I) Milder Forms of Growth Hormone Deficiency gradually appear with age in adults

because of the gradual aging and thus age-related decline of the pituitary gland.

Senescence is associated with lower GH and IGF-1 levels and increased somatostatin


Senescence is associated with alterations in the circadian cycle of serum GH:

a reduced amplitude and apha phase advance


II) Supporting Data on Growth Hormone’s Beneficial Effects in Adults

1) GH is important for psychic well-being

Lower quality of life and fatigue: the association with lower GH and/or IGF-1 levels


Lower quality of life and fatigue: the effect of GH and/or IGF-1 treatment

Lower quality of life and fatigue: the improvement with GH treatment


Depression: the association with lower GH and/or IGF-1 levels

37. Jarrett DB, Miewald JM, Kupfer DJ. Recurrent depression is associated with a persistent reduction in sleep-related growth hormone secretion. Arch Gen Psychiatry. 1990 Feb;47(2):113-8


42. Dinan TG, Barry S. Responses of growth hormone to desipramine in endogenous and non-endogenous depression. Br J Psychiatry. 1990 May;156:680-4


Depression: the improvement with GH treatment


Anxiety: the association with lower GH and/or IGF-1 levels

49. Tancer ME, Stein MB, Uhde TW. Growth hormone response to intravenous clonidine in social phobia: comparison to patients with panic disorder and healthy volunteers. Biol Psychiatry. 1993 Nov 1;34(9):591-5


Anxiety: the improvement with GH treatment


**Memory loss and Alzheimer’s disease: the association with lower GH and/or IGF-1 levels**


**Memory loss and Alzheimer’s disease: the improvement with GH treatment**


**Sleep disorders: the association with lower GH and/or IGF-1 levels**

61. Astrom C, Lindholm J. Growth hormone-deficient young adults have decreased deep sleep. Neuroendocrinology. 1990 Jan;51(1):82-4

**Sleep disorders: the improvement with GH treatment**


**Loss of sexual drive, sensitivity and/or potency: the association with lower GH and/or IGF-1 levels**


**Loss of sexual potency: the improvement with GH treatment**


2) GH is important for the good physical appearance and body composition

**Sarcopenia: the association with lower GH and/or IGF-1 levels**


Sarcopenia: the improvement with GH treatment


Lean body mass: the association with lower GH and/or IGF-1 levels


Lean body mass: the improvement with GH treatment


Physical appearance, body morphology improvement with GH treatment

3) GH may protect – at least partially - against the appearance of age-related diseases

**Hypercholesterolemia: the association with lower GH and/or IGF-1 levels**


**Hypercholesterolemia: the improvement with GH treatment**


**Homocysteinemia: the improvement with GH treatment**


**Atherosclerosis: the association with lower GH and/or IGF-1 levels**


**Atherosclerosis: the improvement with GH treatment**


Arterial hypertension: the association with lower GH and/or IGF-1 levels


Arterial hypertension: the improvement with GH treatment


Coronary heart disease: the association with lower GH and/or IGF-1 levels


Coronary heart disease: the improvement with GH treatment


Stroke and other cerebrovascular disorders: the association with GH and/or IGF-1 levels


Obesity: the association with lower GH and/or IGF-1 levels


Obesity: the improvement with GH treatment


Diabetes: the association with lower GH and/or IGF-1 levels


Diabetes: the improvement with GH treatment


Rheumatism: the association with lower GH and/or IGF-1 levels


Rheumatism: the improvement with GH treatment


**Osteoporosis: the association with lower GH and/or IGF-1 levels**


**Osteoporosis: the improvement with GH treatment**


Infections and lower immunity: the association with low growth hormone/IGF-1 levels


Infections and lower immunity: The improvement with GH treatment


Cancer: the association with lower GH and/or IGF-1 levels

Cancer: opposed by GH treatment?


III) GROWTH HORMONE MAY MAKE A PERSON SURVIVE LONGER:

Longevity: the association with GH and/or IGF-1 levels


Longevity: the improvement with GH treatment


III) ADVERSE SYMPTOMS of PERSISTING LOW GROWTH HORMONE LEVELS have been abundantly reported, as has their improvement or disappearance with growth hormone treatment.

