

"Just remember one thing; God has a plan for each and every one of us. All you have to do... is keep the faith and accept your cause" Ronnie Coleman

## **HUMAN GROWTH HORMONE RESEARCH:**

*The two search engines, Google and Yahoo, who control about 90% of total internet searches, show the terms HGH or Human Growth Hormone, are searched beyond 20,000 times per day online!*

### **INTRODUCTION**

#### **Growth hormone- Normal values:**

##### **Men:**

**0–5 nanograms per milliliter (ng/mL)**

##### **Women:**

**0–10 ng/mL**

##### **Children:**

**0–16 ng/mL**

**After physical or emotional stress (such as exercise or worry about health problems), growth hormone (GH) levels are normally about 20 to 30 ng/mL.**

Growth Hormone is a polypeptide hormone. This means it is composed of a long chain of amino acids, 191 to be exact. Under normal physiologic conditions, growth hormone is secreted by the anterior pituitary gland. This is a gland that lies at the base of the brain in a bony cavity called the Sella Turcica. In addition to growth hormone, the anterior pituitary also secretes prolactin, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, and adrenal corticotropic hormone. The secretion of growth hormone by the pituitary gland is initiated by the hypothalamus, another gland in the brain that lies right next to the pituitary. The hypothalamus initiates growth hormone secretion by secreting growth hormone releasing hormone (GHRH); at the same time it stops secreting a growth hormone inhibitory hormone called somatostatin. When somatostatin is turned off and GHRH is turned on, the pituitary will release growth hormone in bursts of activity. These bursts of growth hormone release occur primarily during deep stages of sleep, such as stage 3 and stage 4. Once released in the blood, growth hormone is very short lived. It is generally completely metabolized and gone within a half-hour. During that time, however, it manages to reach the liver and many other cells in the body, and induce them to make another polypeptide hormone called Insulin-like Growth Factor One (IGF-1). It is really IGF-1 that travels around to the

various tissues of the body to effect most of the benefits that we attribute to growth hormone. The secretion of growth hormone itself is regulated by a classic biofeedback loop. This means when levels of growth hormone in the blood reach a certain threshold, growth hormone stimulates receptors in the pituitary to stop further growth hormone secretion. It also stimulates receptors in the hypothalamus to stop GHRH and turn on somatostatin. IGF-1, which goes up in response to growth hormone, also feeds back on the pituitary and hypothalamus to help control growth hormone secretion. This is nature's system of checks and balances to assure we don't have too much of any one hormone.

### Normal Physiology of Growth Hormone in Adults

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## **INTRODUCTION**

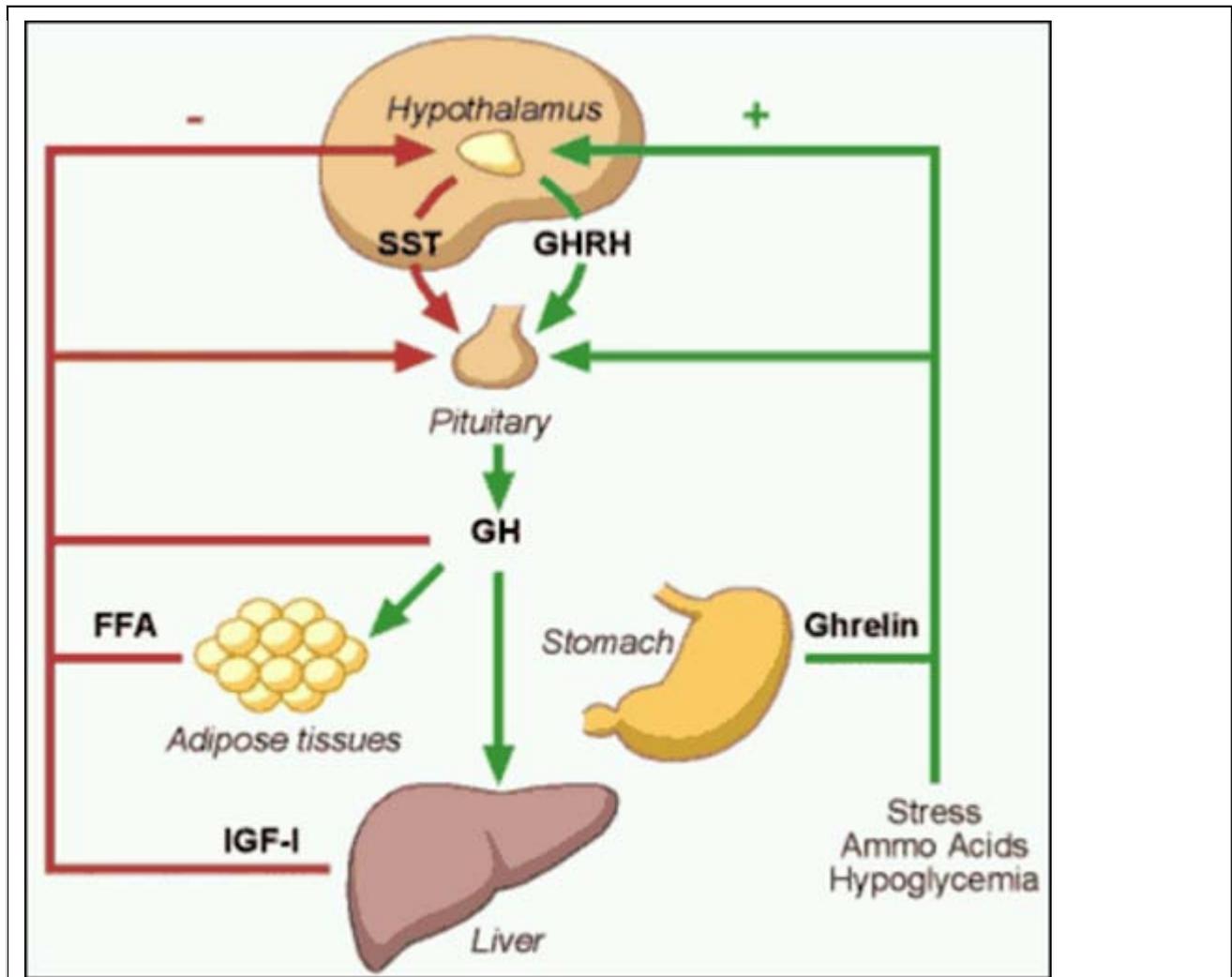
In his monograph from 1912 on "The Pituitary Gland" Harvey Cushing proposed the existence of a "hormone of growth", and was thereby among the first to indicate that the primary action of this hormone was to control and promote skeletal growth. In clinical medicine growth hormone (GH) (also called somatotropin) has until recently primarily been known - and used - for the action suggested by its name - i.e. for the treatment of short stature in hypopituitary children, and for its adverse effects in connection with hyper-secretion as observed in acromegaly. The multiple and complex actions of human GH were, however, acknowledged shortly after the advent of pituitary derived preparation of the hormone in the late fifties - as beautifully reviewed by Maurice Raben in 1962 (1). In the present chapter

we will briefly review normal physiology of GH secretion and the effects of GH on intermediary metabolism throughout adulthood. Other important physiological effects of GH will be dealt with in the review of GH replacement in adults.

## **SECRETION, PHARMACOKINETICS AND PHARMACODYNAMICS**

### **Regulation Of Gh Secretion**

GH is a single chain protein with 191 amino acids and two disulfide bonds. The GH gene is located on chromosome 17. Approximately 75% is secreted in the 22kD form, while the remainder consists of a 20kD variant produced by alternate splicing. GH is secreted by the somatotrope cells located primarily in the lateral wings of the anterior pituitary. The morphological characteristics and number of these cells are remarkably constant throughout life, while secretion changes - as mentioned below. GH secretion occurs in a pulsatile fashion, and in a circadian rhythm with a maximal release in the second half of the night. Two hypothalamic hormones regulate GH secretion: Growth Hormone Releasing Hormone (GHRH) with a stimulatory action at the level of gene transcription and somatostatin (SST) with an inhibitory effect on the GH secretion from the pituitary gland. Various synthetically produced GH releasing compounds and the recently discovered natural hormone ghrelin probably have a dual effect in increasing the release of GHRH and inhibiting SST action, thereby obtaining a very powerful stimulation of GH secretion. Ghrelin in the systemic circulation derives from the stomach, but it remains to be convincingly demonstrated that gut-derived ghrelin is a regulator of GH secretion(2). Interestingly, exogenous ghrelin stimulates food intake and gastric emptying (2) In everyday life it is known, that stress, hypoglycaemia and ingestion of protein (high levels of circulating amino acids) stimulates GH secretion, while high levels of glucose and FFA inhibits secretion (Fig 1).



**Figure 1. Factors that stimulate and suppress GH secretion under physiological conditions**

GH acts both directly through its own receptor and indirectly through the induced production of Insulin-like Growth Factor I (IGF-I). IGF-I is synthesized both in the liver and in the periphery, and is an important mediator of GH actions. It circulates bound to a number of different binding proteins of which IGFBP-3 is the most important.

With the introduction of dependable radioimmunological assays it was recognised that circulating GH was blunted in obese subjects (3), and that normal aging was accompanied by a gradual decline in GH levels (4). The latter observation led Rudman et al. (5) to the hypothesis that many of the senescent changes in body composition and organ function were related to or caused by hyposomatotropinemia. The term "somatopause" may be considered a paraphrase for Rudmans hypothesis although it remains uncertain who introduced this persuasive term.

More recent studies have uniformly documented that hypopituitary adults with severe GH-deficiency are characterised by increased fat mass and reduced lean body mass (LBM) (6). It is also known that normal GH levels can be restored in obese subjects following massive weight loss (7), and that GH substitution in GH-deficient adults normalises body composition (6).

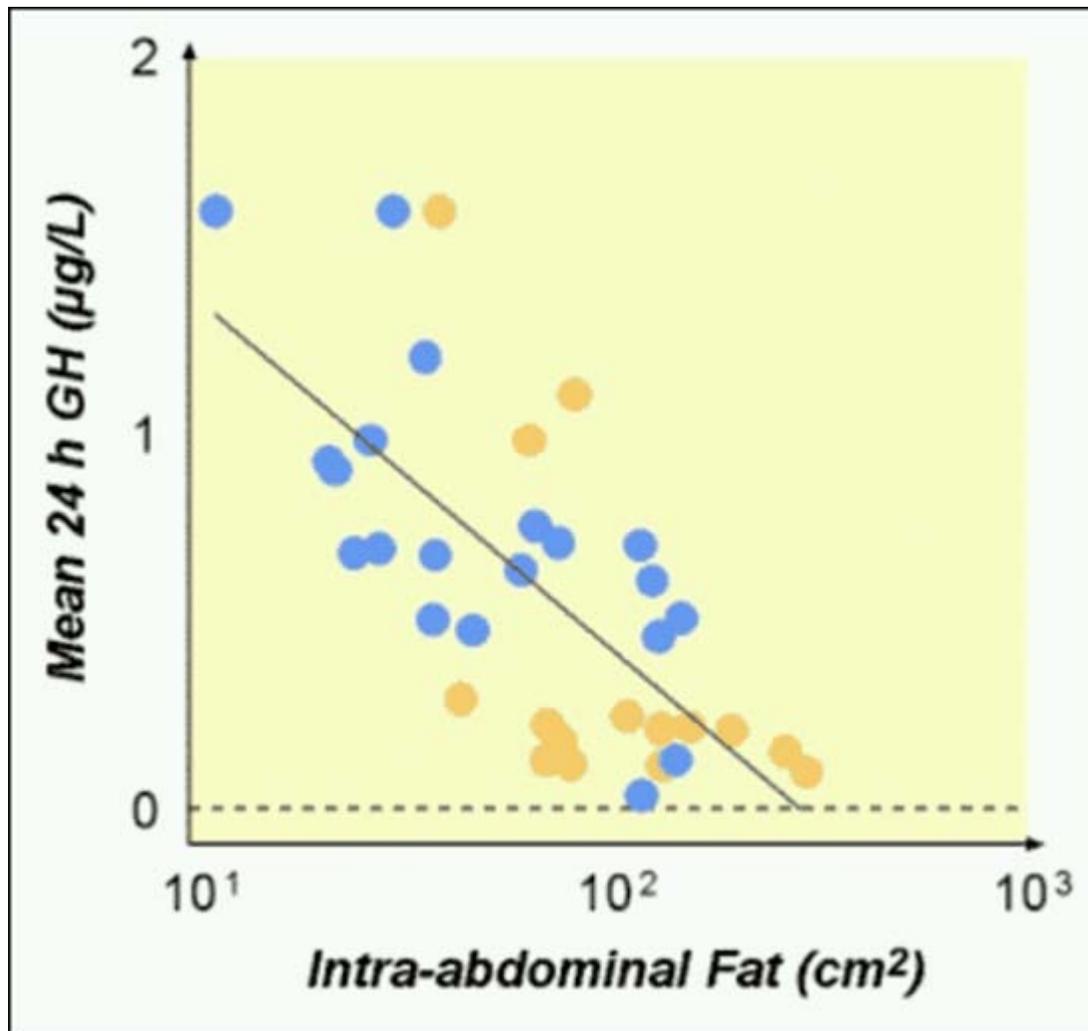
What remains unknown is the cause-effect relationship between hyposomatotropinemia and senescent changes in body composition. Is the propensity for gaining fat and loosing LBM initiated or preceded by a primary age-dependent decline in GH secretion and action or vice versa?: accumulation of fat mass secondary to non-GH dependent factors (e.g. life style, dietary habits) results in a feedback inhibition of GH secretion

Moreover, little is known about possible age-associated changes in GH pharmacokinetics and bioactivity.

### **Influence Of Body Composition, Physical Fitness And Age On Stimulated And Spontaneous Gh Levels In Normal Adults**

Assessment of GH status by means of standardized stimulation tests remains a cornerstone for the diagnosis of GH deficiency in children. The reason for this is that pituitary GH is released in a pulsatile and episodic manner separated by long intervals with low GH levels. A similar approach is used when evaluating hypopituitary adults, in whom it has been shown that stimulated GH release allows a better separation between patients and

normal subjects as compared to 24-h spontaneous GH release (8). It is, however, noteworthy that stimulated GH peak levels are subject to a very pronounced inter- and intra-subject variability. A number of physiological variables such as body composition, nutritional status, physical fitness and sex steroids are known to influence GH release, but the degree to which each of these factors contributes to the individual variation is not clear. In adults it has been reported that the GH response to clonidine declines with age (9), whereas the response to arginine primarily appears to be determined by gender with higher levels in females (10). The association between body composition and stimulated GH release in healthy adults was assessed in a cross-sectional study in 42 clinically non-obese adults between 27-59 years (22 females/20 males) who underwent 2 stimulation tests (clonidine and arginine) in addition to in-depth measures of body composition and physical fitness (VO<sub>2</sub>-max) (11). Elderly people (mean age 50 years) had a lower peak GH response to both secretagogues, and females had a higher response to arginine when compared to males. Body mass index and intra-abdominal fat content (CT scan) was higher in "older" people and in males compared to "young" people and females, respectively and lean body mass was higher in males compared to females, whereas physical fitness was higher in young people compared to older people. Multiple regression analysis, however, revealed that intra-abdominal fat mass was the most important and negative predictor of peak GH levels (Fig.2), whereas both age, gender and physical fitness were of minor importance. Lean body mass was not significantly associated with GH status in either males or females.

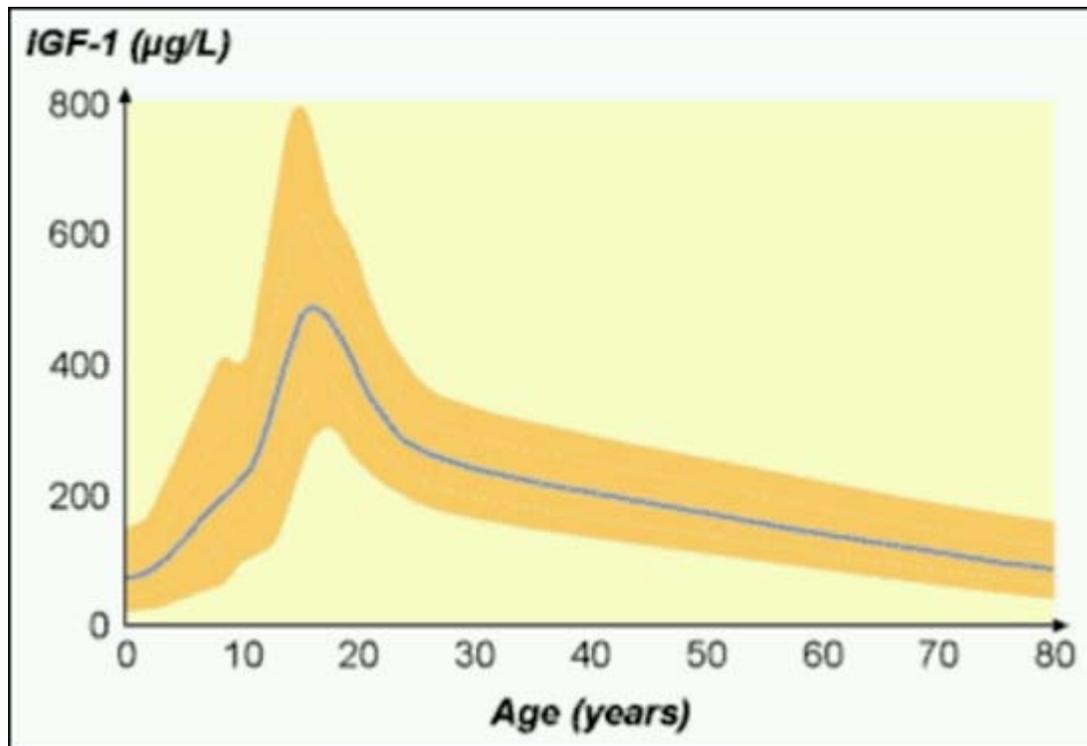


**Figure 2. Correlation between intra-abdominal fat mass and 24 hour GH secretion (from ref. 10).**

In the same population 24-h spontaneous GH levels were also analysed by means of deconvolution analysis of samples obtained every 20 minute. Mean GH levels, GH production rate and GH burst amplitude were higher in young people and in females as compared to older people and males, (12). Multiple regression analysis again suggested that intraabdominal fat mass was the single most important and negative determinant of GH status. Fasting levels

of insulin, IGF-I and free fatty acids did not correlate with either estimates of GH status. Surprisingly, LBM exhibited a weak inverse correlation with mean 24-h GH release, but LBM was not associated with other attributes of GH status and was not an independent determinant by multiple regression analysis.

A detailed analysis of GH secretion in relation to body composition in elderly subjects has, to our knowledge, not been performed. Instead serum IGF-I has been used as a surrogate or proxy for GH status in several studies of elderly men (13-15). These studies comprise large populations of ambulatory, community-dwelling males aged between 50-90 years. Not unexpectedly serum IGF-I declined with age (Fig. 3), but IGF-I failed to show any significant association with body composition or physical performance (13-15). As also pointed out by some of the authors, however, the validity of IGF-I as an indicator of GH secretion is uncertain - in particular in adults. It is evident that serum IGF-I levels are low in GH deficient children and elevated in active acromegaly, but serum IGF-I levels correlate only weakly with GH status in healthy young and mid-life adults, and a large proportion of hypopituitary GH-deficient adults may have IGF-I levels within the normal range (16). The residual or non-GH-dependent determinants of IGF-I in adults remain elusive and merits future research.



**Figure 3. Changes in serum IGF-I with increasing age. Modified from Jull A et al., J. Clin. Endocrinol. Metab. 1994; 78: 744-752.**

### **Influence Of Age, Sex And Body Composition On Gh Action And Pharmacokinetics**

Considering the great interest in the actions of GH in adults surprisingly few studies have addressed possible age-associated differences in the responsiveness or sensitivity to GH. In normal adults the senescent decline in GH levels is paralleled by a decline in serum IGF-I, suggesting a down-regulation of the GH-IGF-I axis. Administration of GH to elderly healthy adults has generally been associated with predictable albeit modest effects on body composition and a high incidence of side-effects (17). Whether this reflects an unfavourable balance between effects and side effects in older

people or employment of excessive doses of GH is uncertain, but it is evident that older subjects are not resistant to GH. Studies in GH deficient adults with pituitary disease strongly suggest that the dose requirement declines with age. Short-term dose response studies clearly demonstrate that older patients require a lower GH dose to maintain a given serum IGF-I level (18-19), and it has been observed that serum IGF-I increases in individual patients on long-term therapy if the GH dosage remains constant (20). It has also recently been reported that hypopituitary patients above 60 years are highly responsive to even a small dose of GH (21). Interestingly, there appears to be a gender difference in GH deficient adults with men being more responsive in terms of IGF-I generation and fat loss during therapy (22).

The pharmacokinetics and short-term metabolic effects of a near physiological intravenous GH bolus (200  $\mu$ g) were compared in a group of young (< 30 years) and older (> 50 years) healthy adults (23). The area under the GH curve was significantly lower in older subjects, whereas the elimination half-life was similar in the 2 groups, suggesting both an increased metabolic clearance rate (MCR) and apparent distribution volume (Vd) of GH in older subjects. Both MCR and Vd showed a strong positive correlation with fat mass, although multiple regression analysis revealed age to be an independent positive predictor. The short-term lipolytic response to the GH bolus was higher in "young" as compared to "older" subjects, respectively. Interestingly, the same study revealed that the GH binding protein (GHBP) correlated strongly and positively with abdominal fat mass (24).

### **"The Somatopause"**

It is obvious that the mechanism underlying the so-called somatopause involves other and perhaps more complex mechanisms than the female menopause, which predominantly is caused by gonadal resistance to

gonadotropins. A prospective long-term study of normal adults with serial concomitant estimations of GH status and adiposity would provide useful information. Evaluation of GH sensitivity as a function of age, sex and body composition would also be worthwhile. In the mean time the following hypothesis may be proposed (Fig. 4): 1. Changes in life-style and genetic predispositions promote accumulation of body fat with aging 2. The increased fat mass increases FFA availability, inducing insulin resistance and hyperinsulinemia 3. High insulin levels suppress IGFBP-1 resulting in a relative increase in free IGF-I levels 4. Systemic elevations in FFA, insulin and free IGF-I suppresses pituitary GH release, which further increases fat mass 5. Endogenous GH is cleared more rapidly in subjects with high amount of fat tissue. The very strong positive correlation between fat mass and GHBP could suggest that GH is cleared in adipose tissue by a receptor mediated mechanism. Clearly, future studies are needed to substantiate or refute this simplified model. At present it is equally premature and unwarranted to recommend GH treatment to reverse the age-associated deterioration in body composition and physical performance.

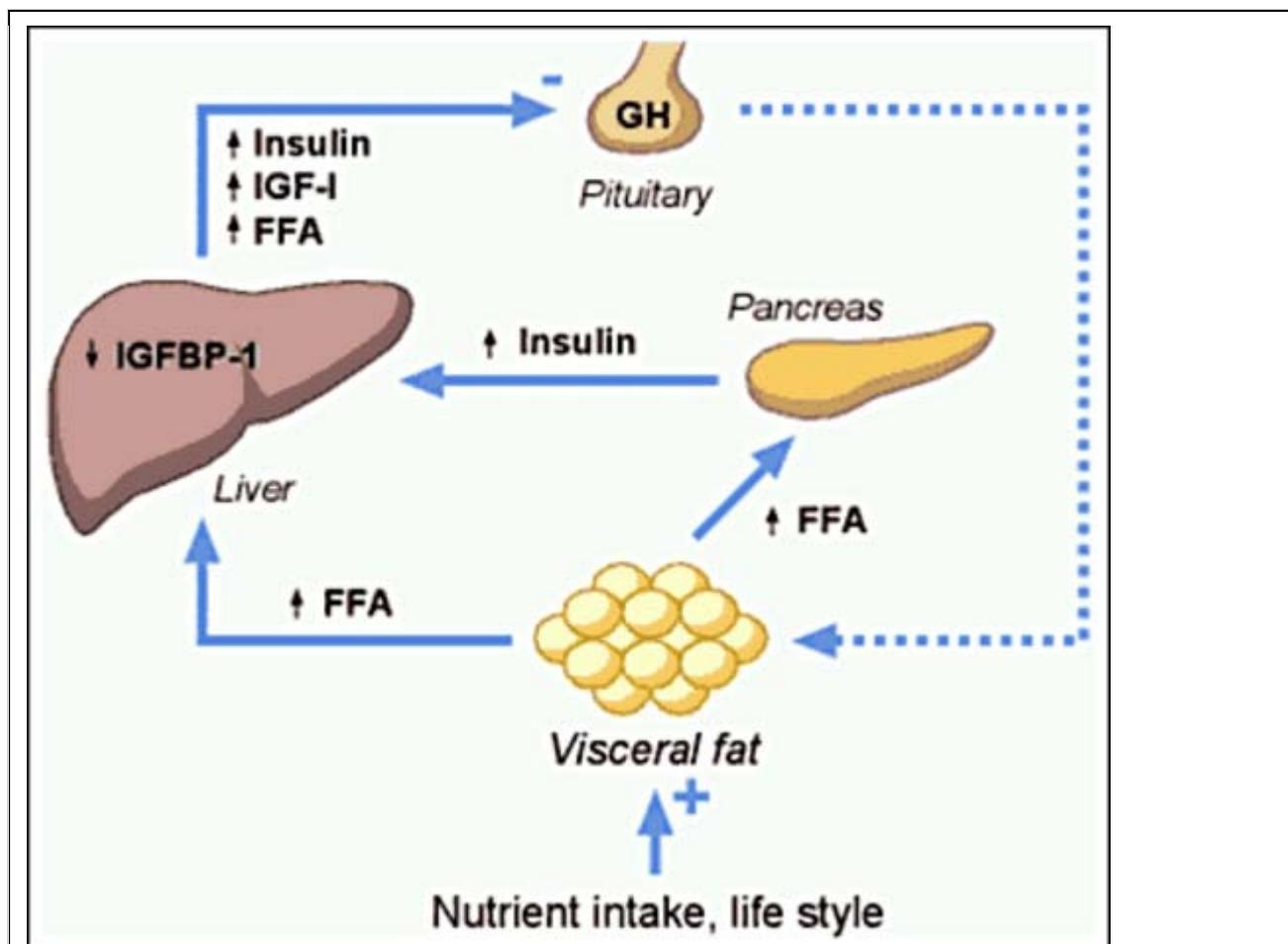


Figure 4. Hypothetical model for the association between GH levels and body composition in adults.

## METABOLIC EFFECTS OF GROWTH HORMONE

### Glucose Homeostasis and Lipid Metabolism

The involvement of the pituitary gland in the regulation of substrate metabolism was originally detailed in the classic dog studies by Houssay (25). Fasting hypoglycaemia and pronounced sensitivity to insulin were described as salient features of hypophysectomised animals. These

symptoms were readily corrected by administration of anterior pituitary extracts. It was also noted that pancreatic diabetes was alleviated by hypophysectomy. Finally, excess of anterior pituitary lobe extracts aggravated or induced diabetes in hypophysectomised dogs.

Luft et al. (26) clearly demonstrated the glycaemic control to deteriorate following exposure to a single supraphysiological dose of human GH in hypophysectomised adults with type 1 diabetes mellitus. Somewhat surprisingly, only modest effects of GH on glucose metabolism were recorded in the first metabolic balance studies involving adult hypopituitary patients (27, 28).

More recent studies on glucose homeostasis in GH deficient adults have generated results, which at first glance may appear contradictory. Insulin resistance may be more prevalent in untreated GH deficient adults (29, 30), whereas the impact of GH replacement on this feature seems to depend on the duration and the dose. Below, some of the metabolic effects of GH in human subjects, with special reference to the interaction between glucose and lipid metabolism, will be reviewed.

### **Studies In Normal Adults**

Almost forty years ago it was shown that infusion of high dose GH into the brachial artery of healthy adults reduced forearm glucose uptake in both muscle and adipose tissue (31). This was paralleled by a drop in RQ and an increase in muscle uptake of FFA, both of which suggest oxidation of FFA by the muscle. This pattern was opposite that of insulin, and co-administration of insulin and GH resulted in only minimal changes in net fluxes of glucose and FFA across the forearm bed. These studies clearly indicated direct insulin antagonistic effects of GH on muscle and adipose tissue.

The introduction of reliable radioimmunoassays for GH revealed the pulsatile and episodic nature of GH release (32) now known to be generated by

alternating secretion of GHRH and SST. A GH pulse is released roughly every second hour with a mean daily secretion of 0.5 mg (33). Apart from a well-known circadian variation in terms of elevated nocturnal GH levels during the early hours of sleep, GH secretion is amplified during fasting and stress, whereas meals suppress GH release. We studied the metabolic effect of a physiological GH bolus in the postabsorptive state, and demonstrated stimulation of lipolysis following a lag time of 2-3 hours to be the most consistent effect (34). Plasma glucose, on the other hand exhibited only minimal fluctuations, and serum insulin and C-peptide levels remained completely stable. This was associated with subtle reductions in muscular glucose uptake and oxidation, which could reflect substrate competition between glucose and fatty acids (i.e. the glucose/fatty acid cycle). In line with this, sustained exposure to high GH levels induces both hepatic and peripheral (muscular) resistance to the actions of insulin on glucose metabolism together with increased (or inadequately suppressed) lipid oxidation. Apart from enhanced glucose/fatty acid cycling, it has been shown that GH induced insulin resistance is accompanied by reduced muscle glycogen synthase activity (35) and diminished glucose dependent glucose disposal (36). Bak et al. (35) also demonstrated insulin binding and insulin receptor kinase activity from muscle biopsies to be unaffected by GH.

