Endocrine, *vol. 12, no. 2, 163–172, April 2000* 0969–711X/00/12:163–172/$12.50

Effects of Growth Hormone on Body Composition and Bone Metabolism

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Physiologic effects of growth hormone (GH) extend beyond the stimulation of linear growth during childhood and adolescence. These effects include building and sustaining lean body mass, facilitating the utilization of fat mass for energy needs, and maintaining bone mineral density. These nongrowth effects of GH appear to be important throughout life. Children and adults with severe GHD demonstrate marked reductions in lean body mass, increases in percent body fat, and subnormal bone mineral density. Replacement of GH attenuates these abnormalities, though it remains unknown whether it does so completely. Children with body composition abnormalities resembling the GHD state (e.g., Prader–Willi syndrome) also appear to respond favorably to administration of GH treatment, and demonstrate concomitant improvements in strength and agility. Long-term body composition benefits of GH supplementation in these and other non-GHD individuals remain unproven.

Key Words: Growth hormone; body composition; bone density.

Introduction

Human growth hormone (GH) is produced as a single chain, 191 amino acid protein, and released in pulses regulated by the interplay of two hypothalamic regulatory peptides, GH releasing hormone (GHRH) and somatostatin (somatotropin release-inhibiting factor). Physiologic effects of GH occur through both direct and indirect (via IGF peptides) mechanisms. In general, linear growth-promoting effects of GH appear to depend upon production of IGF-1 and perhaps other IGF peptides; whether the critical source of IGF-1 is the liver (endocrine effect of circulating IGF-1), the cartilage growth plate itself (paracrine IGF-1 effect), or both, remains unresolved. Conversely, investigations of normal volunteers, or patients with diabetes, GH deficiency, and other disorders reveal that several important physiologic effects of GH not directly related to linear growth occur independent of, (e.g., enhanced lipolysis, amino acid transport in muscle and heart, and hepatic protein synthesis) or even contradictory to, IGF activity (effects on glucose metabolism).

Growth hormone has been administered to GHD children during the past 35 yr to increase growth rate and adult stature; consequently, until recently, GH therapy was discontinued after cessation of growth. However, while linear growth effects of GH are completed with epiphyseal fusion, GH secretion continues into adult life in gradually diminishing amounts. Severe GHD in children and adults is now known to be associated with abnormalities of body composition and bone metabolism which adversely affect strength, endurance, and other quality of life measures. Thus, interest in the multiple "nongrowth" effects of GH and the value of ensuring GH sufficiency in patients who have completed longitudinal growth has increased substantially during the past decade.

Present knowledge regarding effects of GH deficiency or treatment on body composition and bone density derive largely from studies utilizing dual energy X-ray absorptiometry (DXA, which provides practical and accurate measurements of body fat, lean tissue (i.e., muscle), and bone mineral density (BMD), or bone mineral content (BMC). This technique is based on the differential attenuation of two energy photons as they pass through bone and soft tissues *(1)*. Initially, the radioisotope Gadolinium was used as the photon source, since the isotope emits photons at two characteristic energy levels. Newer generation absorptiometers use a broad band X-ray as their source. The DXA body composition measurements are made possible by the fact that the human body is made up of three main compartments distinguishable by their X-ray attenuation properties: fat, bone mineral, and residual (or lean soft tissue) *(2,3)*.

The physiologic effects of GH in adipose tissue, muscle, and bone are discussed below (**Fig. 1**). For each of these sites of GH action, basic effects on cellular growth and metabolism are first described, followed by in vivo effects of GH deficiency and, finally, effects of GH treatment.

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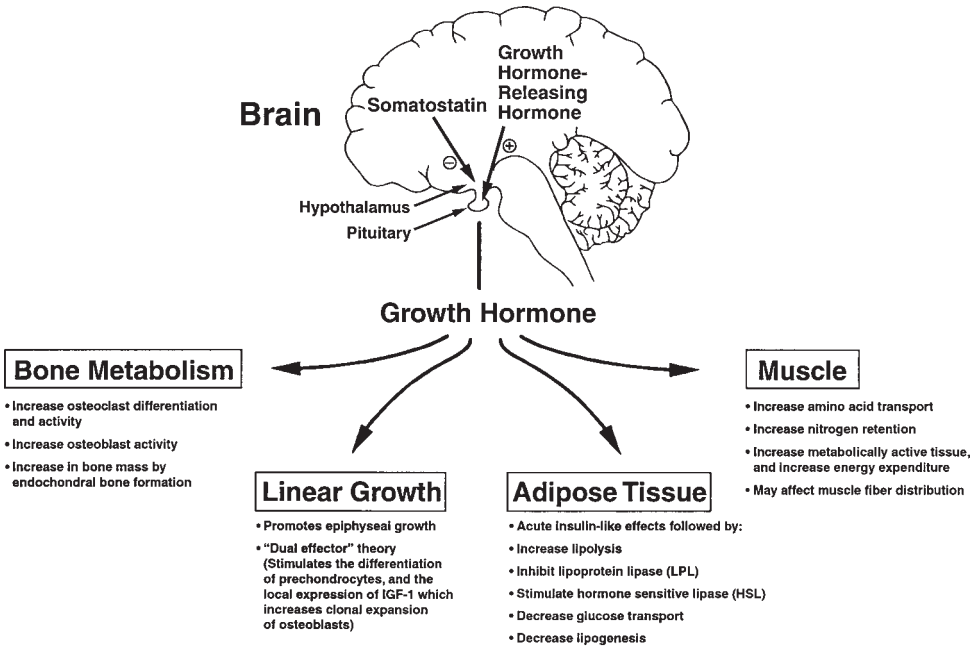

