of QoL is derived from short-term studies of GH replacement in severely GH-deficient adults; these have predominantly reported beneficial effects, although the degree of improvement has often been modest. To date, however, there are few data to demonstrate whether this beneficial effect on QoL is maintained in the long term. PATIENTS AND METHODS: This study consisted of the follow-up of 85 GH-deficient adults who completed the Nottingham Health Profile (NHP) and the Psychological General Well-Being Schedule (PGWB) self-rating questionnaires in 1992, as part of a 12-month double-blind randomized study of GH replacement. In 2001 we attempted to contact all 85 patients and asked them to complete the two questionnaires again. Follow-up data were obtained in 61 patients. The findings were analysed according to whether the individual had received GH continuously since completion of the initial study, received no further GH replacement, or received GH replacement for only part of the intervening time. Both the NHP and the PGWB give a total score and subsection scores for six specific areas of QoL. A high score correlates with increased morbidity in the NHP, and with reduced morbidity in the PGWB. RESULTS: Fifty-nine patients completed the NHP at both time points. The patients who continued GH (n = 17) had significantly greater morbidity at baseline than patients who opted to discontinue therapy (n = 27), as reflected by the higher scores overall (5.7 +/- 4.0 vs. 2.8 +/- 3.5; P = 0.01) and in the energy subsection (47.0 +/- 34.7 vs. 13.2 +/- 28.6; P < 0.001). ***Over the study period energy levels improved in the patients who remained on GH therapy (47.0 +/- 34.7 vs. 25.7 +/- 31.0; P = 0.04). By contrast, a deterioration in the physical mobility subsection (2.4 +/- 5.4 vs. 8.2 +/- 16.7; P = 0.04) occurred in the patients who did not continue GH therapy, and no change occurred in the energy subsection.*** *In the 36 patients who completed the PGWB significant differences were observed at baseline between patients who received GH replacement continuously (n = 10) and those who discontinued therapy (n = 21) in the overall score (67.2 +/- 14.1 vs. 86.8 +/- 14.7; P = 0.001); and in the subsections for anxiety (P =*

0.04), depression (P = 0.04), well-being (P = 0.001), self-control (P = 0.04) and vitality (P < 0.001); the greater morbidity at baseline being observed in the patients who continued GH replacement. ***In the patients receiving GH continuously for 9 years the vitality subsection score improved significantly (7.7 +/- 2.4 vs. 12.5 +/- 3.2; P = 0.003), whereas no change in vitality score occurred in patients who did not continue GH therapy.*** *The change in the energy subsection of the NHP and vitality subsection of the PGWB over the 9 years of the study were significantly different between the patients who opted to continue GH replacement and those who discontinued therapy (P = 0.008 and P < 0.001, respectively). CONCLUSION:* ***During this 9-year study, small but significant declines in health were observed in GH-deficient adults who remained untreated. By contrast, the patients who received GH continuously experienced improvements in energy levels while all other areas of QoL were maintained. The beneficial effects of GH on QoL are therefore maintained with long-term GH replacement and obviate the reduction in QoL seen over time in untreated GH-deficient adults.***

Giavoli C, Porretti S, Ronchi CL, Cappiello V, Ferrante E, Orsi E, Arosio M, Beck-Peccoz P. Long-term monitoring of insulin sensitivity in growth hormone-deficient adults on substitutive recombinant human growth hormone therapy. Metabolism. 2004 Jun;53(6):740-3.

Since the effects of recombinant human growth hormone (rhGH) replacement therapy on glucose metabolism are still a matter of debate, the aim of the present study was to evaluate the impact of long-term rhGH treatment on insulin sensitivity. Simple indices of insulin resistance (IR) and insulin sensitivity (IS), based on fasting glucose and insulin, such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin check index (QUICKI), were used to estimate the degree of IR and IS in 20 normoglycemic patients (11 men and 9 women; mean age, 44 +/- 14 years) with severe adult-onset GH deficiency (GHD). Measurements were determined at baseline and after 1 and 5 years of continuous rhGH therapy. Basal values were compared to those obtained in 20 healthy sex- and age-matched controls. Starting rhGH dose ranged from 3 to 8 microg/kg/d in keeping with sex and age, then doses were titrated according to insulin-like growth factor-I (IGF-I) levels. At baseline all patients had low IGF-I levels (10 +/- 5.4 nmol/L), high body mas index (BMI; 27.5 +/- 4 kg/m(2)), and elevated body fat percentage (BF%; 31.8 +/- 9.6). Fasting glucose and insulin levels, as well as HOMA-IR and QUICKI, did not differ significantly from those recorded in the control group. After 1 year of rhGH replacement therapy, normalization in IGF-I levels and a significant reduction in BF% were observed (P <.001), and these effects were maintained after 5 years of treatment. ***Fasting glucose increased from 79 +/- 10 to 87 +/- 13, and 87 +/- 12 mg/dL (P <.05) after 1 and 5 years of therapy, respectively. Fasting insulin significantly increased after 1 year, without further modifications in the long-term follow-up. HOMA-IR significantly increased from 2.1 +/- 1.7 to 2.5 +/- 1.7 (P <.05) after 1 year, then decreased to 2.3 +/- 1.5 (P = not significant [NS] v basal) after 5 years.*** *A specular decrease in QUICKI from 0.37 +/- 0.05 to 0.34 +/- 0.03 (P <.01) occurred after 1 year, with a trend to increase (0.35 +/- 0.04; P = NS v basal) after 5 years. No patient developed impaired fasting glucose. In conclusion, rhGH therapy determined an increase in fasting glucose and insulin levels, causing in the short-term period a worsening of IS. The sustained reduction in BF%, without further deterioration of IS, suggests that long-term beneficial effects on body composition may overcome the negative influence of GH on glucose metabolism. PMID: 15164321*

Giusti M, Meineri I, Malagamba D, Cuttica CM, Fattacciu G, Menichini U, Rasore E, Giordan G. Impact of recombinant human growth hormone treatment on psychological profiles in hypopituitarv patients with adult-onset growth hormone deficiency. Eur J Clin Invest 1998 Jan;28(1):13-9.

Goeddel DV, Heyneker HL, Hozumi T, et al. Direct expression in Escherichia coli of DNA sequence coding for human growth hormone. Nature 1979; 281:544-8.

Gotherstrom G, Bengtsson BA, Bosaeus I, Johannsson G, Svensson J. A Ten-Year, Prospective Study of the Metabolic Effects of Growth Hormone Replacement in Adults. J Clin Endocrinol Metab. 2007 Feb 6; [Epub ahead of print]

Context. Only a few studies have investigated the effects of growth hormone (GH) replacement in adults for more than 5 years. Objective/Design/Patients. In a prospective, open-label, single-center study, the effects of 10-year GH replacement were determined. Eighty-seven consecutive patients (52 men and 35 women), with a mean age of 44.1 (range 22-74) years with adult onset GH deficiency (GHD) were included. Results. The initial mean dose of GH (0.98 mg/day) was reduced during the study and at year ten was ***0.47 mg/day.*** *The mean insulin-like growth factor-I (IGF-I) SD score increased from -1.81 at baseline to 1.29 at study end. The absolute reduction in total body fat was transient. However, after correction for age and sex using a four-compartment model, the reduction in body fat was sustained during the 10-year study period. There was a sustained improvement in serum lipid profile and after 10 years, blood glycosylated hemoglobin (HbA1c) level was reduced. The treatment responses in IGF-I SD score, serum high density lipoprotein-cholesterol (HDL-C) level, and body composition as measured using dual energy X-ray absorptiometry (DEXA), were more marked in men whereas women had a more marked reduction in blood HbA1c level. Conclusion. The effect on the absolute amount of body fat was seen early and was transient, which could be due to the normal aging of the patients. The effects on metabolic indices were detected later, but they were sustained and even progressive throughout the study period.*

Gotherstrom G, Bengtsson BA, Bosaeus I, Johannsson G, Svensson J. Ten-year GH replacement increases bone mineral density in hypopituitary patients with adult onset GH deficiency. Eur J Endocrinol. 2007 Jan;156(1):55-64.

There are few studies that have determined the effects of long-term GH replacement on bone mineral density (BMD) in GH-deficient (GHD) adults. In this study, the effects of 10 years of GH replacement on BMD were assessed in 87 GHD adults using dual energy X-ray absorptiometry (DEXA). The results show that GH replacement induced a sustained increase in BMD at all the skeletal sites measured. INTRODUCTION: Little is known of the effect of more than 5 years of GH replacement therapy on bone metabolism in GHD adults. PATIENTS AND METHODS: In this prospective, open-label, single-center study, which included 87 consecutive adults (52 men and 35 women; mean age of 44.1 (range 22-74) years) with adulthood onset GHD, the effect of 10 years of GH replacement on BMD was determined. RESULTS: The mean initial dose of GH was 0.98 mg/day. The dose was gradually lowered and after 10 years the mean dose was 0.47 mg/day. The mean insulin-like growth factor-I (IGF-I) SDS increased from 1.81 at baseline to 1.29 at study end. The GH replacement induced a sustained increase in total, lumbar (L2-L4) and femur neck BMD, and bone mineral content (BMC) as measured by DEXA. The treatment response in IGF-I SDS was more marked in men, whereas women had a more marked increase in the total body BMC and the total body z-score. There was a tendency for women on estrogen treatment to have a larger increase in bone mass and density compared with women without estrogen replacement. CONCLUSIONS: ***Ten years of GH replacement in hypopituitary adults induced a sustained, and in some variables even a progressive, increase in bone mass and bone density. The study results also suggest that adequate estrogen replacement is needed in order to have an optimal response in BMD in GHD women.***

Hanaire-Broutin H, Sallerin-Caute B, Poncet MF, Tauber M, Bastide R, Chalé JJ, Rosenfeld R, Tauber JP. Effect of intraperitoneal insulin delivery on growth hormone binding protein, insulin-like growth factor (IGF)-I, and IGF-binding protein-3 in IDDM. Diabetologia. 1996 Dec;39(12):1498-504.

Low plasma insulin-like growth factor (IGF)-I despite high circulating growth hormone (GH) in insulin-dependent diabetes mellitus (IDDM) indicate a hepatic GH resistance. This state may be reflected by the reduction of the circulating GH binding protein (GHBP), corresponding to the extracellular domain of the GH receptor, and the reduction of insulin-like growth factor binding

protein (IGFBP)-3, major IGF-I binding protein, upregulated by GH. We carried out two studies. In the first, plasma GHBP activity was compared in patients with IDDM on continuous subcutaneous insulin infusion (CSII) or on conventional therapy and in healthy subjects. In the second study, the 18 patients on CSII at baseline were then treated by continuous intraperitoneal insulin infusion with an implantable pump (CPII) and prospectively studied for GH-IGF-I axis. Although HbA1c was lower in patients on CSII than in those on conventional therapy, GHBP was similarly reduced in both when compared to control subjects (10.2 +/- 0.8 and 11.6 +/- 0.9% vs 21.0 +/- 1.3, p < 0.01). CPII for 12 months resulted in: a slight and transient improvement in HbA1c (Time (T)0: 7.6 +/- 0.2%, T3: 7.1 +/- 0.2%, T12: 7.5 +/- 0.2%, p < 0.02), improvement in GHBP (T0: 10.2 +/- 0.8%, T12: 15.5 +/- 1.5, p < 0.0001), near-normalization of IGF-I (T0: 89.4 +/- 8.8 ng/ml, T12: 146.9 +/- 15.6, p < 0.002) and normalization of IGFBP-3 (T0: 1974 +/- 121 ng/ml, T12: 3534 +/- 305, p < 0.0001). ***The hepatic GH resistance profile in IDDM does not seem to be related to glycaemic control, but partly to insufficient portal insulinization. Intraperitoneal insulin delivery, allowing primary portal venous absorption, may influence GH sensitivity, and improve hepatic IGF-I and IGFBP-3 generation.*** *PMID: 8960832*

Hardin DS, Woo J, Butsch R, Huett B. Current prescribing practices and opinions about growth hormone therapy: results of a nationwide survey of paediatric endocrinologists. Clin Endocrinol (Oxf). 2007 Jan;66(1):85-94.

BACKGROUND: With the advent of several new treatment indications for recombinant hGH, endocrinologists are being asked to make some difficult decisions regarding eligibility for treatment. The purpose of this study was to summarize prevailing attitudes about GH diagnosis and treatment among paediatric endocrinologists. METHODS: We sent surveys to all active US members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) listed in the 2004-05 directory (excluding our own group of physicians). Thirty-eight per cent of the surveys were returned and 182 met eligibility for analysis. Surveys were divided into four parts: demographic data, answers reflecting current diagnosis practices for GH deficiency and treatment with GH, attitudes and clinical practice for the idiopathic short stature (ISS) diagnosis, and four case studies. Through a series of questions, we elicited the influence towards prescribing GH of current height, growth velocity, predicted height, pubertal progression and other variables. Results were entered into a Microsoft Access database and statistical evaluation was conducted. RESULTS: Eighty-eight per cent of respondents answered 'no' to the statement that there is good consensus on who should be treated with GH and ***over 90% answered 'no' to the statement that secretagogue testing was the best way to determine if a child would benefit from GH.*** *Factors listed by respondents as important for prescribing GH include: growth velocity less than the 25th percentile, target height less than the 5th percentile and pubertal stage greater than Tanner 2. Current height was also important; however, answers varied as to what height percentile indicated the need for treatment. When queried about prescribing practices for nonstraightforward cases, 62% of respondents answered that the cost of GH influenced their decision to treat, 55% responded that concerns of future unknown side-effects affected their decision and 37% noted family persistence influenced their decision. In response to queries about ISS, 82% answered that they were currently using the new indication and 69% answered that there was a need for the indication. The statement that short stature could be a disability received a 'yes' response from 78%. Answers to the four cases reflected lack of consensus, with one-third of all respondents answering that they would treat each case, one-third choosing to treat more than two of the cases and one-third treating less than two of the cases. CONCLUSION:* ***Endocrinologists differed in their answers about cause for treatment with GH but in general favoured use of poor growth velocity, poor target height and low IGF-1 levels as indications to treat a paediatric patient with GH. (Notice, they do not do, or pay much attention to GH-stimulation tests!—HHL)***

Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP; KIMS International Board; 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 Metab. 2001 Nov;86(11):5277-81.

The morbidity associated with GH deficiency (GHD) in adults is now well established. Furthermore, many controlled clinical trials have demonstrated the efficacy of GH replacement therapy. The aim of the present study was to determine whether the effects of GH replacement in adults are reflected in a reduced use of healthcare resources, in addition to improving quality of life (QoL). Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmacoepidemiological survey of hypopituitary adults with GHD, for 6 months before GH treatment and for 6-12 months after the start of treatment. Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. QoL (assessed using a disease-specific questionnaire, QoL-Assessment of GHD in Adults) and satisfaction with physical activity during leisure time were also assessed. ***For the total group (n = 304), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly (P < 0.05) after 12 months of GH therapy. Patients also needed less assistance with daily activities, although this was significant (P < 0.01) only for the men.*** *QoL improved after 12 months of GH treatment (P < 0.001), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months (P < 0.001).* ***In conclusion, GH replacement therapy, in previously untreated adults with GHD, produces significant decreases in the use of healthcare resources, which are correlated with improvements in QoL.***

Hilczer M, Smyczynska J, Stawerska R, Lewinski A. Stability of IGF-I concentration despite divergent results of repeated GH stimulating tests indicates poor reproducibility of test results. Endocr Regul. 2006 Jun;40(2):37-45.