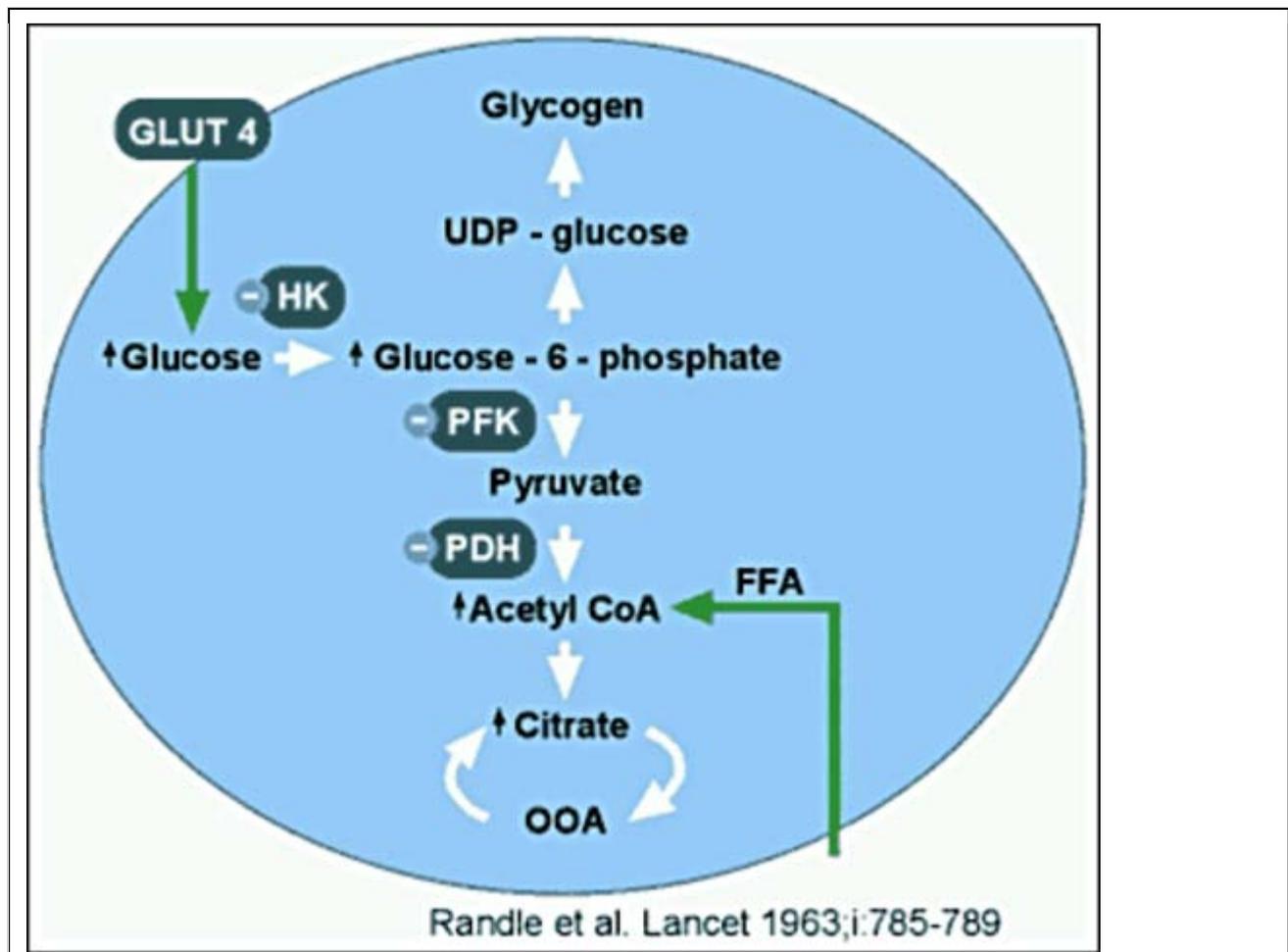
### **Lessons From Acromegaly**

Active acromegaly clearly unmasks the diabetogenic properties of GH. In the basal state plasma glucose is elevated despite compensatory hyperinsulinemia. In the basal and insulin-stimulated state (euglycemic glucose clamp) hepatic and peripheral insulin resistance is associated with enhanced lipid oxidation and energy expenditure (37). There is evidence to suggest that this hypermetabolic state ultimately leads to beta cell exhaustion' and overt diabetes mellitus (38), but a more recent study have demonstrated that the abnormalities are completely reversed after

successful surgery (37). Conversely, it has been shown that only two weeks administration of GH in supraphysiological doses (8 IU/day) induces comparable acromegaloid - and reversible - abnormalities in substrate metabolism and insulin sensitivity (39).

## **INTERACTION OF GLUCOSE AND LIPID METABOLISM**

Relatively few studies have scrutinised the exact sites of action of GH on glucose metabolism. There is no evidence of a net effect of GH on insulin binding to the receptor (35, 40), which obviously implies post receptor metabolic effects. The effect of FFA on the partitioning of intra-cellular glucose fluxes was originally described by Randle et al. (41). According to his hypothesis (the glucose/fatty acid cycle), oxidation of FFA initiates an up-stream, chain-reaction-like inhibition of glycolytic enzymes, which ultimately inhibits glucose uptake (Fig. 5).



**Figure 5. The glucose-fatty acid (Randle) cycle in muscle. Oxidation of fatty acids (FFA) inhibits pyruvate dehydrogenase (PDH). Citrate inhibits phosphofructokinase (PFK). The rise in glucose-6-phosphate inhibits hexokinase. Additional abbreviations: UDP, uridine diphosphate; GLUT 4, Glucose transporter 4.**

When considering the pronounced lipolytic effects of GH the Randle hypothesis remains an appealing model to explain the insulin-antagonistic effects of GH glucose metabolism. In support of this experiments have shown that co-administration of anti-lipolytic agents and GH reverses GH-induced insulin resistance. Similar conclusions were drawn from a recent

study in GH deficient adults, which showed that insulin sensitivity was restored when acipimox (a nicotinic acid derivative) was co-administered with GH (42). It has, however, also been reported that GH-induced insulin resistance preceded the increase in circulating levels and forearm uptake of lipid intermediates (43). This early effect of GH on muscular glucose uptake could reflect intra-myocytic FFA release and oxidation and thus be compatible with the Randle hypothesis. It could also imply alternative (early) effects of GH. Moreover, the inhibitory effect of GH on muscle glycogen synthase activity (35) is not readily explained by substrate competition. According to the Randle hypothesis the fatty acid-induced insulin resistance will result in elevated intracellular levels of both glucose and glucose-6-phosphate. By contrast, muscle biopsies from GH deficient adults after GH treatment have revealed increased glucose but low-normal glucose-6-phosphate levels (44). Moreover, NMR spectroscopy studies in healthy adults indicate that FFA infusion results in a drop in the levels of both glucose and glucose-6-phosphate (45). The latter study, which did not involve GH administration, reported that FFA suppressed the activity of PI-3 kinase, an enzyme stimulated by insulin which is considered essential for glucose transportation into skeletal muscle via translocation of glucose transporter activity (GLUT 4). In a recent study we observed, that GH infusion in healthy subjects, which induced elevated FFA levels and insulin resistance, did not impact insulin-stimulated PI-3 kinase activity (46). Thus, the molecular mechanisms subserving GH-induced insulin resistance remain uncertain.

### **Implications For GH Replacement**

Regardless of the exact mechanisms, the insulin antagonistic effects may cause concern when replacing adult GH deficient patients with GH, since some of these patients are insulin resistant in the untreated state. There is evidence to suggest that the direct metabolic effects on GH may be balanced by long-term beneficial effects on body composition and physical fitness, but

some studies report impaired insulin sensitivity in spite of favourable changes in body composition. There is little doubt that these effects of GH are dose-dependent and may be minimised or avoided if an appropriately low replacement dose is used. Still, the pharmacokinetics of s.c. GH administration is unable to mimic the endogenous GH pattern with suppressed levels after meals and elevations only during postabsorptive periods, such as during the night. This may be considered the natural domain of GH action which coincides with minimal beta-cell challenge. This reciprocal association between insulin and GH and its potential implications for normal substrate metabolism was initially recognised by Rabinowitz & Zierler (47) . The problems arise when GH levels are elevated during repeated prandial periods. The classic example is active acromegaly, but prolonged high dose s.c. GH administration may cause similar effects. Subcutaneous administration of GH in the evening probably remains the best compromise between effects and side effects (48), but it is far from physiological. We know and understand that hypoglycaemia is a serious and challenging side effect of insulin therapy as a consequence of inappropriately high insulin levels (during fasting). As a corollary, we must realise that hyperglycaemia may result from GH therapy. It is therefore important to carefully monitor glucose metabolism and to use the lowest effective dose when replacing adults with GH.

## **EFFECTS OF GROWTH HORMONE ON MUSCLE MASS FUNCTION**

The anabolic nature of growth hormone (GH) is clearly evident in patients with acromegaly and vice versa in patients with GH deficiency. A large number of in vitro and animal studies throughout several decades have documented stimulating effects of GH on skeletal muscle growth (49). The methods employed to document in vivo effects of GH on muscle mass in humans have been exhaustive including whole body retention of nitrogen

and potassium, total and regional muscle protein metabolism using labeled amino acids, estimation of lean body mass by total body potassium or dual x-ray absorptiometry (DEXA), and direct calculation of muscle area or volume by computerised tomography (CT) and magnetic resonance imaging (MRI).

### **Effects Of GH On Skeletal Muscle Metabolism In Vitro And In Vivo**

The clinical picture of acromegaly and gigantism includes increased lean body mass of which skeletal muscle mass accounts for approximately 50 %. Moreover, retention of nitrogen was one of the earliest observed and most reproducible effects of GH administration in humans (1). Thoroughly conducted studies with GH administration in GH deficient children using a variety of classic anthropometric techniques strongly suggested that skeletal muscle mass increased significantly during treatment (49, 50). Indirect evidence of an increase in muscle cell number following GH treatment was also presented (49).

These early clinical studies were paralleled by equally impressive experimental studies in rodent models. GH administration in hypophysectomised rats increased not only muscle mass, but also muscle cell number (i.e. muscle DNA content) (49). Interestingly, the same series of experiments revealed that work-induced muscle hypertrophy could occur in the absence of GH. The ability of GH to stimulate RNA synthesis and amino acid incorporation into protein of isolated rat diaphragm suggested direct mechanisms of actions, whereas direct effects of GH on protein synthesis could not be induced in liver cell cultures (51). Another important observation of that period was made by Goldberg, who studied protein turnover in skeletal muscle of hypophysectomised rats with <sup>3</sup>H-leucine tracer techniques. In these studies it was convincingly demonstrated that GH directly increased the synthesis of both sarcoplasmic and myofibrillar protein without affecting proteolysis (52).

The most substantial recent contributions within the field derive from human in vivo studies of the effects of systemic and local GH and IGF-I administration on total and regional protein metabolism by means of amino acid isotope dilution techniques. Horber and Haymond demonstrated that systemic GH administration for 7 days in normal adults increased whole body protein synthesis without affecting proteolysis (53), and similar data were subsequently obtained in GH deficient adults (54). Fryburg and Barret (55) infused GH (systemically for 8 hours) in normal adults and reported an acute stimulation of forearm (muscle) protein synthesis without any effects on whole body protein synthesis. By contrast Copeland and Nair (56) observed an acute stimulatory effect of GH on whole body protein synthesis, but no stimulatory effect on leg protein synthesis, in a design that also included co-administration of somatostatin to suppress insulin. Finally, Fryburg et al. (57) infused GH into the brachial artery, which was accompanied by a local increase in forearm muscle protein synthesis.

Based on these recent studies it seems that the nitrogen retaining properties of GH predominantly involve stimulation of protein synthesis without affecting (lowering) proteolysis and clues are also provided about the underlying mechanisms. Theroretically, the protein anabolic effects of GH could be either direct, or mediated through IGF-I, insulin or lipid intermediates. GH receptors are present in skeletal muscle (58), which combined with Fryburgs intra-arterial GH studies, makes a direct GH effect conceivable. An alternative interpretation of Fryburgs data could be that GH stimulates local muscle IGF-I release, which subsequently acts in an autocrine/paracrine manner. The effects of systemic IGF-I administration on whole body protein metabolism seem to depend on ambient amino acid levels in the sense that IGF-I administered alone suppresses proteolysis (59) whereas IGF-I in combination with an amino acid infusion increase protein synthesis (60). Moreover, intra-arterial IGF-I in combination with systemic

amino acid infusion increased protein synthesis (61). It is therefore likely that the muscle anabolic effects of GH at least to some extent are mediated by IGF-I. By contrast, it is repeatedly shown that insulin predominantly acts through suppression of proteolysis and this effect(s) appears to be blunted by co-administration of GH (62). The degree to which mobilisation of lipids contributes to the muscle anabolic actions of GH has so far not been specifically investigated.

In conclusion several experimental lines of evidence strongly suggest that GH stimulates muscle protein synthesis. This effect is presumably in part mediated through binding of GH to GH receptors in skeletal muscle. This does not rule out a significant role of IGF-I being produced either systematically or locally.

A interesting recent discovery has been that infusion of GH and IGF-I into the brachial artery increase forearm blood flow several fold (57, 63). This effect appears to be mediated through stimulation of endothelial nitric oxide release leading to local vasodilatation (64, 65). Moreover, co-infusion of a nitric oxide inhibitor with IGF-I appeared to blunt the stimulatory effect of IGF-I on forearm protein synthesis (64). It thus appears that an IGF-I mediated increase in muscle nitric oxide release accounts for some of the effects of GH on skeletal muscle protein synthesis. These intriguing observations may have many other implications. It is, for instance, tempting to speculate that this increase in skeletal muscle blood flow contributes to the GH induced increase in resting energy expenditure, since skeletal muscle metabolism is a major determinant of REE (66). Moreover, it is plausible that the reduction in total peripheral resistance seen after GH administration in GHDA is mediated by nitric oxide (65).

### **Effects Of GH Administration On Muscle Mass And Function In Adults Without Gh-Deficiency**

As previously mentioned the ability of acute and more prolonged GH administration to retain nitrogen in normal adults has been known for decades and more recent studies have documented a stimulatory effect on whole body and forearm protein synthesis.

Rudman et al. was the first to suggest that the senescent changes in body composition were causally linked to the concomitant decline in circulation GH and IGF-I levels (66). This concept, which is known by some as the somatopause, has recently been reviewed (67), and a number of studies with GH and other anabolic agents for treating the sarcopenia of ageing are currently in progress.

Placebo-controlled GH administration in young healthy adults (21-34 years) undergoing a resistance exercise programme for 12 weeks showed a GH induced increase in LBM, whole body protein balance and whole body protein synthesis, whereas quadriceps muscle protein synthesis rate and muscle strength increased to the same degree in both groups during training (68). In a similar study in older men (67 years) GH also increased LBM and whole body protein synthesis, without significantly amplifying the effects of exercise on muscle protein synthesis or muscle strength (69). An increase in LBM but unaltered muscle strength following 10 weeks of GH administration plus resistance exercise training was also recorded by Taaffe et al. (70). A more recent study of 52 older men (70-85 years) treated with either GH or placebo for 6 months, without concomitant exercise, observed a significant increase (4.4 %) in LBM with GH, but no significant effects on muscle strength (71). Thus no significant clinical benefit from administering GH to non-GH-deficient senescent patients has been documented yet.

Numerous studies have evaluated the effects of GH administration in chronic and acute catabolic illness. A comprehensive survey of the prolific literature within this field is beyond the scope of this review, but it is noteworthy, that HIV-associated body wasting is a licensed indication for GH treatment in the

USA. In this patient category GH treatment for 12 weeks has been associated with significant increments in LBM and physical fitness (72, 73).

### **Growth Hormone signaling in humans**

GH receptor signaling is a separate and prolific research field by itself as recently reviewed (74). This section will focus on recent data obtained in human models.

Growth hormone receptors have been identified in many tissues including muscle, fat, liver, heart, kidney, brain and the pancreas (75). Activation of receptor-associated Janus kinase (JAK) 2 is considered the critical step in initiating GH signalling. One GH molecule binds to two GHR molecules, and it is believed that preformed, unliganded GHR dimers exist (74). Following GH binding the intracellular domains of the GHR dimer undergo rotation, which is thought to bring together the two intracellular domains each of which bind one JAK2 molecule. This in turn induces cross-phosphorylation of tyrosine residues in the kinase domain of each JAK2 molecule followed by tyrosine phosphorylation of the GHR. Phosphorylated residues on GHR and JAK2 form docking sites for different signaling molecules including signal transducers and activators of transcription (STAT) 1, 3, 5a and 5b (74). STATs bound to the activated GHR-JAK2 complex are subsequently phosphorylated on a single tyrosine by JAK2 after which they dimerize and translocate to the nucleus, where they bind to DNA and act as gene transcription factors. A STAT5b binding site has recently been characterised in the IGF-I gene promoter region, which mediates GH-stimulated IGF-I gene activation (76). Attenuation of JAK2-associated GH signaling is mediated by a family of cytokine-inducible suppressors of cytokine signaling (SOCS) (77). SOCS

proteins bind to phosphotyrosine residues on the GHR or JAK2 and suppress GH signaling by inhibiting JAK2 activity and competing with STATs for binding on the GHR. As an example, it has been reported that the inhibitory effect of estrogen on hepatic IGF-I production seems to be mediated via upregulation of SOCS-2 (78).

Data on GHR signaling derive mainly from rodent models and experimental cell lines, although GH-induced activation of the JAK2/STAT5b and the MAPK pathways have been recorded in cultured human fibroblasts from normal human subjects (79). STAT5b in human subjects is critical for GH-induced IGF-I expression and statural growth as demonstrated by the identification of mutations in the STAT5b gene of patients presenting with severe GH insensitivity in the presence of normal GHR (80). GHR signaling in human models *in vivo* has been reported in a study in healthy young male subjects exposed to an intravenous GH bolus vs. saline (81). In muscle and fat biopsies significant STAT5b tyrosine phosphorylation was recorded 30-60 minutes after GH exposure (81). Significant GH-dependent IGF-I mRNA expression was only detectable in adipose tissue, whereas SOCS-1 and SOCS-3 mRNA expression tended to increase in muscle and fat, respectively (81). There was no evidence of GH-induced activation of PI 3-kinase, Akt/PKB, or MAPK in either tissue. The latter observation is noteworthy in relation to the insulin antagonistic effects of GH.

There is animal and *in vitro* evidence to suggest that insulin and GH share post-receptor signaling pathways (82). Convergence has been reported at the levels of STAT5 and SOCS3 (83) as well as on the major insulin signaling pathway: insulin receptor substrates (IRS) 1 and 2, PI 3-kinase, Akt and extracellular regulated kinases (ERK) 1 and 2 (84, 85). Studies in rodent

models suggest that the insulin-antagonistic effects of GH in adipose and skeletal muscle involve a suppression in insulin-stimulated PI3-kinase activity (82, 86). One study assessed the impact of a GH infusion on insulin sensitivity and the activity of PI3-kinase as well as PKB/Akt in skeletal muscle in a controlled design involving healthy young subjects (87). The infusion of GH induced a sustained increase in FFA levels and subsequently insulin resistance as assessed by the euglycemic clamp technique. This was, however, not associated with any changes in the insulin-stimulated increase in either IRS-1 associated PI3-kinase or PKB/Akt activity (87). It was subsequently assessed that insulin had no impact on GH-induced STAT5b activation or SOCS3 mRNA expression (88).

**There are at least 3 substances which control HGH secretion:**

<http://www.futurescience.com>

- **Growth hormone releasing hormone (GHRH)**, a substance which declines with age. Increasing levels of GHRH causes the pituitary to increase its output of HGH.
- **Growth hormone releasing peptide (GHRP)** is another substance that declines with age. Increasing levels of GHRP also causes the pituitary to increase its output of HGH.
- **Somatostatin** is a hormone that blocks the release of HGH by the pituitary gland. The natural production of somatostatin increases with age, and causes a corresponding decrease in HGH production by the pituitary gland.

The production of HGH is controlled by GHRH, GHRP, somatostatin, and other substances in the body. The degree to which changes in the levels of each of these substances is responsible for the decline in human growth hormone varies from individual to individual, and is somewhat gender-dependent.

The only naturally-occurring growth hormone releasing peptide appears to be ghrelin. Ghrelin is a hormone with many other effects, including being a powerful appetite stimulant. When given to laboratory animals, the animals eat huge amounts of food. The weight gain induced by overeating completely overwhelms the fat burning caused by the growth hormone

release, and the animals become obese. Pharmaceutical companies have produced synthetic growth hormone releasing peptides, such as GHRP-6 and GHRP-2, which stimulate HGH in humans, but do not increase appetite significantly. These substances are not on the market yet, and probably won't be for many years, if ever.

Pharmaceutical companies have produced a number of other promising analogs of ghrelin that restore the normal pulsatile release of growth hormone without the other unwanted effects of ghrelin. These substances include:

- **Hexarelin**
- **MK-0677 (ibutamoren mesylate, developed by Merck)**
- **Capromorelin (developed by Pfizer)**
- **Tabimorelin**
- **SM-130686 (Sumitomo Pharmaceuticals)**
- **Ipamorelin (Novo Nordisk)**
- **NN703 (Novo Nordisk. Similar to ipamorelin, but more selective)**

Many of the above growth hormone releasing analogs of ghrelin are effective when taken orally. None of them are on the market anywhere in the world. Hexarelin is a peptide that is fairly easy to synthesize, and it is sometimes used outside of legitimate medical channels. The other substances on the above list are only available in rare clinical trials.

Even though the above compounds have all been researched and found effective, it is doubtful if the research will proceed much farther. Most of these compounds are mainly effective against age-related declines in growth hormone. The United States Food and Drug Administration (FDA) does not regard the age-related decline in growth hormone to be a disease, even when it results in serious disability and death. Because of the size of the U.S. market and the worldwide influence of the FDA, these valuable medicines will probably be forever blocked from the market. (Because of the effectiveness of MK-0677, however, there is some hope for it eventually being approved somewhere in the world for a condition other than age-related growth hormone decline.)

Three major analogs of growth hormone releasing hormone have been developed by pharmaceutical companies, and will be discussed later:

- **Sermorelin (Geref, developed by Serono, withdrawn from the market)**

- **Tesamorelin (Theratechnologies. Marketed in the United States by Serono.)**
- **CJC-1295 (ConjuChem Biotechnologies)**

The effects of HGH in the human body have been studied intensively for decades, but the factors that affect HGH production remain rather complex and mysterious. Part of the reason for this is that the quantities of these substances produced by the body are on the order of a milligram per day in adults. Most people only produce about a teaspoonful of these substances during their entire adult lives.

To make the HGH situation even more complex, HGH is normally released in pulses or bursts throughout the day. There are usually 10 to 20 surges of HGH release, with the largest release occurring shortly after you fall asleep. Is there any advantage to having HGH released in pulses? Or is this simply the body's most efficient way of producing HGH? Nobody knows the answer to this important question, although there seems to be some evidence that the pulsatile release of HGH is important for human health.

There are indications, however, that some of the ghrelin analogs or the GHRH analogs may be superior to ordinary HGH replacement. Ordinary HGH therapy does not increase insulin sensitivity or decrease glucose levels, although it logically should be expected to -- since it increases the level of IGF-1 (insulin-like growth factor number 1). IGF-1 **decreases** glucose levels, so there is something about the continuous presence of growth hormone that is offsetting this IGF-1 related decrease in blood glucose. When youthful pulsatile release of growth hormone is restored, often (most notably with Tesamorelin) the **IGF-1 related decrease** in blood glucose is seen in most people, as would be expected. With some people, however, blood glucose levels increase (at least in short-term studies).

### **There are three basic ways for increasing HGH:**

- Taking a substance that increases the natural secretion of HGH by the pituitary gland.
- Using an injectable human growth hormone releasing hormone (GHRH).
- Using injectable human growth hormone.

With current technology and available substances, taking a substance that increases the natural secretion of HGH generally works best for those between the ages of roughly 30 to 45 years.

For most people over 45, injectable HGH is most effective -- and usually the only effective -- of the currently available options (although sermorelin works for some people). Tesamorelin looks very promising, but it is not known how widely available it will become.

### **Growth Hormone Releasing Hormone**

The information here on growth hormone releasing hormone (GHRH) will only be of academic interest to most people, since consistently effective medicines analogous to GHRH are not yet widely available. That situation may change in the future, though.

An injectable GHRH product has been produced with recombinant DNA technology, and was once commonly available by prescription in the United States and many other countries. It was sold under the brand name *Geref* by Serono Labs. GHRH is a protein consisting of a chain of 44 amino acids. *Geref* consists of only a 29 amino acid fragment of the GHRH molecule, but it appears to have the same effect as the full GHRH molecule (at least, for most people for a short period of time). The generic name of *Geref* is sermorelin.

*Geref* (sermorelin) was withdrawn from the market for general use in November, 2002. From 2002 until 2008, *Geref* was available only for diagnostic use and in clinical trials. In mid-2007, a few compounding pharmacies made sermorelin available at a reasonable price for general use by prescription. This sermorelin is no longer available from compounding pharmacies, though. Much of the sermorelin sold in the United States in recent years reportedly came from biotech companies in China, and was not necessarily identical to *Geref*.

*Geref* was totally withdrawn from the market in 2008, with the last sales from Serono occurring on September 30, 2008.

Other than the exception noted above, at adult doses, the cost of *Geref* has always been more than injectable HGH, and it has always been more difficult to obtain. Also, it didn't work for everyone. Some studies indicate that GHRH seems to work better when used in conjunction with L-arginine. If the release of HGH in pulses is important, the use of sermorelin with L-arginine may be superior to the use of HGH, but this varies greatly from individual to individual. The use of sermorelin for anything other than diagnostic use has been generally disappointing.

One problem with sermorelin, as well as many other GHRH analogs, is that they have a very short lifetime in the body, usually with a half-life of only

minutes. (It appears that this half-life problem can be solved for some of these GHRH analogs by chemically combining them with polyethylene glycol, among other methods.)

Sermorelin is a much smaller molecule than HGH, and research has been done on a sermorelin nasal spray. Only 3 to 5 percent of sermorelin is absorbed in the nasal spray form, however. This makes a sermorelin nasal spray far too expensive, so sermorelin was only available in injectable form. Sermorelin for sub-lingual use has recently become available in a few countries. This product may work for some people, but it will have problems with absorption and high cost that are similar to the earlier nasal spray form.

Theratechnologies of Canada has developed what appears to be a much better form of GHRH. **Tesamorelin** contains the same number of amino acids (44) as natural growth hormone releasing hormone, but it has been modified to last longer in the human body. It avoids the short half-life problem of sermorelin, and tesamorelin appears to be much more effective. Tesamorelin was approved by the FDA in the United States on November 10, 2010 for HIV-related fat accumulation. Tesamorelin will be marketed in the United States under the brand name *Egrifta*. It is also currently under investigation for the reduction of abdominal fat in otherwise normal adults with reduced levels of growth hormone. Tesamorelin is also being investigated for mild cognitive impairment.

Tesamorelin has produced many encouraging results, including a small improvement in glucose levels in most patients. Human growth hormone often produces a temporary increase in insulin resistance when it is first started, especially in high doses. Tesamorelin seems to have the opposite effect. (However, under certain conditions, such as when Tesamorelin is discontinued after a short period of time, insulin resistance actually may get worse. This is not surprising from what is known about lipolysis and insulin resistance.)

The manufacturer of Tesamorelin completed an agreement in October, 2008 with the pharmaceutical company Serono for marketing Tesamorelin in the United States, and an official New Drug Application was filed with the FDA on June 1, 2009. On May 27, 2010, the FDA expert advisory board voted unanimously (16-0) to approve Tesamorelin. It received official approval from the United States Food and Drug Administration on November 10, 2010. There are likely to be strict controls on off-label use until a large body of data is available from uses for the FDA-approved indications.

Another long-acting analog of GHRH that looks very promising is CJC-1295, but that product is at least 3 years away from approval by government

agencies. CJC-1295 maintains a much longer half-life in the human body by partially binding to albumin, an important protein that is prevalent in the human bloodstream.

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As stated earlier, pharmaceutical companies have produced growth hormone releasing agents that have been shown to be very effective in reversing the decline in HGH production with age. The one that has consistently worked the best is MK-0677 (ibutamoren mesylate), which is very effective in restoring HGH release in middle-aged and "normally-aging" elderly individuals to the levels of much younger people. MK-0677 is an oral medicine that restores the release of HGH in the pulsatile fashion characteristic of HGH release in young people. Unfortunately, it was not very effective in restoring HGH in the frail elderly, which was its original target market. It appears, in fact, that any form of HGH supplementation in the very frail elderly, and in the critically-ill elderly, is actually quite harmful. Restoring HGH in "normally-aging" people is not a function that the Food and Drug Administration (FDA) considers to be a legitimate function of a medicine; therefore, Merck (the pharmaceutical company) stopped all further development of MK-0677. Other effective oral HGH releasers developed by the pharmaceutical companies have faced a similar fate for similar reasons.

A considerable amount of research has been done on HGH releasers by the pharmaceutical companies, and some very promising substances have been developed, but there is no sign that any of them will be on the market anytime soon. MK-0677 (ibutamoren mesylate) is a substance, though, that seems to be too good to go away. It still appears in successful clinical trials from time to time. It recently completed another successful medical test in normally aging adults, and has been undergoing clinical trials for use in fibromyalgia.

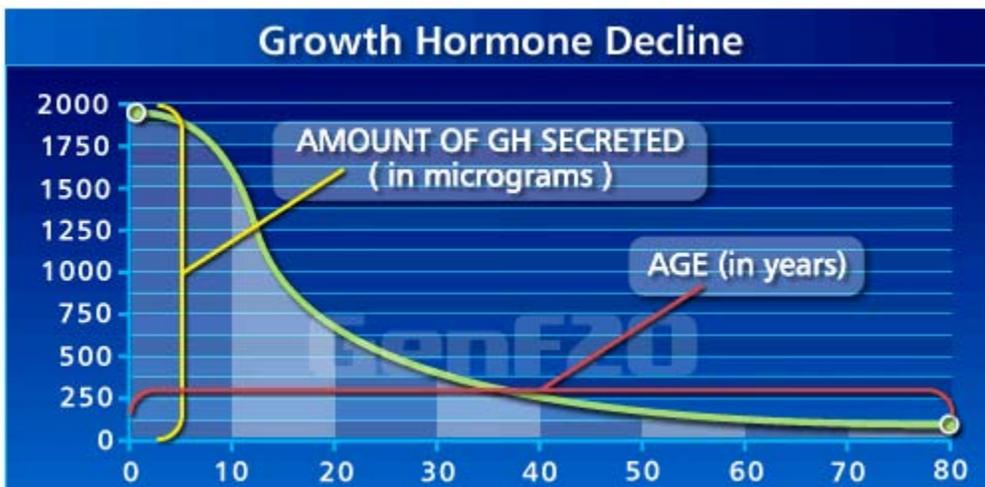
In a free market, MK-0677 (ibutamoren mesylate) would likely have had a revolutionary impact on the health of most people over 40. In fact, it is possible that MK-0677 could have revolutionized health care, prevented great human suffering, and literally saved trillions of dollars in health care. Since a free market in pharmaceuticals does not exist, MK-0677 will probably remain a laboratory curiosity more many years.

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The average person thinks of the damage of aging as an inevitable process of wear and tear. However, if wear and tear were the primary cause of

aging in humans, a 60 year-old should have only twice the signs of aging as a 30 year-old. In healthy adults, it is known that premenopausal women secrete more GH than age-matched men, and that GH secretion is reduced with advancing age and with obesity.

Why do most 30-year-olds show few effects of aging, while the effects of aging are so obvious in a 60 year-old person? If wear and tear were the major cause of aging, a 90-year-old person would only have 3 times as much aging damage as a 30-year-old.



Direct measurement of growth hormone level does pose a significant challenge because of its pulsatile nature. Plasma Insulin-like Growth Factor 1 (IGF-1) level concentrations decline with advancing age in healthy adults paralleling the growth hormone decline (Figure 1). After a great deal of debate, a consensus has been reached to use IGF-1 as an indirect marker for growth hormone level.

**Figure 1. IGF-1 Levels As Individuals Age**

- Starting value IGF-1 levels fall from 500-1000ng/ml
- At age 30 IGF-1 levels typically drop to 400ng/ml
- At age 40 IGF-1 levels typically drop to 300ng/ml
- At age 50 IGF-1 levels typically drop to 200ng/ml
- At age 60 IGF-1 levels typically drop to 100ng/ml
- At age 70 IGF-1 levels typically drop to 50ng/ml
- On average, at death (assuming approximately at age of 80) IGF-1 levels typically drop to 0 (zero) ng/ml

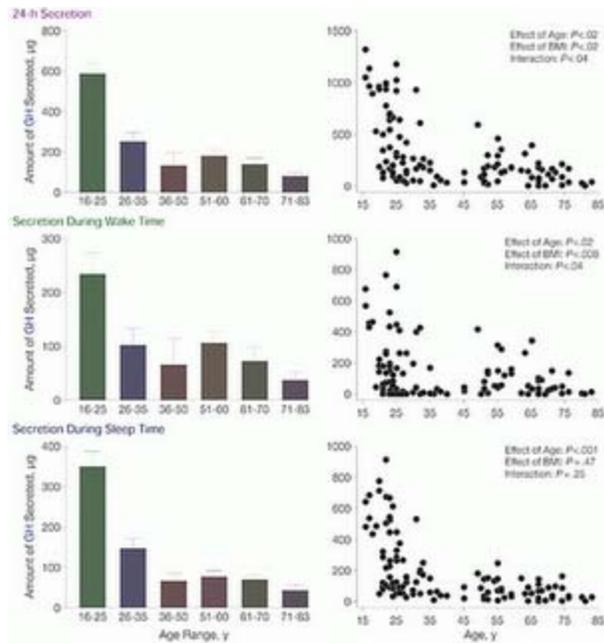
At the age of 30, people have spent most of their lives with fairly high levels of human growth hormone (HGH). HGH is responsible for growth during

childhood -- and for the repair and regeneration of human tissue throughout our lives. By the time we reach the age of 30, our HGH levels are only about 20 percent of their peak levels during childhood, and after the age of 30, they continue to decline at about 12 to 15 percent per decade, and often much more. By the time most of us are 30 years old, our bodies no longer produce enough HGH to repair all of the damage that is occurring in our bodies. As our HGH levels continue to decline, the damage that we call aging continues to accelerate. This human growth hormone reduction, greatly contributes to the acceleration of the aging process.