Fig. 1. Multiple sites of GH action.

Effects of GH on Adipose Tissue

The important influence of GH on body composition results from effects on both adipose and lean body tissues. GH exerts a wide variety of cellular activities mainly mediated by regulating the transcription of specific genes. However, GH also induces rapid changes in the catalytic activity of several enzymes, resulting in acute changes of carbohydrate and lipid metabolism. In adipose tissue, GH has diverse and incompletely understood effects, which influence both the development of and metabolic processes in adipocytes. GH receptors and expression of GH receptor mRNA have been demonstrated both in preadipocyte cultures and in mature adipocytes. The expression of these receptors appears to be higher in mature adipocytes compared to preadipocytes. Increased expression of GH receptors has been demonstrated in hypophysectomized rats, and in patients with Prader–Willi syndrome after treatment with exogenous GH *(4)*. While some actions of GH in adipose tissue are mediated directly through interaction with the GH receptor, other effects appear to be mediated indirectly through IGF-1.

In primary cultures of adipose precursor cells, GH is found to stimulate the proliferation of these immature cells and reduce their differentiation to mature adipocytes. GH also induces IGF-1 production in both mature adipocytes and preadipocytes *(5)*. The level of IGF-1 mRNA in white adipose tissue is normally higher than in most tissues, in a range similar to that in the liver, and IGF-1 produced in adipose tissue contributes significantly to circulating levels. While GH appears to affect adipose tissue growth and metabolism both directly and via local production of IGF-1, the exact biological effect of locally produced IGF-1 in adipose tissue is still not well understood.

The main function of adipose tissue is accumulation of lipid in the fed state, and release of energy during exercise or fasting states. Since adipose tissue has a limited ability for *de novo* synthesis of free fatty acids (FFAs), accumulation of triglycerides is dependent upon lipoprotein lipase (LPL), the enzyme primarily responsible for hydrolyzing triglycerides to free fatty acids which can be transported to adipose tissue *(6)*. GH produces a pronounced *inhibition* of adipose tissue LPL, while insulin and glucocorticoids stimulate LPL activity. GH also directly stimulates hydrolysis of triglycerides into glycerol and free fatty acids *(7)* and fat oxidation, increases free fatty acid concentrations in a dose-dependent manner *(6)*, stimulates fatty acid transport from adipose tissue to the liver, and inhibits free fatty acid re-esterification by adipocytes *(8)*.

Hormone sensitive lipase (HSL) is the rate-limiting step for release of stored triglyceride in adipocytes (lipolysis). Primary regulation of HSL is by the cAMP-mediated phosphorylation cascade, through which catecholamines (via beta-adrenergic receptors) stimulate lipolysis and other compounds, such as adenosine and prostaglandins, inhibit it. GH appears to stimulate HSL activity, stimulate beta-receptors, and inhibit adenylate cyclase via the inhibitory G_I guanine-nucleotide regulatory protein *(6)*. Thus, GH-mediated inhibition of adipocyte differentiation and triglyceride accumulation combine with stimulation of lipolysis to reduce adipose tissue mass *(9)*.