OBJECTIVE: Growth hormone (GH) secretion is routinely assessed in provocative tests. However, some limitations of these tests have been reported, including a weak correlation between spontaneous GH secretion and GH peak in stimulating tests, poor reproducibility of test results and normalisation of previously decreased GH response to stimulation in the repeated provocative tests. The observed discrepancies between the results of consecutive GH stimulating tests in the same patient may be explained either by real changes in GH secretion or by the poor reproducibility of GH response to stimulation. Normalisation of previously decreased GH secretion should entail the increase of insulin-like growth factor-I (IGF-I) concentration, while stability of IGF-I secretion despite divergent GH response to stimulation in repeated tests might indicate the poor reproducibility of GH stimulating tests. The aim of the study was a comparison of GH peak in repeated stimulating tests and of corresponding, simultaneously measured IGF-I concentration. METHODS: The investigation comprised 84 children with short stature who underwent repeated GH tests and IGF-I evaluation. In 60 patients each of two different tests (with clonidine and with glucagon, in standard doses) was performed twice, together with IGF-I measurement during both evaluations. In 20 patients (remaining in the same pubertal stage during the time period between the procedures in question) at least one test, together with IGF-I measurement, was repeated within one year. RESULTS: ***The correlation between the results of GH tests, repeated during the two evaluations, was weak*** *($r=0.22$, $p<0.05$ for all patients and $r=0.25$, $p<0.05$ for the patients examined 2 times within 1 year), with the high within-subject variability (43.4 % and 59.5 %, respectively).* ***Conversely, the correlation between two values of IGF-I SDS was good both for all patients*** *($r=0.65$, $p<0.05$) and especially for the patients examined twice within 1 year ($r=0.96$, $p<0.05$), with low within-subject variability for the latter subgroup of patients (11.2 %).* ***The same GH stimulating tests, performed twice in the same patient, led to different conclusions (either the confirmation of GHD diagnosis or its exclusion) in most of examined patients.*** *Poor reproducibility of GH stimulating tests, rather than the possibility of short-term changes in GH secretion, was confirmed.* ***(Serum IGF-1 is the better test of GH secretion!-HHL)***

Hilding A, Hall K, Wivall-Helleryd IL, Sääf M, Melin AL, Thorén M. Serum levels of insulin-like growth factor I in 152 patients with growth hormone deficiency, aged 19-82 years, in relation to those in healthy subjects. J Clin Endocrinol Metab. 1999 Jun;84(6):2013-9.

Serum insulin-like growth factor I (IGF-I) levels within normal range for age have been reported to be common in adults with GH deficiency (GHD). Therefore, serum IGF-I levels were determined in 152 consecutive patients (71 women and 81 men) with evidence of hypothalamic-pituitary disorders or previous cranial radiation, who fulfilled the presently used criteria for GHD i.e. peak GH response below 3 microg/L at stimulation test. Patients treated for acromegaly were excluded. Forty-three patients, aged 19-63 yr, had childhood onset GHD, and 109, aged 23-82 yr, had adult-onset GHD. Their IGF-I levels were expressed in SD scores in relation to normal reference values based on 448 healthy subjects, aged 20-96 yr (247 women and 201 men). In healthy subjects a linear inverse correlation, without gender difference, was found between logarithmic transformed IGF-I levels and age (r = -0.774; P < 0.001). In contrast, no age dependency was found in GHD patients. All patients with childhood-onset GHD had IGF-I values below -2 SD, significantly lower than those in adult-onset GHD patients (-6.2 +/- 0.3 vs. -3.2 +/- 0.2 SD score; P < 0.001). ***In patients with adult-onset GHD, 34% of the IGF-I levels were within normal range, increasing to 40% in the subgroup above 60 yr of age, in whom 86% were diagnosed with hypothalamic-pituitary tumors.*** *Normal IGF-I was more common in men than in women, but no difference was observed between patients with panhypopituitarism and those with partial pituitary insufficiency. High frequencies of IGF-I levels within the normal range were found in GHD patients with pituitary tumors (20 of 57 nonsecreting pituitary adenomas, 5 of 15 prolactinomas, 6 of 12 Cushing's disease, and 4 of 25 craniopharyngiomas), but in only 2 of 43 patients with GHD due to other causes.* ***In conclusion, an IGF-I level below -2 SD seems to be of diagnostic value in GHD with onset in childhood or early adulthood, whereas values within normal range are common in patients over 60 yr of age, especially those with pituitary tumors.*** *The outcome of GH replacement therapy may reveal whether the addition of IGF-I as a diagnostic criterion is of predictive value in older patients.*

Isidori AM, Kaltsas GA, Perry L, Burrin JM, Besser GM, Monson JP. The effect of growth hormone replacement therapy on adrenal androgen secretion in adult onset hypopituitarism. Clin Endocrinol (Oxf). 2003 May;58(5):601-11.

OBJECTIVE: Growth hormone replacement therapy in GH-deficient children is associated with enhanced adrenal androgen production, raising the possibility that GH might stimulate adrenocortical hormone secretion. This has not been extensively investigated in adults to date. GH is a potent modulator of the activity of the 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) enzyme and by altering cortisol metabolism can affect the function of the hypothalamo-pituitary-adrenal (HPA) axis and therefore potentially of adrenal androgen secretion. This study examined the effects of GH replacement in GH-deficient adults on adrenal androgen secretion. DESIGN: Prospective study of the effect of GH replacement therapy on adrenal androgen production in patients with adult onset hypopituitarism over a 12-month period. PATIENTS AND METHODS: Thirty adult GH-deficient patients were classified into two groups according to their cortisol responses to an insulin-induced hypoglycaemia or a glucagon stimulation test: 13 patients were adrenocorticotropic hormone (ACTH)-sufficient (nine females, age 45.1 +/- 3 years), whereas 17 patients were ACTH-deficient (11 females, age 45.5 +/- 3 years). Serum samples were collected before patients were initiated on GH replacement therapy using a dose titration regimen, and after 6 and 12 months on GH therapy for measurement of serum IGF-I, dehydroepiand-rosterone sulphate (DHEAS), Delta4-Androstenedione (A4), testosterone, cortisol, sex hormone binding globulin (SHBG) and cortisol binding globulin (CBG). RESULTS: Six months after the initiation of GH replacement therapy, serum IGF-I levels were within the normal age-related reference range in both groups of patients and this was maintained at 12 months [in all patients 0 vs. 6 months: median (interquartile range): 92.5 ng/ml (73-116 ng/ml) vs. 191 ng/ml (159-224 ng/ml), P < 0.01]. In both ACTH-sufficient and -deficient groups of GH-deficient patients, pretreatment serum DHEAS levels were lower than the normal age-

*related reference range (P < 0.01); the ACTH-deficient patients had significantly lower DHEAS levels than the ACTH-sufficient patients [median (interquartile range): 0.5 micro mol/l (0.4-1.2 micro mol/l) vs. 1.5 micro mol/l (0.6-2.7 micro mol/l), P < 0.05]. Following GH replacement therapy, median levels of serum DHEAS levels rose from 1.5 micro mol/l (0.6-2.7 micro mol/l) to 1.9 micro mol/l (1.9-3.9 micro mol/l) in ACTH-sufficient patients, increasing in 11 of the 13 patients (P < 0.02). In this group, the median percentage increase from baseline was 32% at 6 months (P < 0.05). In contrast, baseline serum DHEAS levels [0.5 micro mol/l (0.4-1.2 micro mol/l)] declined in or from the measurable range in 47% of ACTH-deficient patients [median -16%; range -36-0] and only in one patient a + 0.2 micro mol/l increase was observed. GH dose requirements tended to be lower in ACTH-sufficient patients [1.2 U/day (0.8-1.4 U/day) vs. 1.6 U/day (1.0-2.0 U/day); P = 0.062]. There were no significant changes in serum testosterone, A4, SHBG and/or CBG levels, compared to the pretreatment levels, in either group of patients over the 12 months of GH replacement. CONCLUSIONS: This study shows that median serum DHEAS levels are significantly lower in GH-deficient patients, even those with intact ACTH reserve, than in aged-matched controls. GH replacement therapy is associated with a significant increase in mean serum DHEAS only in ACTH-sufficient patients. **These findings are consistent with either (i) GH stimulation of adrenal androgen production in the permissive presence of ACTH or (ii) an inhibitory effect of GH on 11beta-HSD type 1 activity leading to enhanced cortisol clearance, subsequent activation of the HPA axis and ACTH-mediated androgen secretion.** PMID: 12699442*

Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? Clin Endocrinol (Oxf). 2006 Feb;64(2):115-21.

*The ability of GH, via its mediator peptide IGF-1, to influence regulation of cellular growth has been the focus of much interest in recent years. In this review, we will explore the association between GH and cancer. Available experimental data support the suggestion that GH/IGF-1 status may influence neoplastic tissue growth. Extensive epidemiological data exist that also support a link between GH/IGF-1 status and cancer risk. Epidemiological studies of patients with acromegaly indicate an increased risk of colorectal cancer, although risk of other cancers is unproven, and a long-term follow-up study of children deficient in GH treated with pituitary-derived GH has indicated an increased risk of colorectal cancer. **Conversely, extensive studies of the outcome of GH replacement in childhood cancer survivors show no evidence of an excess of de novo cancers, and more recent surveillance of children and adults treated with GH has revealed no increase in observed cancer risk.** However, given the experimental evidence that indicates GH/IGF-1 provides an anti-apoptotic environment that may favour survival of genetically damaged cells, longer-term surveillance is necessary; over many years, even a subtle alteration in the environmental milieu in this direction, although not inducing cancer, could result in acceleration of carcinogenesis. Finally, even if GH/IGF-1 therapy does result in a small increase in cancer risk compared to untreated patients with GH deficiency, it is likely that the eventual risk will be the same as the general population. Such a restoration to normality will need to be balanced against the known morbidity of untreated GH deficiency.*

Johansson JO, Landin K, Johannsson G, Tengborn L, Bengtsson BA. Long-term treatment with growth hormone decreases plasminogen activator inhibitor-1 and tissue plasminogen activator in growth hormone-deficient adults. Thromb Haemost. 1996 Sep;76(3):422-8.

*The syndrome of growth hormone deficiency (GHD) in adults is associated with premature atherosclerosis, increased cardiovascular mortality, abnormal lipoprotein patterns and abnormal body composition. We have previously shown that GH-deficient adults have increased concentrations of fibrinogen and plasminogen activator inhibitor (PAI-1) activity. The aim of the present investigation was to study coagulation and fibrinolysis in 17 patients with adult-onset GHD during two years of treatment with recombinant human GH (12 micrograms/kg body weight/day). The impact of the contemporary changes in metabolic variables and body composition on coagulation and fibrinolysis was studied. The patients received conventional thyroid, adrenal and gonadal hormone replacement therapy. **PAI-1 activity, PAI-1 antigen and tissue plasminogen activator (t-PA) antigen***

levels decreased during the GH treatment period (p < 0.05). *The decrease was more pronounced in patients with high pre-treatment levels of the different variables. alpha 2-antiplasmin decreased (p < 0.05), while plasminogen was unchanged during two years of GH treatment.* ***Fibrinogen concentrations tended to decrease after two years of GH treatment*** *(p = 0.06), while the coagulation factors VII and VIII were unchanged. von Willebrand factor demonstrated a transient decrease after 18 months of GH treatment. The coagulation inhibitor, protein C, decreased (p < 0.05), while antithrombin was unchanged. Fasting plasma insulin increased (p < 0.01), but blood glucose did not differ after two years of GH treatment. Serum high-density lipoprotein cholesterol, total cholesterol and triglycerides were unaltered. Body fat decreased during the initial GH treatment but was unaltered after two years, while* ***lean body mass increased (p < 0.001) and the waist over hip circumference ratio tended to decrease*** *(p = 0.06). In conclusion, PAI-1 activity, PAI-1 antigen and t-PA antigen decreased during long-term GH treatment. These changes may be a direct effect of GH itself or may be secondary to the favourable changes in body composition. It remains to be seen whether changes in these fibrinolytic variables during rhGH treatment reduces the cardiovascular risk in patients with GHD. The present results suggest that GH plays a role in the regulation of fibrinolysis.*

Johannsson G, Bengtsson BA, Andersson B, Isgaard J, Caidahl K. Long-term cardiovascular effects of growth hormone treatment in GH-deficient adults. Preliminary data in a small group of patients. Clin Endocrinol (Oxf). 1996 Sep;45(3):305-14.

OBJECTIVE: The long-term cardiovascular effects of GH administration in adults are of major clinical importance, given the increasing use of such treatment. We have evaluated long-term cardiovascular effects of recombinant human GH (rhGH) substitution in GH deficient men. DESIGN: S.c. rhGH 0.5 U/kg/week ***(80kg—40U/week, c/w my starting dose of 4.2U.week!)*** *or placebo was administered in a 6-month double-blind, cross-over study, followed (after a year without substitution) by a 42-month period of open GH substitution. PATIENTS: We evaluated 7 GH-deficient men serially and compared the results with 21 men matched in terms of age and height. MEASUREMENTS: Investigations included exercise tests and Doppler-echocardiography to determine exercise capacity and cardiovascular performance. RESULTS: Heart rate and systolic blood pressure at rest increased with GH substitution to the level of the controls, as did diastolic blood pressure after an initial reduction. Age-adjusted exercise capacity increased during the study and we found no evidence of ischaemic heart disease on exercise ECG. Stroke volume increased with GH substitution, thereby normalizing the initially reduced cardiac index. There was no significant change in left atrial or ventricular internal dimensions, systolic function as measured by fractional shortening, or diastolic function as measured by isovolumic relaxation time and left ventricular filling (A/E ratio). However, a lower atrial emptying index than that seen among controls might indicate some diastolic disturbance and there was a definite increase in left ventricular wall thickness compared with controls (to 25.1 +/- 1.5 vs 19.7 +/- 0.4 mm, P < 0.001). CONCLUSIONS:* ***We found that GH substitution in GH-deficient adults had a beneficial effect on physical performance and cardiac output. The concomitant increase in left ventricular mass index might be an effect of an excessive substitution dose.***

Johannsson G, Svensson J, Bengtsson BA. Growth hormone and ageing. Growth Horm IGF Res. 2000 Apr;10 Suppl B:S25-30.

The proportion of elderly people is steadily growing in Western societies. The result is a disproportionate accumulation of the oldest and most vulnerable sector of the population, suffering from frailty-associated disorders and cardiovascular diseases. ***Growth hormone (GH) secretion declines progressively during adulthood.*** *In ageing and severe GH deficiency, an individual's muscle mass, muscle strength and bone mass are decreased, and the relative proportion of total and visceral fat is increased.* ***An association between reduced GH levels and the catabolism of ageing has been suggested. GH or GH secretagogue treatment could be of value to minimize the health-related consequences associated with the ageing process.***

Johnsen SP, Hundborg HH, Sørensen HT, Orskov H, Tjønneland A, Overvad K, Jørgensen JO. J Clin Endocrinol Metab. 2005 Nov;90(11):5937-41.

Insulin-like growth factor (IGF) I, -II, and IGF binding protein-3 and risk of ischemic stroke. BACKGROUND: Low IGF-I levels may be associated with the development of stroke; however, prospective data appear to be unavailable. METHODS: This was a nested case-control study within a Danish follow-up study, including 57,053 men and women. Baseline data included circulating IGF-I, IGF-II, and IGF binding protein (IGFBP)-3 concentrations as well as lifestyle factors and medical history. We identified 254 cases with incident ischemic stroke and 254 gender- and age-matched controls. RESULTS: ***Participants in the bottom quartiles of IGF-I and IGFBP-3 levels (median concentrations, 72 and 2937 ng/ml, respectively) were at increased risk of ischemic stroke, e.g. adjusted odds ratios (ORs) of 2.06 [95% confidence interval (CI), 1.05-4.03] and 2.29 (95% CI, 1.17-4.49), respectively, when compared with participants in the top quartiles (median concentrations, 125 and 4835 ng/ml, respectively).*** *A negative, although weaker, association was also found for IGF-II (adjusted OR 1.44, 95% CI 0.79-2.64) when comparing the bottom quartile with the top quartile. No substantial associations were seen for IGF-I and IGF-II when also adjusting for IGFBP-3; adjusting IGFBP-3 for IGF-I and -II had only a minor impact on the risk estimates. CONCLUSION: These findings give some support to the hypothesis that the IGF axis is involved in the pathogenesis of ischemic stroke. PMID: 16131586*

Jorgensen JO, Muller J, Moller J, Wolthers T, Vahl N, Juul A, Skakkebaek NE, Christiansen JS. Adult growth hormone deficiency. Horm Res. 1994;42(4-5):235-41.