IV) GROWTH HORMONE TREATMENT OF PARTIAL GROWTH HORMONE DEFICIENCY


GH treatment: safety, side effects, complications


219. Milner RDG, Barnes ND, Buckler JMH, Carson DJ, Hadden DR, Hughes IA, Johnston DI, Parkin JM, Price DA, Rayner PH, Savage DCL, Savage MO, Smith CS, Swift PG


V) JUSTIFIED OR NON JUSTIFIED FEARS ON GROWTH HORMONE TREATMENT?

1) Can growth hormone treatment cause severe discomfort and side effects?

Claim: GH treatment has substantial adverse effects such as edema, etc.

Fact: Substantial adverse effects only appear at overdoses such as is the case for any other medical treatment, it is sufficient to reduce the dose to avoid them.


2. Amato G, Izzo G, La Montagna G, Bellastella A. Low dose recombinant human growth hormone normalizes bone metabolism and cortical bone density and improves trabecular bone density in growth hormone deficient adults without causing adverse effects. Clin Endocrinol (Oxf). 1996 Jul;45(1):27-32 (no adverse effects with doses of 10µg/kg/day or a mean of 500-800 µg /day)

2) Can growth hormone treatment cause or aggravate diabetes?

**Suspicion:** Can GH at physiological doses cause diabetes?

**Facts:** GH’s role is to prevent hypoglycaemia by elevating the low serum glucose levels of GH deficient subjects back to normal. It does not at physiological doses cause diabetes.

**Arguments against GH use**

**GH is a hyperglycemic hormone**


**Treatment of GH-deficient children: higher incidence of diabetes**

2. Cutfield WS, Wilton P, Benmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA. Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. Lancet. 2000 Feb 19;355(9204):610-3 (“GH treatment did not affect the incidence of type 1 diabetes mellitus in any age group. … the higher than expected incidence of type 2 diabetes mellitus with GH treatment may be an acceleration of the disorder in predisposed individuals. Type 2 diabetes did not resolve after GH therapy was stopped.”; critics: very high GH doses are used in children; no increased incidence of type 2 diabetes has been seen in adults taking GH)

**Serum GH levels are higher in diabetes patients** (critics: yes, two times higher serum GH, but -50% lower serum IGF-1, which reflects GH activity; insulin treatment of diabetes significantly increases serum IGF-1 and lower GH)


**Acromegaly is associated with an increased incidence of diabetes**


**Arguments for GH use:**

**Insulin secretion: the tonic secretion of insulin from the beta-cells depends on IGF-1**


**GH is an anti-hypoglycemic hormone:** it neutralizes hypoglycaemia


9. West TE, Sonksen PH. Is the growth-hormone response to insulin due to hypoglycaemia, hyperinsulinaemia or a fall in plasma free fatty acids? Clin Endocrinol (Oxf). 1977 Oct;7(4):283-8 (hypoglycaemia per se was the important stimulus to GH secretion and not hyperinsulinaemia or a lowering of plasma free fatty acids)


**IGF-1 therapy has insulin-like effects:** it reduces glycaemia and serum insulin in controls and type 2 diabetic patients

Diabetes: the association with lower GH and/or IGF-1 levels


Diabetes patients have high GH, but low IGF-1, marker of GH metabolic activity: a lower IGF-1 in insulin-dependent diabetes pubers is associated with a higher serum glycosylated hemoglobin HbA1C


Acromegaly: GH production in acromegaly is 10 to 100 times the normal production; 10 to 300 times the doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a polyhormonal deficit: hypothyroidism, hypogonadism, hypocorticism, ..., endocrine conditions that increase the risk of glucose intolerance and diabetes. These conditions are not found in corrective GH treatment of GH deficiency.

14. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 (“Patients with active acromegaly ... secretion rate per 24 h was 25 times greater in female acromegalics and 100 times greater in male acromegalics than that in the controls”)

15. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. J Clin Endocrinol Metab. 1983 Nov;12(3):509-34 (“The possibility of deficiencies of the other pituitary hormones should then be addressed in patients with secretory tumours. In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order. Basal thyroid function tests, serum oestriadiol or testosterone, and basal gonodotrophins should be routinely obtained in patients with macroadenomas. Additionally, the integrity of the pituitary-adrenal axis should be determined and an overnight water deprivation test for assessment of neurohypophyseal function is also recommended.”)