The decline in HGH is not the only cause of the manifestations of aging. Even if our HGH levels remained at the level of a 25 year-old, we would continue to experience the effects of aging, but those effects would be greatly reduced until we reached a very advanced age. HGH does not affect the root cause of aging, as measured by maximum lifespan, but it can certainly affect many of the manifestations of aging. **Humans normally produce about 500 micrograms of HGH daily at age 20. By age 80, the daily production falls to 60 (or less) micrograms. IGF-1 levels below 200 to be HGH deficient and a diagnosis on Adult Onset Growth Hormone Deficiency Syndrome is made**

Human Growth Hormone (HGH) is produced by somatotropes, which are the cells that make up 50% of the pituitary gland. It is first converted to growth factors in the liver. IGF-1 is the most effective growth factor, causing the majority of the age-reversing effect of HGH. IGF-1 is sent to all parts of the body, affecting every bodily function- sex and reproduction, growth and development, mood and metabolism. By increasing the levels of HGH in our bodies, we can slow, or even reverse, many of the manifestations of aging. It must be done carefully, though, and under medical supervision. Ideally, this HGH replacement should begin at about the age of 30 years, but HGH replacement can be beneficial at any age above 30. In fact, for older people, HGH therapy can reverse the manifestations of aging by 5 to 15 years or more. There is no other single therapy currently available that can have the impact on the aging body that HGH can have.

Actual plots of growth hormone secretion patterns, with age on the horizontal axes, tell a different story. See, for example, the graphs below, from [professionalmuscle.com](http://professionalmuscle.com). They match the graphs one sees in empirical academic papers. The graphs below (click to enlarge) are particularly good at highlighting some interesting patterns of variation.

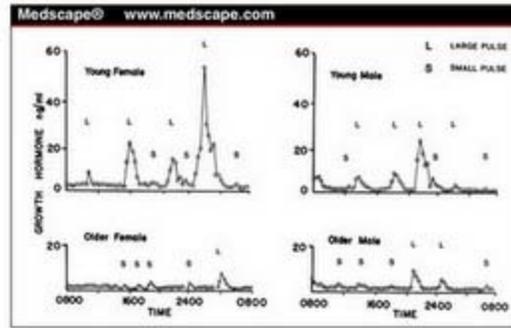


On the left side, bar charts show secretion patterns grouped by age ranges during a 24 h period (at the top), during wake time (at the middle), and during sleep (at the bottom). On the right side is the actual data used to build the bar charts. As you can see from the graphs on the right side, the drop in growth hormone secretion follows a pattern that looks a lot more like an exponential decay than a linear pattern.

The drop is very steep from 15 to 40 years of age, after which it shows some fluctuations, going up and down. Interestingly, people in their 50s and 60s, at least in this dataset, have on average higher growth hormone levels than people in their 40s. Of course this may be due to sample bias, but the graphs suggest that there is a major drop in growth hormone secretion, on average, around age 40.

As you can see, there is a lot of individual variation in growth hormone levels. If you look carefully at the graph on the top-right corner, you will see a 50 year old who has a higher 24 h growth hormone secretion than many folks in 15-30 age range. This pattern of individual variation is common for the vast majority of traits anyway, and often the distribution of traits follows a normal, or bell-shaped, distribution. The bell-shaped distribution becomes clear when the traits are plotted based on frequency.

Growth hormone is secreted in pulses. In case you are wondering, growth hormone secretion in young women is higher than in young men. See the graphs below (click to enlarge), from this excellent article on growth hormone by Cummings and Merrian.



**Figure 2.** Episodic GH secretion in younger and older women and men. In both sexes, the decline in GH primarily reflects a reduction in GH pulse amplitude. (From Ho et al.)<sup>2</sup>

Yet, women do not put on a lot of muscle mass in response to weight training, regardless of the age at which they do weight training. This means that growth hormone, by itself, does not lead to significant gains in muscle mass. Androgenic hormones, like testosterone, play a key moderator role here. Muscle mass gain is the result of a number of things, including the combined action of various hormones. To complicate things further, not only do these hormones act together in an additive fashion, but they also influence each other.

Another reasonable conclusion from the data above on growth hormone secretion in young women and men is that growth hormone must indeed have major health-promoting effects, as most of the empirical data suggests. The reason is that, from an evolutionary standpoint, young (or pre-menopausal) women have always been the evolutionary bottleneck of any population of ancestral hominids. High survival rates among young women were a lot more important than high survival rates among men in general, in terms of the chances of survival of any population of ancestral hominids.

Higher survival rates among young ancestral women may have been enabled by higher levels of growth hormone, among other things. The onset of the metabolic syndrome, which is frequently in modern humans around age 40, may also be strongly influenced by falling growth hormone levels.

How can growth hormone secretion be increased after age 40? A few options are vigorous exercise, particularly resistance exercise; healthy sleep patterns; and some supplements, like niacin.

[J Endocrinol Invest.](#) 1999;22(5 Suppl):58-60.

**Gender difference in growth hormone response in adults.**

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**Abstract**

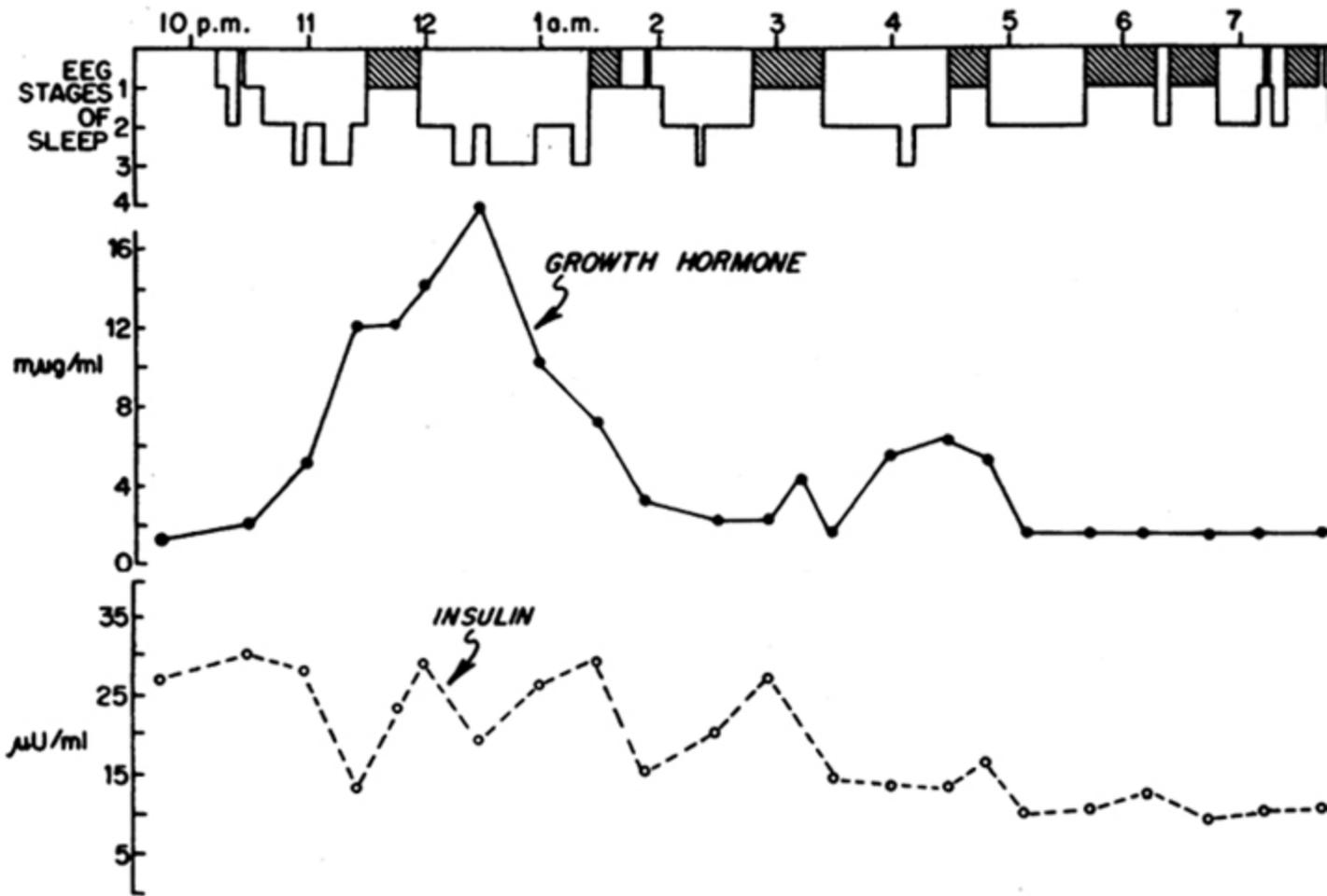
Several trials with growth hormone (GH) replacement therapy in adults with GH deficiency have been conducted during the last 10 years. Beneficial effects of treatment on bone density, physical capacity, body composition, lipid profile and quality of life have been reported. It has long been known that GH secretion is greater in women than in men, despite similar reference ranges of serum insulin-like growth factor (IGF)-I in adult men and women. It has also been reported that sex steroids influence not only GH secretion but also the local synthesis of IGF-I in target tissues and the expression of the GH receptor in various other tissues. However, it has been acknowledged only recently that there is a clinically significant gender difference in the response to GH treatment in adults with GH deficiency and, consequently, a need to adjust the dose of recombinant human GH (rhGH). We report the results of a placebo-controlled study in 36 men and women with GH deficiency who received the same dose of rhGH per body surface area (1.25 U/m<sup>2</sup> per day) for 9 months. We observed significantly greater responses in male patients than in female patients with regard to the changes in serum levels of IGF-I, body composition and biochemical markers of bone metabolism. When these patients continued to receive GH replacement therapy for an additional 24 months, the dose of rhGH was adjusted to the serum levels of IGF-I. As a result, the dose administered to the male

patients was reduced to nearly half that given to the female patients (1.0 vs 1.9 U/day) and the serum levels of IGF-I and of biomarkers of bone turnover increased to the same extent in patients of both sexes. However, an increase in bone density of the hip and the lumbar spine after a total of 33 months of rhGH treatment was observed only in the male patients; no significant changes in bone density were found in the female patients. The reason for the observed difference in GH response between men and women with GH deficiency is not known, although the different sex steroid pattern cannot be excluded as a contributing factor.

### Human Growth Hormone and sleep

The graphs below taken from a 1968 study demonstrate the relationship between sleep and secretion of somatotropin, otherwise known as Human Growth Hormone.

**Chart 1** - Normal secretory pattern of Human Growth Hormone and insulin in relation to sleep cycles.



**Chart 2** - Secretory pattern of Human Growth Hormone and insulin relating to delayed sleep. Notice that the normal peak secretion of hGH does not occur when sleep is delayed from the usual bedtime. Since hGH releases fat and prevents the storage of excess fat, irregular sleep habits are likely to have a major negative impact on a person's ability to maintain their ideal weight. Notice also that insulin takes a lot longer to return to low levels if a person stays awake later than usual at night.

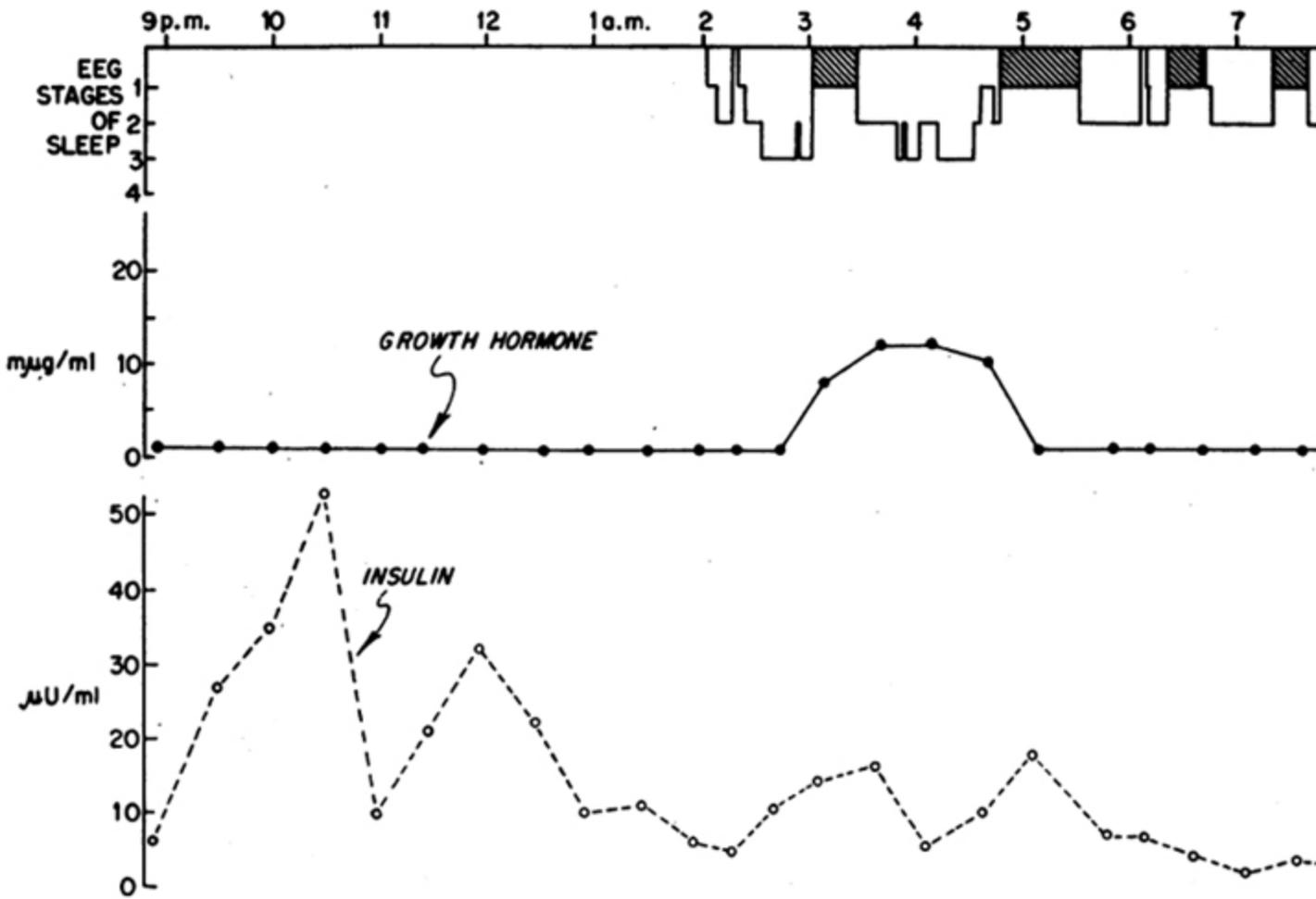


Chart source:

Takahashi Y, Kipnis DM, Daughaday WH, Growth hormone secretion during sleep, Washington University School of Medicine, Department of Medicine, Metabolism Division, St. Louis, Missouri, Published in The Journal of Clinical Investigation, Sep 1968; 47(9): 2079-2090

**Growth Hormone Rating: (1 being the lowest, 5 being the highest)**

- Strength-4
- Weight Gain-4
- Fat Loss-4
- Side Effects-2
- Keep Gains--4

**What HGH therapy can do:**

- Reduce excess body fat, especially abdominal fat. (The reduction of abdominal fat is the single most profound effect of HGH replacement in many people.)
- Increase muscle mass (and physical strength if combined with moderate exercise).
- Reduce wrinkling of the skin and some other effects of skin aging.
- Re-grow certain internal organs that have atrophied with age.
- Increase bone density.
- Strengthen the immune system.
- Reverse cognitive decline.
- Stimulate production of the bone marrow cells that produce red blood cells.
- Reduce the probability that you will spend the last years of your life in a nursing home.
- HGH slows the progression of cardiovascular disease, and reduces the risk of death from cardiovascular disease, in individuals with natural growth hormone levels that are below average for the age of the individual. HGH can also slow the progression of cardiovascular disease by improving one's cholesterol profile. There is increasing evidence over the past year or two that maintaining healthy growth hormone levels results in a stronger heart. Individuals with low growth hormone levels have an overall increased risk of death due to cardiovascular disease. Low growth hormone levels cause a particularly large increase in the risk of stroke as compared with individuals receiving growth hormone replacement.

**Uses of HGH in sports and bodybuilding: (Minimum effective dosages seem to start at 4 I.U. per day).**

1) Human growth hormone provides a potent anabolic effect; it builds muscle. Without turning this into a biochem lesson – especially since that's way over my head – suffice to say that HGH increases the body's ability to synthesize protein, and that this allows for muscle tissue to be built. Human growth hormone use produces the holy grail of all anabolic benefits, *hyperplasia*. Hyperplasia is the permanent increase in the amount of muscle cells. Over the years there have been many steroids that were alleged to result in creating new muscle cells, but HGH is the substance that actually delivers this incredible benefit. HGH also increases the size of existing muscle cells.

So with HGH you have a situation where the size of existing muscle cells are increased AND a permanent creation of new muscle cells. So a person could go on a cycle of human growth hormone therapy, which would create new muscle cells that remain after HGH therapy stops. The longer the person

remains on this regimen the more *new* muscle cells will be produced. This person would then have more muscle than he did before the therapy and reap all of the performance benefits that come with increased muscle even after the end of therapy.

Additionally, human growth hormone has a positive strengthening affect on connective tissues such as ligaments, tendons and cartilage and at an accelerated rate. Old injuries will heal and these tissues will be strengthened which can potentially minimize future injuries as well. There is no doubt that human growth hormone therapy is being used in conjunction with the surgery and rehab of professional athletes, which has had the effect of getting athletes back on the field quicker than ever. These connective tissue benefits make HGH much more attractive than the use of old school steroids, as steroids only positively affect muscle tissue, while having a negative effect on connective tissue.

2) HGH provides metabolic benefits such as helping the body burn more fat than usual, and serves as a protein-sparing agent as well. HGH administration triggers the release of fatty acids from fat stores and the body winds up burning more fat than carbohydrates to meet energy requirements. This is why athletes on human growth hormone can have extremely low levels of body fat while maintaining extremely high levels of muscle mass.

Without drugs, there is a kind of equilibrium between body fat and muscle mass. If body fat is too low, a person's muscle mass will decrease as well. HGH also has an anti-catabolic effect (protein sparing), which means that muscle protein isn't broken down during periods of intense exercise or in the case of calorie restriction. This anti-catabolic effect means that athletes can recovery quicker from competition and training.

And it is worth noting that testosterone when used in similarly appropriate doses; in conjunction with HGH is an extremely potent supplement cocktail from which all athletes would benefit greatly.

Remember, this isn't an effort to rationalize or justify the use of HGH and testosterone. I am simply recognizing and pointing out reasons why athletes – or anybody who works out for that matter – would find these substances so desirable.

### **Effect of the Human Growth Hormone on Reduction of Fat and Cutting Body Weight**

HGH supplements exert a highly beneficial effect on the human body.

These supplements promise to reduce superfluous weight, cut down on fat deposits, attain ideal body mass, build lean muscle and achieve an attractive body contour.

To start the therapy, the dosage of HGH is 2 IU per day. As the body gets adjusted to the treatment, it is better to increase the dose to 3 IU per day and then further increase it to a maximum daily dosage of 4 IU per day. This dose given for six months provides brilliant results for fat loss. This hormone when used for four to six weeks will give satisfactory results if taken along with anabolic androgen steroids. Addition of T3 along with HGH and testosterone would reduce the muscle mass effectively and promptly. Some people, who have been under HGH cycle, also say that following a good diet and a graded exercise regimen is advantageous to attain fat loss.

User testimonials say that taking this hormone at a dosage of 4 IUs per day, in the morning before exercise worked well and proffered successful weight reduction and fat loss. Administering the hormone two to four IU, twice per day along with Metformin was also observed to give good results with weight loss.

It is believed that some people have used the drugs that help cut down fat in a combination of primobolan, dianabol and HGH. There was another successful experience by an individual who was on GH cycle with six IU per day. The dosage was distributed into 3 IUs twice per day and was given for an interval of two months. During this period, the user maintained a strict exercise schedule and appropriate diet, which appreciably enhanced the effect of the hormone.

The glucose level in the body gets blocked by the growth hormone, and that allows the fat reserves to be melted in order to provide adequate energy to meet the requirement of the body. Also, HGH boosts metabolic processes of the body, which in turn burns fat. So there will be significant fat reduction after administering the hormone. This hormone also reduces the need to embark on a strict diet plan and a rigid exercise schedule in order to shed superfluous fat.

Thus, HGH guarantees freedom from obesity and over weighted-ness. It burns excessive and unwanted fat sheds pounds of undesirable weight, simultaneously boosts energy levels and augments lean muscle mass. The therapy provides general health and well being.

### What HGH cannot do:

- It cannot eliminate the effects of oxidation damage, although it may alleviate some of it.
- HGH cannot eliminate the effects of the reduction of other hormones. In fact, a deficiency of certain other hormones will decrease the beneficial effects of HGH.
- It cannot significantly reverse the damage to human proteins caused by glucose, although it may reverse a little of this damage.
- Although it helps skin to look younger, it cannot eliminate all of the damage cause by sunlight and other ultraviolet sources.
- It cannot increase maximum lifespan. For many people with HGH or IGF-1 genetic defects, however, it can significantly extend life *expectancy*.

Studies show that there are specific exercises that are particularly effective at stimulating GH release. As we share them with you, it is important to point out that any exercise will help to enhance the effects of growth hormone. The following exercises are used specifically help to increase GH release and have a rate of effectiveness that, for the most part, is proportionate to the intensity of the exercise.

<b>EXERCISE</b>	<b>INTENSITY</b>	<b>HGH SECRETION</b>
Running (Women)	High	266% increase in trough levels 75% increase in daily secretion
Running (Men)	Moderate	0% - Moderate
Stationary Bike (both sexes)	High	166% increase
Stationary Bike (both sexes)	Moderate	166% increase
Weight Training (both sexes)	85% MLC *	400% increase
Weight Training (both sexes)	70% MLC *	300% increase
Weight Training (both sexes)	Moderate - High	Immediate & Sustained increase
Treadmill (both sexes)	High	Increased GH Pulse

- \*MLC = Maximal Lift Capacity, the maximum amount of weight able to be lifted once.

**Two recent studies show how you can increase hGH levels naturally.** Kang's 1990 research shows that it's the intensity of the workout, not the volume of work, which maximizes growth-hormone secretion. Kang studied a variety of training regimens and found that the greatest hGH production was achieved with relatively heavy weights done in sets of eight to ten repetitions with a one-minute rest between sets. This boosted hGH levels 36 percent higher than regimens that used longer rest periods, higher rep ranges and lower weights. Kang also discovered that hGH secretion peaks 10 to 25 minutes after the start of exercise. After 25 minutes it begins to decline but still remains above baseline levels for an hour. The fat mobilization produced by this additional hGH lasts more than an hour, however.

**A second study**, this one performed by Ballard in 1991, indicates that the timing of your workout may affect total hGH release. Ballard analyzed the amount of growth hormone produced by identical workouts at four different times of the day: 6 am., noon, 6 p.m. and midnight. She found that training sessions at noon and 6 p.m. produced significantly higher levels of hGH secretion than early-morning or late-night workouts. This appears to be related to the body's circadian rhythm and the length of time between the peak secretion during sleep and the workout. While each athlete's biological clock is different, you might want to experiment with midday or early-evening training if you currently work out first thing in the morning or late at night. It could very well make a noticeable difference.

**One thing you should avoid is oral arginine and ornithine.** There has been a lot of hype about these supplements from advertisers, who stand to gain financially from your purchases. Unfortunately, oral supplementation doesn't work at dosages that you can afford unless you've won the lottery. Durk Pearson and Sandy Shaw report in their book *Life Extension* that measurable increases in hGH have been achieved with dosages of five to 10 grams of L-arginine and 2 1/2 to five grams of Lornithine per day. (Try pricing the cost of these dosages on a monthly basis if you want a shock.) Alas, lower doses are only effective if the amino acids are introduced intravenously. So unless you work in a hospital, *chances are you're out of luck.*

All weight-training exercises are effective promoters of GH release, but those that involve the use of high-resistance and major muscle groups

tend to be the most effective. Applying maximum effort to fewer repetitions of squats, leg presses, deadlifts, overhead presses, bench presses, standing curls, and leg curls will optimize your results. In addition, go to MLC for one rep of each of these exercises no more than once a week to create an additional boost of GH. If you are not experienced with weight training, please work with your physician to determine your physical condition and work with a qualified personal trainer who can teach you proper technique.

### **Major Difference Between GH and Steroids:**

Steroids can increase the size of your muscle cells, but cannot I repeat CAN NOT increase the number of muscle cells in your body, which to start with is governed by your genetics. However Growth hormone CAN increase the number of muscle cells in your body, which goes beyond genetics.

### **Half-Life of GH:**

Exogenous (injected) GH has a "half-life" of approximately 2 hours . . . a 4-hour period of activity during which there is a suppression of naturally produced GH.

## **Scientific Review of Growth Hormone**

Kent Holtorf, M.D.

### **Section 1:**

**Growth hormone (GH ) results in decreased body fat, increase lean muscle, decreased heart disease and an increase in quality of life.**

1. "The overall deterioration of the body that comes with growing old is not inevitable...We now realize that some aspects of it can be prevented or reversed." Effects of 10-20 years of aging on lean body mass and adipose tissue reversed in 6 months with testosterone and hGH.

Daniel Rudman, M.D. Effects of Growth Hormone in Men over 60 Years Old," New England Journal of Medicine. New England Journal of Medicine. 1990 Jul 5;323(1):1-6.

2. Life with low growth hormone (GH) is poor both in quantity and quality.  
- GH peaks at puberty and begins to decrease at 21.

"At age 60 most adults have total 24-hour secretion rates indistinguishable from those of hypopituitary patients with organic lesions in the pituitary gland. Almost all adults 40 years of age or older have a growth hormone (IGF-1) deficit."

Savine R. Growth hormone replacement for the somatopause. Horm Res 2000;53 Suppl 3:37-41 Savine R. et al.

3. GH decreased body fat in men and women by 14% and increased lean muscle in both men and women.

Synergistic with testosterone (decreased body fat 17-18%).

GH resulted in substantial increase in aerobic capacity, decreased total and LDL (bad) cholesterol, improved cholesterol coronary risk ratio, and GH lowered PSA.

Mark Blackman of Johns Hopkins University and National Institute on Aging (Due to be published)

4. "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"

Their results (Blackman) showed positive effects of GH on lean body mass, central fat, low-density lipoprotein cholesterol and aerobic capacity.

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

5. Low IGF-1 (measurement of low growth hormone) in older women results in:

Poor muscle strength Slow walking speed Difficulty with mobility tasks

Cappola AR et al. Association of IGF-I levels with muscle strength and mobility in older women.

J Clin Endocrinol Metab 2001 Sep;86(9):4139-46

6. Aging and Adult Growth Hormone Deficiency both have:

- Increased Cardiovascular morbidity and mortality
- Decreased muscle mass and bone mass
- Total and visceral fat increased
- LDL (bad cholesterol) increased

With GH supplementation

Body composition changes - reduction in total and visceral fat and increase in lean body mass

Improvement in cardiovascular function and lipids

Reverse atherosclerotic changes in carotids

Quality of life improves

Bone Mineral Density Increases

Johannsson et al. Growth Hormone and IGF Research 2000, Supplement B 25-30

7. GH deficiency results in abnormal body fat and distribution, and insulin resistance. GH replacement results in increased lean body mass, decreased abdominal fat by up to 50%, and increased insulin sensitivity (prevents diabetes)

Christiansen, J. Effects of GH upon body composition.. Growth Hormone in Adults , 1996, Cambridge University Press

8. GH secretion impaired in obesity

- GH decreases adiposity
- Inhibits lipoprotein lipase
- Enhances lipolysis
- Improves dyslipidemia

Nam SY et al. Growth Hormone and Adipocyte Function in Obesity.

Horm Res 2000 Jul;53 Suppl S1:87-97

9. Middle age men with low GH and abdominal obesity

- 9 months of GH treatment (9.5 microg/kg/day)
- Decreased fat, abdominal visceral 18% and subcutaneous 6%
- Improved insulin sensitivity (prevents diabetes)
- Total Cholesterol, LDL, Triglycerides decreased
- Diastolic BP decreased

Johannsson G et al. GH treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism and reduces diastolic BP. J Clin Endocrinol Metab 1997;82:727-734

10. 5 years GH Replacement

- Significant Increase in
  - Lean body mass
  - Bone mineral density
- HDL-C (good cholesterol)
- Significant decrease in
  - Total Cholesterol
  - LDL-C (bad cholesterol)
  - Triglycerides

- Hemoglobin A1C (lower glucose levels and diabetes preventative)

“5 year GH substitution is safe and well tolerated”

Gotherstrom G et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001 Oct;86(10):4657-65

#### 11. GH +/- Sex steroids and subcutaneous and visceral fat with a combination of growth hormone, HRT and testosterone

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

#### 12. HGH deficiency results in impaired physical performance, and hGH replacement increases exercise capacity

Johansson, J. Psychosocial and CNS effects. *Growth Hormone in Adults* 1996, Cambridge University Press

Juul, A. Adult GH deficiency and effects of GH treatment on muscle strength, cardiac function and exercise performance. *GH in adults*, Cambridge University Press, 1996, p 254-241

#### 13. HGH Deficiency results in chronic fatigue and depression, and hGH Replacement results in:

- Increased sense of well-being

- Improved quality of life

Gibney et al. The effects of 10 years of GH in adult GH deficient patients

*J Endocrin Metab* 1999 August

### Section 2: Growth Hormone and the Brain

#### 1. Adult nerve cells are targets of IGF-1

- IGF-1 increases dendritic formation of cortical neurons (improved mental function)

Riddle D. Role of IGF -1 in cortical dendritic growth *Journal of GH and IGF Research* Oct 99.

Caro, E et al Body to brain signaling mediated by circulating IGF-1. *Journal of GH and IGF Research* Oct 99.

#### 2. IGF-1 reverses age-related D2 (Dopamine) receptor deficits and improve age related impairment in learning and memory

Thornton et al. *Journal of GH and IGF Research* Oct 99.

#### 3. IGF-1 correlated with cognitive function in men average age 69

- GH deficiency correlated with poor emotional and psychosocial functioning

Aleman A et al. Insulin-Like Growth Factor-I and Cognitive Function in Healthy Older Men *J Clin Endocrinol Metab* 84:471–475, 1999.

#### 4 GH increases connexin-43 (improved mental function)

- In cerebral cortex

- In hypothalamus

- IGF-1 does not increase connexin-43

- Connexin-43 forms gap junctions that mediate intercellular communication and improved mental function

- Increased neuronal communication

Aberg ND. Growth hormone increases connexin-43 expression in the cerebral cortex and hypothalamus. *Endocrinology* 2000

#### 5. HGH exerts profound effects on CNS and improves:

- Cognitive capabilities

- Memory

- Alertness

- Motivation, Work Capacity

- GH receptors present in the brain

- Hypothalamus, choroid plexus, hippocampus

- GH crosses BBB

Nyberg F. Growth Hormone in the Brain: Characteristics of Specific Brain Targets for the Hormone and Their Functional Significance. *Front Neuroendocrinol* 2000 Oct;21(4):330-348.