Studies of GH effects on fat metabolism in humans consistently indicate enhancement of lipolysis, with increased concentration of FFA and glycerol in the plasma within 2 h

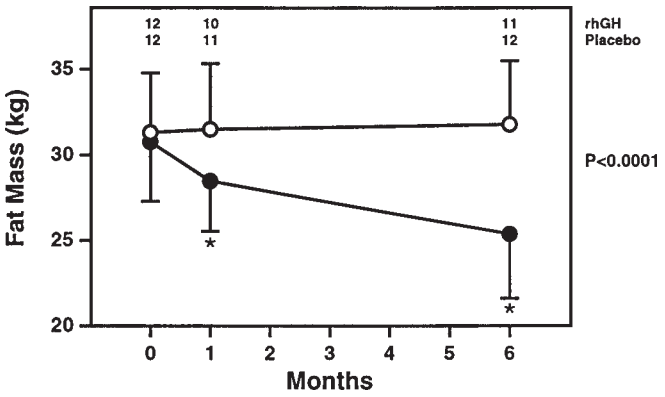

Fig. 2. Effect of GH replacement therapy (0.07 U/kg body weight) on fat mass during the administration of GH (●) or placebo (○) in adults with GHD. The number of patients studied at each time in each group appears at the top of the panel. The horizontal bars indicate the standard error for the mean values shown. Fat mass was estimated using total-body potassium. Reprinted with permission from Salomon, F., et al. (1989). *N. Engl. J. Med.* **321,** 1800. Copyright ©1989 Massachusetts Medical Society. All rights reserved.

of GH infusion. While the predominant effect remains uncertain, multiple GH effects described include enhanced catecholamine-induced lipolysis due to up-regulation of the beta-adrenergic receptor levels *(10)*, enhanced expression of hormone sensitive lipase *(11)*, and inhibition of the alpha-subunit of the inhibitory guanine-nucleotide binding protein. The latter may reduce tonic inhibition of lipolysis induced by locally produced antilipolytic compounds, such as adenosine and prostaglandin *(12)*. GH consistently decreases the activity of LPL in humans. Recent studies indicate that gene expression of LPL is unaffected, suggesting that reduced LPL activity is due to GH-induced post-translator alterations in LPL processing. In summary, both in vitro and in vivo studies indicate that GH-enhanced lipolytic activity in adipose tissue, combined with reduction of triglyceride accumulation via inhibition of the LPL activity are important mechanisms by which GH reduces adipose tissue.

Acute insulin-like effects of GH occur in adipose tissue not previously exposed to GH (e.g., from hypophysectomized rats), in contrast to well-known insulin counter-regulatory effects of chronic GH exposure. Preincubation of adipose tissue from normal rats for 2–4 h in the absence of GH causes increased glucose oxidation and antilipolysis when GH is subsequently added. During continued incubation for longer periods (6–10 h), typical insulin-antagonistic effects of GH are seen. In adipocytes, the intracellular phosphorylation cascade affected by binding of GH to its receptor involves activation of insulin sensitive enzymes, such as IRS-1 and IRS-2, which are bridging molecules with multiple docking sites. Activation of these systems results in short-term activation of a common signaling pathway to promote glucose uptake and inhibition of lipolysis *(13)*. While these short-term effects are intriguing, the biological importance of these insulin-like effects is doubtful.

Normal GH secretion and action during childhood and adolescence promotes growth of lean tissue and limits the formation of fat in the abdominal visceral depot *(14)*. In the adult, visceral fat is associated with hyperlipidemia, insulin resistance, and type 2 diabetes mellitus. The state of GH insufficiency observed in children or adults with severe GHD and some other similarly affected individuals (e.g., Prader–Willi syndrome) is distinguished by a marked decrease in lean body mass accompanied by increased adipose tissue. In the first placebo-controlled study examining the effectiveness of GH treatment on correcting this abnormal body composition, a reduction of fat mass from 30.5 ± 3.3 kg to 25.5 ± 3.6 kg ($p < 0.0001$) occurred during 6 mo of GH therapy in adults with GHD *(15)* (**Fig. 2**). Subsequent controlled studies have revealed consistent reductions in total body fat mass *(16)* (mean reductions of fat mass approx 4–7 kg in GHD adults) *(17)* and particular reductions in abdominal visceral fat (assessed by MRI of CT) in patients with GHD following GH replacement (**Fig. 3**). This reduction occurs in both childhood-onset as well as adult-onset GHD *(18)*. These observations have contributed to a consensus that GH has important effects on fat metabolism in both childhood and adulthood, and that GH replacement in appropriate individuals will lessen health risks associated with increased adiposity.

Effects of GH on Muscle

For biochemical endocrinologists interested in the hormonal control of growth and differentiation, skeletal muscle is one of the more difficult tissues to study. In many cases, the force required to disrupt skeletal muscle exceeds that required to fracture nuclei, so it is difficult to prepare muscle nuclei in ample yields. One approach widely used to minimize such problems is the study of cultured muscle cells, using primary myoblasts (usually from embryonic or neonatal animals) and myogenic cell lines. While these preparations are thought to retain normal physiologic responses, results may not accurately predict in vivo responses. For instance, while stimulation of growth of cultured muscle cells has been demonstrated with IGF-1, GH is generally inactive in this setting *(15)*. Whole-animal preparation studies show that a number of anabolic processes associated with growth are stimulated following GH administration to hypophysectomized animals: muscle weight, protein and RNA content, and the activities of RNA polymerases, ribosomes, and related enzymes are all elevated *(19)*. However, studies in whole animals are, thus far, incapable of distinguishing direct from indirect effects of GH and the IGF-1 system.