GH therapy increases the glycaemia during the first months, then reduces it when given to HIV-infected patients with fat accumulation:


GH therapy at physiological doses to type 1 diabetics: no effect on glycaemia


GH therapy to type 1 diabetics: increased insulin requirements, but improved control of hypoglycaemic attacks


Low dose GH therapy (0.10 mg/day) improves insulin sensitivity in young healthy adults

21. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and
cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. Clin Endocrinol (Oxf). 2005 Oct;63(4):428-36 (“The low GH dose (0.10 mg/day) decreased fasting glucose levels (P < 0.01) and enhanced insulin sensitivity (P < 0.02), the standard GH (mean dose 0.48 mg/day) did not modify insulin sensitivity”)

Diabetes: the improvement with GH treatment


3) Can growth hormone treatment cause or facilitate cancer?

Claim: GH increases the risk of cancer

Facts: The epidemiological studies, which indicate an association between serum IGF-I and cancer risk, have not established causality. An increased cancer risk with GH therapy has not been proven in humans.

Arguments against GH use:

GH LEVELS: Studies with positive associations between higher serum GH and/or IGF-1 levels and an increased risk of prostate or breast cancer

Studies where a higher serum IGF-1 and/or high IGF-I to IGFBP-3 molar ratio was found associated with an increased risk of prostate cancer (critics: the increased IGF-I may be due to local production of IGF-1 by the tumour and may thus be a marker, and not a cause of cancer, or a bias due to nutritional fators - see further)


Studies where a higher serum GH was found associated with an increased risk of breast cancer (critic: based on the measurement of the daytime serum GH level, which is not representative of GH 24-hour secretion)


Studies where a higher serum IGF-1 or IGF-1/IGFBP-3 ratio is found associated with an increased risk of breast cancer, in particular in women with ≥ 19 CA repeats in IGF-1 gene


A study where a lower serum IGFBP-3 was found in breast cancer patients

A study where a higher serum IGF-1 / IGF-BP-3 was found associated with an increased colon cancer risk (the colon cancer risk was 4 times increased only for subjects in the upper tertile of IGF-1 and lower tertile of IGF-BP-3; for other tertiles or a combination of tertiles there was: no significant association)


In acromegaly, the incidence of and/or mortality from digestive cancer is increased


Critics: in acromegaly the GH production is 10 to 100 times the normal production, 10 to 300 times the daily doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a polyhormonal deficit: hypothyroidism, hypogonadism, hypocorticism, ..., endocrine conditions that increase the risk of glucose intolerance and diabetes These conditions are not found in corrective GH treatment of GH deficiency.

12. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 ("Patients with active acromegaly … secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls")

Neutral information and a alternative explanations of a possible GH and cancer relation

Possible bias in the studies with increased prostate and breast cancer risk:

Bias 1: The diagnosis of cancer may be more rapidly made in patients with high IGF-1 because they may undergo more intensive scrutiny: As raised IGF-1 may cause tissue hyperplasia, including increase in size of prostate and breast tissue, the existence of these bigger tissues and possibly of the symptoms they may cause, may lead to more intensive scrutiny, from increased rate of PSA, CEA or C1.25 measurements, to ultrasound and RX examinations, prostate or breast biopsies, and thus an increased rate of detection of very slow, asymptomatic prostate or breast cancers that would have remained undiagnosed or diagnosed much later in patients with low IGF-1. Such higher rate of cancer detection may be particularly the case for prostate cancer, where the number of detected prostate cancer cases is very low compared to the total number of cases found at autotopsy, and premenopausal breast cancer patients who were diagnosed within the 2 years after the first blood sample.

Higher levels of IGF-1 or GH or acromegaly have been associated with benign prostatic hyperplasia, but not necessarily with prostate cancer


GH and IGF-1 treatment of primates can increase breast hyperplasia, not specifically breast cancer


Bias 2: After adjustment for prostate volume, no longer significant associations between serum IGF-I and prostate cancer risk may persist (Serum IGF-I is not useful for diagnosis of prostate cancer, but a marker of benign prostatic hyperplasia and enlargement)


Bias 3: Serum IGF-I may actually be a surrogate marker of nutritional factors that may increase the cancer risk such as meat and milk intake (persons who eat a lot of protein, especially red meat, have higher IGF-1 levels and an increased cancer risk)


Link between meat, milk and/or protein intake, and prostate or breast cancer


Red meat and milk intake is correlated with high IGF-1


Bias 4: The increases of serum IGF-1 may be produced by the malignant tumour and constitute a consequence and not a cause as suggested in some animal studies.