Several reports have focused on the clinical features of the untreated GH-deficient adult and the effect of GH therapy. The results reported are strikingly unanimous. Untreated GH-deficient adults have been shown to have increased cardiovascular mortality, reduced exercise capacity, reduced muscle strength, subnormal glomerular filtration rate and renal plasma flow, defective sweat secretion and defective thermoregulation, reduced energy expenditure and basal metabolic rate, abnormal thyroid hormone metabolism, reduced myocardial function and clinical signs of premature atherosclerosis. Body composition has been found abnormal with increased fat mass, decreased lean body mass, decreased muscle fat ratio, visceral obesity, reduced extracellular fluid volume and reduced bone mineral content. Furthermore, two independent groups have reported impaired psychological wellbeing as compared to normal subjects. Apart from the observation on total mortality, all the above-reported abnormalities improve during GH substitution. The only recognisable side effects so far has been fluid retention, which is usually transient and dose-dependent. It is concluded that GH deficiency has distinct clinical consequences all of which can be totally or partially alleviated by GH replacement therapy.

Juul A, Scheike T, Davidsen M, Gyllenborg J, Jørgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. Circulation. 2002 Aug 20;106(8):939-44.

BACKGROUND: Insulin-like growth factor I (IGF-I) has been suggested to be involved in the pathogenesis of atherosclerosis. We hypothesize that low IGF-I and high IGFBP-3 levels might be associated with increased risk of ischemic heart disease (IHD). METHODS AND RESULTS: We conducted a nested case-control study within a large prospective study on cardiovascular epidemiology (DAN-MONICA). We measured IGF-I and IGFBP-3 in serum from 231 individuals who had a diagnosis of IHD 7.63 years after blood sampling and among 374 control subjects matched for age, sex, and calendar time. At baseline when all individuals were free of disease, subjects in the low IGF-I quartile had significantly higher risk of IHD during the 15-year follow-up period, with a relative risk (RR) of 1.94 (95% CI, 1.03 to 3.66) of IHD compared with the high IGF-I quartile group, when IGFBP-3, body mass index, smoking, menopause, diabetes, and use of antihypertensives were controlled for. Conversely, individuals in the high IGFBP-3 quartile group had an adjusted RR of 2.16 (95% CI, 1.18 to 3.95) of having IHD. Identification of a high-risk population with low IGF-I and high IGFBP-3 levels resulted in markedly higher risk of IHD (RR 4.07; 95% CI, 1.48 to 11.22)

compared with the index group. CONCLUSIONS: ***Individuals without IHD but with low circulating IGF-I levels and high IGFBP-3 levels have significantly increased risk of developing IHD during a 15-year follow-up period. Our findings suggest that IGF-I may be involved in the pathogenesis of IHD.*** *PMID: 12186797*

Kehinde EO, Akanji AO, Mojiminiyi OA, Bashir AA, Daar AS, Varghese R. Putative role of serum insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) levels in the development of prostate cancer in Arab men. Prostate Cancer Prostatic Dis. 2005;8(1):84-90.

INTRODUCTION: The incidence of clinical prostate cancer in the Arab population is among the lowest in the world. High serum IGF-1 level has been implicated as a possible risk factor for the development of prostate cancer in Caucasians. The purpose of this study was to determine serum IGF-1 and IGFBP-3 levels in healthy Arab men and in Arab men with newly diagnosed benign prostatic hyperplasia (BPH) and prostate cancer, and to compare these values with values reported in Caucasians. PATIENTS AND METHODS: Subjects were recruited in two groups: (a) indigenous, healthy Arab men aged 15-90 y (n = 383); (b) Arab men with newly diagnosed prostate cancer (n = 30) or BPH (n = 40). Blood was obtained from fasting patients and volunteers, between 8:00 a.m. and 12:00 noon. The serum concentrations of IGF-1 and IGFBP-3 were determined using Immunoradiometric assay (IRMA) kits. RESULTS: As in Caucasians, serum IGF-1 and IGFBP-3 levels declined with age in Arab men. The mean +/- s.d. of serum IGF-1 levels in healthy Arab men in the age group 15-20, 51-60, 61-70 y were lower (376.2 +/- 153.2, 134.9 +/- 105.7 and 89.6 +/- 48.4 ng/ml, respectively), compared to values reported for similarly aged Caucasians. Arab men with newly diagnosed prostate cancer had significantly higher serum IGF-1 level (P < 0.01) and lower IGFBP-3 levels (P < 0.01) compared to age-matched Arabs without the disease. CONCLUSIONS: Arab men have lower serum IGF-1 levels compared to Caucasians and this may be an important factor in the explanation of the low incidence of prostate cancer in the Arab population. ***(This association is cause for concern, but there is no evidence that GH replacement increases the risk of prostate cancer. There are also many possible explanations for the association that would not imply that GH replacement will cause prostate cancer. —HHL)***

Khan AS, Sane DC, Wannenburg T, Sonntag WE. Growth hormone, insulin-like growth factor-1 and the aging cardiovascular system. Cardiovasc Res. 2002 Apr;54(1):25-35.

There is a large body of evidence that biological aging is related to a series of long-term catabolic processes resulting in decreased function and structural integrity of several physiological systems, among which is the cardiovascular system. These changes in the aging phenotype are correlated with a decline in the amplitude of pulsatile growth hormone secretion and the resulting decrease in plasma levels of its anabolic mediator, insulin like growth factor-1 (IGF-1). ***The relationship between growth hormone and biological aging is supported by studies demonstrating that growth hormone administration to old animals and humans raises plasma IGF-1 and results in increases in skeletal muscle and lean body mass, a decrease in adiposity, increased immune function, improvements in learning and memory, and increases in cardiovascular function.*** *Since growth hormone and IGF-1 exert potent effects on the heart and vasculature, the relationship between age-related changes in cardiovascular function and the decline in growth hormone levels with age have become of interest. Among the age-related changes in the cardiovascular system are decreases in myocyte number, accumulation of fibrosis and collagen, decreases in stress-induced cardiac function through deterioration of the myocardial conduction system and beta-adrenergic receptor function, decreases in exercise capacity, vessel rarefaction, decreased arterial compliance and endothelial dysfunction leading to alterations in blood flow. Growth hormone has been found to exert potent effects on cardiovascular function in young animals and reverses many of the deficits in cardiovascular function in aged animals and humans. Nevertheless, it has been difficult to separate the effects of growth hormone deficiency from age-related diseases and associated pathologies. The development of novel animal models and additional research are required in order to elucidate the specific effects of growth hormone deficiency and assess its contribution to cardiovascular impairments and biological aging.*

Kim KR, Nam SY, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment with diet restriction accelerates body fat loss, exerts anabolic effect and improves growth hormone secretory dysfunction in obese adults. Horm Res 1999;51(2):78-84.

*In obese adults on calorie restricted diet, GH for 12 weeks accelerated body fat loss, exerted anabolic effects, and improved GH secretion. Both groups lost similar amount of weight, but GH group lost half as much lean body mass, had a signif decrease in visceral fat, and an increase in mid-thigh muscle area. No change in oral GTT results. Slight edema and arthralgia occurred in 10 of subjects during 2nd week but resolved spontaneously. (**Dose 0.18U/kg IBW/week or 14.4 U/wk for 80kg man? This is a very high dose!—HHL)***

Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. Am J Clin Nutr 1985;42:1255-1265.

Krentz AJ, Koster FT, Crist DM, et al. Anthropometric, metabolic, and immunological effects of recombinant human growth hormone in AIDS and AIDS-related complex. J Acquir Immune Defic Syndr 1993;6:245-251.

Landin-Wilhelmsen K, Nilsson A, Bosaeus I, Bengtsson BA. Growth hormone increases bone mineral content in postmenopausal osteoporosis: a randomized placebo-controlled trial. J Bone Miner Res. 2003 Mar;18(3):393-405.

*Eighty osteoporotic, postmenopausal women, 50-70 years of age, with ongoing estrogen therapy (HRT), were randomized to recombinant human growth hormone (GH), 1.0 U or 2.5 U/day, subcutaneous, versus placebo. This study was double-blinded and lasted for 18 months. The placebo group then stopped the injections, but both GH groups continued for a total of 3 years with GH and followed for 5 years. Calcium (750 mg) and vitamin D (400 U) were given to all patients. Bone mineral density and bone mineral content were measured with DXA. At 18 months, when the double-blind phase was terminated, total body bone mineral content was highest in the GH 2.5 U group (p = 0.04 vs. placebo). At 3 years, when GH was discontinued, total body and femoral neck bone mineral content had increased in both GH-treated groups (NS between groups). At 4-year follow-up, total body and lumbar spine bone mineral content increased 5% and 14%, respectively, for GH 2.5 U (p = 0.01 and p = 0.0006 vs. placebo). Femoral neck bone mineral density increased 5% and bone mineral content 13% for GH 2.5 U (p = 0.01 vs. GH 1.0 U). At 5-year follow-up, no differences in bone mineral density or bone mineral content were seen between groups. Bone markers showed increased turnover. Three fractures occurred in the GH 1.0 U group. No subjects dropped out. Side effects were rare. **In conclusion, bone mineral content increased to 14% with GH treatment on top of HRT and calcium/vitamin D in postmenopausal women with osteoporosis. There seems to be a delayed, extended, and dose-dependent effect of GH on bone. Thus, GH could be used as an anabolic agent in osteoporosis.***

Lange KH, Isaksson F, Juul A, Rasmussen MH, Bulow J, Kjaer M. Growth hormone enhances effects of endurance training on oxidative muscle metabolism in elderly women. Am J Physiol Endocrinol Metab 2000 Nov; 279(5):989-96.

Lasaite L, Bunevicius R, Lasiene D, Lasas L. Psychological functioning after growth hormone therapy in adult growth hormone deficient patients: endocrine and body composition correlates. Medicina (Kaunas). 2004;40(8):740-4.

Growth hormone replacement in adult growth hormone deficient patients improves psychological well-being and the quality of life. The aim of this study was to investigate relationship between changes in mood, cognitive functioning, quality of life, changes in body composition and hormone concentration at baseline and six months after treatment with human recombinant growth hormone. Eighteen adult patients with growth hormone deficiency syndrome were recruited to the study. Growth

hormone was administered in doses of 12 IU per week in an open design. After 6 months of growth hormone replacement therapy the psychological functioning improved significantly on mood scales (Profile of Mood State) and on a cognitive performance tests. Changes in quality of life scale were trivial. After growth hormone treatment serum concentration of Insulin like growth factor -1 (IGF-1) and triiodothyronine increased and concentration of serum free thyroxine decreased significantly in comparison to basal concentration. There were no significant differences in changes of plasma cortisol, thyrotropin and growth hormone concentrations. Improvement on Profile of Mood State global score as well as on Vigor-Activity subscale correlated significantly with increase in IGF-1 concentration. Improvement on Profile of Mood State Vigor-Activity subscale correlated with increase in water body mass and improvement on Hospital Anxiety and Depression scale depression subscale correlated with decrease in cortisol concentration. ***The study shows that growth hormone replacement improves mood and cognition in adult growth hormone deficient patients. This improvement is related to changes in water body mass as well as to endocrine changes.*** *PMID: 15299990*

Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2004 Jan;89(1):114-20.

The IGF system has been implicated in cardiovascular disease (CVD) development. The prospective association of serum IGF-I and IGF-binding protein-1 (IGFBP-1) with all cause, ischemic heart disease (IHD), and non-IHD CVD mortality was examined in 633 men and 552 nonestrogen-using postmenopausal women, aged 51-98 yr (mean, 74 yr) in 1988-1992, who were followed through July 2001 (96% follow-up). During the 9- to 13-yr follow-up, there were 522 deaths; 224 were attributed to CVD, and 105 were caused by IHD. IGF-I and IGFBP-1 were independently and jointly related to risk of IHD mortality. In a proportional hazards model including both IGF-I and IGFBP-1 and adjusting for CVD risk factors, the relative risk of IHD mortality was 38% higher for every 40 ng/ml (1 SD) decrease in IGF-I (95% confidence interval, 1.09-1.76; P = 0.005) and 3.11 times greater for those in the lowest quintile of IGFBP-1 (95% confidence interval, 1.74-5.56; P < 0.001) compared with those with higher IGFBP-1 levels. IGF-I and IGFBP-1 (alone or in combination) were not related to risk of all cause or non-IHD CVD mortality. ***We conclude that low baseline levels of IGF-I and IGFBP-1 increase the risk of fatal IHD among elderly men and women independent of prevalent IHD and CVD risk factors.*** *PMID: 14715837*

Lombardi G, Di Somma C, Marzulla P, Cerbone G, Colao A. Growth hormone and cardiac function. Ann Endocrinol (Paris) 2000 Feb; 61(1):16-21.

Lonn L, Johansson G, Sjostrom L, Kvist H, Oden A, Bengtsson BA. Body composition and tissue distributions in growth hormone deficient adults before and after growth hormone treatment.Obes Res. 1996 Jan;4(1):45-54.

This study examines short and long-term effects of recombinant human growth hormone (rhGH) on body composition and regional tissue distributions by using a multicompartment technique based on computed tomography. Part I includes nine subjects aged 46 +/- 9 years with adult onset GH deficiency who were examined before and in the end of 6 months treatment with rhGH (0.4 U.kg-1.week-1) in a double-blind crossover trial. Part II is an ongoing open trial including seven of the males in part I. They were treated with rhGH (0.25 U.kg-1.week-1) over an additional period of 24 months. ***Adipose tissue (AT) was reduced by 4.7 kg*** *($p < 0.01$) while the* ***muscle plus skin compartment (M) and visceral organs (V) were increased by 2.4 ($p < 0.05$) and 0.7 kg*** *($p < 0.01$), respectively, over 6 months of treatment with a high rhGH dose. A preferential lipid mobilization occurred in the visceral and subcutaneous trunk depots resulting in a changed AT distribution. Muscles of legs and arms increased while the increase of trunk muscles did not reach significance.* ***The body composition changes were maintained over 2 years additional treatment.*** *The preferential loss in visceral AT was further pronounced while other changes in tissue distributions observed*

during the first 6 months tended to be reversed on the lower rhGH dosage. It is concluded that growth hormone has profound and discordant effects on AT, M and V and with associated changes in tissue distributions. The beneficial effects on body composition seen in short-term treatment is preserved throughout an additional 24 months period of treatment.

Marzullo P, Di Somma C, Pratt KL, Khosravi J, Diamandis A, Lombardi G, Colao A, Rosenfeld RG. Usefulness of different biochemical markers of the insulin-like growth factor (IGF) family in diagnosing growth hormone excess and deficiency in adults. J Clin Endocrinol Metab. 2001 Jul;86(7):3001-8.

The diagnostic approach to acromegaly and GH deficiency frequently includes measurement of several components of the insulin-like growth factor (IGF) system. IGF-I levels are reported to be good predictors of active and cured acromegaly, but are commonly found within the normal age-adjusted range in adult GH-deficient (GHD) patients. Circulating concentrations of IGF-binding protein-3 (IGFBP-3), acid-labile subunit (ALS), and free IGF-I reflect the GH secretory status, but their diagnostic accuracy is still debated. In this study serum levels of total and free IGF-I, IGFBP-3, ALS, and IGFBP-3-IGF-I and IGFBP-3-ALS complexes were determined in patients previously diagnosed with active (n = 67) or inactive (n = 16) acromegaly and adult GHD (n = 34) and compared with results obtained in 58 healthy controls. In healthy subjects, IGF-I, IGFBP-3, ALS, and both IGFBP-3 complexes declined with age; a correlation was found between IGF-I and IGFBP-3 (r = 0.59; P < 0.001), ALS (r = 0.67; P < 0.001), and free IGF-I (r = 0.40; P < 0.05). Active acromegalic patients showed a significant increase in all parameters tested. IGF-I concentrations were above +2 SD in 100% of patients, whereas slightly lower sensitivities were shown for IGFBP-3 (85%), ALS (88%), and free IGF-I (94%). In this group, IGF-I exhibited a slightly higher correlation with IGFBP-3 (r = 0.83; P < 0.001) than with ALS levels (r = 0.78; P < 0.001). In cured acromegalic patients, we observed the normalization of all parameters but free IGF-I levels. Adult GHD patients showed a significant reduction of all hormones. Unlike active acromegalic patients, all parameters had only a modest sensitivity in GHD; suppression below -2 SD was observed in 41% of GHD patients for IGF-I, 47% for IGFBP-3, 32% for ALS, and 35% for free IGF-I measurements. Previous radiotherapy and GH peak response below 3 microg/L were associated with significantly lower IGF-I, IGFBP-3, and ALS levels. IGF-I levels were significantly correlated to ALS (r = 0.68; P < 0.001) and IGFBP-3 (r = 0.64; P < 0.001) as well as with free IGF-I (r = 0.67; P < 0.001) levels. By multiple regression analysis, the number of anterior pituitary hormones impaired was the most predictive indicator of IGF-I, IGFBP-3, and free IGF-I levels in GHD patients; conversely, the GH peak response better anticipated ALS concentrations. The pattern of IGFBP-3 complexes paralleled previous hormonal findings. In active acromegalic patients, IGFBP-3-IGF-I levels were 5.4-fold higher than in controls and were above +2 SD in 95% of patients, whereas IGFBP-3-ALS levels were elevated in 15% of cases. On the other hand, both IGFBP-3 complexes were able to predict GHD in only a minority of cases. Taken together, these data support the diagnostic role of IGF-I in acromegaly and suggest that free IGF-I and the IGFBP-3-IGF-I complex can assist diagnostic strategies in this condition. All markers are of limited predictive value in adult GHD, as hormonal values are commonly found within the normal limits. In these patients, low IGFBP-3 and IGF-I concentrations can add further clinical information on the residual GH activity.