## 6. IGF-I exerts cytoprotection against A beta-amyloid induced neuronal cell death (prevents Alzheimer's disease)

Takako Niikura et al. Insulin-Like Growth Factor I (IGF-I) Protects Cells from Apoptosis by Alzheimer's V642I Mutant Amyloid Precursor Protein through IGF-I Receptor in an IGF-Binding Protein-Sensitive Manner The Journal of Neuroscience, March 15, 2001, 21(6):1902-1910

### Section 3: Growth Hormone and Bone

#### 1. GH Deficiency causes reduced bone density

- GH Replacement reverses osteoporosis

Logobardi, J Endocrinol Invest, May 1999.

#### 2. Bone density significantly improved with hGH therapy

- Increases formation and strength of cortical bone.
- Synergistic effect with exercise
- Lower growth hormone levels are found in patients with bone fractures

Growth Hormone and Mild Exercise in Combination Markedly Enhance Cortical Bone Formation and Strength in Old Rats H. Oxlund, et al Endocrinology, April 1998, p. 1899-1904 Vol. 139, No 4.

Colao A. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. J Clin Endocrinol Metab 1999 Jun;84(6):1919-24.

Hedstrom M. Hip fracture patients, a group of frail elderly people with low bone mineral density, muscle mass and IGF-I levels. Acta Physiol Scand 1999 Dec;167(4):347-50.

#### 3. Effect of hGH on body composition and bone turnover in women with osteoporosis

- Increase in handgrip strength
- Decrease in waist/hip ratio
- Increased bone formation
- Decreased osteoporosis

Sugimoto T et al. Effect of recombinant human growth hormone in elderly osteoporotic women. Clin Endocrinol (Oxf) 1999 Dec;51(6):715-724.

#### 4. Growth hormone replacement in men (18 month study)

- Increase bone density and lean body mass
- Body fat decreased
- Low incidence of side effects

#### 5. 42 month study

- Increases of bone mineral density in spine and femoral neck
- Patients with osteopenia (low bone mass) were reduced by 50%
- Better results in males and younger
- *"GH deficient patients with osteoporosis or osteopenia should be considered candidates for GH replacement"*

Valimaki MJ et al 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

### Section 4: Growth Hormone and the Heart

#### 1. GH deficiency associated with

- Increased Cardiovascular (CV) Deaths
- GH Replacement results in:
  - Increased CV function
  - Improves lipid profile
  - Reverses arteriosclerosis
  - Reduced carotid intima thickness
  - Improves dilated cardiomyopathy

Gibney et al. The effects of 10 years of GH in adult GH deficient patients J Endocrin Metab 1999 August

## 2. GH and Atherosclerosis

- GH normalized Intima Media thickness (IMT) of carotid artery in 3 months and improvement continued 18 months of study
- IMT negatively correlated with IGF-1
- No significant change in lipids
- Direct effect on arterial wall via Nitric oxide

Pfeifer M et al. Growth Hormone (GH) Treatment Reverses Early atherosclerotic Changes in GH-Deficient Adults J Clin Endocrinol Metab 84: 453-457, 1999.

Borson-Chazot F. et al. Decrease in Carotid Intima-Media Thickness after One Year Growth Hormone (GH) Treatment in Adults with GH Deficiency J Clin Endocrinol Metab 84: 1329-1333, 1999.

## 3. Growth hormone improves cardiac performance

- Increases contractility and cardiac output
- Improves cardiac function in dilated cardiomyopathy

Fazio et al. A preliminary study of GH in the treatment of dilated cardiomyopathy. NEJM 1996;334:809-814.

Isgaard J et al. GH improves cardiac function in rats with experimental MI. Eur J Clin Invest 1997;27:517-525.

Tivesten, A The Growth Hormone Secretagogue Hexarelin Improves Cardiac Function in Rats after Experimental Myocardial Infarction. Endocrinology, January 2000, p. 60-66 Vol. 141, No. 1.

## 4. Growth hormone treatment in heart failure patient increased

- Ejection fraction 13% to 28% (doubled heart function)
- Heart medications able to be discontinued

Bocchi EA et al. Growth hormone for optimization of refractory heart failure treatment. Arq Bras Cardiol 1999 Oct;73(4):391-8

## 5. Cardiac Performance Impaired in GH deficiency

- Reduction of LV mass
- Reduction of ejection fraction
- Reversed after GH replacement

Colao A et al. Impaired cardiac performance in elderly patients with growth hormone deficiency J Clin Endocrinol Metab 1999 Nov;84(11):3950-5

## 6. GH decreases coronary inflammation and prevents heart attacks

- GH deficient adults have increased cardiovascular mortality
- Inflammatory markers are predictive of cardiovascular events
- C-Reactive protein increased in GH deficiency
- With hGH Replacement therapy
- C reactive protein decreased
- Visceral and subcutaneous fat decreased
- Lipoprotein(a) decreased

Sesnilo G et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med 2000 Jul 18;133(2):111-22

## 7. IGF-1 and the heart

- Improves cardiac contractility, cardiac output, stroke volume, ejection fraction.
- Improves cardiac function after myocardial infarction by stimulating contractility and promoting tissue remodeling.
- Facilitates glucose metabolism, lowers insulin levels, increases insulin sensitivity, and improves the lipid profile

Ren J et al. Insulin-like growth factor I as a cardiac hormone: physiological and pathophysiological implications in heart disease. J Mol Cell Cardiol 1999 Nov;31(11):2049-61

## 8. HGH Increases coronary blood flow and capillary density

- Decline in GH leads to decline in tissue growth, maintenance and repair in older animals (and humans)
- Deterioration of cardiovascular function contributes to decline of physical function and quality of life
- Decreased coronary flow and capillary density with aging reversed by GH

Khan AS et al. Growth hormone increases regional coronary blood flow and capillary density in aged rats. J Gerontol A Biol Sci Med Sci 2001 Aug;56(8):B364-71.

## Section 5: Growth Hormone and Immune System

### 1. Connection between neuroendocrine and immune and GH/IGF-1

- IGF-1 needed for lymphocyte maturation and function
- IGF-1 restores age-related thymic involution in rodents
- IGF-1 restores damaged immune system
- Decline in T and B cells are restored by GH

Clark R. The somatogenic hormones and insulin-like growth factor-1: stimulators of lymphopoiesis and immune function. *Endocr Rev.* 1997 Apr;18(2):157-7.

Burgess W et al. The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-I. *Neuroimmunomodulation* 1999 Jan-Apr;6(1-2):56-68.

### Section 6: Growth Hormone and Crohn's Disease

#### 1. Significant improvement in patients treated with GH

Slonim AE et al. A preliminary study of growth hormone therapy for Crohn's disease. *N Engl J Med* 2000 Jun 1;342(22):1633-7

### Section 7: GH and Chronic Fatigue and Fibromyalgia (See CFIDS and Fibromyalgia page)

#### 1. GH deficiency mimics Fibromyalgia

- Low GH secretion, IGF-1 and IGFBP3 in Fibromyalgia
- Rx with HGH or GHRH produced increases in IGF-1 and IGFBP3
- Can be significant improvement with GH replacement

LEAL-CERRO A. et al. The Growth Hormone (GH)-Releasing Hormone - GH -Insulin-like Growth Factor-1 Axis in Patients with Fibromyalgia Syndrome *J Clin Endocrinol Metab* 84: 3378–3381, 1999

#### 2. Growth hormone deficiency more common in fibromyalgia patients

- Supplementation with hGH can result in improvement in symptoms
- Bennett RM, *Z Rheumatol* 1998;57 Suppl 2:72-6.

#### 3. Growth hormone supplementation results in significant improvement in symptoms

“Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of fibromyalgia.”

Bennett RM; Clark SC; Walczyk *J Am J Med* 1998 Mar;104(3):227-31

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## Jintropin 10iu : usage

**Active Life:** Varies by injection method

**Drug Class:** Growth Hormone/IGF-1 Precursor (for injection)

**Average Dose:** Men 2-6 i.u. total daily

**Acne:** No

**Water Retention:** Rare

**High Blood Pressure:** Rare

**Liver Toxic:** No

## MIXING

Always release the water slowly and down the side of the glass, whenever adding water to the powder. This ensures that the compound remains intact. Growth Hormone by nature is quite fragile. Once the water is in, gently swirl the solution. DO NOT SHAKE. Continue to swirl slowly until all is dissolved.

### **WHERE TO INJECT**

The inner thigh is the most readily absorbed area. This should be done, carefully pinching a small fold and injecting in the middle. I would not recommend the abdomen as the fat tends to slow the absorption process. Growth Hormone can be injected anywhere however.

### **LENGTH OF USE**

The Growth Hormone does not elicit results immediately. It might take 2 to 3 months before you can see results. The better matched compounds to human DNA (Jintropin) is much quicker than say Serostim with regards to the results. If you cannot determine yourself to stay on Growth Hormone for at least 4 months, do not waste your money. This would usually mean about 4 kits. Not cheap.

Result of well being, some lipolysis, improved skin appearance: 2iu daily

Moderate lipolysis, better sleep, more energy: 3iu daily

Begin to see fullness in the muscle, advanced lipolysis: 4iu daily

Muscular hypertrophy, feeling like a king, full as hell: 5iu daily

### **SIDE-EFFECTS**

**Side effects of growth hormone are generally mild and are largely associated with salt and water retention. The minority of patients that experience this typically complain of mild weight gain from water retention associated with a vague feeling of puffiness. This is sometimes accompanied by joint discomfort, particularly in the**

fingers, with a feeling of tightness when making a fist. Other joints may also become uncomfortable. Carpal Tunnel Syndrome is a well-known side effect of growth hormone that was more common in the early days when growth hormone was given in higher dose with lower frequency. Carpal Tunnel Syndrome is also a function of fluid retention, which causes water to accumulate in the closed carpal tunnel compartment of the wrist, compressing the median nerve. This results in numbness and tingling in the palm and fingers. **These side effects are easily remedied by abstaining from growth hormone for about a week, and then resuming the treatment with a 20% dose reduction. Older patients are more subject to side effects and are generally started at a low dose of growth hormone than younger adults.** Another potential side-effect of growth hormone is the elevation of blood sugar. Growth hormone mobilizes body fat, causing our fat cells to break themselves down and release free fatty acids into the blood stream. These free fatty acids are energy molecules which can be taken up by organs and many of our organs to be used for energy. When our muscles are consuming free fatty acids as a fuel, they are far less interested in sugar, therefore they tend to resist the effects of insulin, and extract less sugar from the blood. At the same time, growth hormone can increase glucose output from the liver to the blood. This combination of effects can raise blood sugar and raise insulin levels, neither of which is good. Fortunately, this is only a problem in people who eat a diet high in sugar and starch, and do little exercise. At Cenegenics® we teach our patients to eat a low glycemic diet (low in sugar and starch) and exercise regularly. The effect of our nutrition and exercise program in lowering blood glucose and insulin levels far outweighs the effect of growth hormone in raising glucose and insulin levels. The net

effect in our patients, therefore, is the lowering of glucose and insulin levels. This is a very health-promoting benefit that prevents disease and extends life span.

## **ACROMEGALY**

Acromegaly and gigantism are diseases of growth hormone excess. These are typically seen by persons who have growth hormone secreting tumors. Gigantism refers to the condition of growth hormone excess in children, where their ultimate height is far above normal because the growth hormone excess occurs when the epiphyseal plates of the bones are still open and the bones are growing. Acromegaly refers to growth hormone excess in adulthood after the epiphyses are closed and the bones are no longer growing. In these people the cartilage continues to grow, and the disease is characterized by enlargement of the nose, chin, ears, supra-orbital ridge (eyebrow area), hands and feet. Patients occasionally ask if acromegaly can result from growth hormone supplementation in adulthood. The answer is absolutely not. Acromegaly results in growth hormone levels that are two to ten times that of a normal adult. Keep in mind that when we supplement growth hormone in a controlled and monitored medical program, we bring the level only up to the mid-normal range of an adult. In fact, one would have to use ridiculously high doses by today's standards to achieve the growth hormone levels seen in acromegaly.

## **HGH AND METFORMIN EFFECTS:**

Effects of a combination of recombinant human growth hormone with metformin on glucose metabolism and body composition in patients with metabolic syndrome.

[Herrmann BL](#), [Berg C](#), [Vogel E](#), [Nowak T](#), [Renzing-Koehler K](#), [Mann K](#), [Saller B](#).

Division of Endocrinology, University of Essen, Germany. [burkhard.herrmann@uni-essen.de](mailto:burkhard.herrmann@uni-essen.de)

## Abstract

Abdominal obesity and insulin resistance are central findings in metabolic syndrome. Since treatment with recombinant human growth hormone (rhGH) can reduce body fat mass in patients with organic GH deficiency, rhGH therapy may also have favourable effects on patients with metabolic syndrome. However, due to the highly increased risk for type 2 diabetes in these patients, strategies are needed to reduce the antagonistic effect of rhGH against insulin. We conducted a 18-month randomised, double-blind, placebo-controlled study to assess the effect of rhGH in combination with metformin (Met) in patients with metabolic syndrome. 25 obese men (55 +/- 6 years, BMI 33.4 +/- 2.9 kg/m<sup>2</sup>) with mildly elevated fasting plasma glucose (FPG) levels at screening (6.1-8.0 mmol/l) were included. All patients received metformin (850 mg twice daily) either alone or in combination with rhGH (daily dose 9.5 microg/kg body weight). An oGTT was performed at baseline, after 6 weeks, and after 3, 6, 12, and 18 months of therapy. Glucose disposal rate (GDR) was measured by euglycemic hyperinsulinemic clamp at 0 and 18 months and body composition was measured by DEXA every 6 months. In the Met + GH group, IGF-I increased from 146 +/- 56 microg/l to 373 +/- 111 microg/l (mean +/- SD) after 3 months and remained stable after that. BMI did not change significantly in either group during the study. Total body fat decreased by -4.3 +/- 5.4 kg in the Met + GH group and by -2.7 +/- 2.9 kg in the Met + Placebo group (differences between the two groups: p = n. s.). Waist circumference

decreased in both groups (Met + GH: 118 +/- 8 cm at baseline, 112 +/- 10 cm after 18 months; Met + Placebo: 114 +/- 7 cm vs. 109 +/- 8 cm; differences between the two groups:  $p = 0.096$ ). In the Met + GH group, FPG increased significantly after 6 months (5.9 +/- 0.7 vs. 6.7 +/- 0.4 mmol/l;  $p = 0.005$ ), but subsequently decreased to baseline levels (18 months: 5.8 +/- 0.2 mmol/l). FPG remained stable in the Met + Placebo group until 12 months had elapsed, and then slightly decreased (baseline: 6.2 +/- 0.3, 18 months: 5.5 +/- 0.6 mmol/l,  $p = 0.02$ ). No significant changes were seen in either group regarding glucose and insulin AUC during oGTT or HbA (1c) levels. GDR at 18 months increased by 20 +/- 39% in Met + GH-group and decreased by -11 +/- 25% in the Met + Placebo group (differences between the two groups:  $p = 0.07$ ). In conclusion, treatment of patients with metabolic syndrome and elevated FPG levels did not cause sustained negative effects on glucose metabolism or insulin sensitivity if given in combination with metformin. However, since our data did not show significant differences between the two treatment groups with respect to body composition or lipid metabolism, future studies including larger numbers of patients will have to clarify whether the positive effects of rhGH on cardiovascular risk factors that have been shown in patients with GH deficiency are also present in patients with metabolic syndrome, and are additive to the effects of metformin

***For the most part, the pituitary has completed its function and is at rest by 5 a.m. Therefore injecting after awakening in the morning results in injecting "on top of the peak" of endogenous (our own) growth hormone, so as not to suppress the pituitary. By the time the pituitary is ready again for its nighttime activity, the growth hormone given in the morning injection has been completely metabolized. This eliminates the risk of pituitary suppression. I do believe that splitting them to early morning (on waking up at 7am) and early evening (around about 4pm), is a great idea over morning/night... this way it leaves your body and opening to possibly produce its own GH, post workout and during deep***

*night REM sleep - even though it probably won't with the supplementation of GH (depending on your age, etc.). When you take it at night, there is no way you will produce anything while you sleep...*

### A comparison of subcutaneous and intramuscular administration of human growth hormone in the therapy of growth hormone deficiency.

The sc and im administration of human GH (hGH) was compared in the therapy of GH deficiency. The peak and integrated concentrations of hGH in the plasma of the patients were similar after sc and im injection of an initial dose (0.1 U/kg) of hGH. The peak hGH concentration occurred at 2 h in both groups. The posttreatment height velocity and the change in height velocity at 3-month intervals were also similar in the im and sc groups. The somatomedin generation test resulted in a higher mean peak of somatomedin C after sc injection; however, if the individual peaks of somatomedin C were averaged, there was no difference between sc and im injection. A cross-over at 9 months of therapy to determine patient acceptance of im vs. sc injections indicated overwhelming acceptance of the sc route. The antibody responses to hGH were similar in both groups. We conclude that sc injection of hGH is an effective and safe mode of therapy for GH deficiency. The lipoatrophy that occurred infrequently at the injection site can be eliminated by rotation of sites. Subcutaneous administration of hGH will be more acceptable by the patients with less pain and less noncompliance. The mean half-life of intravenous somatropin is 0.36 hours, whereas subcutaneously and intramuscularly administered somatropin have mean half-lives of 3.8 and 4.9 hours, respectively. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

#### Recap:

- More HGH will be available Sub-Q than IM.
- Sub-Q and IM are equals in effectivity.
- Localized lipoatrophy from Sub-Q (it occurs to loose fat where do you inject Sub-Q...mid-section is the best target for Sub-Q). :)
- Less pain and risk from Sub-Q compared to IM.

### Subcutaneous (SC) vs. Intramuscular (IM)

Even though many people, including the HGH manufacturers, recommend SC injections of HGH, I do not agree. I prefer IM injections. This is based on pharmacology and clinical observation. First, many people report pain, irritations, redness, nodules at the site of injection. There is also an adipose layer in virtually every SC site. injection of a substance with pH lower than 7 (neutral) can cause these adverse effects. All water-based and alcohol-based injectible solutions are slightly acidic--some more than others. It is the low pH factor that causes the

problem. oil-based injectibles are neutral or slightly basic and do not cause any of the adverse sides. to combat this problem, I have recommended injecting HGH into the quad muscle. Some people can achieve this with a 1/2" needle, some have to use a longer needle to get past the adipose layer and into the muscle.

The advantages of injecting IM is one--less discomfort and adverse effects, and two--a greater increase in IGF levels than injecting into SC tissue (adipose). You still get the same fat burning effects that you would injecting SC, but you also get greater IGF levels doing so. SC injection does not allow the HGH to get into the bloodstream to raise IGF levels. The HGH stays localized in the adipose tissue, only providing fat-burning.

Intramuscular GH not only peaked higher, but also earlier— so, despite being cleared more rapidly, a greater total amount of GH is delivered when injected into muscle. Not only does the body benefit from receiving more total drug/hormone, the cells of the body are able to prime themselves to respond to the next dose of GH more quickly as the drug is cleared. Perhaps the time is overdue in this article to remind the reader that GH is most effective when released in pulses, not as a steady, continuous signal. So although it was not seen with the single-dose study, it is likely that intramuscular GH would offer a more “lifelike” signal and possibly greater physiologic benefits over time. The downside to this is a greater risk of injury (striking a nerve, injecting into a blood vessel, suffering a deep tissue infection), more pain and potential interference with anabolic steroid injections in those who use the two drugs during the same period.

**COMMENT:** APPROXIMATELY 350,000 NANOGRAMS (0.375 MILLIGRAMS) EQUALS ONE UNIT OF HGH. A 4-UNIT VIAL CONTAINS APPROX 1.52 MG PURE HGH (1,520,000 NANOGRAMS ).

HGH is sometimes measured in international units, and sometimes measured in milligrams (mg).

**3 International Units = 1 milligram**  
(its really more precisely 1mg=2.7IU).

1. Many people experience increases in blood glucose levels when starting HGH. This effect usually goes away with time, but there appears to be a definite advantage to taking the prescription medicine metformin along with HGH to keep glucose levels under control. (Also, there is evidence that metformin can slow the aging process at a more fundamental level than HGH.) Alpha-lipoic acid or R-lipoic acids, which are both similar nutritional supplements, can also help to keep blood glucose levels under. You need to have a empty stomach when taking GH the presence of insulin

lowers the effect of GH... Typically females require 2 to 4 units of HGH per week more than men.

- **DIFFERENT AREAS TO INJECT:** Different areas of the body absorb HGH at different rates. The fastest absorbing area is the stomach; the arms and then the legs are the next fastest. The slowest is in the buttocks. Because of this, rotating injection spots in the same area-- just in slightly different locations--will help regulate the distribution of the medication. Do not use an injection site within two inches of the navel or scar tissue.

**SOME RECOMMENDED DOSAGE PROTOCOLS:** *Qualified physicians begin with low doses such as 0.5 IU per day and slowly increase the patient's dosage in 0.5 IU monthly increments as needed. Usual maximum dosage for life extension purposes 2IU's per day 5-7 days per week. For Fat burning purposes about 3-4 IU's per day would be effective. For most sports recommended Human Growth Hormone dosage would be 6+ IU's a day. 4 to 6 iu ed is sufficient. Most people take it 5 days on 2 days off at their designated dosage. There is no reason or evidence why you cannot stay on for various lengths of time; there is no need to go 5 on 2 off other than cost. Considering that our natural production is only .5 to 1.5iu a day, this is still a huge bump for the body. Research has shown that the body's natural defense systems render mega doses of GH ineffective, anyway. GH does not cause gains in mass...it allows you to put on a great deal of lean mass in combination with proper steroid and insulin use. The user before taking must know this. One or two kits are not enough, you need at least 3 to make you happy, GH takes a while to make its effects, but remember they are long lasting, what you see is what you keep. It takes 6 to 8 weeks to notice a dramatic change in body comp using GH on an ED or 5/2 split. Lighter doses for long periods of time are better than large doses for short cycles. Like any other drug, the more you take the more the benefits, but likewise also more risks. 4-6 iu is a standard dose but many people take more, the*

***most repulsing side effects happen at or beyond 12 iu a day but like anything else it depends on your predisposition for it***

**These are the typical HGH doses that people use:** (For comparison: the hypophysis of a healthy; adult, releases 0.5-1.5 I.U. growth hormones daily).

Anti-Aging: 2iu-4iu daily

Fat loss: 4iu-8iu daily

Muscle building: 8iu-24iu daily

The dosage should be between 2-3IU per day if you are using GH primarily for fat loss, 4-8 IU's a day for both fat loss and muscle growth, and approximately 1.0 – 2.0 IU's a day for females. When starting out with HGH, for most people it is wise to begin your dose at 1.5 – 2.0IU per day for the first couple of weeks, and then begin increasing your dose by 0.5 unit every week or two until you reach your desired level. While it isn't an absolute necessity to do this, if you are sensitive to the type of sides HGH present you will often times avoid these sides of joint pain/swelling, CTS, and bloating/water retention by slowly acclimating to your ultimate 4-5 IU/day goal. It is best to split your injections 1/2 first thing in the morning, 1/2 early afternoon if your dose is above 3.0 IU's per day. Your pituitary will naturally produce an average of 6 or so pulses of GH per day, the mega pulse being 2 hours after we fall asleep. Each injection you take will create a negative feedback loop that as suggested by a couple of studies will suppress these pulses for an approximate 4 hours. By taking your injections first thing in the morning and early afternoon you will still allow your body to release its biggest pulse, which normally occurs shortly after going to sleep at night, as well as blunting the effects of cortisol, the two biggest peaks of which are occurring at these same times (early morning, early afternoon).

For maximum benefit in this regard, the addition of Testosterone and/or other anabolic should strongly be considered. For advanced use, other supplements like Insulin, and low-dose T3 or T4 would also be considerations.

Regardless of your goal, as a general rule the best way to begin your HGH program is to start with a low dose and ease your body

into the higher doses. This will allow you to avoid (or at least minimize) many of the more common (and unpleasant) sides of HGH such as bloating and joint pain & swelling. Most people can tolerate up to approximately 2 IU's per day with few sides, so that would be a good place to start.

For many using this as a general health supplement, that is as high as you will need to go. For others this will be only the start. Above 4 IU's, I would definitely suggest that you split your injections into two per day instead of one unless it is just not feasible to do so. If you are splitting your doses, the two times of the day when your cortisol levels are at peak are when you wake up and in the early afternoon. This being the case, another good strategy is to take your HGH injections at these times. Cortisol is very catabolic by nature and a well -timed HGH injection can go a long way toward blunting this effect.

## **The Best HGH Injection Sites**

By [Sandy Keefe](#), eHow Contributor

updated: January 3, 2010

1. Human growth hormone (HGH) is a hormone secreted by the pituitary gland that has a powerful effect on a child's growth. According to The Magic Foundation, HGH also contributes to bone density, immune system function, heart strength, and lung capacity. When a child doesn't produce enough HGH, her doctor may prescribe injections of synthetic HGH (somatropin) to be given subcutaneously, or between his skin and muscle layers. It's important to rotate HGH injection sites to prevent damage to the skin and subcutaneous tissue.

### **Abdomen**

2. Genentech, the company that manufactures the Nutropin brand of somatropin, says the tissue under the abdominal skin does a great job of

absorbing the drug.

Choose a site below the waist but above the hipbones, and between the area where the body curves on the side and two inches from the center of the abdomen. Stay away from the navel when you inject HGH.

You may find abdominal injections less painful than those in other areas, but it's important to avoid injecting at your waistline so your clothes don't irritate the site.

### **Thighs**

3. The front and outside surfaces of the thighs are also good injection sites.

To identify the right spot, Genentech recommends that you "divide" the leg between the hip bone and knee into thirds. Give the HGH injection into the skin on the middle third of the thigh, either on the front of the leg or on one of the outside areas. Gently pinch up one to two inches of skin before injecting the medication.

### **Buttocks**

4. The upper, outer aspect of the buttocks tends to be a good spot for relatively pain-free injections. While it's tough to inject yourself properly on these sites, the patient can lie down on a flat surface on their stomach and point their toes inward so a caregiver can find the right spot. Select a spot below the waist but above the buttocks crack, and between the side curve of the body and a few inches from the spine.

### **Upper Arms**

5. Genentech suggests using the largest part of the back part of the upper arms as an alternative injection site for HGH. This site will be effective only if you can grasp enough skin to administer the drug subcutaneously. This means you'll need to hold enough skin between your thumb and index finger to insert the needle under the skin at a 45 to 90 degree angle. If you're giving the HGH injection to someone else, stand beside and a little behind the person and ask her to place his hand on her hip.

#### **How to Prepare an Injection of HGH.**

**Step 1** Clean the surface (i.e. table) and organize everything you need.

**Step 2** Wash your hands with soap and warm water. If someone else is giving you the injection, he or she should put on a pair of disposable gloves now.

**Step 3** Remove the plastic flip tops from Human Growth Hormone ampoule and sterile water vials and throw them away. Clean rubber stoppers on both vials with a fresh alcohol swab and throw it away. Don't touch the tops after being sterilized! (otherwise clean them again using a new alcohol swab)

**Step 4** Unwrap the syringe and a long needle (without touching a needle!) Take the plastic tip protector from the syringe, hold the syringe and twist tightly into place on the needle and then remove the plastic cap from the needle. Set it aside as you will need it later on. Pull back the plunger in the syringe until it reaches the 1 cc line on the barrel.

**Step 5** Place the vial of sterile water on the clean work surface. Take the syringe with a longer needle on and push it straight down through the middle of the rubber stopper on top of the vial. Push on the syringe plunger all the way down, which will push the 1cc of previously pumped air into the vial. This will create some pressure in it. While holding the plunger down, pick up the vial and the syringe with your other hand and turn it upside down. Slide the needle tip below the level of water in the vial. Then release the plunger, which will fill the syringe with water automatically. Alternatively pull back on the plunger until it reaches the 1cc mark on the syringe barrel. If air bubbles get in the syringe, tap the barrel with your fingertips, and then gently push the plunger in to move the air bubble(s) back into the vial. When the syringe is filled with sterile water remove the vial off the needle without touching the needle tip.

6. **Step 6** In the next step mix the sterile water with the Human Growth Hormone vial. To do this hold the needle and syringe containing sterile water and push the needle through rubber stopper on HGH vial and inject the Sterile Water into it. The needle tip should rest against the wall of the vial. Push the syringe plunger gently and slowly to allow the water to flow down the side of the vial.
7. **Step 7** Remove the needle from HGH vial and put the syringe aside. Shake the HGH vial mixed with Sterile water gently in slow round motion. Pull back the plunger to get some air into the syringe and insert it back into a HGH vial. Push the plunger to create pressure in the vial, which will help you pump the solution out. When a vial is empty, turn around the syringe that needle is at the top.
8. **Step 8** Take the empty plastic cap from larger needle and remove it. Place a smaller needle needed to inject and make sure there are no air bubbles in the syringe. And you are ready to inject.
9. **How to Inject**

10. Choose the injection site for subcutaneous injection. Probably the most convenient, easiest and comfortable site is the anterior abdomen (belly). It is important to avoid the area directly around the belly button (umbilicus). When the spot is selected, clean it with a new, fresh alcohol sponge and allow the area to air dry.
11. Use your non-dominant hand (left hand for right handed people) pinch a fold of skin and hold it up. Use your dominant hand to pick up the syringe and dart it in to the skin fold quickly. Insert the entire needle perpendicular to the skin and keep it there. If you can pinch a 1-inch (2.5-cm) tissue fold, insert the needle at a 45-degree angle; for a 2-inch (5-cm) fold, insert it at a 90-degree angle. Make sure fluid is injected slowly, followed by quick needle removal. Additionally use a clean alcohol sponge to hold pressure on the injection site for a moment or two.
12. **Don't-s**
13. When injecting Human Growth Hormone subcutaneously it is important not to aspirate after inserting the needle to prevent tissue damage, hematoma formation, and bruising. After the taking HGH don't massage the site as it may cause damages to the underlying tissue and increase the medication absorption rate to an undesired (fast) rate.
14. **Conclusion**
15. Human Growth Hormone, can bring a lot of benefits, however when it is prepared and administered in the right way. The injection preparation may seem complicated, but will become a routine after repeating it several times. It is worth to be persistent, as it brings excellent results on the long run

**FIRST PROTOCOL:** The injections are taken daily for four successive days. The time of injections may not be much important, as human growth hormone is normally produced in our body by pituitary gland during the early hours of sleep and that's why evening dosages are preferred followed by a three day rest. According the several years of experience this schedule found to be more effective and safe. *3iu at once as soon as you get up in the am. From what I have read and discussed with other folks on HGH, they usually don't split doses until 4iu. Then they do 2iu in the am and 2 iu post workout.*

## **OR:**

ALMOST THE SAME AS THE EVERY DAY INJECTION PROTOCOL ABOVE BUT WITH WEEKENDS OFF: HGH 1- 1.5 IU one injection every day five days a week. Some patients prefer to take one unit of HGH every day. That is safe and increases the benefit, but it also increases the cost. Then two rest days are given theoretically so as to give the pituitary time to recover from the inhibition of the high serum levels of exogenously administered HGH.

The GH dosage given by the physician for anti-aging purposes was in the range of 0.01 mg – 0.02 mg /kg/ week or (2 IU/m<sup>2</sup> day). This was given as subcutaneous injections, distributed into three to five times a week.