Bias: the variability of serum IGF-1 makes that if two weeks after the initial blood test another measurement of IGF-1 was done, the results of the studies would have been different (about 40% of participants of the study would have switched from one quartile to the other)

36. Milani D, Carmichael JD, Welkowitz J, Ferris S, Reitz RE, Danoff A, Kleinberg DL. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. J Clin Endocrinol Metab. 2004 May;89(5):2271-4 (“If fasting serum IGF-1 is measured twice, two weeks apart, individual differences range from -36.25 to +38.24%, while the mean value for the group of 84 shows high correlation between the two IGF-Is (r=0.922; p<0.0001) and varies much less (mean 120 at first visit) versus 115; p=0.03) in normal volunteers between the ages of 50 and 90 years. When considered in quartiles, IGF-1 changed from one quartile to another in 34/84 (40.5%) of the volunteers. When the group was divided in halves, tertiles, quartiles, or quintiles there was an increasing number of subjects who changed from one subdivision to another as the number of gradations increased. These results suggest that the predictive outcomes of earlier studies that used single IGF-I samples for analysis of risk ratios according to tertiles, quartiles, or quintiles could have been different if a second IGF-I was used to establish the risk ratio.”)

No significant associations of serum levels and prostate cancer risk

No difference in plasma GH or IGF-1 between prostate cancer patients and controls


40. Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalgleish AG, Kirby RS. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. BJU Int. 1999 Jun;83(9):996-9

41. Ismail HA, Pollak M, Behloul H, Tanguay S, Begin LR, Aprikian AG. Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples. BJU Int. 2003 Nov;92(7):699-702


In acromegaly, the incidence of cancer, other than possibly colon cancer, does not appear to be significantly increased; in one study it was even significantly reduced by -14%. Overall mortality is normal for patients with low posttreatment GH, but increased for patients with high posttreatment GH.


47. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4 (“The overall cancer incidence rate was 24% lower than that in the general population of
the U.K.; the overall cancer mortality rate was not increased, but the colon cancer mortality rate was increased.")

No difference in serum IGF-1 between breast cancer patients and controls


GH transgenic mice with high serum IGF-1 do not develop breast, prostate, or colonic malignancies


Arguments for GH use:

Inverse (protective) associations of serum GH/IGF-1 levels and overall cancer risk

Untreated GH deficient patients have an increased overall cancer incidence (2x the normal incidence) and cancer mortality (4x)


A high serum IGF-1 is found associated with a lower risk of prostate cancer


No significant association between serum IGF-1 and prostate cancer:


A high serum IGFBP-3 is associated with a reduced prostate cancer risk (-30%), and/or prostate cancer recurrence


Studies where GH therapy given to cancer patients reduced the cancer recurrence, and reduces the cancer mortality or increases survival time


**Long-term GH replacement** (60 months) reduced the increased cancer risk and mortality of GH deficient patients by half


**GH or IGF-1 therapy to animals with cancer: may reduce the tumour incidence and/or progression**

**Combined GH- insulin therapy reduced the development of mammary carcinoma in female rats**


**GH-therapy reduced the development of lung metastases in rats with prostate cancer**


A lower serum GH level is found in gastric cancer patients


**GH-therapy inhibits the development of liver cancer due to carcinogens ( aflatoxin B1 or N-OH-acetyl-amino fluoren) in male rats**


**IGF-1-therapy preserved lean mass in rats with sarcoma and cachexia**


**Conclusion on the cancer studies and GH**

- GH therapy raises both the levels of both IGF-I and IGFBP-3. IGFBP-3 is a potent inhibitor of IGF action in breast and prostate tissues.
- **Autocrine production of IGF's and GH**, have been identified in cancer cells and tissues. Thus, serum IGF-I may actually be a confounding variable, serving as a marker for local prostatic IGF-I production.
- Since GH-deficient patients often have a subnormal IGF-I serum level, which normalizes on therapy, the cancer risk on GH therapy does not substantially increase above that of the normal population. On the contrary, the evidence points to a normalization of the risk.
- It seems prudent that when we treat adult GH deficiency, we should aim to maintain serum IGF-1 in the normal range.