Molitch ME. Diagnosis of GH deficiency in adults--how good do the criteria need to be? J Clin Endocrinol Metab. 2002 Feb;87(2):473-6.

Monson JP. Long-term experience with GH replacement therapy: efficacy and safety. Eur J Endocrinol. 2003 Apr;148 Suppl 2:S9-14.

Demonstration of the long-term efficacy of GH replacement in GH-deficient adults has depended on a combination of single-centre studies and data from large multinational databases, which, by virtue of their size, are likely to detect rare adverse events and also permit analysis of mortality rates. The Pharmacia International Metabolic Surveillance (KIMS) study (a pharmacoepidemiological survey of

the safety and efficacy of GH replacement in adults, sponsored by Pharmacia) is currently the largest database, with information on over 8000 patients from a total of 27 countries. Abundant epidemiological evidence confirms that hypopituitarism is associated with premature mortality, with an increase in cardiovascular and cerebrovascular disease as a primary underlying cause. Central adiposity, hyperlipidaemia, insulin resistance, and diabetes mellitus are common in adults with hypopituitarism. ***GH replacement is associated with improvements in central fat mass and mean reductions in serum total and low-density lipoprotein cholesterol*** *which may be additive to those achieved with hydroxymethylglutaryl-coenzyme A reductase inhibitors. These beneficial effects are maintained for at least 2 Years after initiation of therapy, as are reductions in central adiposity, with similar benefits seen in men and women when the GH dose is titrated to achieve a serum IGF-I between the median and the upper end of the age-related reference range.* ***Fasting plasma glucose and glycated haemoglobin increase, usually within the reference range, during prolonged GH replacement, but do not tend to rise further*** *above baseline in subjects with pre-existing impaired glucose tolerance. Bone remodelling increases during GH replacement therapy, but indices tend to return to baseline within 5 Years of commencing treatment. Bone mineral density increases in men whereas, in women, improvement is limited to stabilisation of bone density. Data from the KIMS study demonstrate that prolonged GH replacement is associated with a reduction in the number of patients requiring assistance with daily living and a significant reduction in sick leave and hospital admissions.* ***GH replacement therapy improves psychological well-being, particularly in those patients with the greatest deficit prior to treatment, with improvement maintained beyond 6 Months of therapy and sustained during long-term follow-up.*** *Data from the KIMS population show that there is no increase in the overall occurrence of de novo neoplasia or the rate of regrowth of primary pituitary tumours. There is an apparent increase in intracranial neoplasia, which may be an artefact of comparing a surveillance population with general population data. Unlike mortality in untreated hypopituitary GH-deficient patients, mortality in the KIMS study is currently similar to that predicted for the normal population. PMID: 12670295*

Munzer T, Harman SM, Hees P, Shapiro E, Christmas C, Bellantoni MF, Stevens TE, O'Connor KG, Pabst KM, St Clair C, Sorkin JD, Blackman MR. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. J Clin Endocrinol Metab. 2001 Aug;86(8):3604-10.

Aging is associated with reduced GH, IGF-I, and sex steroid axis activity and with increased abdominal fat. We employed a randomized, double-masked, placebo-controlled, noncross-over design to study the effects of 6 months of administration of GH alone ***(20 microg/kg BW (double my usual starting dose-HHL)****, sex hormone alone (hormone replacement therapy in women, testosterone enanthate in men), or GH + sex hormone on total abdominal area, abdominal sc fat, and visceral fat in 110 healthy women (n = 46) and men (n = 64), 65-88 yr old (mean, 72 yr). GH administration increased IGF-I levels in women (P = 0.05) and men (P = 0.0001), with the increment in IGF-I levels being higher in men (P = 0.05). Sex steroid administration increased levels of estrogen and testosterone in women and men, respectively (P = 0.05). In women, neither GH, hormone replacement therapy, nor GH + hormone replacement therapy altered total abdominal area, sc fat, or visceral fat significantly. In contrast, in men, administration of GH and GH + testosterone enanthate decreased total abdominal area by 3.9% and 3.8%, respectively, within group and vs. placebo (P = 0.05). Within-group comparisons revealed that sc fat decreased by 10% (P = 0.01) after GH, and by 14% (P = 0.0005) after GH + testosterone enanthate. Compared with placebo, sc fat decreased by 14% (P = 0.05) after GH, by 7% (P = 0.05) after testosterone enanthate, and by 16% (P = 0.0005) after GH + testosterone enanthate. Compared with placebo, visceral fat did not decrease significantly after administration of GH, testosterone enanthate, or GH + testosterone enanthate. These data suggest that in healthy older individuals, GH and/or sex hormone administration elicits a sexually dimorphic response on sc abdominal fat. The generally proportionate reductions we observed in sc and visceral fat, after 6 months of GH administration in healthy aged men, contrast with the disproportionate reduction of visceral fat reported after a similar period of GH treatment of nonelderly GH deficient men and women. Whether longer term administration of GH or testosterone enanthate, alone or in*

combination, will reduce abdominal fat distribution-related cardiovascular risk in healthy older men remains to be elucidated.

Muniyappa R, Sorkin JD, Veldhuis JD, Harman SM, Münzer T, Bhasin S, Blackman MR. Long-term testosterone supplementation augments overnight growth hormone secretion in healthy older men. Am J Physiol Endocrinol Metab. 2007 Sep;293(3):E769-75.

Circulating testosterone (T) and GH/IGF-I are diminished in healthy aging men. Short-term administration of high doses of T augments GH secretion in older men. However, effects of long-term, low-dose T supplementation on GH secretion are unknown. Our objective was to evaluate effects of long-term, low-dose T administration on nocturnal GH secretory dynamics and AM concentrations of IGF-I and IGFBP-3 in healthy older men (65-88 yr, n = 34) with low-normal T and IGF-I. In a double-masked, placebo-controlled, randomized study we assessed effects of low-dose T supplementation (100 mg im every 2 wk) for 26 wk on nocturnal GH secretory dynamics [8 PM to 8 AM, Q(20) min sampling, analyzed by multiparameter deconvolution and approximate entropy (ApEn) algorithms]. The results were that T administration increased serum total T by 33% (P = 0.004) and E(2) by 31% (P = 0.009) and decreased SHBG by 17% (P = 0.002) vs. placebo. T supplementation increased nocturnal integrated GH concentrations by 60% (P = 0.02) and pulsatile GH secretion by 79% (P = 0.05), primarily due to a twofold increase in GH secretory burst mass (P = 0.02) and a 1.9-fold increase in basal GH secretion rate (P = 0.05) vs. placebo. There were no significant changes in GH burst frequency or orderliness of GH release (ApEn). IGF-I levels increased by 22% (P = 0.02), with no significant change in IGFBP-3 levels after T vs. placebo. ***We conclude that low-dose T supplementation for 26 wk increases spontaneous nocturnal GH secretion and morning serum IGF-I concentrations in healthy older men.*** *PMID: 17550998*

Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Shalet SM. Dose titration and patient selection increases the efficacy of GH replacement in severely GH deficient adults. Clin Endocrinol (Oxf). 1999 Jun;50(6):749-57.

OBJECTIVE: Previous studies of GH replacement in adults have used unselected cohorts of GH deficient (GHD) adults and weight-based dosing regimens resulting in supraphysiological serum IGF-I levels and a high frequency of side-effects and withdrawal from these studies. By choosing patients with a high level of morbidity at baseline and using a low dose GH titration regimen we aimed to avoid over-replacement and increase the efficacy of treatment. DESIGN: ***An open study of GH replacement, initiating treatment with a dose of 0. 8 U/day and titrating the dose by 0.4 U increments to normalize the IGF-I SDS between - 2.0 and + 2.0 SD of the age-related normal range.*** *PATIENTS: 65 severely GHD patients (peak GH < 9 mU/l to provocative testing), 25 males, of mixed adult and childhood-onset and mean age 38.7 (range 17-72) years. Inclusion criterion was that of subjectively poor quality of life on clinical interview. MEASUREMENTS: Height, weight, waist and hip circumference were measured to allow calculation of body mass index (BMI) and waist-hip ratio (WHR). Bone mineral density (BMD) was measured by dual X-ray absorptiometry (DEXA). Serum haemoglobin A1C (HbA1C), lipid profile and insulin like growth factor 1 (IGF-I) were measured. The Psychological General Well-Being Schedule (PGWB) and Adult Growth Hormone Deficiency Assessment (AGHDA) self-rating questionnaires (SRQ) were used to assess quality of life. RESULTS: Baseline characteristics were consistent with those previously described in severely GHD adults; mean IGF-I SDS - 2.4 (+/- 2.7), BMI 28.8 (+/- 5. 4) kg/m2, total cholesterol 6.17 (+/- 1.2) mmol/l, reduced BMD z-scores at the lumbar spine (- 0.8 +/- 1.2) and femoral neck (- 0. 44 +/- 1.4), and SRQ scores considerably lower than reported in previous studies of GH deficient adults and normal controls. Following initiation of GH serum IGF-I SDS was increased significantly from baseline to a mean level of 0.15 +/- 2.7 (P < 0. 001) and 0.31 +/- 2.0 (P < 0.001) at three and eight months, respectively.* ***The mean PGWB score increased from 59.7 +/- 19.9 to 75. 8 +/- 15.0 (P < 0.001) and 73.7 +/- 19.5 (P = 0.001) at three and eight months, respectively. An increase of 14 points represents the largest improvement in quality of life, using this index, that has been reported in GHD adults.*** *The mean AGHDA score also demonstrated considerable improvement, falling from 15.3 +/- 6.0 to*

10.4 +/- 6.2 (P < 0.001) and 9.8 +/- 6.5 (P < 0.001) at three and eight months, respectively. The changes observed in both the PGWB and AGHDA scores between baseline and at both three and eight months were shown to correlate significantly with the respective baseline score. A significantly greater improvement was observed in the PGWB following GH replacement in those with a baseline PGWB score of < 60 than in those with a score > 60. This observation was significant at both three (27.1 vs 6.7, P = 0.0001) and eight (25.6 vs 3.3, P = 0.0003) months. All PGWB subscales showed significant improvement though that of vitality was of greatest magnitude. A strong correlation was observed between the generic and disease-specific SRQ (r = - 0.73, P < 0.001). CONCLUSIONS: ***The observed improvement in quality of life in GH deficient adults is proportional to the degree of impairment before commencing therapy. The use of low-dose titration and selection of a population with greater morbidity reduces the occurrence of over-replacement and increases the efficacy of treatment. This allows direction of resources to those in greatest need.***

Ninh NX, Thissen JP, Maiter D, Adam E, Mulumba N, Ketelslegers JM. Reduced liver insulin-like growth factor-I gene expression in young zinc-deprived rats is associated with a decrease in liver growth hormone (GH) receptors and serum GH-binding protein. J Endocrinol. 1995 Mar;144(3):449-56.

Zinc depletion attenuates growth and decreases circulating IGF-I. *To investigate the mechanisms responsible for the IGF-I decline, we determined the effects of dietary zinc (Zn) deficiency on body and organ growth, serum IGF-I, serum GH-binding protein (GHBP), liver GH receptors and liver expression of their corresponding gene. After 1 week of adaptation to a normal zinc diet, a zinc-deficient diet (ZD; Zn, 0 p.p.m.) or a zinc-normal diet (CTR; Zn, 75 p.p.m.) was available ad libitum to 4-week-old Wistar rats for 4 weeks. Pair-fed animals (PF) received the zinc-normal diet in the same absolute amount as that consumed the day before by the ZD group. The food intake of ZD and PF rats was reduced by 32% (P < 0.001) compared with the CTR group.* ***Zinc depletion specifically reduced body weight gain (-22%, P < 0.05), serum IGF-I concentrations (-52%, P < 0.001),*** *hepatic GH receptors (-28%; P < 0.05) and serum GHBP levels (-51%; P < 0.05), compared with the PF group. GH concentrations were reduced in ZD animals compared with CTR rats (P < 0.01). The caloric restriction of PF animals also decreased body weight gain (-50%, P < 0.001), serum IGF-I concentrations (-21%, P < 0.05), liver GH receptors (-38%, P < 0.001) and serum GHBP levels (-38%, P < 0.01), when compared with the CTR group. Both ZD and PF groups had reduced liver IGF-I and GH receptor/GHBP mRNA levels in comparison with the CTR group (P < 0.01).(ABSTRACT TRUNCATED AT 250 WORDS)*

Raben MS. Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab 1958; 18:301-3.

Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004 Apr 24;363(9418):1346-53.

BACKGROUND: Insulin-like growth factor (IGF)-I and its main binding protein, IGFBP-3, modulate cell growth and survival, and are thought to be important in tumour development. Circulating concentrations of IGF-I might be associated with an increased risk of cancer, whereas IGFBP-3 concentrations could be associated with a decreased cancer risk. METHODS: We did a systematic review and meta-regression analysis of case-control studies, including studies nested in cohorts, of the association between concentrations of IGF-I and IGFBP-3 and prostate, colorectal, premenopausal and postmenopausal breast, and lung cancer. Study-specific dose-response slopes were obtained by relating the natural log of odds ratios for different exposure levels to blood concentrations normalised to a percentile scale. FINDINGS: We identified 21 eligible studies (26 datasets), which included 3609 cases and 7137 controls. High concentrations of IGF-I were associated with an increased risk of prostate cancer (odds ratio comparing 75th with 25th percentile 1.49, 95% CI 1.14-1.95) and premenopausal breast cancer (1.65, 1.26-2.08) and high concentrations

of IGFBP-3 were associated with increased risk of premenopausal breast cancer (1.51, 1.01-2.27). Associations were larger in assessments of plasma samples than in serum samples, and in standard case-control studies compared with nested studies. INTERPRETATION: ***Circulating concentrations of IGF-I and IGFBP-3 are associated with an increased risk of common cancers, but associations are modest and vary between sites.*** *Although laboratory methods need to be standardised, these epidemiological observations could have major implications for assessment of risk and prevention of cancer. PMID: 15110491*

Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 1990 Aug 4;336(8710):285-8.

Rosen T, Wiren L, Wilhelmsen L, Wiklund I, Bengtsson BA. Decreased psychological well-being in adult patients with growth hormone deficiency. Clin Endocrinol (Oxf.) 1994;40:111-116.

Rosenfalck AM, Fisker S, Hilsted J, Dinesen B, Volund A, Jorgensen JO, Christiansen JS, Madsbad S. The effect of the deterioration of insulin sensitivity on beta-cell function in growth-hormone-deficient adults following 4-month growth hormone replacement therapy. Growth Horm IGF Res. 1999 Apr;9(2):96-105.