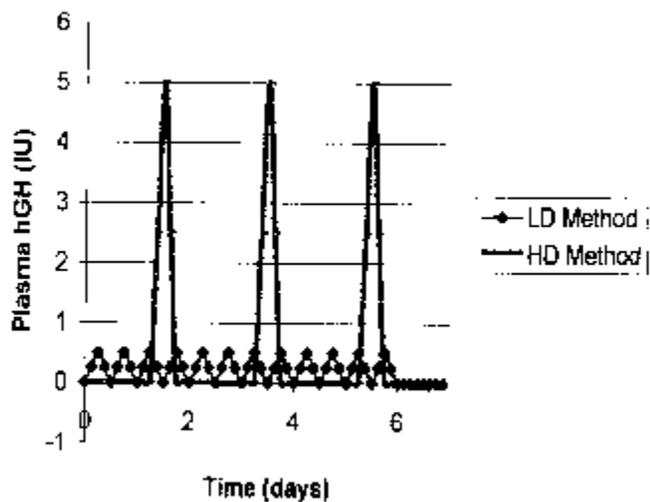
**Example:** A 200 lb man would be @ 1.5 to 2 iu of Humatrope per day. A 115 lb woman would be at 1/2 to 1 iu per day of Humatrope. This is injected subcutaneously (just under the skin) divided into usually 3 to 6 injections per week. Experience has shown that sensitivity varies considerably between individuals, with elderly individuals being most sensitive.

**Since the largest natural HGH release in healthy young people occurs shortly after the onset of sleep, most doctors originally suggested that HGH be injected just before bedtime. Some people (especially those between 40 and 65 years old) report better results taking the HGH in the morning (or at some other time of the day), and letting their pituitary gland supply the nighttime HGH dose. Most people over the age of 65 or 70 have a very small natural production of HGH after sleep onset, so injecting HGH just before bedtime is probably best for these older people.**

In one study patients were randomly assigned to receive either GH (0.125 U/kg per week for 1 month and 0.25 U/kg per week after (for a 90kg man like myself that would read as 11IU per week for 1 month to be increased to 22IU after that- somewhat high compared to most other dosing directives) . Most people using HGH to replace declining levels of growth hormone use one unit per day or less. Most can tolerate 1-2 IU per day with few sides.

While there are studies that suggest that the suppression from exogenous HGH is short lived (about 4 hours from injection), there are no large-scale studies to indicate safety of everyday injections in long-term use. There are studies by anti-aging groups demonstrating that a day or two off per week is adequate to protect the pituitary and its triggers over long cycles. If your use of HGH becomes more a lifestyle than a single cycle, I would consider running it 5 on/2 off, or 6 on/ 1 off until such time as we have reliable data demonstrating long-term safety sans any degradation of your own output or the triggers initiating that output.

**Theoretical plasma levels of hGH using high-dose, low-frequency (HD) and low-dose, high-frequency (LD) treatment regimens.**



**SECOND RECOGNISED PROTOCOL:**

Shooting HGH every other day more accurately replicates the pulsatile frequency of HGH, and thus gave better results for growth (height) deficient children, HGH pulsatility is necessary for proper function of the HGH receptor. Dosing in the EOD nature reduces incidence of any sort of withdrawal problems associated with normal HGH use, including regression or retardation of growth after cessation of therapy.

Therefore, I feel very comfortable speculating that the use of HGH in this manner, which more closely simulates the natural secretion pattern of it, allows the HGH receptors and the rest of the body to more efficiently recover from it, and this will result in much more muscle growth over time (although height was examined in the previous study). **EOD GH with twice the dosage had you been taken it ED means higher GH blood levels at a given time. GH taken sub-q is active for about 2-3 hours. GH that your body secretes on it's own is active for much less but with higher fluctuations, the researchers concluded that the body acts better to GH that is raised rapidly in blood. The EOD GH group maintained "sensitivity" to endogenous (your body's own) GH quickly after the GH inj. stopped. The ED GH group on the other hand seemed to be non-responsive to your body's own GH for long time after the study ended. In even simpler English, to translate what it may mean to us is that using hGH everyday will only negligibly give better short-term results. Yet using alternate day hGH will give radically better long-term results and much better recovery, as the body may get back to homeostasis much faster.**

**The prevention of GH tolerance and withdrawal syndrome by alternate day therapy may implicate the pulsate nature of GH secretion and serum profile. The latter is preserved in the alternate day regimen and is abrogated by daily treatment. We have previously shown the essential role of GH pulsatility for proper function of the GH receptor.** *My recommendations therefore are 2shots per day of .056iu/kg of bodyweight (5IU), taken every other day, for a minimum of 3months, and preferably for 2-3x that long, and preferably with the other synergistic compounds as well, such as AAS.*

### **THIRD RECOGNISED PROTOCOL: 3/week Protocol**

In recent times through experimentation lifters have discovered a new and exciting way of extracting even better results from the same amount of GH, and as an added benefit without the all too often experienced negative side

effects like carpal tunnel syndrome, water retention or aching joints. This method involves taking your weekly total of GH you would use over a 7 day period, dividing it by 3 and using 1/3 post workout after 3 selected workouts each week. Now obviously the individual shots will be bigger, but because their infrequent the body doesn't grow accustomed to them and the side effects never show. In the 2 plus years I've been counseling lifters on their GH usage not 1 has experienced any side effects using GH this way, yet the muscle gains and fat loss results they experience are far better than ever. I've had guys who couldn't get any results from daily injects suddenly gain a solid 15lbs in 4-8 weeks by doing nothing more than switching their cycle from daily shots to the 3/week protocol.

The cycle would look like this.

9-10ius GH 3 times per week, post workout, preferably IM injection

500mg/week Testosterone

12.5- 25mcg/day T3

Again you see that the 3 components are the same, GH, Testosterone and T3. The only differences between this option and option #1 is that you are doing shots only post workout and only on 3 workout days, on the "off days" you are not shooting anything. You are also only shooting your GH once that day, right after your workout, not upon rising from sleep. The idea here is to hit it hard and infrequently, causing the body to react in a favorable way and then let it rest. I can state emphatically that I haven't had 1 person I've recommended this to over the past 2 plus years not be far more pleased with the results than with the daily injection method.

**Conclusion**

As you can see I've laid out what I feel are the 2 most popular methods of cycling GH, the decision is yours in which to try but I would make this recommendation to you if your goals are to gain muscle mass use the 3 times a week protocol, if fat loss is more your goal use the daily injection method. That's said, I've said this a hundred times so I may as well say it again, I don't like using GH for fat loss it's much too expensive for the amount of fat loss you'll experience, there are far better and cheaper chemicals you can use like T3, Clenbuterol and the ECA Stack. Also, you'll hear of the 5 on/2 off method, that is simply the daily injection method outlined above only you skip every 6th and 7th day, this isn't to keep things fresh in the body like with the 3 times a week protocol it's just so you save some money by doing 5 injections a week vs. 7. If you are going to do this save a few extra dollars and to it 7 days a week don't skimp and do it ½ way, go all the way and do it right.

One last thing, many people will tell you that you need to stack insulin with GH to get it to work, this is bull crap plain and simple. Will you get better results using Insulin, yes, but not because it makes the GH work any better but because Insulin is a very potent drug and the extra gains come from that. I've purposely left it out because these cycles are aimed at early users of GH and at this point Insulin shouldn't even be considered. Save that for years from now when you are struggling to get results from the chemicals you are using now. Use it now and you won't have anything to turn to later. Hopefully one of the cycles I've laid out will help you reach your goals, work hard and it will come!

***An example of a good, safe protocol to follow in my opinion could be: I will start with 5IU's s/c on Monday, Wednesday and Fridays –with Saturday and Sundays***

***off(using this regime one would be three days on and four days off, this should definitely be more than enough to increase the chance of full Pituitary recovery) divided between early morning- 7am and 4pm - to be increased after 1 month to 8IU's (4iuS EACH INJECTION SPLIT)- Total 24IU's per week!***

*J Endocrinol Invest. 2003 May;26(5):420-8.*

***Three weekly injections (TWI) of low-dose growth hormone (GH) restore low normal circulating IGF-I concentrations and reverse cardiac abnormalities associated with adult onset GH deficiency (GHD).***

*Pincelli AI, Bragato R, Scacchi M, Branzi G, Osculati G, Viarengo R, Leonetti G, Cavagnini F.*

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***GH replacement therapy given 3 times weekly (TWI) and adjusted to allow serum IGF-I concentrations in the mid-normal range for sex and age has been shown to be as effective as the daily regimen in improving lipid profile, body composition, bone mass and turnover in adult GH deficient (GHD) patients. Only one study has investigated so far the short-term (6 months) effect of a fixed weight-based TWI dosing schedule on heart structure and function in childhood onset (CO) GHD patients, whereas such a schedule in adult onset (AO) GHD patients has not been studied as yet. Aim of this study was to investigate whether a 1-yr low-dose titrated TWI GH-replacement***

*regimen aimed at achieving and maintaining IGF-I levels within the low normal limits for age and sex is able to affect cardiovascular and heart parameters in a group of AO GHD patients. Eight adult patients (4 women and 4 men, age 35.8 +/- 3.37 yr, body mass index, BMI, 28.7 +/- 2.62 kg/m<sup>2</sup>) with AO GHD were included in the study, along with 10 healthy subjects, matched for age, sex, BMI and physical activity (6 women and 4 men, age 35.2 +/- 4.05 yr, BMI 28.4 +/- 2.34 kg/m<sup>2</sup>). M- and B- mode ecocardiography and pulsed doppler examination of transmitral flow were performed in GHD patients at baseline and after 3 and 12 months of GH therapy (mean GH dose 6.7 +/- 0.8 microg/kg/day given thrice a week), while normal subjects were studied once. Treatment with GH for 1 yr induced a significant increase in left ventricular (LV) diastolic and systolic volumes (+11.1 and +16.5%, respectively). Systolic LV posterior wall thickness and LV mass were increased (+10.2 and +7.7%, respectively) by GH administration. Systemic vascular resistance was significantly decreased by 1-yr GH therapy (-13.8% after 1 yr), while stroke volume, cardiac output and cardiac index were increased (+9.4, +11.6 and + 11.9%, respectively). LV end-systolic stress was decreased at the end of GH therapy (-11.2%). E and A wave, significantly reduced at baseline, were increased by 1 yr of GH therapy (+23.3% and +28.1%, respectively); likewise, the abnormally high E peak deceleration time was partially reversed by GH administration (-10.7%). Our study, though conducted in a small sample size, demonstrates that a TWI GH treatment schedule is able to reverse the cardiovascular abnormalities in AO GHD patients and to improve body composition and lipid profile. The maintenance of circulating IGF-I concentrations within the low normal range allows*

*to avoid most of the side-effects reported with higher GH doses while being cost-effective and improving the patient's compliance.*

In fact, it has been shown that a single year of treatment can turn back the clock by ten years. Adverse effects from injectable HGH therapy are very rare as long as the amount of HGH used averages 1 unit or less per day. Most physicians familiar with adult HGH replacement therapy believe that 1.5 units per day reaches the point of diminishing returns, and more than 2 units per day begins to put you at some risk of side effects. (The clinical studies that resulted in frequent side effects from HGH used much larger doses. In fact, all of the most frequently-quoted clinical studies have used doses that we now know are ridiculously high doses.) In general, side effects of HGH are very rare in doses of 1 unit per day or less and common in doses above 2 units per day.

Reconstituting common HGH, one vial contains powdered freeze-dried HGH and the other vial contains sterile water with a bacteriostatic preservative. When the user is ready to begin, a certain amount of the sterile water is drawn out of the second vial (with a needle and syringe) and injected into the first vial to dissolve the powdered HGH. The solution is then ready for injection. The unused portion is to be kept refrigerated. Use reconstituted HGH within 3 or 4 weeks.

Half life of HGH is 2 hours when injected sub-q with a four hour period which there is suppression of naturally produced GH. Intramuscular injections shorten the half life. Subcutaneous injections over the long term can lead to spot reduction. Whether or not HGH has any localized benefit from IM injection is unknown, but speculated.

**Remember the two groups got the same weekly total hGH dosage,**

**so your every other day hGH injections would be twice as if you used it every day.**

**STILL ANOTHER PROTOCOL: TWICE WEEKLY INJECTIONS- TOTAL WEEKLY INJECTION DOSAGE REMAINS THE SAME: (THEORY BEHIND THIS PROTOCOL)**

*The natural secretion of GH plasma levels of growing children where huge spurts of growth were noticed but only 4-5 per days per month*

**PLAN: To inject 5ius twice weekly on Tuesdays and Saturdays - TOTAL 10IU's per week- For three months and then consider increasing dosage also twice weekly to give twice weekly GH spurts and leave the other days for sensitization and natural Pituitary GH secretion to recover. Maximum weekly dose to be experimented with: 15IU's!**

### Timing

As described above, the body produces HGH in a pulsatile fashion throughout the day with the heaviest pulses occurring approximately 2-3 hours after going to bed as you fall into a deep sleep; and what is its frequency?" HGH is primarily released in pulses that take place during the beginning phases of sleep, with the highest release at the latest stages of sleep, which is why it is important to get a minimum of eight hours of restful sleep. People who do not get proper sleep have shorter life spans and sometime suffer from HGH deficiencies. During the 24-hour cycle of the day, HGH is released in smaller pulses, about 30 in total.

Injectible HGH is completely absorbed and put to use within approximately 3 hours. The strategy with respect to timing depends somewhat on our age and the other elements of our cycle. As you will see below, there is no single best strategy and it depends a lot on your individual situation.

For those that are between their late 20's and early 50's, there is still a reasonable chance that your own endogenous production of HGH is still at a reasonable level. The best time to take an injection, this being the case, would be early morning? After your body's own

release of HGH in the night. If you get up to go to the bathroom in the early morning, this is probably the perfect time to take a couple of units of HGH. This will be the least disruptive time to take an injection of HGH. The second best time would be first thing in the morning when you wake up.

If you are in your late 50's or beyond, or if for some reason you have a condition that has rendered your pituitary incapable of a normal release of HGH, a great time to take HGH is right before bed. This allows you to closely mimic the natural pattern that would occur if your pituitary were functioning properly. For the rest of us, taking your HGH right before bed is going to end up creating a negative feedback loop, robbing you of your body's own nightly pulse of HGH.

The easiest way to measure growth hormone in the body is by measuring plasma IGF-1 levels.

Under 350 IU is considered evidence of deficiency. Between the ages of 20 to 40 years, less than 5% of healthy men have less than 350 IU per liter of IGF-1 levels. But after 60, 30% of apparently healthy men have this low amount. And after age 65, about half the population is partially or wholly deficient in growth hormone.

### **Long-term care**

Although insufficient information is currently available, GH replacement (as with other hormones) is most likely for life. It is possible that the dose requirement may decrease over time. Some studies have suggested HGH replacement therapy might possibly extend the human lifespan 10 to 20 years, as long as a health conscious lifestyle is included as a part of the doctor monitored HGH therapy program.

### **HGH "Blockers" (called Somatostatin<sup>5</sup>) increase with age**

Some research scientists believe the problem of HGH deficiency lies with **somatostatin** (HGH "blockers"), the natural inhibitor (blocker) of HGH. With age, and may act to block the pituitary's release of HGH. When researchers eliminated somatostatin production in old rats, they found growth hormone secretion, as great as those of young rats. This might indicate, theoretically, that the Pituitary Gland has a life-long ability to produce any healthy level of HGH we might desire.

### HGH Stimulators Decrease with Age

A second theory concerning the decrease of HGH as we age is that the precursor hormone, growth hormone-releasing hormone (GH-RH), which stimulates HGH release by the Pituitary Gland, becomes less sensitive to signals from the Hypothalamus. Hence, insufficient GH-RH is released, resulting in a decrease of growth hormone secretions over time and age. A third theory concerning HGH decline or deficiency is that, not only does the growth hormone secreted and available to receptors in our cells decrease with aging, but that the cell receptors become more resistant and less responsive to the HGH. Under this theory, aging can be viewed as a disease of growth hormone resistance within our cell receptors, similar to the way in which diabetes is a disease of insulin resistance.

- **Drugs that can increase GH include: amphetamines, arginine, dopamine, estrogens, glucagon, histamine, insulin, levodopa, methyldopa, and nicotinic acid ect.**
- **The following is a chart adapted from Basic and Clinical Endocrinology, 5th Edition depicting other factors influencing the GH secretion spike:**

<u>Factors Increasing</u>	<u>Factors Decreasing</u>
<b><u>GH Secretion:</u></b>	<b><u>GH Secretion:</u></b>
<b>Physiological:</b>	<b>Physiological:</b>
Sleep	Hyperglycemia
Fasting	Elevated Blood Free
Exercise	Fatty Acids
High Amino Acids	Obesity
in the Blood	Hyper or
Low Blood Sugar	Hypothyroidism
<b>Pharmacologic</b>	<b>Pharmacologic</b>
Any hypoglycemic agent	GH itself
Estrogens	Somatostatin
Alpha-agonists	Alpha antagonists
Beta antagonists	(yohimbine)
Serotonin	Beta agonists
Dopamine	(ephedrine, clenbuterol)
GABA	Serotonin antagonists
	Dopamine antagonists

### HGH and Exercise: Exercise Stimulates Natural HGH Production

Regular exercise is the best way to naturally increase you GH production and with weaker muscles, lower bone mass and less flexibility; therefore making stretching (like yoga) a part of your daily routine. Several studies have shown that exercise prolongs life, decreases heart disease, and lowers high blood pressure and stroke rates. Aerobic exercise is very important for maintaining a healthy vascular system, which is a central factor in longevity, vitality and health.

### **(L-DIHYDROXYPHENYLALANINE) L-Dopa: Growth hormone releaser:**

Studies in 1970 discovered and clinically proved that Parkinson's disease patients using **L-Dopa** had significant increases in plasma *hGH* levels. This was a wonderful and breakthrough discovery that offered those afflicted with this dreadful and devastating disease hope for an improved quality of life. **L-Dopa** supplementation was later tested on children that were short in stature and was found to significantly elevate the *hGH* levels. **It should be pointed out, however, that the L-dopa used in the human growth hormone studies was "plain" L-dopa, while the "gold standard" L-dopa (Sinemet ®) used in PD, and which is the most widely used form of L-dopa worldwide, is a combination of L-dopa with a peripheral decarboxylase inhibitor (PDI). The PDI prevents L-dopa from being converted to dopamine outside the brain, thereby reducing side effects (such as nausea) while simultaneously getting more L-dopa to the brain (where the PDI cannot enter). It is generally accepted that 100mg Sinemet ® L-dopa is equal to 400-500mg L-dopa alone (19). Thus 100mg Sinemet ® will approximately provide the typical 500mg L-dopa alone dose used in the human growth hormone studies. However, if the Sinemet ® used is a sustained release variety, it will need to be carefully chewed up (sublingualised) to mimic the fast release L-dopa used in the growth hormone studies. For the movement regulation benefits, as well as for the "warming" neurotransmitter benefits, the sustained-release form is preferable. To maximise the benefit/risk ratio, anyone using L-dopa/ Sinemet ® without medical supervision/monitoring, should probably restrict the dosage to 100mg daily.**

### **Human growth hormone release:☆**

#### **Comparison of provocative test procedures:**

[« PreviousNext »](#) **The American Journal of Medicine**  
[Volume 56, Issue 2](#) , Pages 179-185, February 1974

#### **Abstract**

Twenty normal adult volunteers were systematically tested with five known provocative agents of human growth hormone (HGH) release in order to ascertain which procedure was the most effective stimulus for pituitary testing purposes. Ninety-five per cent responded normally (5 ng/ml increment) to levodopa (l-dopa) and 90 per cent to insulin-hypoglycemia.

Arginine, vasopressin and glucagon were less potent stimuli; however, arginine (80 per cent response rate) was superior to vasopressin and glucagon (60 and 55 per cent, respectively).

Nine subjects were retested with the same stimuli. Again, the incidence of normal HGH responses was highest with the L-dopa and insulin tolerance tests (100 and 89 per cent, respectively). Results with arginine, vasopressin and glucagon were significantly less consistent.

Because of the important additional features of greater simplicity and safety, and until hypothalamic releasing substances become generally available, the routine use of L-dopa as a pituitary test agent warrants great attention.

Table Mean age, peak plasma GH concentrations after levodopa 1 g or Sinemet one tablet (25 mg L-alpha methyl dopa hydrazine and 250 mg levodopa):

No. of patients - without Parkinsonism: 8Nos

-All male-34yrs (mean age) GH levels  $32 \pm 4^*$  (ng/ml)

**Oral doses (0.5 g) caused a significant rise in plasma growth hormone in patients initially starting therapy or on chronic therapy for as long as 11 months (dose: 250 mg for subjects < 70 lb and 500 mg for subjects > 70lb). The rise in plasma growth hormone persisted for 120 minutes after the administration of the drug. The L-dopa-induced rise in plasma growth hormone could be blocked by either oral or intravenous glucose administration. The data suggest that a dopaminergic mechanism in the median eminence or a norepinephrine-sensitive site in the hypothalamus or limbic system may be involved in the regulation of growth-hormone secretion. Furthermore, patients with Parkinson's disease, on L-dopa therapy, appear to be under the influence of elevated plasma growth hormone for a substantial part of the day. Other clinical studies found that L-Dopa supplementation in healthy young adults (ages 31 to 44) increased hGH levels by a staggering 221% and healthy older adults (ages 64 to 88) increased their hGH levels by an impressive 167%! **The growth hormone response to levodopa is normal in patients with Parkinson's disease and not altered by long-term levodopa treatment.** A 1976 National Institute on Aging study by Joseph Meites, one of the most distinguished researchers in hormone and aging, found that .500 mg of the drug per day increased the Gh output of men over sixty who did not have Parkinson's to levels approaching that of young adult! And there were no adverse effects at this dosage. A 1982**

**study by Sonntag and his colleagues found that L-dopa restored the growth hormone pulses that had decreased in old rats to those of young rats. According to Pearson and Shaw, .250 to 0.500 mg of L-dopa can cause Growth Hormone release as shown by fat loss and muscle gain.**

If L-dopa were useful only as a PD treatment, it would be of little interest to most people. Yet L-dopa has uses beyond PD. It has been known for over 30 years that it is an effective stimulant of human growth hormone (HGH) release. In 1970, Boyd and colleagues found that a 500mg oral dose ..."caused a significant rise in plasma growth hormone in PD patients, initially starting therapy or on chronic L-dopa therapy for as long as 11 months. 1982 study by Sonntag and his colleagues found that L-dopa restored the growth hormone pulses that had decreased in old rats to those of young rats. According to Pearson and Shaw, .25 to .5 grams of L-dopa can cause GH release as shown by fat loss and muscle gain. The rise in plasma growth hormone persisted for 120 minutes after the administration of the drug." (4). Boden and his co-workers gave 500mg of the drug orally to four male and five female volunteers. "HGH levels rose sharply at 45 minutes from the basal value of 0.8mg/ml, to a maximum of 10.0mg/ml at 90 minutes ( $p < 0.001$ ) and declined thereafter. This rise occurred in eight of the nine subjects." (5). Hayek and Crawford reported that six out of seven "constitutionally short children" responded to oral L-dopa (200-500mg), "...with elevations in HGH concentration above 7mg/ml, peak levels occurring between 30 and 120 minutes after drug administration..". (6).

In 1975, Ajlouni and colleagues reported the effects of 500mg of oral L-dopa on eight normal and 8 non-obese insulin-dependent diabetic subjects. The normal subjects increased their plasma HGH from 1.5mg/ml before L-dopa, to an average 21mg/ml at 90 minutes post L-dopa, with all subjects showing at least a 10 mg/ml increase. The diabetics increased from 2.5mg/ml to 20mg/ml from 60-90 minutes post L-dopa. Giving 100 grams (3 ounces) of glucose with, or 30 minutes after the drug totally suppressed the expected HGH increase (7).

Obesity has been shown to blunt HGH release after oral L-dopa. Laurian and his co-workers tested 17 obese, non-diabetic and six normal weight volunteers. All 17 obese subjects failed to respond to L-dopa, while the normal weight subjects had HGH increases of 10-11mg/ml at 90 and 120 minutes after the drug was administered. The 17 obese men and women subsequently lost 12-50kg. After weight loss, 8 people secreted HGH in response to L-dopa, but at levels only 50-60% of the normal weight people. 9 formerly obese people still failed to respond to it (8).

Barbarino and colleagues gave 500mg orally to 12 obese people, with no significant HGH increases. **When some of the subjects were given 40mg oral Propranolol, two hours before L-dopa- Pretreatment with atenolol (50 or 100 mg orally in subjects with body weight less than or greater than 40 kg, respectively)** they then showed HGH response, although at only 50-75% of the level shown by 12 normal weight subjects given L-dopa, whose serum HGH levels reached 7 to 32mg/ml 60-120 minutes after L-dopa (9).

Greenspan et al. compared HGH response to L-dopa in 44 young patients (31-44 years of age) and 42 older patients (64-88 years of age). All were considered "healthy participants". Plasma HGH increased by 221% in the young patients and 167% in the older patients. The post L-dopa HGH levels were similar in young and old (4.5 and 4.8mg/ml) (10).

The preceding studies illustrate some of the studies showing that 500mg oral L-dopa is an effective stimulator of HGH release. Whether a person is male or female, young or old, diabetic or not, thin or obese (possibly with Propranolol), a PD patient or not, L-dopa is a natural HGH-releasing agent when taken on an empty stomach. For those who can't afford HGH injections, or just don't like self-injecting, L-dopa may provide a reasonable alternative.

### **Supplements to be taken along with L-Dopa:**

Reasonable doses for ascorbate are 250-1000mg, four times daily. Vitamin E: 100-400 IU, d-alpha tocopherol plus 100-400mg gamma tocopherol. Glutathione: 1000-2000mg daily on empty stomach. N-acetylcysteine (NAC): 600-1200mg daily. CoQ10: 100-400mg daily taken with fat-containing meal. EGCG (green tea polyphenol): 100-200mg daily.

### **Final note:**

Growth hormone (HGH) release occurs maximally in the first few hours of sleep (around 10pm – 2am).

***The GH stimulation induced by levodopa/carbidopa (Sinemet) is so consistent that this combination is used as a screening test for GH deficiency in man. GH response elicited by Madopar was consistently lower than that would have been anticipated after administration of levodopa alone to normal old subjects, and in sharp contrast with the clear-cut GH rise present in normal individuals given the***

**companion drug, Sinemet. If Sinemet (100mg of L-dopa and 25mg of Carbidopa) is being taken to increase levels of growth hormone, the tablets are best taken prior to bedtime.**

For most people, taking Sinemet ® at bedtime to release GH will probably not be a viable option, since it will probably be so stimulating they won't get to sleep. An alternative strategy for those into strength training exercises might be to take Sinemet ® (chewed up) 60-90 minutes before exercising since GH release should then peak during the exercise (e.g. weight training), amplifying any GH release/anabolic benefits from the strength training exercise.

The stimulatory effect of **Nacom (250 mg L-Dopa and 25 mg LCarbidopa)** on the HGH secretion was evaluated in 75 short stature patients. The number of blood samples was restricted to only three (0, 45 and 90 min). 63 patients reached adequate HGH concentrations after the ingestion of 1 tablet Nacom (84%). Somatotropin levels increased from 2.08 (s~ 0.28) to a maximal HGH value of 14.22 (sx 0.87) ng/ml. When the stimulatory effect of Nacom was compared with the standard method of arginine infusion in children with normal stature the arginine test was not superior to the Nacom-test.

The Nacom-test appears to be a simple and reliable screening method for HGH deficiency, particularly in outpatients.

### Media in This Article

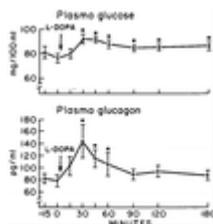


Figure 1 Plasma Glucose and Glucagon Responses after 0.5 G of Oral L-Dopa in Eight Male and Three Female Subjects (Mean ± S.E.).

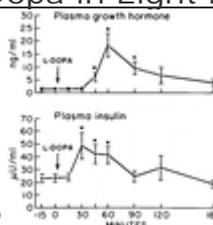


Figure 2 Plasma Insulin and Growth Hormone Responses after 0.5 G of Oral L-Dopa in Six Subjects (Mean ± S.E.).

## **Metabolic Responses to Acute and Chronic L-Dopa Administration in Patients with Parkinsonism**

Cesare R. Sirtori, M.D., Ph.D., Per Bolme, M.D., and Daniel L. Azarnoff, M.D.

N Engl J Med 1972; 287:729-733 [October 12, 1972](#)

### Abstract

The metabolic effects of L-dopa were studied in 23 patients with Parkinsonism. Levels of plasma growth hormone were elevated two hours after administration of 0.5 to 1.0 g of L-dopa, and this response persisted for at least one year. Plasma glucose was increased at two hours, and free fatty acids at four hours. Chronic therapy significantly increased serum cholesterol (approximately 10 per cent), but no change in serum triglycerides, thyroxine, fasting blood sugar, and 24-hour urinary excretion of 17-keto and 17-ketogenic steroids was observed. After one year of chronic L-dopa therapy, there was a decrease in glucose tolerance associated with a delayed and exaggerated insulin response. The changes in growth hormone and carbohydrate tolerance suggest that patients receiving L-dopa for long periods should be monitored for the possible development of frank acromegaly

## **Human Growth Hormone Response to Levodopa**

### **Relation to Menopause, Depression, and Plasma Dopa Concentration**

Edward J. Sachar, MD; Norman Altman, MD; Peter H. Gruen, MD; Alexander Glassman, MD; Frieda S. Halpern, MA; Jon Sassin, MD

*Arch Gen Psychiatry.* 1975; 32(4):502-503.

### **Abstract**

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After ingestion of 500 mg of levodopa, postmenopausal women had significantly diminished human growth hormone (HGH) responses (mean, 4.6 ng/ml), as compared with those of age-matched men (mean, 9.1 ng/ml;  $p < .05$ ). The differences between the groups were not related to plasma dopa concentrations.

The HGH responses to levodopa of age-matched unipolar and bipolar depressed men, and of unipolar depressed postmenopausal women, did not differ significantly from their respective normal control groups. Depressive illness of these types does not appear to affect the HGH response to levodopa, once the effect of the menopause is taken into account.

### **Stimulation of Human-Growth-Hormone Secretion by L-Dopa**

A. E. Boyd, III, M.D., Harold E. Lebovitz, M.D., and John B. Pfeiffer, M.D.

N Engl J Med 1970; 283:1425-1429 [December 24, 1970](#)

#### Abstract

The effect of L-dopa, a precursor of Central-nervous-system catecholamines, on growth-hormone secretion was studied in a group of patients with Parkinson's disease undergoing treatment with the drug. Oral doses (0.5 g) caused a significant rise in plasma growth hormone in patients initially starting therapy or on chronic therapy for as long as 11 months. The rise in plasma growth hormone persisted for 120 minutes after the administration of the drug. The L-dopa-induced rise in plasma growth hormone could not be blocked by either oral or intravenous glucose administration. The data suggest that a dopaminergic mechanism in the median eminence or a norepinephrine-sensitive site in the hypothalamus or limbic system may be involved in the regulation of growth-hormone secretion. Furthermore, patients with Parkinson's disease, on L-dopa therapy, appear to be under the influence of elevated plasma growth hormone for a substantial part of the day.

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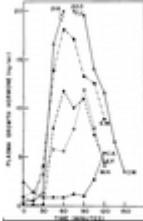


Figure 1 Effect of L-dopa on Plasma Growth Hormone in Five Patients with Parkinson's Disease during the Initial Therapy with the Drug (Each Patient Received 0.5 G of L-dopa by Mouth at 0 Time).

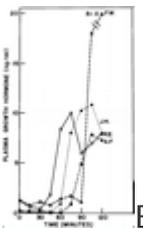


Figure 2 Effect of L-dopa on Plasma Growth Hormone in Four Patients with Parkinson's Disease Who Had Been Taking the Drug for Six to 11 Months (Each Patient Received 0.5 G of L-dopa by Mouth at 0 Time).