4) CAN GROWTH HORMONE TREATMENT REDUCE THE LIFESPAN?

**Claim:** GH may have adverse effects on lifespan

**Facts:** GH treatment appears to reduce mortality, except for special mice species and humans put in extreme conditions.

**Arguments against GH use**

**Studies where higher GH and/or IGF-1 levels were found associated with premature death**

A high serum GH was associated with premature death in humans (critics: an old fashioned technique, which lacked assay precision, was used to measure GH; the daytime serum GH were measured, which is not accurate except for acromegaly patients; serum GH does not reflect GH activity; serum IGF-1 does it, but up to a certain
degree; an increased serum GH may possibly reflect increased binding of GH to increased serum GHBP and thus inactivation of GH, but the serum GHBP level was not checked in the study.


Acromegaly adults have premature death only when they keep high posttreatment GH and thus a probably continuing active growth hormone-secreting tumor that crushes down all the other pituitary cells, overall mortality is normal for patients with low posttreatment GH.


Mice models of genetic pituitary failure with multiple hormone deficiency (Ames and Snell mice) and GH receptor knockout mice (primary IGF1-deficiency) may have a significant higher longevity (critics: the heterozygous IGF-I receptor knock-out mutants are special mice species, as are Ames and Snell mice. They react in a completely different way to GH than normal mice species. They have a 50% decrease in IGF-1 receptors, but a 32% higher serum IGF-1; they have more glucose intolerance; are slightly smaller; the lifespan was only significantly longer in female mice (+33%), not in male mice (+16%); the results based on a shortliving species (mise) may not be necessarily true for species with a long life such as humans).


Can GH therapy increases mortality?

GH therapy to critically ill patients: doubles the mortality rate

7. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999 Sep 9;341(11):785-92 (Critics on the study: the doses used were too high doses: 10 to 70 times the normal dose in very weak persons; the control group had an abnormally lower mortality rate than predicted; combined to the high mortality rates of the treatment group, the average mortality rate was very similar to that of a historical cohort; GH treatment lowers cortisol levels, which are crucial to critically ill patients)

BUT: Studies where GH therapy lowered the levels of cortisol and its metabolites by 20 to 40 %, which is dangerous for critically-ill patients who desperately need cortisol for their survival


...and a study where patients who have poor responsive adrenals (poorly able to increase their cortisol production) and are in septic shock, die easier

.. and studies where glucocorticoid treatments considerably increased survival of critically-ill patients

**survival of HIV patient from pneumonia**


**survival from typhus**


**NEUTRAL information on GH and longevity**

No increased mortality in acromegaly if levels of GH are less than 2.5 ng/ml


**Arguments for GH use**

**GH/IGF-1 LEVELS: Higher serum GH and IGF-1 levels are associated with a higher survival**

Persistent GH deficiency (without GH therapy) in humans, is associated with a shorter life expectancy: increased overall and cardiovascular mortality


**Higher mortality in GH deficient women**


Higher mortality in 11 GH deficient adults suffering from a genetic defect (6.7-kb spanning deletion of genomic DNA of the GH-1 gene) that causes isolated GH deficiency (hereditary dwarfism), untreated men lost 21 years of life (-25% compared to the unaffected brothers) and women 34 years less (-44% versus unaffected sisters)


Patients with hypopituitarism have increased overall and cardiovascular mortality; the increased mortality from cerebrovascular disease (esp. in women) was the main contributor to the increased cardiovascular mortality


**GH TREATMENT: Corrective GH hormone treatment increases survival**

GH replacement therapy of GH deficient adults lowers the excessive mortality back to normal


GH treatment of normal elderly mice, extended the mean and maximal life span\(^9\).


GH treatment of GH deficient mice extended life span, but lifespan of (non GH treated) mice was similar to that of normal mice.


Conclusion: Persistent GH deficiency reduces the life expectancy, while GH treatment of GH-deficient patients improves it. Caution should be applied when using GH treatment in critically-ill patients.