The purpose of the present study was to evaluate the combined effect of GH treatment on body composition and glucose metabolism, with special focus on beta-cell function in adult GHD patients. In a double-blind placebo-controlled design, 24 GHD adults (18M/6F), were randomized to 4 months treatment with biosynthetic GH 2 IU/m2s.c. daily (n =13) or placebo (n =11). At inclusion and 4 months later an oral glucose tolerance test (OGTT), a frequently sampled intravenous glucose tolerance test (FSIGT) and dual-energy X-ray absorptiometry (DXA) whole-body scanning were performed. During the study period, body weight decreased 1.6 kg from 94.0 +/- 18.7 to 92.4 +/- 19.4 kg (mean +/- SD) (P<0.05) in the GH-treated group, but remained unchanged in the placebo group. Fat mass decreased from 32.4 +/- 9.6 to 28.1 +/- 10.5 kg (P<0.001), whereas lean body mass increased from 58.3 +/- 11.5 to 61.0 +/- 11.7 kg (P<0.01) in the GH-treated group. Treatment with GH for 4 months resulted in a significant increase in fasting blood glucose (before GH 5.0 +/- 0.3 and after 5.4 +/- 0.6 mmol/l, P<0.05), fasting plasma insulin (before GH 38.4 +/- 30.2 and after 55.3 +/- 34.7 pmol/l, P<0.02) and fasting proinsulin (before 8. 1 +/- 6.7 and after 14.6 +/- 16.1 pmol/l, P<0.05). The insulin sensitivity index SI, estimated by Bergmans Minimal Model, decreased significantly [before GH 1.1 +/- 0.7 and after 0.4 +/- 0.2 10(-4)(min x pmol/l), P<0.003]. The non-insulin-dependent glucose uptake (glucose effectiveness SG did not change (before GH 0.017 +/- 0.005 and after 0.015 +/- 0.006 min-1, NS). Insulin secretion was enhanced during GH therapy, but insufficiently to match the changes in SI, resulting in a higher blood glucose level during an OGTT. Blood glucose at 120 min was 5.5 and 6.3 mmol/l before and after GH treatment, respectively (P = 0.07). One patient developed impaired glucose tolerance. Short-term GH replacement therapy in a dose of about 2 IU/m2 daily in GHD adults induces a reduction in insulin sensitivity, despite favourable changes in body composition, and an inadequate enhancement of insulin secretion. (NOTE-This study used a very high daily dose of 2iu/m2. For a 6'6", 80kg man whose SA is 2.1 m2, that amounts to over 4iu/day. Normal replacement doses is 1iu/day!)

SA calculation: $(\text{height[cm]} \cdot \text{weight[kg]} / 3600)^{1/2}$ -or- $(\text{height[in.]} \cdot \text{weight[lb.]}) / 3131)^{1/2}$

Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. N Eng J Med 1990 Jul, 323 (l):l-6.

Landmark study of adults not diagnosed with growth hormone deficiency: *6 month baseline and 6 month treatment period for 21 healthy men with IGF-1 levels below 350U/L. Results: and 8.8% increase in lean body mass, a 14.4 percent decrease in adipose-tissue mass, a 1.6% increase in avg. lumbar vertebral bone density, and a 7.1% increase in skin thickness. Conclusion: Diminished*

secretion of growth hormone is responsible in part for the decrease in lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur with old age.

Russell-Jones DL, Watts GF, Weissberger A, Naoumova R, Myers J, Thompson GR, Sonksen PH. The effect of growth hormone replacement on serum lipids, lipoproteins, apolipoproteins and cholesterol precursors in adult growth hormone deficient patients. Clin Endocrinol (Oxf). 1994 Sep;41(3):345-50.

OBJECTIVE: Adult patients with growth hormone deficiency are thought to be at higher risk of mortality from cardiovascular disease. We therefore investigated the effect of recombinant human growth hormone (rhGH) replacement therapy on fasting serum concentrations of lipids, lipoproteins and cholesterol precursors in adult growth hormone deficient patients. DESIGN: Double-blind placebo controlled trial. Patients were randomly allocated to placebo or rhGH replacement therapy (0.018 U/kg/day for 1 month followed by 0.036 U/kg/day for 1 month). PATIENTS: Eighteen patients with severe growth hormone deficiency. MEASUREMENTS: Fasting lipid, lipoprotein and cholesterol precursors (lathosterol and mevalonic acid) were measured at baseline and after 2 months. RESULTS: In the rhGH treated group ***there was a significant fall in serum cholesterol*** *(P < 0.01) (6.44 +/- 0.49 to 5.71 +/- 0.48 mmol/l),* ***LDL cholesterol*** *(P < 0.02) (4.29 +/- 0.49 to 3.62 +/- 0.44 mmol/l),* ***LDL cholesterol/HDL cholesterol ratio*** *(P < 0.02) (3.99 +/- 0.62 to 3.26 +/- 0.39),* ***apolipoprotein B*** *(P < 0.01 (1.30 +/- 0.11 to 1.15 +/- 0.11 g/l) and* ***mevalonic acid*** *(P < 0.05) (13.4 +/- 10.96 to 6.21 +/- 1.91 micrograms/l). There were no significant changes in triglycerides, HDL cholesterol, apolipoprotein A1, lipoprotein (a) or lathosterol concentrations. In the GH treated group the rise in serum insulin was inversely correlated with the fall in cholesterol (P < 0.05), LDL cholesterol (P < 0.01) and apolipoprotein B (P < 0.01). There were no significant changes in any of the measured variables in the placebo group. CONCLUSION: We conclude that GH may be involved in the regulation of lipid and lipoprotein metabolism and that rhGH replacement therapy of adult GHD patients is associated with beneficial changes in lipid and lipoprotein profiles. The reduction in mevalonic acid is consistent with up-regulation of hepatic LDL receptors caused by GH and this may explain the fall in LDL cholesterol and apolipoprotein B concentrations.*

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. N Engl J Med 1989 Dec 28; 321(26):1797-803.

Lean body mass increased by 5.5kg, fat mass decreased by 5.7kg, basal metabolic rate increased significantly, plasma cholesterol decreased.

Savine R, Sonksen P. Growth hormone - hormone replacement for the somatopause? Horm Res. 2000;53 Suppl 3:37-41.

Twenty-four-hour growth hormone (GH) secretion reaches a peak at around puberty and by the age of 21 has begun to decrease. ***Thereafter the fall in GH secretion is progressive such that by the age of 60 most adults have total 24-hour secretion rates indistinguishable from those of hypopituitary patients with organic lesions in the pituitary gland.*** *Patterns of GH secretion are similar to those in younger people but GH pulses are markedly reduced in amplitude. Sleep and exercise remain the major stimuli for GH secretion. The fall in GH secretion seen with ageing coincides with changes in body composition and lipid metabolism that are similar to those seen in adults with GH deficiency. In elderly subjects, although GH secretion is markedly reduced, remaining GH secretion correlates closely with body composition (particularly with lean body mass and inversely with central abdominal fat). Pioneering studies carried out by Rudman showed that GH administration to elderly subjects with low insulin-like growth factor-I levels resulted in reversal of many of the changes associated with GH deficiency, namely an increase in lean body mass and bone mineral density and a reduction in body fat and plasma cholesterol. These changes were remarkably similar to those shown a year earlier in adults with GH deficiency given GH replacement. Subsequent studies of GH replacement in elderly adults have confirmed Rudman's initial observations but have been dominated by side effects*

which have led to a high number of dropouts. It is now clear that the elderly are very sensitive to GH and the doses used need to be very low, increased very slowly and tailored to the individual needs of each patient. Using this more cautious approach, recent studies have been very positive. A series of papers from Blackman's group, presented at the US endocrine meeting in San Diego in 1999, investigated the effects of GH with or without testosterone supplements (in men) and oestrogen supplements (in women). Their results showed positive effects of GH on lean body mass, central fat, low-density lipoprotein cholesterol and aerobic capacity. In many instances there was a positive interaction between GH and hormone replacement with testosterone and oestrogen, but it appeared that GH showed the most potent anabolic effects. Clearly more studies are needed before GH replacement for the elderly becomes established. Safety issues will require close scrutiny, but the data available so far are sufficiently positive to undertake large multicentre, placebo-controlled trials, particularly looking at endpoints associated with prevention of frailty and loss of independence.

Savine R, Sönksen PH. Is the somatopause an indication for growth hormone replacement? J Endocrinol Invest. 1999;22(5 Suppl):142-9.

In the normal population, a gradual and progressive fall in spontaneous growth hormone (GH) secretion occurs with increasing age and is reflected in a parallel fall in circulating insulin-like growth factor (IGF)-I, reduction in lean body mass, increase in body fat and rise in low-density lipoprotein (LDL) cholesterol. Aging is also associated with a progressive failure of body functions and particularly with an increasing lack of physical strength and mobility. Many problems of aging are attributable to the progressive loss of lean tissues and to catabolic events. This can be and often is associated with a progressive decline in independence and quality of life, leading eventually to a prolonged dependence on others, followed by a distressing process of death. By analogy with the fall in ovarian function that inevitably eventually occurs in women with increasing age, this fall in GH secretion has been termed the somatopause. In cross-sectional studies on elderly people, the amount of GH secreted spontaneously correlates well with "good risk factors" such as body composition, mobility, lipid profiles and blood pressure. The important question that these scientific facts raises is whether this fall in GH secretion with increasing years is an important physiological safety event of the normal aging process, or whether it marks the development of GH deficiency which would benefit from GH replacement. It is established that a number of the clinical features of the somatopause are shared with the syndrome of adult-onset GH deficiency and Rudman first proposed the importance of GH in maintaining health and vitality with increasing age many years ago. In 1989, GH replacement was shown to be beneficial in adults with GH deficiency, and in 1990 Rudman showed remarkably similar beneficial effects in a group of elderly men with low plasma IGF-I values, but no underlying pituitary pathology, who were administered GH. In these adults, low doses of GH increased lean body mass and bone mineral density, decreased body fat and lowered LDL cholesterol. Sleep and exercise are the two major stimuli for secretion of GH in normal people and there is evidence to indicate that the GH response to exercise is essential for developing and maintaining physical fitness. There is also some evidence to suggest that adults who continue to exercise with increasing age better maintain lean body mass and physiological GH secretion. So, is the somatopause due to lifestyle changes consequent upon indolence, too much TV and modern living? Is it better to chase our patients (and colleagues?) down to the gym three times a week or should we give them an injection of GH before they sit down with a can of lager to watch the World Cup? Should the fact that elite athletes in virtually all sports have decided from their own "clinical trials" that GH is a performance-enhancing drug, when combined with exercise, have any influence on our strategy? The long-term safety of GH replacement is clearly a matter for concern but we do now know that life without GH is poor both in quantity and quality. ***Is there a safe therapeutic window that allows GH replacement in the somatopause to add years to life, quality to these years, and maybe even improves the quality of death?*** *PMID: 10442584*

Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV associated wasting: a randomized, placebo-controlled trial. Ann Intern Med 1996;125:873-882.

Skaggs SR, Christ DM Exogenous human growth hormone reduces body fat in obese women Horm Res 1991; 35(1):19-24.

Exogenous GH reduces body fat in obese women in the apparent absence of significant kilocaloric restriction.

Sigurjonsdottir HA, Andrew R, Stimson RH, Johannsson G, Walker BR. Lack of regulation of 11beta-hydroxysteroid dehydrogenase type 1 during short-term manipulation of GH in patients with hypopituitarism. Eur J Endocrinol. 2009 Sep;161(3):375-80.

OBJECTIVE: Evidence from long-term clinical studies measuring urinary steroid ratios, and from in vitro studies, suggests that GH administered for longer than 2 months down-regulates 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1), thereby reducing cortisol regeneration in liver and adipose tissue. We aimed to measure acute effects of GH on 11beta-HSD1 in liver and adipose tissue in vivo, including using a stable isotope tracer. DESIGN: Observational studies of GH withdrawal and reintroduction in patients with hypopituitarism. METHODS: Twelve men with benign pituitary disease causing GH and ACTH deficiency on stable replacement therapy for >6 months were studied after GH withdrawal for 3 weeks, and after either placebo or GH injections were reintroduced for another 3 weeks. We measured cortisol kinetics during 9,11,12,12-(2)H(4)-cortisol (d4-cortisol) infusion, urinary cortisol/cortisone metabolite ratios, liver 11beta-HSD1 by appearance of plasma cortisol after oral cortisone, and 11beta-HSD1 mRNA levels in subcutaneous adipose biopsies. RESULTS: GH withdrawal and reintroduction had no effect on 9,12,12-[(2)H](3)-cortisol (d3-cortisol) appearance, urinary cortisol/cortisone metabolite ratios, initial appearance of cortisol after oral cortisone, or adipose 11beta-HSD1 mRNA. ***GH withdrawal increased plasma cortisol 30-180 min after oral cortisone,*** *increased d4-cortisol clearance, and decreased relative excretion of 5alpha-reduced cortisol metabolites. CONCLUSIONS:* ***In this setting, GH did not regulate 11beta-HSD1 rapidly in vivo in humans. Altered cortisol metabolism with longer term changes in GH may reflect indirect effects on 11beta-HSD1.*** *These data do not suggest that glucocorticoid replacement doses need to be increased immediately after introducing GH therapy to compensate for reduced 11beta-HSD1 activity, although dose adjustment may be required in the longer term. PMID: 19549748*

Slonim AE, Bulone L, Damore MB, Goldberg T, Wingertzahn MA, McKinley MJ. A preliminary study of growth hormone therapy for Crohn's disease. N Engl J Med. 2000 Jun 1;342(22):1633-7.

BACKGROUND: Crohn's disease is a chronic inflammatory disorder of the bowel. In a preliminary study, we evaluated whether the administration of growth hormone (somatropin) as well as a high-protein diet would ameliorate the symptoms of the disease. METHODS: We randomly assigned 37 adults with moderate-to-severe active Crohn's disease to four months of self-administered injections of growth hormone (loading dose, 5 mg per day subcutaneously for one week, followed by a maintenance dose of 1.5 mg per day) or placebo. We instructed all patients to increase their protein intake to at least 2 g per kilogram of body weight per day. Patients continued to be treated by their usual physicians and to receive other medications for Crohn's disease. The primary end point was the change in scores on the Crohn's Disease Activity Index from base line to month 4. Scores can range from 0 to 600, with higher scores indicating more disease activity. RESULTS: At base line, the mean (+/-SD) score on the Crohn's Disease Activity Index was somewhat higher among the 19 patients in the growth hormone group than among the 18 patients in the placebo group (287+/-134 vs. 213+/-120, P=0.09). Three patients in the placebo group withdrew before their first follow-up visit and were not included in the data analysis. ***At four months, the Crohn's Disease Activity Index score had decreased by a mean of 143+/-144 points in the growth hormone group, as compared with a***

decrease of 19+/-63 points in the placebo group (P=0.004). *Side effects in the growth hormone group included edema (in 10 patients) and headache (in 5) and usually resolved within the first month of treatment. CONCLUSIONS: Our preliminary study suggests that growth hormone may be a beneficial treatment for patients with Crohn's disease.* ***(Side effects due to very high dose(1.5mg/day). The question is whether a small physiologic dose (0.2-0,4mg/day) would be just as effective.—HHL)***

Smith JC, Evans LM, Wilkinson I, Goodfellow J, Cockcroft JR, Scanlon MF, Davies JS. Effects of GH replacement on endothelial function and large-artery stiffness in GH-deficient adults: a randomized, double-blind, placebo-controlled study. Clin Endocrinol (Oxf). 2002 Apr;56(4):493-501.