**Modest L-dopa supplementation (typically 100mg Sinemet ®/day) has increased their sense of neuromuscular co-ordination, strength, vigour and greater “drive to action”.**

### L-DOPA as a reliable GHG provocative test procedure:

#### L-dopa stimulation test:

- L-dopa: 500 mg orally (children 10 mg/kg) (preferably fasting)
- serum growth hormone baseline, 30, 60, 90 & 120 minutes after L-dopa
- factors contributing to a decreased response:
  - release inhibited by phenothiazines & TRH
  - hypopituitarism
  - hyperglycemia ( serum glucose > 120 mg/dL)
- vertigo & nausea may occur in 1st 30 minutes
- a paradoxical fall in GH may occur in acromegaly

- tolerance to L-dopa may be improved by giving L-dopa 250 mg PO TID with meals for 2 days prior to the test & by giving the test dose 500 mg with food

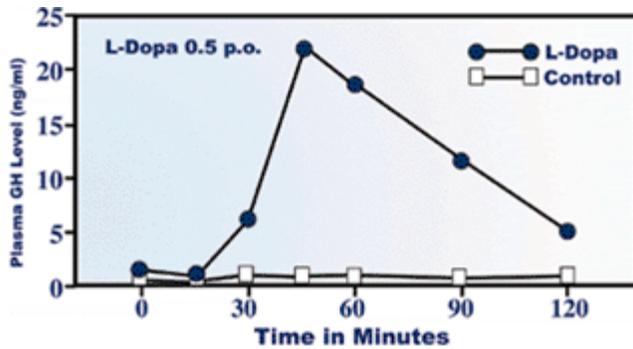


Fig. 2 Effect of L-dopa administration on plasma GH concentrations in normal subjects.

### Abstract

Twenty normal adult volunteers were systematically tested with five known provocative agents of human growth hormone (HGH) release in order to ascertain which procedure was the most effective stimulus for pituitary testing purposes. Ninety-five per cent responded normally (5 ng/ml increment) to levodopa (l-dopa) and 90 per cent to insulin-hypoglycemia. Arginine, vasopressin and glucagon were less potent stimuli; however, arginine (80 per cent response rate) was superior to vasopressin and glucagon (60 and 55 per cent, respectively).

Nine subjects were retested with the same stimuli. Again, the incidence of normal HGH responses was highest with the l-dopa and insulin tolerance tests (100 and 89 per cent, respectively). Results with arginine, vasopressin and glucagon were significantly less consistent.

Because of the important additional features of greater simplicity and safety, and until hypothalamic releasing substances become generally available, the routine use of l-dopa as a pituitary test agent warrants great attention.

**Endurance exercise modulates levodopa induced growth hormone release in patients with Parkinson's disease**

**Thomas Müller**  <sup>a</sup>, , **Jacob Welnic**<sup>a</sup>, **Dirk Voitalla**<sup>a</sup> and **Siegfried Muhlack**<sup>a</sup>

<sup>a</sup>Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany

## Abstract

**Acute levodopa (LD) application and exercise release human growth hormone (GH).** An earlier trial showed that combined stimulus of exercise and LD administration is the best provocative test for GH response in healthy participants. Objective was to show this combined effect of LD application and exercise on GH response and to investigate the impact on LD metabolism in 20 previously treated patients with Parkinson's disease (PD). We measured GH- and LD plasma concentrations following soluble 200 mg LD/50 mg benserazide administration during endurance exercise and rest on two separate consecutive days. GH concentrations significantly increased on both days, but GH release was significantly delayed during rest. LD metabolism was not altered due to exercise in a clinical relevant manner. Exercise induced a significant faster LD stimulated GH release in comparison with the rest condition. We did not find the supposed increase of LD induced GH release by endurance exercise. We assume that only a limited amount of GH is available for GH release in the anterior pituitary following an acute 200 mg LD administration. GH disposal also depends on growth hormone releasing hormone (GHRH), which is secreted into hypothalamic portal capillaries. During the exercise condition, the resulting higher blood pressure supports blood flow and thus GHRH transport towards the GH producing cells in the pituitary. This might additionally have caused the significant faster GH release during exercise. **Findings suggest that: (1) hypothalamic**

dopamine function is impaired in Parkinsonian subjects on Madopar therapy, preserved in unmedicated patients and enhanced in patients on Sinemet therapy.

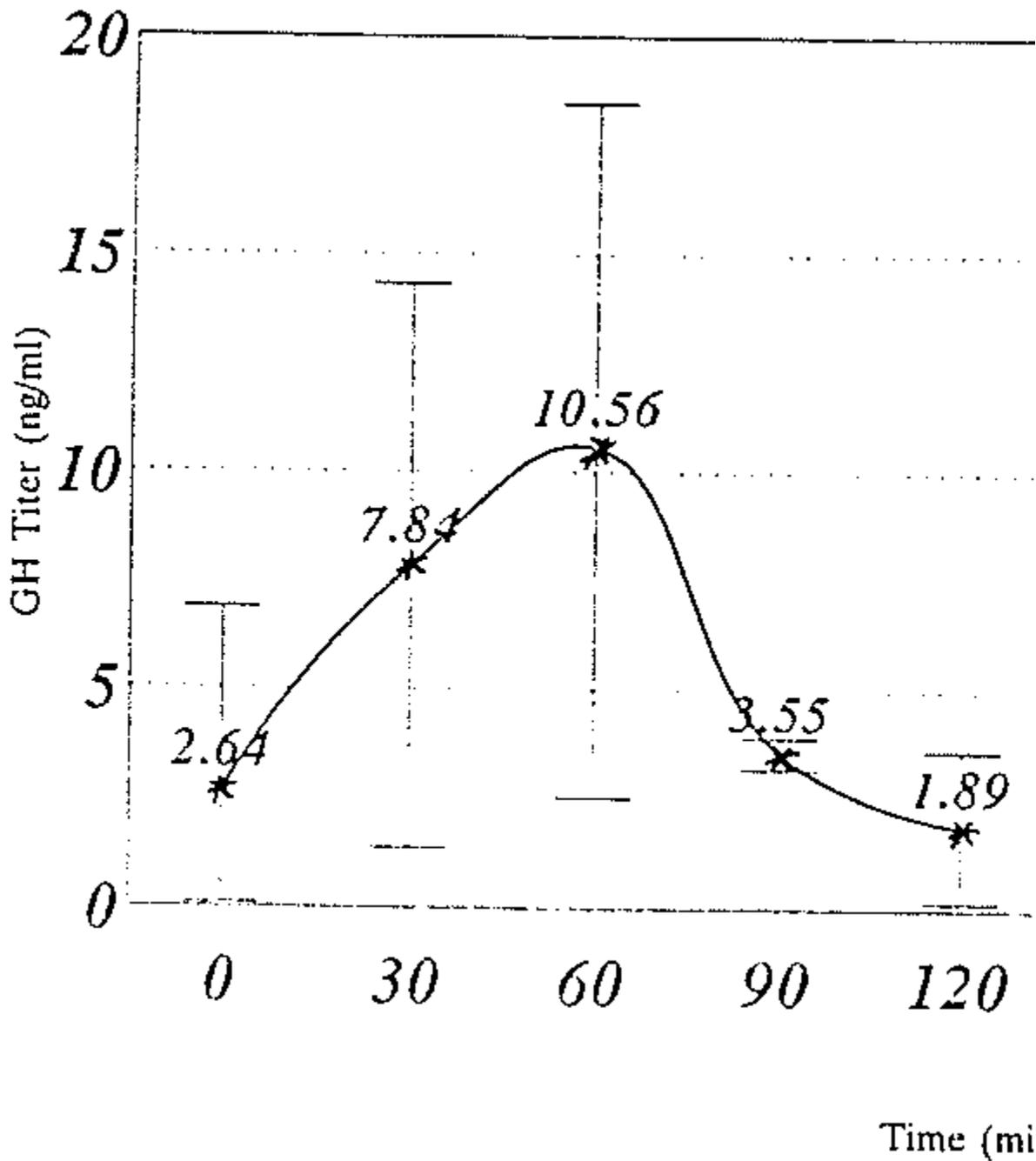


Figure 2. GH Titer (ng/ml) vs Time (mi)

### Fig. 3. Growth hormone titers in L-Dopa test

**DOSAGE OF CLONIDINE HYDROCHLORIDE TO RELEASE HGH IN ADULTS:** 0.25 – 0.30 mgs orally (very reliable in children-0.15mg /Sq m-but not so in adults)

#### **Growth hormone and cortisol secretion after oral clonidine in healthy adults**

Glenn E. Hunt<sup>\*\*</sup>, Brendan T. O'Sullivan<sup>\*\*</sup>, Gordon F. S. Johnson<sup>\*\*</sup>,   
and George A. Smythe<sup>\*\*\*</sup>

<sup>\*\*</sup> Department of Psychiatry, University of Sydney, Sydney, N.S.W.,  
Australia

<sup>\*\*\*</sup> Garvan Institute of Medical Research, St. Vincent's Hospital,  
Darlinghurst, N.S.W., Australia

**(.NB: Either beta adrenergic blockade or alpha stimulation enhances HGH secretion and inhibits insulin secretion and fat mobilization, whereas either alpha blockade or beta stimulation stimulates insulin secretion and fat mobilization and inhibits HGH secretion.)**

#### **Abstract**

The purpose of this study was to evaluate oral clonidine for testing growth hormone (GH) responsiveness in healthy adults. Oral clonidine (0.15 mg) produced a satisfactory GH response (> 4 ng/ml from basal) in eight out of 10 subjects, which is similar to rates reported after an equivalent intravenous dose. Elevated GH levels at baseline occurred in four out of five

female subjects; this did not affect the clonidine-induced GH release. There were no significant differences at any time point in plasma prolactin or cortisol levels following clonidine, compared to placebo controls. Adequate plasma clonidine levels ( $> 0.4$  ng/ml) were achieved in all subjects, with corresponding reductions in mean arterial blood pressure, but with only minimal adverse effects. Results from this study indicate that oral clonidine is a reliable method for testing GH responsiveness in adult subjects.

**Author Keywords:** Clonidine; growth hormone; cortisol; prolactin; blood pressure; pharmacokinetics; humans

### [Basal plasma HGH and cortisol levels and the effect of clonidine administration in female migrainous patients.](#)

[Weizman A](#), [Gil-Ad I](#), [Weizman R](#), [Hering R](#), [Bechar M](#), [Tyano S](#), [Laron Z](#).

#### **Abstract**

Clonidine, a central alpha-adrenergic agent and prophylactic antimigraine drug is known to stimulate human growth hormone (HGH) release and to suppress cortisol secretion. A possible association between basal hormonal levels and response to either acute clonidine test or chronic treatment in female migrainous patients was investigated. 15 females, aged 18-43 years, suffering from migraine, underwent an acute clonidine test by administration of a single oral dose of 0.15 mg. High basal HGH levels (greater than or equal to 9 ng/ml) were observed in 6 patients, while the other 9 patients demonstrated normal low basal HGH levels. Acute clonidine administration induced a marked rise of HGH in 8 of the 9 patients with low basal HGH. In 4 of the 8 responders HGH levels exceeded 20 ng/ml and 3 subjects reached the acromegalic range (greater than 90 ng/ml). The mean response in this group was higher than in a reference group consisting of children and adolescents. It is suggested that the basal hypersecretion and the

hyperresponsiveness of HGH to clonidine provocation test in some migrainous patients results from a hypersensitivity of the central alpha-adrenergic receptors. 12 of the 15 females were treated for 10 weeks with clonidine at gradually increased doses of 0.05 mg/day up to a maximal dose of 0.15 mg/day. A marked suppressive effect on cortisol secretion was observed in the migrainous patients after acute and chronic administration of clonidine. No correlation was observed between HGH and cortisol response to acute or chronic clonidine administration and the prophylactic effect of clonidine on migraine

### **Plasma growth hormone response to oral clonidine as compared to insulin hypoglycemia in obese children and adolescents.**

[Topper E](#), [Gil-Ad I](#), [Bauman B](#), [Josefsberg Z](#), [Laron Z](#).

#### **Abstract**

The response of plasma growth hormone (hGH) to a single oral dose of clonidine (0.15 mg/m<sup>2</sup>) was compared with that obtained with insulin hypoglycemia (ITT) induced by administration of double the usual dose (0.2 U/kg i.v.) in 13 obese subjects aged 5-17 years (7 males, 6 females) with a subscapular skinfold greater than 20 mm and a weight greater than 2 SD of the median. Six healthy subjects (3 males, 3 females), aged 8-14 years who served as controls received the usual dose of 0.1 U/kg i.v. in the ITT.

Clonidine induced an increase of more than 10 ng/ml in the plasma hGH levels in 10 (4 males, 6 females) of the 13 obese subjects and in all of the healthy controls, with peak levels ranging from 14.3 to 31.0 ng/ml (m +/- SD 21.0 +/- 5.2 ng/ml); the ITT elicited a similar rise in only 6 of the 13 subjects and 3 of the healthy controls, with peak levels ranging from 9.8 to 20.0 ng/ml (m +/- SD 14.4 +/- 4.5 ng/ml). Clonidine decreased plasma insulin levels in all the obese female subjects (by a mean of 65%) whereas

in the obese males the insulin pattern was variable. There was no change in blood glucose levels following the administration of clonidine; during the ITT all subjects showed a decrease to less than 50 mg/dl. Blood pressure decreased by a mean of 20 mmHg during the clonidine test. This study demonstrates that clonidine is a more effective hGH stimulus than insulin induced hypoglycemia in normal and in obese children and that the lower hGH secretion of the obese is confirmed by the clonidine test.

### **Effect of prolonged clonidine administration on growth hormone concentrations and rate of linear growth in children with constitutional growth delay**

- Sixteen prepubertal children with constitutional growth delay (10 boys and six girls, mean age  $7.2 \pm 2.1$  years) were administered a daily dose of clonidine ( $0.15 \text{ mg/m}^2$ ) for a period of 1 year. Growth hormone levels, plasma somatomedin C, and linear growth rate were significantly increased at the end of the treatment. Six of the children maintained the higher growth rate even 6 months after treatment. These and other studies suggest that prolonged stimulation of the hypothalamus by clonidine may ameliorate the impairment of growth hormone release seen in some children with constitutional growth delay. Because of the low cost and the convenience of the oral route, administration of clonidine could be a mode of treatment in some children with poor growth. **GH Values after Clonidine Stimulation**

#### **Measured by Immunofluorometric Assay in Normal Prepubertal Children and GH-Deficient Patients**

Eveline G.P. Silva, Natasha Shessarenko, Ivo J.P. Arnhold, Marcelo C. Batista, Vivian Estefan, Maria G.F. Osorio, Suemi Marui, Berenice B. Mendonca

*Objective:* To establish the cut-off values of GH measured by immunofluorometric assay, a more sensitive and specific assay, in normal prepubertal children and compare their values with those of proven GH-deficient patients. *Methods:* 30 normal children (20 males) and 26 patients with known causes of GH deficiency were submitted to the clonidine test and their GH values were compared. A powdered clonidine tablet (0.1 mg/m<sup>2</sup>) was given orally and blood samples for GH measurements were drawn at times –30, 0, 60, 90 and 120 min. *Results:* GH peak values presented a wide variation ranging from 1.7 to 25 µg/l (mean ± SD = 12.87 ± 5.8 µg/l) in the normal group. The cut-off values for the 5th and 10th percentiles of the distribution curve were 3.3 and 5.5 µg/l, respectively. In the GH deficiency group, maximum GH levels after clonidine stimulation ranged from <0.1 to 2.1 µg/l (0.56 ± 0.58 µg/l). *Conclusions:* The cut-off values obtained with the immunofluorometric method are lower than the ones obtained by radioimmunoassay. We suggest a cut-off value of 3.3 µg/l (5th percentile) that ensures 100% of sensitivity along with 93% of specificity to exclude the diagnosis of GH deficiency when using this immunofluorometric method.

### **Age- and gender-related growth hormone responses to intravenous clonidine in healthy adults**

J. Kimber<sup>b, a</sup>, M. Sivenandan<sup>a</sup>, L. Watson<sup>b, a</sup> and C. J. Mathias<sup>b, a</sup>

<sup>a</sup> Neurovascular Medicine Unit, Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine at St Mary's Hospital, London, UK

<sup>b</sup> Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square and University Department of Clinical Neurology, Institute of Neurology, University College London, UK

### **Abstract**

The  $\alpha_2$ -adrenoceptor agonist clonidine stimulates growth hormone (GH) release in both animals and humans. It has been used to test for GH deficiency in children, to assess central  $\alpha_2$ -adrenoceptor function in adults and to determine the pathophysiological basis and to confirm diagnosis in neurological diseases with autonomic failure. The dose and mode of administration, however, may be important, as in some studies in adults oral clonidine has minimal effects on GH. We report our experience following intravenous (i.v.) clonidine (2  $\mu\text{g}/\text{kg}$ ) in 98 normal adults on the neuroendocrine (GH, insulin, glucose and catecholamine) and cardiovascular (blood pressure) responses. In males between 25 and 89 years and females between 25 and 64 years there was a significant rise in GH secretion ( $P < 0.05$ ) after clonidine. Males showed an age-sensitive secretory pattern, with the greatest response between 25 and 35 years ( $P < 0.02$ ). Younger males ( $< 45$  years) had significantly higher peak GH levels post-clonidine than younger females  $< 45$  years ( $P < 0.03$ ). No sex-related change was observed in older subjects ( $> 45$  years). Clonidine caused a significant fall in plasma noradrenalin and adrenalin in all age–sex groups ( $P < 0.001$ ). There were no significant changes in glucose or insulin. There were no effects of age on the fall in blood pressure induced by clonidine. In conclusion, i.v. clonidine stimulated GH in all age groups and there was a marked sexually dimorphic pattern in adults  $< 45$  years. The results overall suggest that i.v. clonidine–GH testing provides a reliable method for investigation of central  $\alpha_2$ -adrenergic function in adult humans.

### **Comparison of growth hormone response after clonidine and insulin hypoglycemia in affective illness**

Jay D. Amsterdam  and Greg Maislin

From the Depression Research Unit, Department of Psychiatry, University of Pennsylvania

#### **Abstract**

Abnormal growth hormone (GH) responses have been observed after several neuroendocrine challenge tests. In the present study, we examined the relationship between GH response after clonidine and insulin administration within the same subject to see if consistent response patterns were evident. Though there was a significant reduction in the mean GH response after clonidine ( $p=0.0002$ ), similar differences were not observed after insulin ( $p=0.10$ ). Furthermore, there were no apparent within-subject correlations for GH response between the clonidine and insulin challenge tests. Although the present findings indicate an inherent variability in GH response patterns after different neuroendocrine challenge tests, it appears from prior studies that GH may be more consistently blunted after clonidine in depression when compared to other GH provocative tests.

### **Measurement of the GH and other responses to clonidine at different times of the day in normal subjects**

**W. G. Honer<sup>a</sup>, I. B. Glass<sup>a</sup>, C. Thompson<sup>a</sup>, T. Corn<sup>a</sup> and S. A. Checkley<sup>\*</sup>**

<sup>a</sup> Institute of Psychiatry Denmark Hill, London, SE5 8AF, U.K.

<sup>\*</sup> Maudsley Hospital, Denmark Hill, London SE5 8AF, U.K.

### **Abstract**

The growth hormone response to clonidine may be impaired in some patients with endogenous depression. To determine whether or not this change is due to a circadian variation in the GH response to clonidine, this measure has been studied in normal subjects at 0900, 1800 and 2100 hr. Similar responses were obtained at 0900 and 1800 hr. The responses at 2100 hr could not be interpreted, as the baseline plasma GH was raised. At no time of day were there impaired GH responses similar to those found in endogenous depression.

The effects of clonidine upon blood pressure and alertness were similar at the three times studied, providing no support for any circadian rhythm in the function of the  $\alpha_2$ -adrenoceptors that mediate these effects of clonidine.

### **Effect of aging on human plasma growth hormone response to clonidine**

**Irit Gil-Ad<sup>a</sup>, Rachel Gurewitz<sup>a</sup>, Ozias Marcovici<sup>b</sup>, Joseph Rosenfeld<sup>b</sup> and Zvi Laron , <sup>a</sup>**

<sup>a</sup>Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, Petah Tikva, and the Sackler School of Medicine, Tel Aviv University Israel

<sup>b</sup>Hypertension Unit, Beilinson Medical Center, Petah Tikva, and the Sackler School of Medicine, Tel Aviv University Israel

#### **Abstract**

The effect of the oral administration of 0.150 mg/m<sup>2</sup> clonidine on the plasma level of human growth hormone (hGH) was studied in 53 adults (25 males and 28 females) aged from 28 to 68 years, of which 15 were healthy volunteers and 38 were hypertensive. Both the normal and hypertensive subjects of both sexes showed an age-related responsiveness of hGH to clonidine, with a normal or partial response in the younger subjects and blunting or lack of response in the more elderly subjects. In the females the blunting of the hGH response appeared at an earlier age than in the males. It is speculated that an alteration in the sensitivity of the central alpha-adrenergic receptors and a decrease in the sex steroid hormones may account for the progressive reduction in hGH secretion with advancing age.

**NB:** Clonidine and L-dopa stimulate GH secretion mainly through the release of hypothalamic GHRH, and that arginine- and insulin-induced hypoglycaemia stimulate GH secretion mainly through the inhibition of hypothalamic somatostatin release. However, the presence of endogenous hypothalamic GHRH seems to be essential for the maximal stimulation of GH

release induced by arginine and insulin.

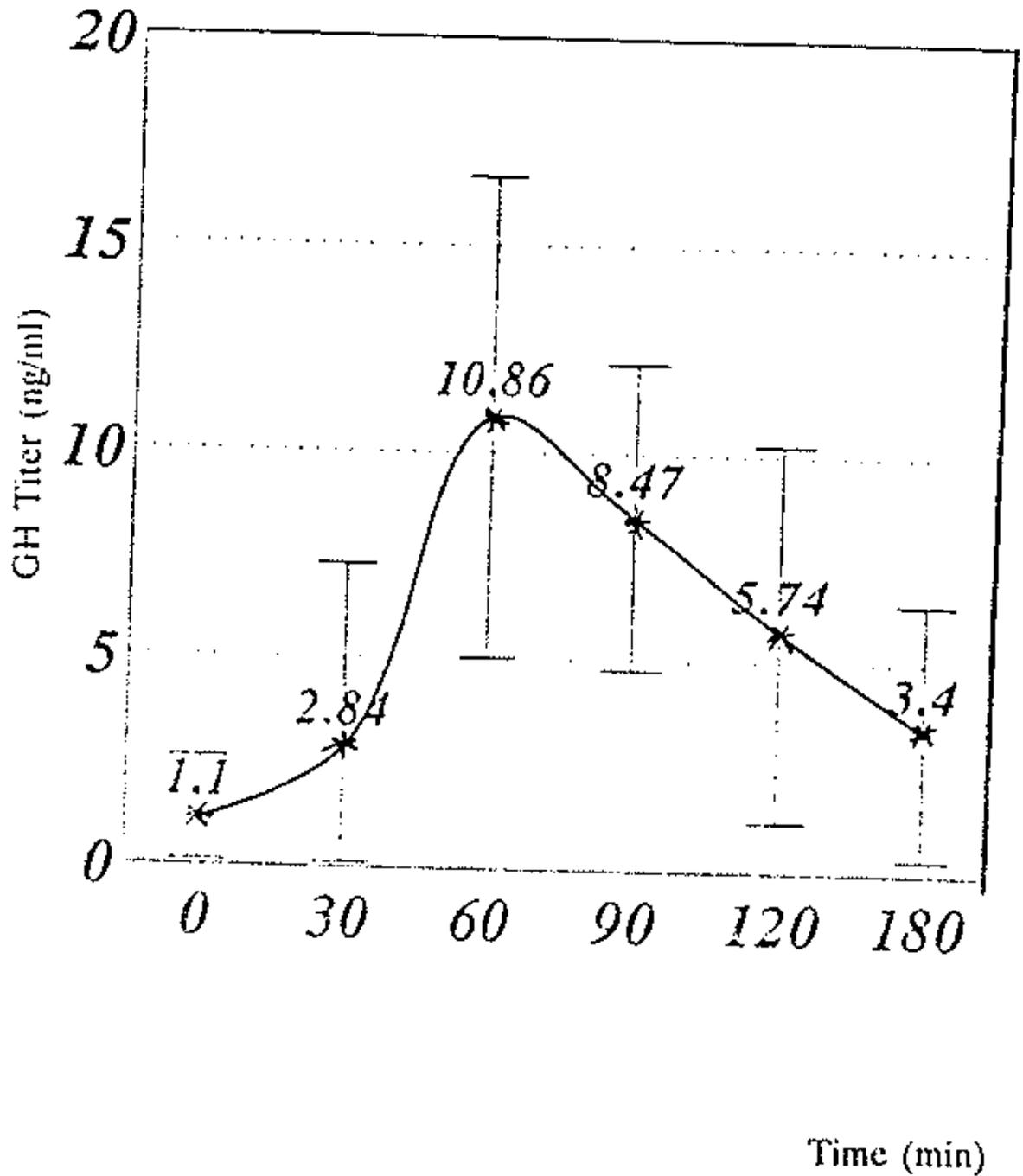


Fig. 1. Growth hormone titers in clonidine test

**GRAPH OF DIFFERENT GH STIMULATION TESTS:**

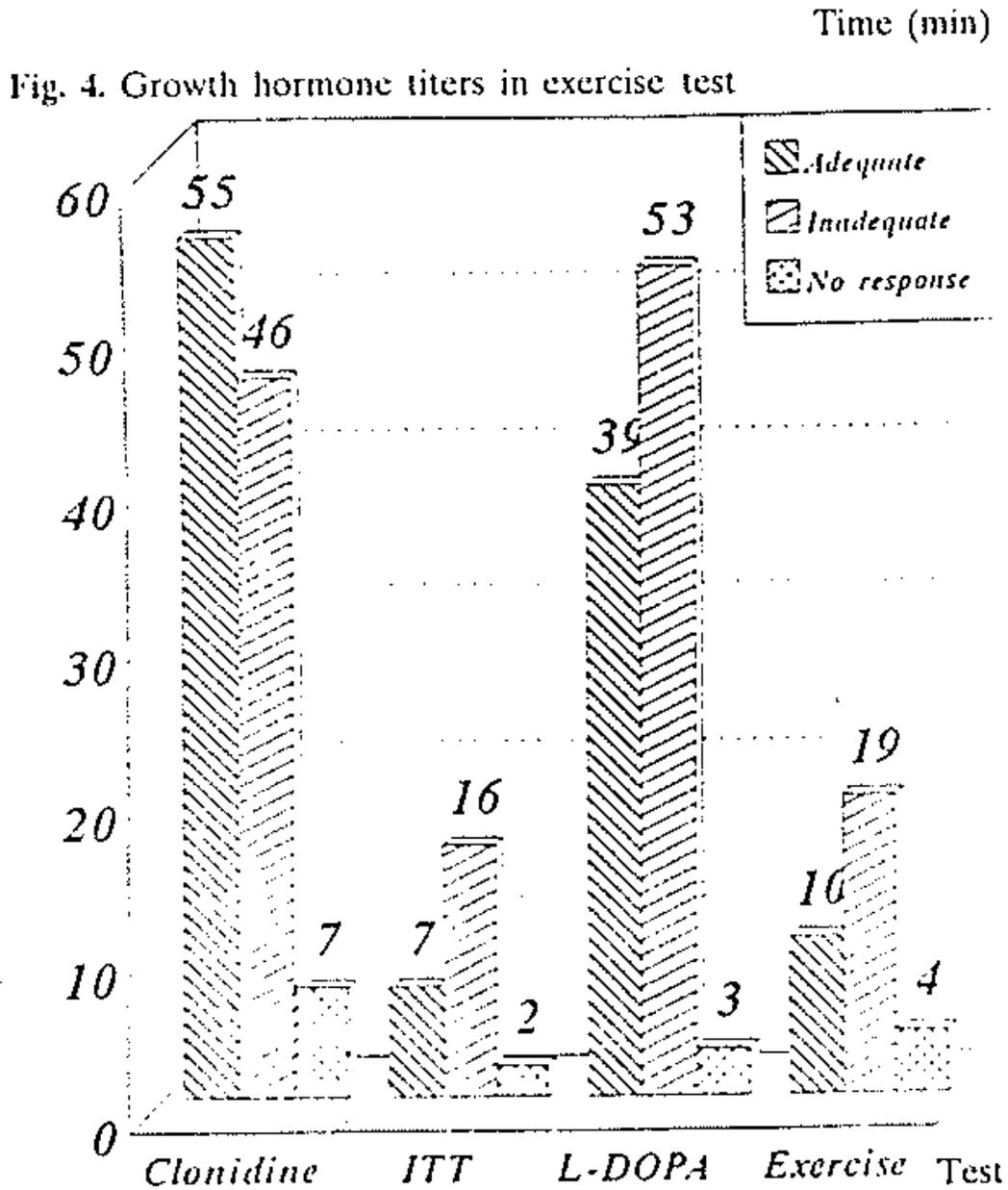


Fig. 5. Test responses

**TABLE**

**Pediatric GHD diagnostic: GH stimulation testing**

GH stimulation testing; peak GH concentration <10 µg/L supports diagnosis of GHD; GHRH currently unavailable.

**Stimulus Dosage Side effects**

Levodopa (PO) <15 kg: 125 mg Nausea

15–30 kg: 250 mg >30 kg: 500 mg- **The enhancement of the L-dopa-stimulated GH release by L-deprenyl is in good agreement with the clinically observed beneficial effects of L-deprenyl in combination with L-dopa therapy.**

Propranolol (PO) 0.75mg/KG- Maximum dose 40mgs:Bradycardia and Hypoglycaemia

Clonidine (PO) 0.15 mg/mb Tiredness, postural hypotension

Arginine HCl (IV)\* 0.5 g/kg (max 30 g)

10% arginine HCl in 0.9% NaCl over 30 min

Insulin (IV) 0.05-0.1 U/kg Hypoglycemia;  
use with caution in children

Glucagon (IM) 0.03 mg/kg IM Nausea;  
(max 1 mg) use with caution in children

- **IGF-1 and IGFBP-3 assays are supportive for diagnosis of GHD**
- **Low levels suggestive of GHDa**

Tests should be performed after overnight fast. Patients should be euthyroid.

\*GHRH is often used in combination with arginine.

GH=growth hormone, GHD=growth hormone deficiency, GHRH=growth hormone releasing hormone,

IM= intramuscular, IV=intravenous, PO=by mouth.

aAdapted from Rosenfeld 2002. bGharib 2003.

### **Selegiline:**

---

1. The antioxidant action of Selegiline may be antiatherogenic and cardioprotective.
2. In conjunction with inhibition of LDL oxidation, Selegiline is unique in that it demonstrates protective effects on both vascular and neuronal tissue.
3. The influence of Selegiline on the cytokine biosynthesis may also contribute to its putative neuroprotective properties.
4. The monoamine oxidase B inhibitor Selegiline effectively inhibits SOD activity.
5. The rate of occurrence of side effects with Selegiline is no greater than with placebo.

6. Selegiline does not result in hypertensive crises.
7. The conversion of Selegiline to amphetamine and methamphetamine may contribute to some of its therapeutic benefits.
8. An acute 10mg dose of Selegiline does not stimulate the basal GH secretion but causes a potentiating effect of L-dopa-induced GH release on chronic therapy.
9. 5-10mg/day for 3 days causes complete inhibition of MAO
10. The amount of stage 2 sleep is increased.
11. There are no effects due to drug withdrawal
12. Selegiline is an irreversible selective MAO-B inhibitor without  $\blacklozenge$ cheese effect $\blacklozenge$ .