OBJECTIVES: Hypopituitary adults with growth hormone deficiency (GHD) have an increased cardiovascular mortality, although the mechanisms remain unclear. Endothelial dysfunction, characterized by reduced nitric oxide (NO) bioavailability, is a key early event in atherogenesis and is associated with increased vascular smooth muscle tone and arterial stiffening. DESIGN AND PATIENTS: In a randomized, double-blind, placebo-controlled study, we investigated the effects of GH replacement on endothelial function and large-artery stiffness in 32 GHD adults (19 males, 13 females) (age range 19-64 years) over a 6-month period. Thirty-two age- and sex-matched healthy controls were also studied. MEASUREMENTS: Endothelial function was assessed using ultrasonic wall tracking to measure flow-mediated dilatation (FMD) of the brachial artery. Large artery stiffness was assessed by pulse wave analysis of the radial artery pressure waveform, allowing determination of the corresponding central arterial pressure waveform and derivation of the augmentation index. Fasting lipid profiles, glucose and insulin were also measured. RESULTS: At baseline, FMD (mean +/- SD) was impaired in GH-deficient subjects vs. controls (3.4 +/- 2.3 vs. 5.7 +/- 2.0%, P < 0.0001), although endothelium-independent dilatation was similar. The augmentation index was higher in GH-deficient subjects vs. controls (23 +/- 12 vs. 14 +/- 14%, P < 0.01). GH-deficient subjects had higher LDL cholesterol (4.1 +/- 0.8 vs. 3.5 +/- 0.8 mmol/l, P < 0.01) and lower HDL cholesterol (1.1 +/- 0.3 vs. 1.4 +/- 0.4 mmol/l, P < 0.01). In GH-deficient subjects, there were inverse correlations between LDL cholesterol and FMD (r = -0.40, P < 0.05) and between FMD and the augmentation index (r = -0.58, P < 0.01). Regression analysis identified FMD as an independent predictor of the augmentation index (P < 0.0001). In comparison with baseline, GH replacement resulted in an increase in FMD (5.0 +/- 2.6 vs. 2.8 +/- 1.9%, P < 0.01). There were decreases in central aortic systolic pressure (117 +/- 15 vs. 123 +/- 17 mmHg, P < 0.01), diastolic pressure (82 +/- 10 vs. 86 +/- 8 mmHg, P < 0.01) and the augmentation index (22 +/- 8% vs. 26 +/- 10%, P < 0.05) despite unchanged brachial pressure indices. LDL cholesterol also decreased (3.5 +/- 0.8 vs. 4.2 +/- 0.8 mmol/l, P < 0.01). There were no significant changes in the placebo group. CONCLUSIONS: ***Adult GHD is associated with endothelial dysfunction and increased large-artery stiffness. An improvement in endothelial function and a reduction in arterial stiffness following GH replacement suggests an important therapeutic role for GH in reducing cardiovascular risk associated with adult GHD.***

Sonntag WE, Lynch CD, Cooney PT, Hutchins PM. Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. Endocrinology. 1997 Aug;138(8):3515-20.

Several reports have demonstrated that cerebral blood flow decreases with age and may contribute to neurodegenerative changes found in aging animals and man. Because GH and insulin-like growth factor 1 (IGF-1) decrease with age and have an important role in vascular maintenance and remodeling, we hypothesized that the decrease in cerebral blood flow is associated with a rarefaction of cerebral blood vessels resulting from a decline in GH and IGF-1. Measurements of vascular density (number of vessels/cortical surface area) in both Brown-Norway and Fisher 344/Brown-Norway rats were made at 5, 13, and 29 months of age using chronic cranial window chambers that allowed viewing of the cortical surface and its corresponding vasculature. Correlations were made with plasma levels of IGF-1. In Brown-Norway rats, arteriolar density decreased from 15.53 +/- 1.08 to 9.49 +/- 0.62 endpoints/mm2 in 7- and 29-month-old animals, respectively (P < 0.05). A decline was

observed also in arteriolar anastomoses [3.05 +/- 0.21 to 1.42 +/- 0.24 connections/mm2 in 7- and 29-month-old animals (P < 0.05)]. Venular density did not decrease with age. Similar changes were observed in Fisher 344/Brown-Norway rats. The number of cortical surface arterioles was correlated with plasma IGF-1 levels at the time of vascular mapping (r = 0.772, P < 0.05), and injection of bovine GH (0.25 mg/kg, s.c., twice daily for 35 days) to 30-month-old animals increased both plasma IGF-1 and the number of cortical arterioles. These data indicate that: 1) vascular density on the surface of the cortex decreases with age; 2) vascular density is correlated with plasma levels of IGF-1; and 3) injection of GH increases cortical vascular density in older animals. ***We conclude that GH and IGF-1 have an important role in the decline in vascular density with age and suggest that decreases in vascular density may have important implications for the age-related decline in cerebral blood flow and brain function.***

Spielhagen C, Schwahn C, Möller K, Friedrich N, Kohlmann T, Moock J, Kołtowska-Häggström M, Nauck M, Buchfelder M, Wallaschofski H. The benefit of long-term growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency: Results of the German KIMS database. Growth Horm IGF Res. 2010 Nov 18. [Epub ahead of print]

OBJECTIVE: To evaluate the treatment effects of long-term growth hormone (GH) replacement therapy in adults with GH deficiency (GHD) who were followed in KIMS Germany (Pfizer International Metabolic Database), a national surveillance study. DESIGN: The analysis was performed using baseline and ***long-term data (range: 4-10years)*** *of 440 consecutively documented patients (216 women and 224 men) with GHD, aged 20 to 49years, enrolled in KIMS Germany. Serum insulin-like growth factor I (IGF-I), fasting blood glucose, fasting serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) as well as body mass index (BMI), waist circumference (WC) and hip circumference (HC) at baseline and at last visit were studied. Furthermore, QoL-AGHDA score was determined to assess quality-of-life (QoL). RESULTS:* ***The mean dose of GH over all years was 0.41mg per day in women and 0.37mg per day in men.*** *IGF-I and IGF-I SDS levels (standard deviation score) increased significantly (p<0.001) during GH treatment. The QoL-AGHDA score decreased significantly (p<0.001), indicating long-lasting improvement in QoL. In total cholesterol, LDL-C and fasting blood glucose, no significant changes were found. Only six patients developed type 2 diabetes during follow-up. Females and males similarly increased significantly in BMI, WC and HC. During GH treatment, recurrences of pituitary or central nervous system tumours or further de novo neoplasia were reported in 6 or 11 patients, respectively. The number of the most frequently reported GH treatment-associated adverse events was low. CONCLUSION: These observational data show long-term beneficial effects of GH replacement therapy on QoL and show no significant effects on total cholesterol, LDL-C or BMI, WC and HC. Additionally, our data indicate that GH replacement therapy in adults is well tolerated. PMID: 21093334* ***(The reason that more benefits are not seen is that such patients generally have multiple hormone deficiencies that are not corrected at all, or not corrected properly—thyroid, cortisol, DHEA, testosterone, estradiol, progesterone, etc.-HHL)***

Stewart PM, Toogood AA, Tomlinson JW. Growth hormone, insulin-like growth factor-I and the cortisol-cortisone shuttle. Horm Res. 2001;56 Suppl 1:1-6.

In peripheral tissues, corticosteroid hormone action is determined, in part, through the activity of 11beta-hydroxysteroid dehydrogenases (11beta-HSD), two isozymes of which interconvert hormonally active cortisol (F) and inactive cortisone (E). 11beta-HSD type 2 (11beta-HSD2) inactivates F to E in the kidney, whilst 11beta-HSD type 1 (11beta-HSD1) principally performs the reverse reaction activating F from E in the liver and adipose tissue. Alteration in expression of these 11beta-HSD isozymes in peripheral tissues modifies corticosteroid action: loss of 11beta-HSD2 activity in the kidney results in cortisol-induced mineralocorticoid excess, and loss of hepatic 11beta-HSD1 activity improves insulin sensitivity through a reduction in cortisol-induced gluconeogenesis and hepatic glucose output. Conversely, overexpression of 11beta-HSD1 in omental adipose tissue can stimulate glucocorticoid-induced adipocyte differentiation which may lead to central obesity. Patients with hypopituitarism have many clinical features in common with patients with Cushing's syndrome--

notably visceral obesity, insulin resistance, osteoporosis and increased vascular mortality. Our hypothesis was that many of these features may be explained by an effect of growth hormone (GH) on the 11beta-HSD isozymes. As assessed by urinary free cortisol/urinary free cortisone ratios and endorsed through in vitro studies, neither GH nor insulin-like growth factor (IGF)-I affect 11beta-HSD2 activity. Patients with acromegaly show a reduction in hepatic-derived metabolites of cortisol/cortisone - levels return to normal when GH concentrations are normalized. Conversely, patients with GH deficiency in the setting of hypopituitarism demonstrate an increased cortisol/cortisone metabolite ratio and reduction in circulating cortisol concentrations in patients on hydrocortisone replacement. Treatment with low-dose GH replacement reverses these abnormalities. These clinical data suggest that GH (and/or IGF-I) inhibits 11beta-HSD1 (i.e. E to F conversion) (parallel in vitro studies suggest that IGF-I and not GH inhibits 11beta-HSD1). These findings have important clinical ramifications. Firstly, the GH-mediated increase in cortisol metabolism (mediated via reduced E to F conversion) may precipitate adrenal insufficiency in hypopituitary patients with partial adrenocorticotropic hormone deficiency commencing GH therapy. Secondly, many of the phenotypic features of hypopituitarism can be explained by an alteration in 11beta-HSD1 activity: ***GH deficiency effectively increases cortisol production in key target tissues including liver and adipose tissue, promoting insulin resistance and visceral adiposity.*** *Thirdly, the reported beneficial effects of GH on cardiovascular risk factors in patients with hypopituitarism may be an indirect effect via alterations in cortisol metabolism. Finally, the GH/IGF-I modulation of cortisol metabolism may underpin the pathogenesis of common diseases such as central obesity and idiopathic osteoporosis. Patients with central obesity but with no evidence of hypopituitarism have relative GH deficiency and* ***it is exciting to speculate that low-dose GH treatment in this group, by inhibiting cortisol generation within omental fat, may offer a novel therapeutic approach.***

Svensson J, Sunnerhagen KS, Johannsson G. Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. J Clin Endocrinol Metab. 2003 May;88(5):2061-9.

GH replacement therapy in adults with adult-onset GH deficiency (GHD) has been shown to increase isometric and isokinetic muscle strength in a few trials with limited numbers of patients. In this single center, prospective, open-label study, the effects of 5-yr GH replacement therapy on muscle function were determined in 109 consecutive adults (61 men and 48 women) with adult-onset GHD. The mean initial GH dose was 0.88 mg/d. The dose was gradually lowered, and after 5 yr the mean dose was 0.46 mg/d. The mean IGF-I SD score increased from -1.54 at baseline to 1.53 at study end. A sustained increase in lean body mass and decrease in body fat was observed. The GH treatment induced persistent increases in isometric knee flexor strength, concentric knee flexor strength at an angular velocity of 60 degrees/sec, and right-hand peak grip strength. After correction for age and gender using observed/predicted value ratios, a sustained increase was also observed in isometric (60 degrees) and concentric (180 degrees/sec) knee extensor strength, average right-hand grip strength for 10 sec, and left-hand grip strength. At study end, knee flexor and extensor strength was 96-104% of predicted and hand grip strength was 84-90% of predicted values. The local muscle endurance was transiently decreased after correction for age and gender. No gender difference was found in the treatment responses in muscle strength. However, muscle strength (also after correction for age and gender) was lower in women than men throughout the study period. ***In conclusion, GH replacement therapy in adults with adult-onset GHD normalized isometric and isokinetic knee flexor and extensor strength. Hand grip strength increased but was not fully normalized.***

Svensson J, Bengtsson BA, Rosen T, Oden A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12.

A retrospective comparison was performed between 1411 hypopituitary adults without GH replacement [mean age, 56.9 (sd 18.6) yr] and the normal population in terms of fatal and nonfatal morbidity. A similar prospective comparison was then made in 289 hypopituitary patients on long-

term GH replacement [mean age, 47.6 (sd 14.8) yr; mean duration of GH treatment, 60 months].In the 1411 hypopituitary patients without GH replacement, overall mortality (P < 0.001), and the rates of myocardial infarctions (P < 0.01), cerebrovascular events (P < 0.001), and malignancies (P < 0.001) were increased compared with the normal population. Colorectal cancer was the most common malignancy in this cohort (P < 0.001 vs. the background population). In the 289 hypopituitary patients on GH replacement, overall mortality and the rate of malignancies were similar to the normal population. In the hypopituitary adults on GH therapy, the rate of myocardial infarctions was lower than that in the background population (P < 0.05), and there was a tendency toward an increased rate of cerebrovascular events. In conclusion, overall mortality and the rate of myocardial infarctions were increased in hypopituitary patients without GH replacement. ***An increased rate of malignancies was observed in the hypopituitary adults without GH therapy, with a predominance of colorectal cancer.*** *GH replacement appeared to provide protection from myocardial infarctions. The rate of cerebrovascular events tended to be increased also in hypopituitary adults on GH therapy.*

Svensson J, Bengtsson BA, Taskinen MR, Wiklund O, Johannsson G. A nine-month, placebo-controlled study of the effects of growth hormone treatment on lipoproteins and LDL size in abdominally obese men. Growth Horm IGF Res. 2000 Jun;10(3):118-26.

Abdominal/visceral obesity is associated with blunted growth hormone (GH) secretion and an unfavourable lipoprotein pattern. In this study, the effect of GH treatment on LDL size and on serum lipoprotein concentrations was determined in abdominally obese men. Thirty men, aged 48-66 years, with a body mass index (BMI) of 25-35 kg/m(2)and a waist:hip ratio of >0.95, received treatment with GH (9. 5 microg/kg/day) or placebo for 9 months. ***Serum concentrations of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB) were reduced*** *(P<0.05, P<0.05 and P<0.001 vs placebo, respectively). Serum lipoprotein(a) [Lp(a)] concentration increased (P<0.05 vs. placebo). Mean low density lipoprotein (LDL) particle diameter was marginally increased by active treatment as compared with placebo (P =0.08). No changes were observed in the serum concentrations of high density lipoprotein-cholesterol (HDL-C), apolipoprotein A-I (apoA-I) and apolipoprotein E (apoE). In conclusion, 9 months of GH treatment in abdominally obese men beneficially reduced serum concentrations of TC, LDL-C and apoB, and marginally increased mean LDL diameter, while serum Lp(a) increased. The ultimate effect of GH therapy on the cardiovascular risk remains, however, to be determined.*

Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet. 2002 Jul 27;360(9329):273-7.

BACKGROUND: Growth hormone raises serum concentrations of insulin-like growth factor IGF-I, which is mitogenic and antiapoptotic. There is evidence that raised endogenous levels of growth hormone and IGF-I might be associated with increased risk of certain solid cancers, but there have been no data on long-term risks of solid cancers after growth hormone treatment. METHODS: We did a cohort study to investigate cancer incidence and mortality in 1848 patients in the UK who were treated during childhood and early adulthood with human pituitary growth hormone during the period from 1959 to 1985. Patients were followed up for cancer incidence to December, 1995 and for mortality to December, 2000. Risk of cancer in the cohort was compared with that in the general population, controlling for age, sex, and calendar period. FINDINGS: Patients treated with human pituitary growth hormone had significantly raised risks of mortality from cancer overall (standardised mortality ratio 2.8, 95% CI 1.3-5.1; ten cases), colorectal cancer (10.8, 1.3-38.8; two cases), and Hodgkin's disease (11.4, 1.4-41.3; two cases). Incidence of colorectal cancer was also greatly raised (7.9, 1.0-28.7). After exclusion of patients whose original diagnosis rendered them at high risk of cancer, the significance and size of the risks of colorectal cancer incidence and mortality, and of Hodgkin's disease mortality were increased. INTERPRETATION: Although based on small numbers, the risk of colorectal cancer is of some concern and further investigation in other cohorts is needed.

We have no evidence as to whether growth hormone in modern dosage regimens is associated with an increased risk of colorectal cancer.

Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critical ill adults. N Engl J Med 1999;341:785-792.

BACKGROUND: The administration of growth hormone can attenuate the catabolic response to injury, surgery, and sepsis. However, the effect of high doses of growth hormone on the length of stay in intensive care and in the hospital, the duration of mechanical ventilation, and the outcome in critically ill adults who are hospitalized for long periods is not known.METHODS: We carried out two prospective, multicenter, double-blind, randomized, placebo-controlled trials in parallel involving 247 Finnish patients and 285 patients in other European countries who had been in an intensive care unit for 5 to 7 days and who were expected to require intensive care for at least 10 days. The patients had had cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure. The patients received either growth hormone (mean [+/-SD] daily dose, 0.10 +/- 0.02 mg per kilogram of body weight) or placebo until discharge from intensive care or for a maximum of 21 days. RESULTS: The in-hospital mortality rate was higher in the patients who received growth hormone than in those who did not (P<0.001 for both studies). In the Finnish study, the mortality rate was 39 percent in the growth hormone group, as compared with 20 percent in the placebo group. The respective rates in the multinational study were 44 percent and 18 percent. The relative risk of death for patients receiving growth hormone was 1.9 (95 percent confidence interval, 1.3 to 2.9) in the Finnish study and 2.4 (95 percent confidence interval, 1.6 to 3.5) in the multinational study. Among the survivors, the length of stay in intensive care and in the hospital and the duration of mechanical ventilation were prolonged in the growth hormone group. CONCLUSIONS: In patients with prolonged critical illness, high doses of growth hormone are associated with increased morbidity and mortality.PMID: 10477776

(GH therapy increased mortality in critically ill patients, however, the doses given were HUGE. Patients less than 60kg received ***5.3mg*** *or* ***15.9U/day****, those weighing >60kg were given* ***8mg*** *or* ***24U/day!*** *GH has strong anti-cortisol effects, and critically ill persons are often cortisol-deficient. This study is often cited when the author wants to highlight how "dangerous" GH is. The normal replacement GH dose for adults is* ***0.2 to 0.6mg/day****-HHL).*

Tschöp M, Lahner H, Feldmeier H, Grasberger H, Morrison KM, Janssen OE, Attanasio AF, Strasburger CJ. Effects of growth hormone replacement therapy on levels of cortisol and cortisol-binding globulin in hypopituitary adults. Eur J Endocrinol. 2000 Dec;143(6):769-73.

OBJECTIVE: To determine if human growth hormone (hGH) replacement therapy alters pharmacokinetics of hydrocortisone (CS) substitution in hypopituitary adults. DESIGN: To this aim, we analysed serum and salivary CS profiles 270 min after oral CS administration at baseline and 6 and 12 months after initiation of hGH replacement therapy. METHODS: Serum IGF-I, cortisol-binding globulin (CBG), thyroxine-binding globulin (TBG) and sex hormone-binding hormone (SHBG) were measured using commercially available radioimmunoassays. In-house immunofluorometric assays were employed for measurements of CS and hGH. RESULTS: hGH replacement did not change total serum CS bioavailability (area under the serum cortisol profile curve). ***Interference of orally administered CS with salivary measurement of free CS (fCS) caused significant bias.*** *Therefore, fCS levels were calculated from their total CS and cortisol-binding globulin (CBG) levels.* ***CBG decreased by approximately 30% after both 6 and 12 months of hGH*** *replacement therapy (n=20, P<0.01). A significant negative correlation between deltaCBG (CBG6months-CBGbaseline) and deltaIGF-I (IGF-I6months-IGF-Ibaseline) was observed (P=0.04).* ***The calculated values of free CS tended to increase with physiological hGH replacement, but this effect was marginal and did not reach statistical significance.*** *In contrast to the CBG concentrations, plasma levels of sex hormone-binding globulin and thyroxine-binding globulin were essentially stable. CONCLUSION: Given that no clinically relevant alterations in pharmacokinetics of CS were evoked by initiation of hGH replacement in hypopituitary adults, we conclude that CS substitution does not require dose adjustment after initiation of hGH replacement. PMID: 11124860*

Toogood AA, Taylor NF, Shalet SM, Monson JP. Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab. 2000 Apr;85(4):1727-30.

11 beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) functions as a net reductase converting cortisone to cortisol. GH inhibits 11beta-HSD1, resulting in a shift in cortisol metabolism favoring cortisone, an observation that may have significance in patients with ACTH deficiency who are unable to compensate for such changes. We have studied the effect of three doses of GH replacement (0.17, 0.33, and 0.5 mg each given for 12 weeks in ascending order) on cortisol metabolism in nine patients, aged 62-70 yr, with hypopituitarism who were receiving fixed doses of oral hydrocortisone. Serum insulin-like growth factor I levels rose in a dose-dependent manner over the course of the study. Fat mass decreased significantly at 24 weeks (P = 0.02), a change that was maintained at 36 weeks. Fasting serum insulin levels did not change significantly over the course of the study. ***The ratio of urine cortisol to cortisone metabolites (Fm/Em) fell significantly at 12 weeks (GH dose, 0.17 mg/day) from 1.32 (0.91-2.20) at baseline to 1.08 (0.89-2.11) (P < 0.05).*** *Although it did not fall further as the dose of GH was increased, the reduction in the Fm/Em ratio persisted at 24 weeks (GH dose, 0.33 mg/day), 1.09 (0.8-2.11) (P < 0.05 vs. baseline), and 36 weeks (GH dose, 0.5 mg/day), 1.19 (0.82-2.31) (P < 0.05 vs. baseline).* ***The Fm/Em ratio did not correlate with serum insulin-like growth factor I, fat mass, or fasting insulin levels at any time during the study.*** *This study confirms the inhibitory effect of GH on 11beta-HSD1 but has shown that the effect occurs maximally at very low GH doses and is not mediated indirectly by change in circulating insulin. Patients with partial or total ACTH deficiency, in whom cortisol replacement is suboptimal, may be at risk of the clinical manifestations of cortisol deficiency when they are commenced on GH therapy.*

Valimaki MJ, Salmela PI, Salmi J, Viikari J, Kataja M, Turunen H, Soppi E. Effects of 42 months of GH treatment on bone mineral density and bone turnover in GH-deficient adults. Eur J Endocrinol. 1999 Jun;140(6):545-54.

OBJECTIVE: To study the effects of GH treatment ***(2.5IU/day target for 70kg person, increased IGF-1 on avg. from 91 to 303ng/ml-HHL)*** *for up to 42 months on bone mineral density (BMD) and bone turnover. DESIGN AND METHODS: BMD with dual energy X-ray absorptiometry, serum type I procollagen carboxy-terminal propeptide (PICP), serum type I collagen carboxy-terminal telopeptide (ICTP) and serum IGF-I were assessed in 71 adults with GH deficiency. There were 44 men and 27 women, aged 20 to 59 (median 43) years. Thirty-two patients completed 36 months and 20 patients 42 months of treatment. RESULTS: The BMD increased for up to 30-36 months and plateaued thereafter.* ***In the whole study group, the maximum increase of BMD was 5.0% in the lumbar spine*** *(P<0. 001),* ***5.9% (P<0.01) in the femoral neck, 4.9% (NS, P>0.05) in the Ward's triangle and 8.2% (P<0.001) in the trochanter area.*** *The serum concentrations of PICP (202.6+/-11.5 vs 116.3+/-5.4 microg/l; mean+/-s.e.m.) and ICTP (10.5+/-0.6 vs 4.4+/-0.3 microg/l) doubled (P<0.001) during the first 6 months of GH treatment but returned to baseline by the end of the study (130.0+/-10.4 and 5.6+/-0.7 microg/l respectively), despite constantly elevated serum IGF-I levels (39. 6+/-4.1 nmol/l at 42 months vs 11.9+/-0.9 nmol/l at baseline; P<0.001). The responses to GH treatment of serum IGF-I, PICP, ICTP (P<0.001 for all; ANOVA) and of the BMD in the lumbar spine (P<0.05), in the femoral neck and the trochanter (P<0.001 for both) were more marked in men than in women. At the end of the study the BMD had increased at the four measurement sites by 5.7-10.6% (P<0.01-0.001) in patients with at least osteopenia at baseline and by 0.1-5.3% (NS P<0.05) in those with normal bone status (P<0.001 for differences between groups; ANOVA). Among patients who completed 36-42 months of treatment, the number of those with at least osteopenia was reduced to more than a half. The response of BMD to GH treatment was more marked in young than in old patients at three measurement sites (P<0. 05-<0.001; ANOVA). In the multiple regression analysis the gender and the pretreatment bone mass appeared to be independent predictors of three measurement sites, whereas the age independently determined only the vertebral BMD. CONCLUSIONS: GH treatment in GH-deficient adults increased BMD for up to 30-36 months, with a plateau thereafter. Concurrently with the plateau in BMD the bone turnover rate normalized.* ***From the skeletal point of view GH-deficient***

patients exhibiting osteopenia or osteoporosis should be considered as candidates for GH supplementation of at least 3-4 years.

Van Cauter E, Leproult R, Plat L Age-related changes in slow wave sleep and REM sleep in relationship with growth hormone and cortisol levels in health men.

GH is secreted during slow wave sleep. The decline in slow wave sleep from early adulthood to midlife was paralled by a major decline in GH secretion. From mid-life to late life, GH secretion further declined at a slower rate. Increasing age was also associated with a rise in evening cortisol levels that became significant only after 50 years when sleep became more fragmented and REM sleep declined. Strategies to enhance sleep quality could serve as an indirect form of hormone therapy.

Vance ML, Mauras N. Growth Hormone Therapy in Adults and Children. N Eng J Med 1999;341(16):1206-14.

Review of growth hormone use in children and in GH-deficient adults. "In adults the goals are to restore normal body composition, improve

van der Klaauw AA, Romijn JA, Biermasz NR, Smit JW, van Doorn J, Dekkers OM, Roelfsema F, Pereira AM. Sustained effects of recombinant GH replacement after 7 years of treatment in adults with GH deficiency. Eur J Endocrinol. 2006 Nov;155(5):701-8.

CONTEXT: The goal of GH replacement with recombinant human GH (rhGH) is to ameliorate symptoms, signs, and complications of adult GH deficiency (GHD) in the long term. To determine whether the observed short-term beneficial effects of rhGH treatment are sustained in the long term, we evaluated biochemical and anthropometric parameters after 7 years of rhGH replacement. PATIENTS AND METHODS: After 2, 5, and 7 years of rhGH replacement, 63 adult GHD patients (30 men, 52 adult-onset GHD) were assessed. IGF-I increased during rhGH replacement, and a stable dose of rhGH was reached within 1 year of rhGH substitution. Thereafter, this individualized dose was continued. RESULTS: Plasma levels of total cholesterol and low-density lipoprotein cholesterol decreased even after 5 years of rhGH replacement (11% decrease, P < 0.001; 22% decrease, P < 0.001 respectively). High-density lipoprotein cholesterol levels increased during 7 years of rhGH replacement (1.4 +/- 0.5 mmol/l at baseline vs 1.7 +/- 0.5 mmol/l after 7 years, P < 0.001), whereas triglyceride concentrations remained unchanged. Fasting glucose levels increased during follow-up, mainly during the first 2 years of rhGH replacement (4.4 +/- 0.7 mmol/l to 5.0 +/- 1.0 mmol/l, P < 0.001). Body mass index increased during follow-up, whereas waist circumference and waist-to-hip ratio remained unchanged. Diastolic blood pressure decreased (P = 0.002), but when patients using antihypertensive medication were excluded this decrease did not reach significance (P = 0.064). Systolic blood pressure remained unchanged. CONCLUSION: The beneficial effects of rhGH replacement, described after short-term rhGH replacement, are sustained in the long term up to 7 years.

Vasan RS, Sullivan LM, D'Agostino RB, Roubenoff R, Harris T, Sawyer DB, Levy D, Wilson PW. Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study. Ann Intern Med. 2003 Oct 21;139(8):642-8.

BACKGROUND: Several experimental investigations have emphasized the favorable effects of insulin-like growth factor I (IGF-I) on left ventricular remodeling, partly through its antiapoptotic effects. Cross-sectional clinical studies have reported that low serum IGF-I levels in patients with heart failure correlate with cachexia and severity of ventricular dysfunction. It is unclear whether low serum IGF-I is a risk factor for heart failure. OBJECTIVE: To prospectively study the association between serum IGF-I level and the incidence of congestive heart failure. DESIGN: Community-based, prospective cohort study. SETTING: Framingham, Massachusetts. PARTICIPANTS: 717 elderly individuals (mean age, 78.4 years; 67% women) who did not have myocardial infarction and

congestive heart failure at baseline. Measurement: Incidence of a first episode of congestive heart failure on follow-up. RESULTS: During follow-up (mean, 5.2 years), 56 participants (35 women) developed congestive heart failure. In multivariable Cox regression models adjusting for established risk factors at baseline, there was a 27% decrease in risk for heart failure for every 1 standard deviation increment in log IGF-I. ***Individuals with serum IGF-I level at or above the median value (140 microg/L) had half the risk for heart failure (hazard ratio, 0.49 [95% CI, 0.26 to 0.92]) of those with serum IGF-I levels below the median.*** *These comparisons were maintained in analyses adjusting for the occurrence of a myocardial infarction on follow-up. CONCLUSIONS: In our prospective, community-based investigation, serum IGF-I level was inversely related to the risk for congestive heart failure in elderly people without a previous myocardial infarction. Additional investigations are warranted to confirm these findings. PMID: 14568852*

Veldhuis JD, Keenan DM, Bailey JN, Adeniji A, Miles JM, Paulo R, Cosma M, Soares-Welch C. Estradiol supplementation in postmenopausal women attenuates suppression of pulsatile growth hormone secretion by recombinant human insulin-like growth factor type I. J Clin Endocrinol Metab. 2008 Nov;93(11):4471-8.

BACKGROUND: Why pulsatile GH secretion declines in estrogen-deficient postmenopausal individuals remains unknown. One possibility is that estrogen not only enhances stimulation by secretagogues but also attenuates negative feedback by systemic IGF-I. SITE: The study took place at an academic medical center. SUBJECTS: Subjects were healthy postmenopausal women (n=25). METHODS: The study included randomized assignment to estradiol (n=13) or placebo (n=12) administration for 16 d and randomly ordered administration of 0, 1.0, 1.5, and 2.0 mg/m2 recombinant human IGF-I sc on separate days fasting. ANALYSIS: Deconvolution analysis of pulsatile and basal GH secretion and approximate entropy (pattern-regularity) analysis were done to quantify feedback effects of IGF-I. OUTCOMES: Recombinant human IGF-I injections increased mean and peak serum IGF-I concentrations dose dependently (P<0.001) and suppressed mean GH concentrations (P<0.001), pulsatile GH secretion (P=0.001), and approximate entropy (P<0.001). Decreased GH secretion was due to reduced secretory-burst mass (P=0.005) and frequency (P<0.001) but not basal GH release (P=0.52). ***Estradiol supplementation lowered endogenous, but did not alter infused, IGF-I concentrations while elevating mean GH concentrations (P=0.012) and stimulating pulsatile (P=0.008) and basal (P<0.001) GH secretion.*** *Estrogen attenuated IGF-I's inhibition of pulsatile GH secretion (P=0.042) but was unable to restore physiological GH pulse frequency or normalize approximate entropy. CONCLUSION:* ***Short-term estrogen replacement in postmenopausal women selectively mutes IGF-I-mediated feedback on pulsatile GH secretion.*** *Disinhibition of negative feedback thus confers a novel mechanism by which estrogen may obviate hyposomatotropism.*

Veldhuis JD, Keenan DM, Bailey JN, Adeniji A, Miles JM, Paulo R, Cosma M, Soares-Welch C. Testosterone supplementation in older men restrains insulin-like growth factor's dose-dependent feedback inhibition of pulsatile growth hormone secretion. J Clin Endocrinol Metab. 2009 Jan;94(1):246-54.

BACKGROUND: Pulsatile GH secretion declines in older men. The causal mechanisms are unknown. Candidates include deficient feedforward (stimulation) by endogenous secretagogues and excessive feedback (inhibition) by GH or IGF-I due to age and/or relative hypoandrogenemia. HYPOTHESIS: Testosterone (T) supplementation in healthy older men will restrain negative feedback by systemic concentrations of IGF-I. SUBJECTS: Twenty-four healthy men (ages, 50 to 75 yr; body mass index, 24 to 30 kg/m(2)) participated in the study. METHODS: We performed a prospectively randomized, double-blind, placebo-controlled assessment of the impact of pharmacological T supplementation on GH responses to randomly ordered separate-day injections of recombinant human IGF-I doses of 0, 1.0, 1.5, and 2.0 mg/m(2). Analysis: Deconvolution and approximate entropy analyses of pulsatile, basal, and entropic (pattern-sensitive) modes of GH secretion were conducted. RESULTS: Recombinant human IGF-I injections 1) elevated mean and peak serum IGF-I concentrations dose-

dependently (both P < 0.001); 2) suppressed pulsatile GH secretion (P = 0.003), burst mass (P = 0.025), burst number (P = 0.005), interpulse variability (P = 0.032), and basal GH secretion (P = 0.009); and 3) increased secretory pattern regularity (P = 0.020). ***T administration did not alter experimentally controlled IGF-I concentrations, but it elevated mean GH concentrations (P = 0.015) and stimulated pulsatile GH secretion (frequency P = 0.037, mass per burst P = 0.038).*** *Compared with placebo, T attenuated exogenous IGF-I's inhibition of GH secretory-burst mass (P < 0.038) without restoring pulse number, basal secretion, or pattern regularity. CONCLUSION: The capability of systemic T to mute IGF-I feedback on pulsatile GH secretion suggests a novel mechanism for augmenting GH production.*

Verhelst J, Abs R, Vandeweghe M, Mockel J, Legros JJ, Copinschi G, Mahler C, Velkeniers B, Vanhaelst L, Van Aelst A, De Rijdt D, Stevenaert A, Beckers A. Two years of replacement therapy in adults with growth hormone deficiency. Clin Endocrinol (Oxf). 1997 Oct;47(4):485-94.