### **Effects of L-deprenyl on human growth hormone secretion**

M. Koulu and R. Lammintausta

#### ***Abstract***

The effects of L-deprenyl on L-dopa-, apomorphine- and L-tryptophan-induced growth hormone (GH) secretion were studied in thirteen healthy male volunteers.

An acute 10 mg dose of L-deprenyl did not stimulate the basal GH secretion. Short-term L-deprenyl premedication significantly enhanced the L-dopa-stimulated GH release. In contrast, L-deprenyl premedication did not change the GH response to apomorphine or L-tryptophan.

Potentialiation of L-dopa-induced GH release by L-deprenyl indicates an increased availability of dopamine at the receptor level without a direct agonistic effect by the drug. Furthermore, L-deprenyl does not change the function of postsynaptic dopamine receptors involved in human GH release.

## Evidence for dopaminergic stimulation of growth velocity in some hypopituitary children.

Huseman CA, Hassing JM.

### **Abstract**

The purpose of this study was to determine if endogenous hGH release, hence growth, in hypopituitary children could be potentiated by therapy with dopaminergic (DA) drugs namely, L-dopa or bromocriptine. The effect of DA therapy on other endocrine function was also examined. Subjects were nine prepubertal children (four girls and five boys) with bone ages (BA) ranging from 1.5-9.5 yr. They were diagnosed as having idiopathic GH deficiency on the basis of: 1) failure to grow at normal rates 2) lack of GH response to two provocative stimuli (oral L-dopa, and insulin-induced hypoglycemia) and 3) low somatomedin-C concentrations for sex and age. They were divided into two groups. Group I (n = 4) received L-dopa (15 mg/kg, orally, every 6 h) for 6 months. Group II (n = 5) received bromocriptine (1.25 mg, orally, every 12 h) for 6 months. At the end of 6 months of DA therapy, both groups received human GH (hGH) im (0.1 IU/kg, thrice weekly) for 6 months. The growth rate in group I increased to 5.7 +/- 0.6 (+/- SE) cm/yr during the 6 months from a pretreatment rate of 3.4 +/- 0.2 cm/yr. Individual increments ranged from 30-94% above pretreatment growth rates. Three of the four children had significantly increased height increments, and two children achieved growth rates normal for their BA. Similarly, the growth rate in group II increased to 4.8 +/- 0.8 cm/yr from the pretreatment rate of 2.9 +/- 0.3 cm/yr. Individual increments ranged from 46-100% above pretreatment growth rates. Three children in group II had significantly increased height increments, and two children had normal growth rates for BA. The growth increments during L-dopa therapy occurred in the three children who had significant increases in hGH and somatomedin-

C; of the three children with significant growth increments during bromocriptine therapy, two had increases in somatomedin-C, and one achieved a normal peak hGH value. hGH therapy caused further acceleration of growth velocities in the majority of patients. DA therapy had no significant effect on basal gonadotropin, gonadal steroids, T4, TSH, or morning cortisol concentrations in the majority of children compared with their pretreatment values. The following conclusions were reached. Dopaminergic therapy by itself, i.e. L-dopa or bromocriptine administration, induced linear growth in some hypopituitary children without significantly affecting basal concentrations of LH, FSH, gonadal steroids, T4, TSH, or cortisol. The effect this therapy could have in potentiating exogenous GH and/or possible GRH therapy is worthy of further investigation.

### [Endogenous dopaminergic dysfunction: a novel form of human growth hormone deficiency and short stature.](#)

[Huseman CA](#), [Hassing JM](#), [Sibilia MG](#).

#### **Abstract**

The purpose of this study was to determine if combined therapy with dopaminergic drugs (DA), i.e. L-dopa or bromocriptine, and exogenous human GH (hGH) could increase growth velocity in hypopituitary children. Twelve prepubertal hypopituitary children (eight boys and four girls; bone age, 1.5-9.5 yr), divided into two groups, each received hGH alone, DA alone, and DA and hGH. Group I (n = 6) received L-dopa (15 mg/kg, orally) at 6-h-intervals during DA and combined DA and hGH therapy. Group II (n = 6) received bromocriptine (1.25 mg, orally) every 12 h during DA and combined DA and hGH therapy. Both groups were given hGH (0.1 IU/kg) three times per week during hGH and combined hGH and respective DA treatment. The study included three 6-month treatment periods of DA, hGH,

and combined DA and hGH therapy. The mean growth rates (centimeters per 6 months, +/- SD) before treatment and during the three study periods for group I were 1.7 +/- 0.2, 3.3 +/- 0.8, 3.4 +/- 0.4, and 3.9 +/- 0.7, respectively. Group II results were 1.4 +/- 0.3, 2.3 +/- 0.8, 5 +/- 1.6, and 3.7 +/- 1.1. Mean and peak hGH concentrations, measured every 30 min for 9 h at the end of each study period, increased significantly in five patients, from 15 +/- 3 (+/- SE) ng/ml during hGH therapy to 30 +/- 5 ng/ml during DA and hGH treatment. The mean peak hGH values rose from 24 +/- 4 to 45 +/- 5 (+/- SE) ng/ml. In conclusion, addition of dopaminergic agents to hGH therapy potentiates growth in some hypopituitary children. The increased growth and hGH responses to L-dopa or bromocriptine suggest impaired endogenous GH release. Dopaminergic therapy alone or in combination with exogenous hGH may be efficacious in some hypopituitary children.

### **Levodopa and Growth Hormone Secretion**

"Glucagon and Growth Hormone" (27 January, p. 188): glucagon stimulation is an effective test of growth hormone release but, since it is less reliable and takes longer to perform than the insulin test, it should be regarded only as "a good second-line test." Though Drs. C. T. Sawin and M. L. Mitchell (1 September, p. 499) have pointed out that the reliability of the glucagon provocative test can be improved by pretreatment with propranolol, we should like to draw attention to another reliable test of growth hormone release, using levodopa as the stimulant, which has recently been investigated by several authors, including ourselves. 2-4 The preliminary results of our study of the effect of levodopa on growth hormone release in elderly normal subjects and in elderly subjects with cerebrovascular hemiplegia are reported briefly here. Plasma growth hormone levels before and after a single oral dose of levodopa (500 mg) were measured by a double antibody radioimmunoassay technique in seven clinically normal elderly subjects aged 64-83 (average 77.0) years and in seven elderly patients aged 66-76 (average 72.4) years with arteriosclerotic hemiplegia of at least three months' duration. Mild side effects of levodopa (nausea) were noted in only four of the 14 subjects. Significant peak levels of growth hormone were found, usually between 60 and 90 minutes after levodopa administration, in 11 of the 14 subjects investigated. There was no significant difference in response between the hemiplegic patients (mean peak plasma growth hormone level ( $\pm$  S.D.) 21.7  $\pm$  6.41 ng/ml) and the

control group ( $26-14 \pm 5-43$  ng/ml). Nor was any significant difference noted between the responses of these two groups of subjects and those of normal adults previously studied. These results confirm that levodopa stimulation should be regarded as a reliable test of growth hormone release in patients of all ages. Moreover, the test is short in duration, does not require any intravenous infusion or injection, and does not involve any risk of hypoglycaemia.-We are, etc.,

By: C. F. COLUCCI

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I Bellastella, A., Cafaro, M. R., Colucci, C. F.,  
D'Alessandro. B., and Gasbarro, R., *Bollettino*

### Relative usefulness of three growth hormone stimulation screening tests.

[Fass B](#), [Lippe BM](#), [Kaplan SA](#).

#### **Abstract**

One hundred ninety-one children were tested by one of three screening procedures for growth hormone deficiency over a five-year period. Sleep screen yielded a 31.3% false-positive rate; levodopa administration alone yielded a 20.5% false-positive rate and levodopa in combination with propranolol yielded a 5.2% false-positive rate. These results support the

view that the combined levodopa-propranolol hydrochloride screen test is superior to either the sleep or the levodopa screen tests in limiting the number of false-positive results and thus the need for further, more extensive testing.

PMID: 474543 [PubMed - indexed for MEDLINE]

### **Stimulation of Growth Hormone Secretion by Levodopa-Propranolol in Children and Adolescents**

**Robert Collu M.D.<sup>1</sup>, Gilles Leboeuf M.D.<sup>1</sup>, Jacques Letarte M.D.<sup>1</sup>, , Jacques R. Ducharme M.D.<sup>1</sup>**

<sup>1</sup> Division of Endocrinology and Metabolism, Department of Pediatrics, Hôpital Sainte-Justine and the University of Montreal, Montreal, Quebec, Canada

Levodopa, 0.5 gm/1.73 sq m, and propranolol, 0.75 mg/kg, were administered orally to 23 children with short stature and 10 children suffering from various disorders. Glucose and insulin tolerance tests and arginine infusions were also utilized in some of these subjects to determine growth hormone (GH) response. Seventeen subjects with short stature had a GH peak greater than 5 ng/ml to the combined levodopa-propranolol provocative test (DPPT). The mean GH peak concentration obtained in this group was  $19.6 \pm 1.8$  (SEM) ng/ml, and in 94.1% of these children the peak was obtained at either 30, 60, or 90 minutes following the administration of the two drugs. Six subjects with short stature who failed to respond to the DPPT had abnormal responses to at least two other stimulatory tests and were classified as GH-deficient. Two subjects among the ten suffering from various disorders failed to respond to the DPPT. The first was a case of chromophobe adenoma of the pituitary gland with primary amenorrhea and luteinizing hormone deficiency, and the second a case of Hand-Schüller-Christian disease.

The DPPT appears to be a reliable, safe, and easy-to-perform **test** to determine GH reserve

**Circadian influence on effect of propranolol on exercise-induced tachycardia in healthy subjects**

A. Fujimura, Y. Kumagai, K. Sugimoto, H. Nakashima, H. Kajiyama, A. Ebihara and K. Ohashi

European Journal of Clinical Pharmacology, 1986, Volume 31, Number 6, Pages 667-672

Following a cross-over design propranolol 20 mg p.o. was given to 7 healthy subjects at 09.00 h and 21.00 h at an interval of 1 week. Heart rate (HR) during submaximal ergometer exercise was measured at four intervals during 10 h after treatment. Plasma propranolol concentrations were also determined.

The suppressive effect (%R) of propranolol on the rise in HR during exercise after the morning dosage was significantly greater at 1.5 h and tended to be greater 3 h after administration than at comparable times in the evening trial. Mean plasma propranolol concentrations during the early phase were higher after the morning than the evening dose. The maximum plasma concentration ( $C_{max}$ ), area under the plasma concentration-time curve from 0 to 10 h (AUC (0–10)) and absorption rate constant ( $k_a$ ) were significantly greater after the morning dose. The time to maximum concentration ( $t_{max}$ ) and elimination half-life ( $t_{1/2}$ ) of the morning and evening dosages did not differ. A significant correlation was observed between plasma propranolol concentration and %R in HR during exercise in the morning ( $r=0.74$ ) and evening ( $r=0.63$ ) trials, and the regression lines of the morning and evening treatments did not differ.

The data indicate that the suppressive effect of propranolol on exercise-induced tachycardia was relatively greater after a morning than an evening dose; that propranolol was more rapidly absorbed from the gastrointestinal tract after the morning than the evening dosage; that diurnal changes in the

activity of propranolol depend in part on the time of administration and its subsequent effect on plasma concentrations of the drug; and that the antagonist activity of propranolol relative to a given drug concentration may not differ between morning and evening treatments.

### Reevaluation of levodopa-propranolol as a test of growth hormone reserve in children.

[Collu R](#), [Brun G](#), [Milsant F](#), [Leboeuf G](#), [Letarte J](#), [Ducharme JR](#).

#### **Abstract**

The growth hormone (GH) reserve of 15 short children was evaluated with the levodopa-propranolol test (DPT) and the sequential arginine-insulin test (AIT). Four patients failed to respond to both tests and were classified as hyposomatotropic. In the other 11 children, the mean GH peak response to the DPT was significantly higher than that to the AIT, mainly because five subjects who a normal response to the DPT had failed to respond to the AIT. These children had a generally poor yearly growth increment prior to testing associated in three with an obvious emotional problem, and were found at follow-up to have resumed a normal growth pattern. These data confirm the effectiveness of the DPT as a test of GH reserve. Although hypoglycemia can occur occasionally during test, this procedure is safer and easier to perform than the widely used AIT. Finally, the DPT seems to detect a category of children who have a temporary growth failure and nonresponse to the usual GH tests but who are not hyposomatotropic and consequently do not require human GH.

#### **Specific GH provocative tests are described below:**

##### **Insulin tolerance test**

Insulin-induced hypoglycemia is the most potent stimulus for GH secretion and the most dangerous tool for provocative GH testing in patients who may have GH deficiency. Insulin tolerance testing makes advantage of the hormonal counterregulatory response to hypoglycemia. In patients without GHD, plasma concentrations of glucagon, epinephrine, norepinephrine, cortisol, corticotropin, and GH are elevated in response to acute hypoglycemia.

To perform the test, patients fast for 8 hours. Then, lispro insulin 0.1 U/kg of body weight is administered rapidly as an intravenous bolus. Serial blood samples are subsequently obtained to measure GH, cortisol, and glucose concentrations at 0 minutes, 15 minutes, 30 minutes, 60 minutes, 75 minutes, 90 minutes, and 120 minutes. With each sample, the blood glucose level is simultaneously determined by using a bedside glucometer to document an appropriate reduction and to ensure safety. Performance of the test is considered adequate when the blood glucose level decreases below 50% of its baseline value.

Adverse effects expected during the procedure include symptoms secondary to hypoglycemia, such as lethargy, shaking, confusion, headache, abdominal pain, nausea, vomiting, syncope, and seizure activity. The test must be performed under the watchful eye of the physician who can begin prompt resuscitation with glucose and/or glucagon as soon as the diagnostic samples have been obtained. To date, the insulin tolerance test is the only provocative test associated with fatalities; therefore, personnel must be trained and conduct the test judiciously.

### **Clonidine stimulation test**

Clonidine acts centrally to stimulate alpha-adrenergic receptors, which are involved in regulating GH release. Serum GH levels are obtained at baseline and at 60 minutes and 90 minutes after the oral administration of clonidine 0.1 mg/kg. Clonidine may induce hypotension during the test. Therefore, warn parents that they may experience lethargy and/or depression for 24 hours after clonidine is administered.

### **Levodopa-propranolol HCl test**

Levodopa is a dopamine receptor agonist. Dopamine is involved in the stimulation of GH secretion. In the converse, beta-adrenergic control negatively regulates GH release.

Propranolol is a beta-blocker used to hinder inhibitory input affecting GH release while levodopa simultaneously stimulates GH release by means of the dopaminergic pathway. Propranolol 0.75-1 mg/kg is orally administered before levodopa. The dosage of levodopa for levodopa-propranolol HCl

testing varies with weight so that children weighing less than 15 kg receive 125 mg, children weighing 10-30 kg receive 250 mg, and children weighing less than 30 kg receive 500 mg.

Blood samples for GH testing are drawn at 0 minutes, 60 minutes, and 90 minutes after the administration of levodopa. Adverse effects include nausea and, in rare cases, emesis. In addition, the patient's heart rate may decrease because of the use of propranolol. Closely monitor his or her vital signs, and ensure that appropriate resuscitative measures are available.

### **Arginine HCl test**

Arginine appears to exert a direct depolarizing action on somatotropic neurons, increasing GH secretion. After an overnight fast, patients are given 10% arginine HCl in 0.9% NaCl 0.5 g/kg (not to exceed 30 g) as a constant intravenous infusion over 30 minutes. Blood samples for GH testing are obtained at 0 minutes, 15 minutes, 30 minutes, 45 minutes, and 60 minutes after the infusion of arginine is begun. Arginine has historically been used as a primer before insulin is administered during insulin tolerance testing.

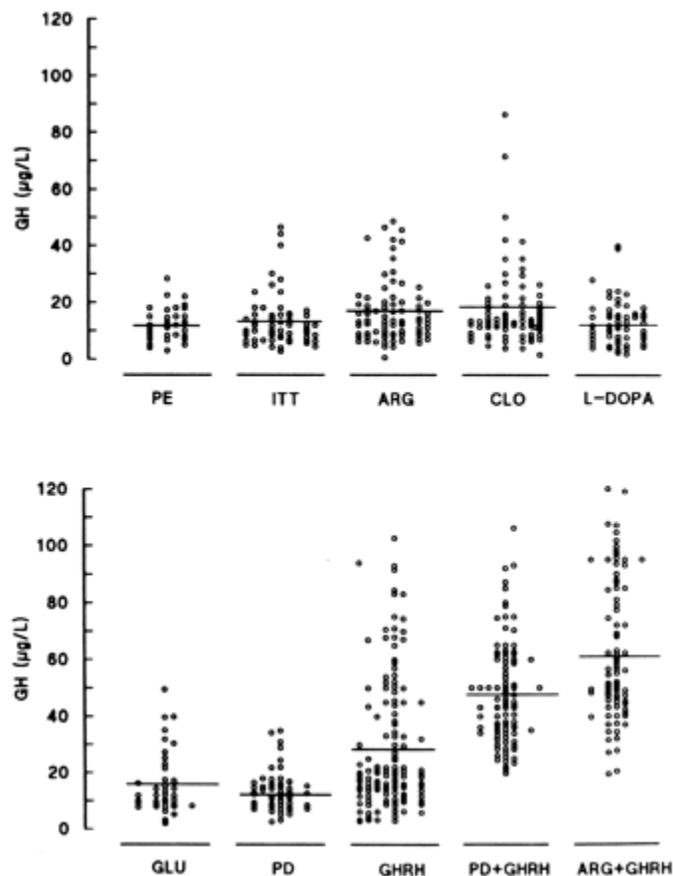
### **Glucagon test**

Glucagon increases peripheral glucose concentrations by means of glycogenolysis and gluconeogenesis. Because glucagon is rapidly metabolized, an abrupt reduction in serum glucose concentration ensues and triggers the release of counterregulatory hormones.

After fasting overnight, patients receive an intramuscular injection of glucagon 0.03 mg/kg (not to exceed 1 mg). Some clinicians advocate the concomitant use of propranolol to inhibit the catecholaminergic response to hypoglycemia. Serum GH concentrations are determined at 0 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes, and 180 minutes after glucagon administration. Nausea and, occasionally, emesis may occur.

### **Expected Results**

Most clinicians use a peak serum GH concentration of more than 10 ng/mL (30 IU) to exclude GHD in children.



**Figure 3.** Individual peak GH responses to physical exercise, ITT, arginine, clonidine, L-dopa, glucagon, pyridostigmine, GHRH, pyridostigmine and GHRH, and arginine and GHRH in normal children of either short or normal height. Serum GH levels were measured in duplicate at each time point by immunoradiometric assay. The sensitivity of the assay was 0.1 µg/liter, whereas the inter- and intraassay coefficients of variation were between 4.9 and 6.5% and 1.5 and 2.9%, respectively. Samples from different individuals for a single provocative stimulus or from the same individual over multiple provocative stimuli were not run in the same GH assay. [Reproduced from E. Ghigo *et al.*: *J Clin Endocrinol Metab* 81: 3323–3327, 1996 (52). © The Endocrine Society.]

### **The effect of nacom (L-dopa and L-carbidopa) on growth hormone secretion in 75 patients with short stature**

The stimulatory effect of Nacom<sup>®</sup> (250 mg L-Dopa and 25 mg L-Carbidopa) on the HGH secretion was evaluated in 75 short stature patients. The number of blood samples was restricted to only three (0, 45 and 90 min). 63 patients reached adequate HGH concentrations after the ingestion of 1 tablet

Nacom (84%). Somatotropin levels increased from 2.08 ( $S \times 0.28$ ) to a maximal HGH value of 14.22 ( $S \times 0.87$ ) ng/ml.

When the stimulatory effect of Nacom was compared with the standard method of arginine infusion in children with normal stature the arginine test was not superior to the Nacom-test.

The Nacom-test appears to be a simple and reliable screening method for HGH deficiency, particularly in outpatients.

**\*\*\*\*\*Chronic treatment with oxprenolol or propranolol in active hypertensive patients was associated with elevation of serum growth hormone (GH).** Propranolol, 80 mg orally, caused a marked rise in GH in 3 of 4 acromegalic patients. Propranolol may increase the GH response to many stimuli including moderate exercise (Maclaren et al., 1975); however, more detailed studies are necessary to determine whether GH remains elevated for a greater part of the day in patients receiving 5-blockers. It is concluded that either beta adrenergic blockade or alpha stimulation enhances HGH secretion and inhibits insulin secretion and fat mobilization, whereas either alpha blockade or beta stimulation stimulates insulin secretion and fat mobilization and inhibits HGH secretion.

[Dtsch Med Wochenschr.](#) 1979 Dec 21;104(51):1811-3.

**[Improvement of growth-hormone stimulation with l-dopa/l-carbidopa by simultaneous administration of propranolol (author's transl)].**

[Article in German]

[Schönberger W](#), [Grimm W](#), [Ziegler R](#).

### **Abstract**

The effect of simultaneous administration of 250 mg L-dopa + 25 mg L-carbidopa (Nacom) and 1 mg propranolol/kg body weight (maximal dose 40 mg propranolol) on growth-hormone secretion was tested in 96 children with growth retardation. The results were compared with those in a group of children that had been receiving only L-dopa and L-carbidopa. The additional

administration of propranolol reduced the number of children unresponsive to adequate growth-hormone stimulation from 16% to 9.5%. There was no significant difference in mean maximal growth-hormone level between both groups, but the addition of propranolol caused a more long-lasting rise in serum growth hormone levels. Some of the children who previously had failed to have a satisfactory rise in growth-hormone level after L-dopa and L-carbidopa showed satisfactory stimulation when propranolol was added. Since only three blood samples need be taken (0, 45 and 90 minutes) and no significant side effects were noted, the combined treatment is suitable for out-patient use.

[J Clin Endocrinol Metab.](#) 1976 Jun;42(6):1188-91.

### **Growth hormone refractory interval to levodopa stimulation.**

[Parker KM, Eddy RL.](#)

#### **Abstract**

The GH response to repeat L-dopa stimulation was studied in three phases. In phase I and phase II, 16 normal adults divided into four groups were restimulated at 3, 4, 5, and 6 hours with 500 mg L-dopa and 1000 mg L-dopa, respectively. No response could be elicited at 3 hours and only at 6 hours (500 mg L-dopa) and 5 hours (1000 mg L-dopa) did the repeat responses return in magnitude to that of the initial. The period of decreased responsiveness to GH was termed the "refractory interval". In phase III, addition of an inhibitor of peripheral L-aromatic amino acid decarboxylase (50 mg MK-486) to the restimulation dose shortened but did not eliminate the refractoriness. Our results suggest that the refractory interval is not due to a peripherally located mechanism.

[Nippon Naibunpi Gakkai Zasshi.](#) 1987 Aug 20;63(8):934-46.

**[Effect of oral administration of L-dopa on the plasma levels of growth hormone-releasing hormone (GHRH) in normal subjects and patients with various endocrine and metabolic diseases].**

[Article in Japanese]

[Mitsuhashi S](#), [Yamasaki R](#), [Miyazaki S](#), [Saito H](#), [Saito S](#).

First Department of Internal Medicine, School of Medicine, University of Tokushima, Japan.

**Abstract**

The responses of plasma growth hormone-releasing hormone (GHRH) and growth hormone (GH) to oral administration of L-dopa were studied in normal subjects and patients with various endocrine and metabolic diseases to clarify the pathophysiological role of the GHRH-GH axis. In normal subjects, the plasma GHRH concentration was increased from the basal value of  $9.8 \pm 1.4$  pg/ml (mean  $\pm$  SE) to  $34.8 \pm 3.1$  pg/ml at 30 approximately 90 min after oral administration of 500 mg L-dopa, followed by a rise of GH release (plasma GH level from less than 1 ng/ml to  $21.7 \pm 4.7$  ng/ml) in most cases, indicating that L-dopa stimulates GH secretion via hypothalamic GHRH. In subjects with simple obesity, the responses of plasma GHRH (peak  $13.2 \pm 1.2$  pg/ml) and GH (peak  $4.3 \pm 1.7$  ng/ml) to L-dopa were significantly lower than those in normal subjects ( $p$  less than 0.01).

[Isr J Med Sci](#). 1982 May;18(5):625-9.

**Growth hormone response to L-dopa in the thinned obese.**

[Laurian L](#), [Oberman Z](#), [Hoerer E](#), [Wiznitzer T](#), [Harell A](#).

## Abstract

The response of plasma growth hormone (GH) to 0.5 g L-dopa was studied in 17 obese nondiabetic subjects and in 6 normal-weight subjects, aged 16 to 46 yr. The test was repeated after the obese subjects were thinned 12 to 50 kg, either with a hypocaloric diet or by a jejunoileal shunt. All the obese subjects had a blunted response to L-dopa stimulation. Nine of the thinned obese continued to exhibit the same blunted GH response, while the other eight responded with a significant GH rise after L-dopa stimulation, although the increase was smaller than that in the controls. No correlation between the initial or final weight or the extent of weight loss and the response to L-dopa was observed. It is assumed that a hypothalamic underresponsiveness is responsible for the blunted response in the obese subjects and its persistence in some of the thinned obese.

## Comparison of Stimulated Growth Hormone Levels in Primed versus Unprimed Provocative Tests

### Effect of Various Testosterone Doses on Growth Hormone Levels

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*Horm Res* 2001;56: 32-37 (DOI: 10.1159/000048087)

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### Key Words

- Priming
  - Transient growth hormone deficiency
  - Growth hormone stimulation test
  - Testosterone
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## Abstract

*Objective:* To show the importance of priming prior to growth hormone (GH) stimulation tests in the diagnosis of GH deficiency, the effect of different doses and schedules of testosterone (T) on GH levels. *Patients and Methods:* Eighty-four prepubertal and early pubertal boys whose heights were 2 SD below the mean and height velocities  $<4$  cm per year and who failed in GH stimulation tests were included in the study. The boys were divided into two groups: the first group consisting of 41 boys was primed with  $62.5 \text{ mg/m}^2$  (low dose testosterone – LDT) and the second group consisting of 43 boys with  $125 \text{ mg/m}^2$  depot testosterone (conventional dose testosterone – CDT) intramuscularly 1 week before the stimulation test. Twenty-one boys out of 36 who failed in GH stimulation tests after one dose T injection were treated with three doses of  $62.5 \text{ mg/m}^2$  T (multiple dose testosterone – MDT) injections monthly and retested. *Results:* The GH levels increased from  $4.80 \pm 2.78$  to  $11.50 \pm 8.84$  ng/ml and from  $4.76 \pm 2.46$  to  $12.98 \pm 8.30$  ng/ml by priming with LDT and CDT respectively. The increment of mean GH levels by both LDT and CDT were found to be similar ( $p = 0.443$ ). The peak GH levels were found to be elevated  $>10$  ng/ml in 22/41 (54%) and 26/43 (60%) who received LDT and CDT respectively ( $p = 0.528$ ). The mean GH level of 21 boys who received MDT was increased from  $5.38 \pm 2.50$  ng/ml (by priming with one dose T) to  $10.19 \pm 6.13$  ng/ml ( $p = 0.004$ ). Twelve (57%) of 21 boys who received MDT responded to GH stimulation test  $>10$  ng/ml. The T level increased from  $0.71 \pm 0.97$  to  $4.54 \pm 2.80$  ng/ml by LDT ( $p < 0.001$ ) and from  $0.65 \pm 0.71$  to  $7.18 \pm 3.18$  ng/ml by CDT ( $p < 0.001$ ). The increment of T level was higher by CDT than LDT ( $p = 0.001$ ). There was no correlation between T and peak GH levels after priming. *Conclusion:* LDT is as effective as CDT in priming of GH stimulation tests. The ones who failed in GH stimulation tests after one dose T injection can be

primed with MDT. The stimulated GH level after priming was related neither to the plasma level of T nor the dose of T.

### **Amantadine enhancement of L-DOPA induced growth hormone stimulation.**

F Massara, F Camanni, G M Molinatti  
Horm Metab Res

#### **Abstract**

Oral amantadine (3 × 100 mg/day for 3 days) had no effect on basal GH values in 6 subjects (3 with untreated Parkinson's disease). The drug did, however, boost L-DOPA stimulation of GH, so that a positive response was also obtained in 2 subjects who had failed to respond to L-DOPA alone.

#### **Key words**

Growth Hormone - L-Dopa - Amantadine - Dopamine - Noradrenaline

### **Endurance exercise modulates levodopa induced growth hormone release in patients with Parkinson's disease**

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#### **Abstract**

Acute levodopa (LD) application and exercise release human growth hormone (GH). An earlier trial showed, that combined stimulus of exercise and LD administration is the best provocative test for GH response in healthy

participants. Objective was to show this combined effect of LD application and exercise on GH response and to investigate the impact on LD metabolism in 20 previously treated patients with Parkinson's disease (PD). We measured GH- and LD plasma concentrations following soluble 200 mg LD/50 mg benserazide administration during endurance exercise and rest on two separate consecutive days. GH concentrations significantly increased on both days, but GH release was significantly delayed during rest. LD metabolism was not altered due to exercise in a clinical relevant manner. Exercise induced a significant faster LD stimulated GH release in comparison with the rest condition. We did not find the supposed increase of LD induced GH release by endurance exercise. We assume, that only a limited amount of GH is available for GH release in the anterior pituitary following an acute 200 mg LD administration. GH disposal also depends on growth hormone releasing hormone (GHRH), which is secreted into hypothalamic portal capillaries. During the exercise condition, the resulting higher blood pressure supports blood flow and thus GHRH transport towards the GH producing cells in the pituitary. This might additionally have caused the significant faster GH release during exercise.

**Keywords:** Parkinson's disease; Levodopa; GH; Exercise

## **INHIBITORY EFFECT OF CIMETIDINE ON L-DOPA-STIMULATED GROWTH HORMONE RELEASE IN NORMAL MAN**

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## **SUMMARY**

Some evidence suggests the existence of a histaminergic influence on GH secretion in animals and man. We used cimetidine, a specific H<sub>2</sub>-receptor antagonist, to study the possible interference of H<sub>2</sub>-receptor blockade on plasma GH release by L-dopa and on PRL inhibition by L-dopa in normal man. Seven healthy normal male volunteers aged 23–36 years received a single oral dose of L-dopa (500 mg) or an i.v. bolus of cimetidine (300 mg) or both (L-dopa 30 min before cimetidine). Blood samples were taken at various times over 2 h and plasma GH and PRL levels measured. Cimetidine alone did not alter basal plasma GH values; L-dopa elicited the well-known GH releasing effect with peak values at 75 min ( $15.65 \pm 2.8$  ng/ml); cimetidine injected 30 min after L-dopa ingestion significantly blunted the GH response to L-dopa and peak values ( $4.7 \pm 1.6$  ng/ml) were delayed to 105 min. Cimetidine provoked a rapid rise in plasma PRL with the peak value of  $15 \pm 3$  ng/ml at 15 min, followed by a return to near basal values in 90–120 min. L-Dopa completely inhibited the PRL response to cimetidine. We conclude that there is an inhibitory influence of the H<sub>2</sub>-receptor antagonist cimetidine on GH release by L-dopa. This, together with the action of cimetidine on PRL secretion (with or without L-dopa), suggests a possible antidopaminergic effect of H<sub>2</sub>-receptor blockade at the level of the central nervous system.