OBJECTIVES: Although several studies have shown beneficial short-term effects of recombinant human growth hormone (rhGH) therapy in adult GH deficient (GHD) patients, few data are available on large groups of patients treated for more than one year. In addition, the optimal dose of rhGH for each patient and the baseline parameters that predict which patients will benefit most from therapy or will have adverse events are not entirely elucidated. DESIGN: 148 adult GHD patients were enrolled in a multicentre 2-year rhGH replacement study which was placebo controlled for the first six months. rhGH (Genotropin/Genotonorm Pharmacia & Upjohn) was given in a dose of 0.25 IU/kg/week sc (1.5 IU/m2/day). ***(80kg—20IU/week, my starting dose is 0.6IU/day, only 4.2IU/week)*** *MEASUREMENTS: Every 3-6 months body composition was measured using body impedance analysis and general well being was assessed using the Nottingham Health Profile (NHP) and social self-reporting questionnaire. At the same time patients had a full clinical examination and blood was sampled for glucose, HbA1c, IGF-1, creatinine, full blood count, thyroid hormones and liver function tests. RESULTS: With rhGH therapy IGF-1 levels increased from -2.00 +/- 2.60 SDS to 1.47 +/- 2.6 SDS after six months (P < 0.001), continued to rise despite no change in dose to 1.84 +/- 2.8 SDS after one year and remained constant thereafter (1.98 +/- 2.4 after 2 years).* ***56% of patients ultimately attained supranormal IGF-1 levels*** *(+2 SD), 22% had levels below the mean, of which 9% were below -2 SD. Within 3 months lean body mass (LBM) increased by +5.09% (P < 0.001), total body water (TBW) by +5.40% (P < 0.001), while body fat (BF) dropped by -10.89% (P < 0.001) and waist circumference by -1.42% (P < 0.004). These effects were maintained during the first year of therapy, but the effect was attenuated after 24 months: LBM, +3.91% (P < 0.001); TBW, +3.28%, P < 0.001, BF, -6.42% (P < 0.001) and waist -2.22% (P < 0.009). Individual differences in response were large and could not be predicted by any of the baseline parameters, except for a better response in males. Treatment resulted in a large and progressive improvement on the NHP scale, especially energy, emotions and sleep, but a similar change was also found in patients during placebo treatment. With rhGH the number of* ***full days of sick leave/6 months decreased*** *from 12.17 +/- 3.90 days (SEM) to 7.15 +/- 3.50 days after six months (P = 0.009), 2.93 +/- 1.55 days after 12 months (P = 0.01), 0.39 +/- 0.17 days after 18 months (P < 0.001) and 3.3 +/- 2.51 days after 24 months (P = 0.026). Similarly, the hospitalization rate went down from 14.9 to 7% after 6 months and remained at this level thereafter (P = 0.12). About one third of patients on rhGH experienced fluid-related adverse events, most often within the first 3 months. They usually disappeared spontaneously or responded well to dose reduction. Cumulative dropout rates were 29% after 1 year and 38% after two years. Two thirds of these patients stopped treatment because of insufficient subjective improvement. Neither drop-outs nor fluid retention could not be predicted by any of the baseline parameters. CONCLUSIONS: We confirmed in a large group of patients the beneficial effects of rhGH therapy on body composition, metabolic parameters and general well-being and found a consistent drop in number of sick days and hospitalization rate. These effects were maintained during two years of therapy, except for an attenuation in body composition changes after 24 months. The high incidence of*

fluid-related adverse events suggests that it may be better to start with lower doses of rhGH and to increase the dose more slowly over a number of weeks. The finding of suboptimal high or low IGF-1 levels in many patients reinforces guidelines not to give rhGH in a weight-dependent dose but to titrate it individually for each patient. ***(Comment: Two year study of 148 GHD adults confirmed beneficial effects on body composition, metabolic parameters and general well-being. Dose should start low and increase gradually. Adjust dosage based on IGF-1 levels.--HHL)***

Vitiello MV, Moe KE, Merriam GR, Mazzoni G, Buchner DH, Schwartz RS. Growth hormone releasing hormone improves the cognition of healthy older adults. Neurobiol Aging. 2006 Feb;27(2):318-23. Epub 2005 Mar 23.

Declines in the activity of the somatotrophic axis have been implicated in the age-related changes observed in a number of physiological functions, including cognition. Such age-related changes may be arrested or partially reversed by hormonal supplementation. We examined the effect of 6 months treatment with daily growth hormone releasing hormone (GHRH) or placebo on the cognition of a group of 89 healthy older (68.0+/-0.7) adults. ***GHRH resulted in improved performance on WAIS-R performance IQ (p<0.01), WAIS-R picture arrangement (p<0.01), finding A's (p<0.01), verbal sets (p<0.01) and single-dual task (p<0.04).*** *GHRH-based improvements were independent of gender, estrogen status or baseline cognitive capacity.* ***These results demonstrate that the age-related decline in the somatotrophic axis may be related to age-related decline in cognition.*** *Further they indicate that supplementation of this neuro-hormonal axis may partially ameliorate such cognitive declines in healthy normal older adults and potentially in individuals with impaired cognitive function (i.e., mild cognitive impairment and Alzheimer's disease).*

Wilhelm B, Kann PH. [Long-term effects of 7-year growth hormone substitution on bone metabolism, bone density, and bone quality in growth hormone-deficient adults]Med Klin (Munich). 2004 Oct 15;99(10):569-77.

BACKGROUND AND PURPOSE: Subnormal bone mineral density (BMD) and increased fracture risk are described in patients with growth hormone deficiency (GHD). Growth hormone (GH) has been reported to have beneficial effects on bone in GHD. The aim of this study was to investigate the long-term effects of GH replacement therapy on bone metabolism, BMD, and bone quality in patients with GHD. PATIENTS AND METHODS: 20 adult patients with GHD (eleven male, nine female, mean age 42.5 years) were included in the study and randomized to either GH or placebo in a dose of 0.25 U/kg body weight/week. After 6 months all patients received GH. After a 1-year double-blind, placebo-controlled study the patients were followed for another 72 months in an open study. The patients were compared to 20 age- und sex-matched healthy controls. Bone turnover was determined by ICTP (type I collagen carboxyterminal cross-linked telopeptide) as parameter of bone resorption and PICP (carboxyterminal propeptide of type I procollagen) as marker of bone formation. BMD was measured at the lumbar spine by dual-photon absorptiometry (DPA) and at the forearm by single-photon absorptiometry (SPA). Apparent phalangeal ultrasound transmission velocity (APU) was assessed as parameter of bone quality independent of BMD. RESULTS: At the beginning of the study BMD at both measuring sites was lower in patients with GHD than in healthy controls. During the 1st year of GH replacement therapy BMD decreased, followed by a continuous increase in BMD (about 12%) up to 60 months which remained unchanged thereafter, building up a plateau. After 72 months no significant difference between the patients and the healthy controls could be detected. Concerning parameters of bone turnover, first ICTP as marker of bone resorption showed a significant increase, later on the marker of bone formation increased as well. APU decreased during the first 6 months of treatment, but had returned to its baseline value after 24 months and remained unchanged throughout the rest of the study. CONCLUSION: ***BMD is subnormal in adults with GHD. GH replacement therapy stimulates bone turnover in patients with GHD and in the long term such stimulation results in an increased BMD. Thereby, GH shows a triphasic action on BMD: an initial decrease in BMD during the 1st year, followed by a continuous increase in BMD with buildup of a stable plateau after 60 months. The newly formed bone seems to have normal bone elasticity.***

Wuster C, Abs R, Bengtsson BA, Bennmarker H, Feldt-Rasmussen U, Hernberg-Stahl E, Monson JP, Westberg B, Wilton P; The KIMS Study Group and the KIMS International Board. Pharmacia & Upjohn International Metabolic Database. The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. J Bone Miner Res 2001 Feb;16(2):398-405.

To assess the influence of factors affecting fracture risk and bone density in adult hypopituitary patients with growth hormone deficiency (GHD), data from a large-scale pharmacoepidemiological survey (the Pharmacia & Upjohn International Metabolic Database [KIMS]) were analyzed and compared with data from a control population (the European Vertebral Osteoporosis Study [EVOS]). The KIMS group consisted of 2084 patients (1112 men and 972 women) with various types of pituitary disease and EVOS consisted of 1176 individuals (581 men and 595 women). Fracture and bone mineral density (BMD) data were available from 2024 patients from the KIMS group and 392 patients from EVOS. The prevalence of fractures in patients with hypopituitarism was 2.66 times that in the non-GH-deficient EVOS population. Adult-onset hypopituitarism with GHD was associated with a higher fracture risk than childhood-onset disease, and patients with isolated GHD had a similar prevalence of fractures to those with multiple pituitary hormone deficiencies. Hormonal replacement therapy with L-thyroxine, glucocorticoids, and sex steroids did not affect the risk of fracture in KIMS patients. In addition, fracture rates in KIMS were independent of body mass index (BMI) and the country of origin. However, smoking was associated with a higher fracture rate in this group. ***In summary, this is the first large-scale analysis to support the hypothesis of an increased fracture risk in adult patients with hypopituitarism and GHD. This increased risk appears to be attributable to GHD alone, rather than to other pituitary hormone deficiencies or to their replacement therapy.***

Wyatt DT, Gesundheit N, Sherman B. Changes in thyroid hormone levels during growth hormone therapy in initially euthyroid patients: lack of need for thyroxine supplementation. J Clin Endocrinol Metab. 1998 Oct;83(10):3493-7.

The occurrence of central hypothyroidism in previously euthyroid children during GH therapy has been reported with widely varying incidence. We monitored the acute effects on the hypothalamic-pituitary-thyroid axis in 15 euthyroid children with classic GH deficiency during the first year of GH therapy. All were initially euthyroid, as assessed by normal baseline TSH, T4, free T4, and T3 levels and negative antithyroid antibodies. A thyroid profile (T4, free T4 index, T3, rT3, and TSH) was performed at baseline and 1, 3, 6, 9, and 12-15 months after GH therapy began; a TRH stimulation test was performed at baseline and after 1, 3, and 9 months of therapy. By 1 month, there were ***significant decreases in T4, free T4 index, and rT3, and significant increases in T3 and the T3/T4 ratio. The changes from baseline values were greatest at 1 month, were almost universal for all thyroid values, and showed a gradual return to baseline from 3-12 months.*** *There were no clinical signs of hypothyroidism and no change in baseline or TRH-stimulated TSH levels or in cholesterol levels, and all patients grew at velocities expected for the treatment schedule. There is little evidence for the development of clinically significant hypothyroidism in the great majority of initially euthyroid patients after GH therapy is begun. T4 supplementation is seldom needed in such patients.PMID:9768652*

Yang R, Bunting S, Gillet N, Clark R, Jin H. Growth hormone improve cardiac performance in experimental heart failure. Circulation 1995;92(2):262-7.

Yuen KC, Bennett RM, Hryciw CA, Cook MB, Rhoads SA, Cook DM. Is further evaluation for growth hormone (GH) deficiency necessary in fibromyalgia patients with low serum insulin-like growth factor (IGF)-I levels? Growth Horm IGF Res. 2007 Feb;17(1):82-8. Epub 2007 Feb 6.

OBJECTIVE: Fibromyalgia (FM) is characterized by diffuse pain, fatigue, and sleep disturbances; symptoms that resemble the adult growth hormone (GH) deficiency syndrome. Many FM patients have low serum GH levels, with a hypothesized aetiology of dysregulated GH/insulin-like growth factor (IGF)-I axis. The aim of this study was to assess the GH reserve in FM patients with low serum IGF-I levels using the GH-releasing hormone (GHRH)-arginine test. DESIGN: We retrospectively reviewed the GHRH-arginine data of 77 FM patients with low serum IGF-I levels referred to our tertiary unit over a 4-year period. RESULTS: Of the 77 FM patients, 13 patients (17%) failed the GHRH-arginine test. Further evaluation with pituitary imaging revealed normal pituitary glands (n=7), coincident microadenomas (n=4), empty sella (n=1) and pituitary cyst (n=1), and relevant medical histories such as previous head injury (n=4), Sheehan's syndrome (n=1), and whiplash injury (n=1). In contrast, the remaining 64 patients (83%) that responded to the GHRH-arginine test demonstrated higher peak GH levels compared to age and BMI-matched controls (n=24). CONCLUSION: ***Our data shows that a subpopulation of FM patients with low serum IGF-I levels will fail the GHRH-arginine test.*** *We, thus, recommend that the GH reserve of these patients should be evaluated further, as GH replacement may potentially improve the symptomatology of those with true GH deficiency.* ***Additionally, the increased GH response rates to GHRH-arginine stimulation in the majority of FM patients with low serum IGF-I levels further supports the hypothesis of a dysregulated GH/IGF-I axis in the pathophysiology of FM.***

Yuen K, Ong K, Husbands S, Chatelain P, Fryklund L, Gluckman P, Ranke M, Cook D, Rosenfeld R, Wass J, Dunger D. The effects of short-term administration of two low doses versus the standard GH replacement dose on insulin sensitivity and fasting glucose levels in young healthy adults. J Clin Endocrinol Metab. 2002 May;87(5):1989-95.

GH has both diabetogenic and insulin-like actions. Supraphysiological GH doses are known to reduce insulin sensitivity (S(I)), but lower doses are less well studied. ***We therefore compared the effects of two physiological GH doses (intermediate, 0.0033 mg/kg x d; low, 0.0017 mg/kg x d) with the standard adult GH deficiency replacement dose (standard, 0.008 mg/kg x d)*** *on S(I), beta-cell function, IGF-I, and IGF binding proteins (IGFBPs)-1 and -3 in healthy adults. Eleven healthy nonobese volunteers (4 males and 7 females, aged 21-38 yr) received 7 daily injections of the standard and intermediate GH doses, and 10 (5 males and 5 females, aged 21-38 yr) received the low dose. Fasting blood samples were collected daily (days 1-8). S(I) and beta-cell function were calculated using the Homeostasis model assessment. All GH doses increased IGF-I and IGFBP-3 levels, with the standard dose inducing the greatest rise ($P < 0.001$). At day 2 vs. baseline, all three doses increased the IGF-I/IGFBP-3 ratio, but only the standard dose lowered IGFBP-1 levels ($P = 0.03$). The standard dose reduced S(I) ($P = 0.01$), whereas the intermediate dose increased S(I) ($P < 0.005$) and lowered fasting insulin levels ($P < 0.01$). The low dose did not modify S(I), but reduced fasting glucose levels ($P < 0.0001$) and increased beta-cell function ($P = 0.001$). Males demonstrated higher IGF-I and IGFBP-3 responsiveness to the standard dose than females. Males also showed greater increase in S(I) and decrease in fasting glucose levels on both intermediate and low doses. In conclusion, the metabolic effects of GH are dose- and gender-dependent.* ***The standard adult GH deficiency replacement dose induced insulin resistance, whereas lower doses improved S(I), especially in males.*** *The low GH dose lowered fasting glucose levels and could represent the optimal dose to stimulate beta-cell function without compromising S(I) in insulin-resistant GH-deficient adults.****(The 0.2mg dose I use is in the low-intermediate range, which in this study improves insulin sensitivity in most persons.—HHL)***