## **DEPRENYL- EXTENDING LIFESPAN**

By James South MA

Deprenyl is a drug that was discovered around 1964-65 by Dr. Joseph Knoll and colleagues. It was originally developed as a psychic energizer, designed to integrate some amphetamine-like brain effects with antidepressant effects. (1) Also known as L-deprenyl, (-)-deprenyl, and selegiline, deprenyl (DPR) has been intensively researched over the past 36 years - many hundreds of research papers on DPR have been published. Knoll has stated that DPR ...is an exceptionally lucky modification of PEA [phenylethylamine], an endogenous ... member of the family to which also the transmitters noradrenaline and dopamine belong. (13)

DPR has shown a unique and exciting pharmacologic/clinical profile. It is the only potent, selective MAO-B inhibitor in medical use. (1) DPR is a catecholamine activity enhancer. (2) DPR has been shown to protect nerve cells against a wide (and growing) number of neurotoxins. (3,4) DPR has also been shown to be a neuroprotection/ neurorescue agent when nerve cells are exposed to damaging or stressful conditions. (5)

DPR has become a standard treatment for Parkinsons disease. (6) DPR is also useful in treating drug-resistant depression. (8,9) In aged rats, DPR has proven to be a highly effective sexual rejuvenator. (10) DPR also shows promise as a cognitive enhancement agent. (10) DPR has also proven in four different rat studies and one dog study to be an effective life-extension agent, even increasing the technical lifespan in Knolls rat experiments. (11,12) and these are just some of DPRs reported benefits.

### **DEPRENYL: MAO-B INHIBITOR EXTRAORDINAIRE**

By 1971 Knoll had shown that DPR was a unique kind of MAO inhibitor - a selective MAO-B inhibitor, without the cheese effect. To fully appreciate what this means, some technical background is necessary.

Some of the most important neurotransmitters in the brain are the monoamine (MA) transmitters: serotonin, dopamine and noradrenalin. After being secreted into the synaptic gap, where one neuron connects to another, many of the transmitter molecules are reabsorbed by the secreting neuron and then disposed of by enzymes called monoamine oxidases (MAO). This prevents excessive levels of transmitters from accumulating in the synaptic gap and over-amping the brain. However, with aging MAO activity significantly increases in the human brain, often to the point of severely depressing necessary levels of MA transmitters. (1)

In the 1950s the first antidepressant drugs to be developed were MAO inhibitors (MAOI). By the 1960s however, MAOIs began to drop out of medical use due to a dangerous side-effect - the so-called cheese effect. When most MOIs are used in people consuming a diet rich in a substance called tyramine, a dangerous, even fatal, high blood pressure crisis can be triggered. Tyramine is found in many foods, including aged cheeses, some wines, beans, yeast products, chicken liver and pickled herring, to name just

a few. (23)

By 1968, further research had shown that there were two types of MAO-A and B. It is primarily intestinal MAO-A that digests incoming tyramine. Most of the MAOIs that have been used clinically inhibit both MAO-A and MAO-B, thus setting up the danger of the cheese effect by inhibiting intestinal and brain MAO-A, allowing toxic tyramine levels to accumulate. DPR is unique among clinically used MAO-Is. At normally used clinical dosages (10-15 mg/day), DPR is a selective MAO-B inhibitor, so it doesn't prevent intestinal MAO-A from digesting dietary tyramine. (1)

In addition, DPR has the unique ability to prevent tyramine from getting into noradrenalin-using nerve cells, and it's only when tyramine enters noradrenalin nerve cells that control arterial blood pressure that it triggers the cheese effect. (1) DPR thus has a dual safety lock in preventing the cheese effect, making it far safer than other MAOIs. At doses over 20-30 mg/day, however, DPR does start to significantly inhibit MAO-A, so there is some risk of the cheese effect at these higher (rarely clinically used) doses. (1)

MAO-A enzymes break down serotonin (5-HT) and noradrenalin (NA), and to a lesser extent dopamine (DA). MAO-B breaks down DA and the trace amine phenylethylamine (PEA). At doses of 5-10 mg per day DPR will inhibit MAO-B about 90%. (1) It was initially presumed that DPR would increase synaptic levels of DA in DA-using neurons, and this led to its use to treat Parkinson's disease in the late 1970s, Alzheimer's disease in the 1980s-90s, and depression starting in the late 1970s. In his 1983 paper on the history of DPR's clinical benefits to its unique MAO-B effects. (1)

Yet many experts have questioned whether DPR's MAO-B inhibition can significantly increase synaptic DA levels. (14,15) This is due to the fact that MAO-B is found only in glial cells in the human brain, non-nerve cells that support, surround and feed the brain's billions of neurons. (1) And whether there is any exchange of DA between these glial cells and the DA-using neurons is still an unanswered question. It is commonly believed that it is MAO-A in DA neurons that breaks DA down. By the 1990s Knoll believed he had discovered the real basis of DPR's being a MAO-B inhibitor. (2)

Yet as will be made clear shortly, even if DPRs originally hypothesized mode of action - directly increasing synaptic DA levels through MAO-B inhibition - is false, DPRs MAO-B inhibition still provides part of its benefit.

### **DEPRENYL: CATECHOLAMINE ACTIVITY ENHANCER**

During the 1990s Knolls DPR research took a new direction. Working with rat brain stems, rabbit pulmonary and ear arteries, frog hearts and rats in shuttle boxes, Knoll discovered a new mode of action of DPR that he believes explains its widespread clinical utility. (2,16) Knoll discovered that DPR (and its cousin, PEA) are catecholamine activity enhancers (CAE).

Catecholamines (CA) refers to the inter-related neurotransmitters dopamine (DA), noradrenalin (NA) and adrenalin. CAs are the transmitters for key activating brain circuits - the mesolimbic-cortical circuit (MLC) and the locus coeruleus (LC). The neurons of the MLC and LC project from the brain stem, through the mid-brain, to the cerebral cortex. They help to maintain focus, concentration, alertness and effortful attention. (17) DA is also the transmitter for a brainstem circuit - the nigrostriatal tract - which connects the substantia nigra and the striatum, a nerve tract that helps control bodily movement and which partially dies off and malfunctions in Parkinsons disease. (1)

When an electrical impulse travels down the length of a neuron - from the receiving dendrite, through the cell body, and down the transmitting axon - it triggers the release of packets of neurotransmitters into the synaptic gap. These transmitters hook onto receptors of the next neuron, triggering an electrical impulse which then travels down that neuron, causing yet another transmitter release. What Knoll and colleagues discovered through their highly technical experiments is that DPR and PEA act to more efficiently couple the release of neurotransmitters to the electrical impulse that triggers their release. (2,16)

In other words, DPR (and PEA) cause a larger release of transmitters in response to a given electrical impulse. Its like turning up the volume on CA nerve cell activity. And this may be clinically very useful in various contexts - such as Parkinsons disease and Alzheimers disease, where the nigrostriatal tract (PD) and MLC circuits (AD) under-function (1,17), as well as in depression, where they may be under-activity of both DA and NA neurons.

(18,19)

Knolls research also indicates that after sexual maturity the activity of the CA nervous system gradually declines, and that the rate of decline determines the rate at which a person or animal ages. (10,20) Knoll therefore believes that DPRs CAE effect explains its anti-aging benefit. (10,20) Knoll also believes that DPRs CAE activity is independent of its MAO-B inhibition effect, because in rats he has shown CAE effect at doses considerably lower than that needed to achieve MAO-B inhibition.

Knolls work indicates that PEA is also a CAE substance. (16) PEA is a trace amine made in the brain that modulates (enhances) the activity of DA/NA neurons. (16,21) Autopsy studies have shown that while DPR increases DA levels in Parkinson patient brains by only 40-70%, DPR increases PEA levels 1300 - 3500%! (14,22) PEA is the preferred substrate for MAO-B, the MAO that DPR inhibits. Paterson and colleagues have shown that PEA has an extremely rapid turnover due to its rapid and continuous breakdown by MAO-B. (21) Thus DPRs CAE activity has a dual mode of action. At low, non-MAO-B inhibiting doses, DPR has a direct CAE activity.

At higher, MAO-B inhibiting doses, DPR creates an additional CAE effect, due to the huge increases in brain PEA levels that DPR causes, PEA also being a CAE substance. Many authors have pointed out the probable DA neuron activity enhancing effect of PEA in Parkinson patients taking DPR. (14, 15, 22) Knolls discovery of PEAs CAE effect now explains this PEA DA-enhancing effect.

### **DEPRENYL: THE NEUROPROTECTOR**

DPR has been shown to protect nerve cells from an ever-growing list of neurotoxins. Some of these neurotoxins can actually be produced within the brain under certain conditions, while others come from the environment or diet.

MPTP is a chemical first identified as a contaminant in synthetic heroin. In the 1980s young men using synthetic heroin suddenly developed a Parkinson-like disease. It was then discovered that the MPTP was taken up by glial cells surrounding nigrostriatal neurons, where it was converted by glial MAO-B enzymes into the real toxin, MPP+. The nigral neurons then

absorbed MPP<sup>+</sup> into their mitochondria, where MPP<sup>+</sup> poisoned the mitochondria, killing the DA-using neurons. (15) The MAO-B inhibiting dose of DPR (10 mg/day) has been shown to prevent MPTP from being converted to the neurotoxin MPP<sup>+</sup>. (4) And as Lange and colleagues note, Compounds with a chemical structure similar to MPTP include both natural and synthetic products (e.g. paraquat) that are used in agriculture! (15)

6-hydroxydopamine (6-OHDA) is a potent neurotoxin that can spontaneously form from DA in DA-using neurons. (11,13) 6-OHDA may then further auto-oxidize to generate toxic superoxide and hydroxyl free radicals and hydrogen peroxide. (11,13) Knolls research has shown that pre-treatment of striatal DA-neurons with DPR can completely protect them from 6-OHDA toxicity. (4,11,13) Even in those not suffering from Parkinsons disease, the nigrostriatal neurons are the fastest aging neuron population in the human brain - an average 13% loss every decade from the 40s on. (1,13) Knoll and others believe that 6-OHDA neurotoxicity is a key cause of this normal nigral death, and that DPR may be just what the doctor ordered to retard this debilitating downhill neural slide.

DSP-4 is a synthetic NA-nerve toxin. In rodents DPR has been shown to prevent the depletion of NA in NA-using neurons and NA-nerve degeneration that DSP-4 causes. (4) AF64A is a cholinergic toxin - it damages brain cells that use acetylcholine. DPR pre-treatment has been shown to protect cholinergic neurons from AF64A toxicity. (4)

DPR has also protected human nerve cells from peroxynitrite and nitric oxide toxicity. Peroxynitrite is formed naturally in the brain when nitric oxide reacts with superoxide radical. Peroxynitrite causes apoptosis, a programmed suicide cell death that can be triggered in neurons by various agents. DPR was found to inhibit peroxynitrite-caused apoptosis, even after the DPR was washed from DPR pre-treated cells. (3)

Methyl-salsolinol is another MAO-B produced endogenous neurotoxin. Salsolinol is a tetra-hydroisoquinoline produced from the interaction of DA and acetaldehyde, the first-stage breakdown product of alcohol. Once formed, salsolinol can then be further modified by MAO-B to generate methyl-salsolinol. DPRs MAO-B inhibiting activity can prevent the DNA damage caused by this toxin. (3,4)

By inhibiting MAO-B, DPR reduces the toxic load on the brain that is routinely produced through the normal operation of MAO-B. MAO-B digests not just DA and PEA, but also tryptamine, tyramine and various other secondary and tertiary amines. (15)

As noted earlier, PEA is the substance MAO-B is most efficient at digesting, so that the half-life of PEA is estimated at only 0.4 minutes. (21)

This continuous high level breakdown of PEA (and other amines) produces aldehydes, hydrogen peroxide and ammonia as automatic MAO-B reaction products, and they are all toxins. (4) Thus by reducing age-elevated MAO-B activity, DPR reduces the toxin burden on DA/NA neurons (where PEA is primarily produced).

...L-deprenyl provides neuroprotection against growth factor withdrawal in PC12 cells, oxidative stress in mesencephalic neurons, and the genotoxic compound, Ara C, in cerebellar granule neurons, and against axotomy-induced motoneuronal degeneration and delayed neuronal death in hippocampus after global ischaemia. (24) And these are just some of the many reports in the scientific literature on DPRs versatile neuroprotection.

### **DEPRENYL: PARKINSONS DISEASE**

Parkinsons disease (PD) is one of the two major neurodegenerative diseases of the modern world - Alzheimers disease is the other. PD affects up to 1% of those over 70, a lesser percent of those 40-70, and rarely anyone below 40. (23) PD is caused by a severe loss of DA-using nigrostriatal neurons, with symptoms manifesting after 70% neuronal loss, and death usually ensuing after 90% loss. (23)

The physiologic role of the nigral neurons is the continuous inhibition of the firing rate of the cholinergic interneurons in the striatum. (13) When the nigral neurons fail in this negative feedback control, voluntary movement and motor control is scrambled, leading to the typical PD symptoms: shuffling gait, stooped posture, difficulty initiating movement, freezing in mid-movement, and the shaking palsy. By the late 1960s the standard treatment for PD was the amino-acid precursor of DA, L-dopa. The L-dopa increased the DA levels in the few remaining nigrostriatal neurons in PD patients (80% of brain DA is normally located in nigral neurons (11), thus at

least partially restoring normal movement and motor control.

However by 1980 A. Barbeau, after analyzing results of 1052 PD patients treated over 12 years, wrote that long-term side effects are numerous.... although we recognize that levodopa is still the best available therapy, we prefer to delay its onset until absolutely necessary. (1)

DPR became a standard therapy to treat PD by the late 1970s. In 1985 Birkmayer, Knoll and colleagues published a paper summarizing the results of long term (9 years) treatment with L-dopa alone or combined with DPR in PD. (25) They found a typical 1 to 2 year life extension over the average 10 years from L-dopa onset until death in the L-Dopa/DPR group. The 1996 DATATOP study found that To the extent that it is desirable to delay levodopa therapy, deprenyl remains a rational therapeutic option for patients with early PD. (26) In a 1992 paper Lieberman cited 17 studies supporting the claim that ... with levodopa-treated patients with moderate or advanced PD... the addition of selegiline [DPR] is beneficial. (6)

Thus by the 1980s-1990s DPR had become a standard PD therapy, used either to delay L-dopa use, or in combination with L-dopa. Yet in 1995 a report published in the British Medical Journal seriously questioned the use of DPR in combination with L-dopa to treat PD. (27)

The UK-PD Research Group study followed 520 PD patients for 5-6 years. Several hundred patients initially received 375 mg L-dopa, while several hundred others received 375 mg L-dopa plus 10 mg DPR daily. After 5-6 years, the mortality rate in the L-Dopa/DPR group was almost 60% higher than in the L-dopa only group. The study authors therefore recommended DPR not be used in PD treatment. Yet the UK-PD study is the only one ever to find increased mortality with DPR use in PD, and the study has been severely criticized on multiple grounds by various PD experts. In response to the study, the BMJ published 8 letters in 1996 criticizing the study on various methodological and statistical grounds. (28) And a 1996 Annals of Neurology article by 4 PD experts provided an exhaustive analysis of the BMJ study, raising many questions and criticisms. (29)

One key criticism is that the UK-PD study was open label and patients could be reassigned to treatment groups during the study. 52% of the L-dopa

group and 45% of the L-Dopa/DPR group changed treatment groups, yet the allocation of end points (deaths) was based on patients original drug assignment, regardless of which drugs the patient was actually taking at time of death! When the death rate was compared only between those remaining on their original drug assignment, there was no statistically significant difference in mortality between the L-dopa and DPR/L-Dopa groups.

Another criticism levelled against the UK study is based on the dosage of L-dopa. It is generally accepted that DPR reduces L-dopa need by about 40%. (14) Thus, to achieve bio-equivalent L-dopa doses, the DPR/L-Dopa group should have only received 225 mg L-dopa, compared to 375 mg in the L-dopa only group. As evidence that the initial L-dopa dose was too high in the DPR/L-Dopa group, after 4-5 years the median L-dopa dose remained at 375 mg in the DPR group, while it had increased to 625 mg in the L-dopa only group. And a growing body of evidence has shown L-dopa to be neurotoxic in PD patients. In a 1996 review paper, S. Fahn briefly reviews 20 in vitro and 17 in vivo studies showing L-dopa to be toxic, especially in neurologically compromised, oxidant-stressed individuals, such as PD patients. (30) Thus if there were any real increased mortality in the DPR/L-Dopa group in the UK study, it is more likely due to L-dopa toxicity than DPR.

This is further borne out by a 1991 study by Rinne and colleagues, who studied 25 autopsied PD brains. (31) When they compared the substantia nigra of 10 patients who had received L-dopa plus DPR with 15 patients who had received L-dopa only, they discovered that there were significantly more nigral neurons remaining in the DPR/L-Dopa brains, i.e. the DPR had actually acted to preserve nigral neurons from L-dopa toxicity. Olanow and co-authors conclude their paper reviewing the UK study: It is our opinion that the evidence in support of discontinuing selegiline [DPR] in levodopa-treated patients, because of fears of early mortality, is not persuasive. Accordingly, we do not recommend that selegiline be withheld in PD patients based solely on the results of the UK study. (29)

### **DEPRENYL: ALZHEIMERS DISEASE**

Alzheimers disease (AD) is the most widespread neurodegenerative disease of modern times, affecting several million people in the U.S. alone. AD is

characterized not only by severe memory loss, but by verbal dysfunction, learning disability and behavioral difficulties - even hallucinations. AD is known to involve damage to the cholinergic neurons of the hippocampus, but In [AD], in addition to the reduction of acetylcholine, alterations have been observed in the activities of other neurotransmitters. More specifically, the deterioration of the dopaminergic [DA] and noradrenergic [NA] systems... seems particularly relevant to the cognitive manifestations.... cerebral depletion of dopamine (DA) can easily lead to memory and attention deficits. In [AD] there is significant increase in type-B cerebral and platelet monoamine oxidases (MAO-Bs)... [Therefore] pharmacological inhibition of MAO-B could result in an improvement in the cognitive functions normally mediated by the catecholaminergic systems. (17)

Thus, with its combined MAO-B inhibition effects and catecholamine activity enhancing effects, DPR would seem tailor-made to treat AD. And indeed that is the conclusion of a 1996 review paper on AD and DPR.

Tolbert and Fuller reviewed 4 single-blind and 2 open label DPR trials in AD, as well as 11 double-blind DPR/AD studies. (7) They noted that all 6 single-blind/open label studies reported positive results, while 8 of the 11 double-blind studies reported favorable results, typically with a 10 mg DPR/day dosage. In 3 of the single-blind studies DPR was compared to 3 nootropics - oxiracetam, phosphatidylserine and acetyl-L-carnitine - and was superior to all 3. Tolbert and Fuller were so impressed with DPR that they concluded ...in our opinion, selegiline is useful as initial therapy in patients with mild-to-moderate Alzheimer disease to manage cognitive behavioral symptoms. In patients with moderate-to-severe Alzheimer disease, selegilines efficacy has not been adequately assessed; however, given the lack of standard treatment, selegiline should be considered among the various treatment options. (7)

### **DEPRENYL: DEPRESSION**

DPR has been used experimentally as a treatment for depression since the late 1970s. While the causes of depression are diverse and still under investigation, it is by now accepted that dysfunction of DA and NA neural systems is a frequent biochemical cause of depression. (18,19)

In addition the research of A. Sabelli and colleagues has established that a

brain PEA deficiency also seems to be strongly implicated in many cases of depression. (32) Given that DPR is a catecholamine (DA and NA) activity enhancer, and that DPR strongly increases brain PEA through MAO-B inhibition, DPR would seem a rational treatment for depression.

Studies with atypical depressives (33), treatment-resistant depressives (34), and major depressives (35) have shown DPR to be an effective, low side-effect depression treatment. However, such studies have often required DPR dosages in the 20-30, even 60 mg range. While these dosages caused little problem in short-term studies, it is dubious to consider using such high, non-selective MAO-B inhibition doses for long term (months - years) treatment. Three studies have shown antidepressant promise at selective, MAO-B inhibiting doses.

In 1978 Mendelwicz and Youdim treated 14 depressed patients with 5 mg DPR plus 300 mg 5-HTP 3 times daily for 32 days. (1) DPR potentiated the antidepressant effect of 5-HTP in 10/14 patients. 5-HTP enhances brain serotonin metabolism, which is frequently a problem in depression (37), while DPR enhances DA/NA activity. Under-activity of brain DA, NA and serotonin neural systems are the most frequently cited biochemical causes of depression (18,19,37), so DPR plus 5-HTP would seem a natural antidepressant combination.

In 1984 Birkmayer, Knoll and colleagues published their successful results in 155 unipolar depressed patients who were extremely treatment-resistant. (8) Patients were given 5-10 mg DPR plus 250 mg phenylalanine daily. Approximately 70% of their patients achieved full remission, typically within 1-3 weeks. Some patients were continued up to 2 years on treatment without loss of antidepressant action. The combination of DPR plus phenylalanine enhances brain PEA activity, while both DPR and PEA enhance brain catecholamine activity. Thus DPR plus phenylalanine is also a natural antidepressant combination.

In 1991 H. Sabelli reported successful results treating 6 of 10 drug-resistant major depressive disorder patients. (9) Sabelli used 5 mg DPR daily, 100 mg vitamin B6 daily, and 1-3 grams phenylalanine twice daily as treatment. 6 of 10 patients viewed their depressive episodes terminated within 2-3 days! Global Assessment Scale scores confirmed the patients subjective

experiences. Vitamin B6 activates the enzyme that converts phenylalanine to PEA, so the combination of low-dose DPR, B6, and phenylalanine is a biological way to enhance both PEA and catecholamine brain function, and thus to diminish depression.

### **DEPRENYL: THE ANTI-AGING DRUG**

4 series of rat experiments, as well as an experiment with beagle dogs, have shown that DPR can extend lifespan significantly, even beyond the technical lifespan of a species. Knoll reported that 132 Wistar-Logan rats were treated from the end of their second year of life with either saline injections or 0.25 mg/kg DPR injection 3 times weekly until death. (11)

In the saline-treated group the oldest rat reached 164 weeks of age, and the average lifespan of the group was 147 weeks. In the DPR group, the average lifespan was 192 weeks, with the shortest-living rat dying at 171 weeks, and the longest-lived rat reaching 226 weeks.

In a second series of experiments Knoll treated a group of 94 low-performing (LP) sexually inactive male rats with either saline or DPR injections (0.25 mg/kg) from their eighth month of life until death. (11) Knoll had already established a general correlation between sexual activity status and longevity in the rats. The saline-treated LP rats lived an average 135 weeks, while the DPR-treated LP rats averaged 153 weeks of life. The saline treated HP rats lived an average 151 weeks of life, while the DPR - treated HP rats averaged 185 weeks of life, with 17/50 HP-DPR rats exceeding their estimated technical lifespan of 182 weeks. (20)

Knolls experiments were partially replicated by Milgram and co-workers and Kitani and colleagues. (11) Milgrams group used shorter-living Fischer 344 rats, while still starting DPR treatment at 2 years of age - in effect later in their lives - and found a marginally significant 16% lifespan extension. The Kitani group, also using the shorter-lived Fischer rats, started their DPR treatment at 1.5 years of age, and found a 34% life increase.(11)

Ruehl and colleagues performed an experiment with beagle dogs and DPR, administered at 1 mg/kg orally per day, for up to 2 years 10 weeks. In a subset of the oldest dogs tested (10-15 years of age), 12 of 15 DPR-treated dogs survived to the conclusion of the study, while only 7 of 18 placebo-

treated dogs survived. By the time the first DPR-treated dog died on day 427 of the study, 5 placebo-treated dogs had already died, the first at day 295. (12) Ruehl et al note that dogs provide an excellent model of human aging, so their study takes on added significance.

Knoll has repeatedly emphasized that the nigrostriatal tract, the tiny DA-using nerve cluster in the basal ganglia (old brain), typically dies off at an average rate of 13% per decade starting around age 45 in humans.

This fact literally sets the human technical lifespan (maximum obtainable by a member of a species) at about 115 years, since by that age the nigral neuron population would have dropped below 10% of its original number, at which time death ensues even if in all other respects the organism were healthy. (23) Based on the sum total of the animal DPR literature, as well as the 1985 study showing life-extension in DPR-treated PD patients (25) Knoll has suggested that if DPR were used from the 40s on, and only modestly lowered the nigrostriatal neuron death rate - i.e. from 13% to 10% per decade - then the average human lifespan might increase 15 years, and the human technical lifespan would increase to roughly 145 years. (23)



Professor Joseph Knoll, discover of the pharmacological activity of [Deprenyl](#)

After 45 years of research, Knoll has concluded that ...the regulation of lifespan must be located in the brain, (20) His research has further convinced him that ... it is the role of the catecholaminergic neurones to keep the higher brain centres in a continually active state, the intensity of which is dynamically changed within broad limits according to need. (20) Knolls research has shown that catecholaminergic nerve activity reaches a maximum at sexual maturity, and then begins a long, gradual downhill slide

thereafter. Knolls animal research has shown catecholaminergic activity, learning ability, sexual activity and longevity to be inextricably interlinked. (11,20)

Knoll argues that the quality and duration of life is a function of the inborn efficiency of the catecholaminergic brain machinery, i.e. a high performing longer living individual has a more active, more slowly deteriorating catecholaminergic system than [his/her] low performing, shorter living peer. (20) And his key conclusion is that ... as the activity of the catecholaminergic system can be improved at any time during life, it must be essentially feasible to ... [transform] a lower performing, shorter living individual to a better performing, longer living one. (20)

It is on this basis that Knoll consistently, throughout his DPR papers (11,20,23), recommends the use of 10 - 15 mg oral DPR/week, starting in the 40s, to help achieve this goal in humans. Knolls research clearly convinces him that DPR is both a safe and effective preserver of the nigrostriatal tract, as well as a catecholamine activity enhancer. DPR may not be the ultimate anti-aging drug, but it is one that is safe and effective, well validated theoretically and experimentally, and it is available now.

### **DEPRENYL: DOSAGE & SIDE-EFFECTS**

Both Dr. Joseph Knoll and the Life Extension Foundation (37) recommend a 10-15 mg weekly (i.e. 1.5 - 2 mg/day) oral DPR dosage for humans, starting around age 40, possibly even in the 30s. 10 mg/day is a relatively standard DPR dose for treatment of PD and AD, but this higher dose should only be used with medical supervision. Some DPR experts believe this dosage is excessive, and that with long term DPR use lower doses may still be effective and safer. (22)

Knoll has noted that the human MAO-B inhibiting DPR dose ranges from 0.05 to 0.20 mg/kg of bodyweight. (1) Thus, even in those wishing to use DPR at an effective MAO-B inhibiting dose, it should not be necessary to use more than 3-5 mg/day. Because DPR is a potent and irreversible MAO-B inhibitor, it may even turn out in many individuals that the suggested 1.5-2 mg/day life extension DPR dose may achieve MAO-B inhibition with long term use.

DPR is reported in most human studies to be well tolerated. (7) Typically, no

abnormalities are noted in blood pressure, laboratory values, ECG or EEG. (7) The most common side effects reported for DPR are gastrointestinal symptoms, such as nausea, heartburn, upset stomach, etc. (7) Some studies have found side effects such as irritability, hyper-excitability, psychomotor agitation, and insomnia, (7,8) These effects are probably due to DPRs catecholamine-enhancing effect, over-activating DA/NA neural systems at the expense of calming/sleep-inducing serotonergic systems, so taking magnesium and tryptophan or 5-HTP may suffice to counter these psychic effects.

Healthy individuals looking at [Deprenyl](#) for life-extension purposes are advised moderate doses. Over the long term, proper dosage appears to be a crucial factor and research is underway to pin-point optimum dosage. Very high doses are not advised for healthy people. The following rate is currently recommended for starting dosage and should be lowered after several months of treatment:

**Deprenil -age related recommended dosage:**

Age	Dosage	Age	Dosage
30-35	1mg twice a week	60-65	5 mg every day
35-40	1mg every other day	65-70	6mg every day
40-45	1mg every day	70-75	8mg every day
45-50	2mg every day	75-80	9mg every day
55-60	3mg every day	80 and over	10mg every day

## **Recovery of growth hormone secretion following cabergoline treatment of macroprolactinomas**

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### **OBJECTIVE**

Cabergoline therapy normalizes prolactin levels and reduces the size of macroprolactinomas. However there are no data indicating whether cabergoline can normalize growth hormone secretion in patients who were growth hormone deficient at the time of diagnosis of a macroprolactinoma.

### **SUBJECTS AND METHODS**

We studied nine patients with biochemical and radiological evidence of a macroprolactinoma who were also growth hormone deficient (peak growth hormone response to insulin-induced hypoglycaemia < 10 mU/l). Patients were assessed before and after cabergoline therapy to assess their growth hormone secretory status, IGF-I levels, cortisol response and change in tumour size.

### **RESULTS**

Treatment with cabergoline was associated with a significant reduction in prolactin concentration ( $74341 \pm 31939$  mU/l vs.  $265.9 \pm 86.3$ ,  $P = 0.009$ ). The mean change in peak growth hormone response to insulin-induced hypoglycaemia was significantly greater following cabergoline therapy compared with pretreatment levels ( $33.5 \pm 11.8$  mU/l vs.  $4.34 \pm 1.21$  mU/l,  $P = 0.022$ ). However IGF-I levels were not different after treatment when compared with baseline although a nonsignificant trend towards improvement was noted ( $24.2 \pm 3.97$  nmol/l vs.  $18.4 \pm 4.94$  nmol/l,  $P = 0.058$ ). The mean peak cortisol concentration was  $407.7 \pm 64.1$  nmol/l before treatment with a nonsignificant rise to  $477.4 \pm 84.8$  nmol/l,  $P = 0.813$  after treatment. These changes were associated with a significant reduction in mean maximal tumour diameter ( $21.2 \pm 2.9$  mm vs.  $29.1 \pm 2.8$  mm,  $P = 0.009$ ). There was no significant difference in either

prolactin concentration or tumour size pre- or post-treatment between those who recovered growth hormone secretion and those that did not. Six of the nine (67%) patients recovered a normal growth hormone response (> 10 mU/l) after cabergoline therapy. Those that remained growth hormone deficient after treatment were all panhypopituitary at baseline while those that recovered showed only partial anterior hypopituitarism.

## **CONCLUSION**

These data indicate that growth hormone secretion may recover following successful reduction of prolactin levels after cabergoline therapy for a mean of 22 months (range 6–28 months) in most but not all subjects with a macroprolactinoma. It is therefore advisable that individuals with a macroprolactinoma in whom growth hormone replacement therapy is being considered undergo repeat assessment of growth hormone secretion following medical treatment.

**Jintropin AQ [somatropin (rDNA origin) injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Jintropin AQ has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence and structure of the product is identical to that of pituitary-derived human growth hormone.**

**Jintropin AQ is available in 5 mg and 10 mg cartridges. Each cartridge contains 3 mL of 5 mg (approximately 15 IU) somatropin or 10 mg (approximately 30IU) somatropin.**

**Jintropin AQ has been determined to be bioequivalent to Jintropin based on the statistical evaluation of AUC and C max.**

### Advantages of Jintropin AQ

Advanced production techniques

Patented proprietary secretion technology \*\*\*12288;\*\*\*12288;

\*\*\*12288; Secretion of expressed rhGH from the E. coli cytoplasm can simplify \*\*\*12288;  
\*\*\*12288; purification and improve the rhGH biological activity.

Special protectant and buffer

### **Bioequivalence between liquid Jintropin and freeze-dried Jintropin**

\*\*\*12288;

\*\*\*12288;\*\*\*12288;Jintropin AQ shows bioequivalence with Jintropin in the powder form.

First ready-to-use rhGH in liquid formulation together with a pen injection system

\*\*\*12288; More convenient by avoiding the need for reconstitution before administration

\*\*\*12288; More accurate by combining with an advanced Jintropin Pen delivery system

Excellent patient compliance.

**Jintropin comes in vials with yellow tops now. The latest batch with green tops and those paper labels Ret talking about was 20020515 (thats mean it was produced almost 1 year ago). I didn't see green tops since last fall.**

**Used saizen, jintropin, humatrope(straight from the pharmacy) and kefei blue tops. In all honesty I havent noticed much difference.**