Growth hormone exerts a marked short-term effect on amino acid transport and uptake by muscle cells in vitro, as

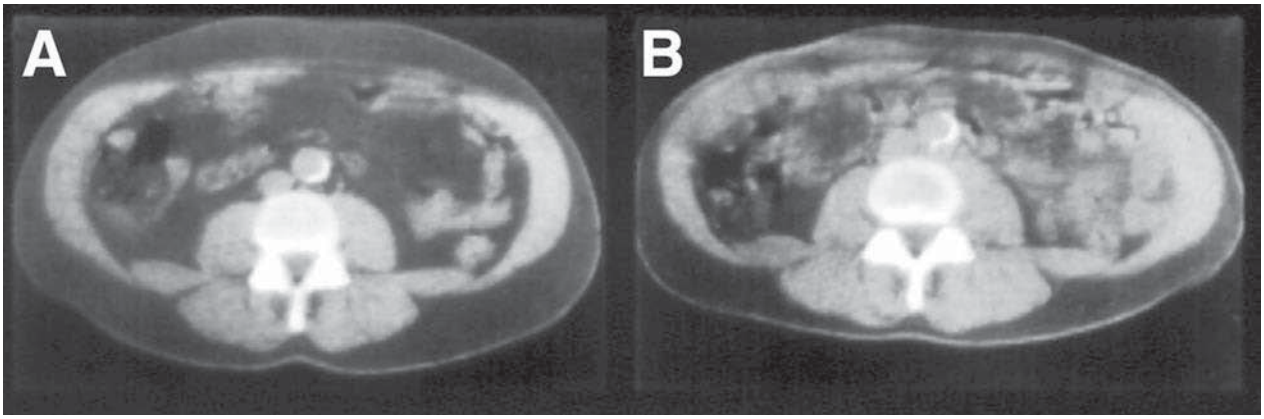

Fig. 3. Computed tomography scan at the L3/L4 level before (a) and after (b) 26 weeks of GH therapy. Both subcutaneous and visceral adipose tissue decrease with therapy. Reprinted with permission from Bengssson, B. A. et al. (1993). *J. Clin. Endocrinol. Metab.* **76,** 315.

does insulin. This effect has been extensively studied using transport of a nonmetabolizable amino acid, amino isobutyl acid *(20)*. GH increases net muscle protein synthesis primarily by enhancing amino acid transport, and hence the availability of amino acids for protein synthesis. GH also promotes retention of phosphate, and thereby contributes to maintenance of the cellular ATP homeostasis critical to muscle function. Relative concentrations of inorganic phosphate, ATP, phosphocreatine, and intracellular pH can be measured with noninvasive phosphorus nuclear magnetic resonance (^{31}P-MRS) and utilized to assess muscle bioenergetics and exercise tolerance. The ^{31}P-MRS measured ratio of inorganic phosphate (Pi) to phosphocreatine (PCr) reflects the cellular bioenergetic state and energy potential, and is positively correlated with the percentage of type 2 muscle fibers. Utilizing this technique, adults with GHD have been found to have low quadriceps volume and isometric strength and low isokinetic muscle strength compared to age and height matched controls; each was increased following GH therapy *(44)*. Interestingly, there was no difference in muscle energy store (as measured by ^{31}P-MRS) and muscle energy store did not change during GH therapy.

Growth hormone may also influence the differential development of muscle fiber distribution *(21)*. It is known that skeletal muscle fibers can undergo adaptational changes, including fiber-type conversion, in response to a variety of stimuli including exercise, chronic stimulation, and denervation. Skeletal muscle properties are also affected by thyroid hormones; hypothyroidism results in a pattern of fast to slow fiber conversion with the reverse occurring in hyperthyroidism *(22)*. In hypophysectomized rats, the administration of GH increased and restored the proportion of slow twitch, fatigue resistant, type 1 muscle fibers *(23)*, suggesting that contractile properties of the muscle in GHD patients might be disrupted by an excessive proportion of fast twitch, type 2 muscle fibers. While some studies in humans support the existence of this effect *(24)*, two studies of GHD adults do not *(25,26)*. While relatively little is known about direct effects of GH upon fiber distribution, the tyrosine kinase of the IGF-1 receptor in rat skeletal muscle is two- to threefold more active in response to IGF-1 in red muscle than in white muscle *(27)*. This may provide one mechanism by which alterations in GH or IGF-1 levels selectively alter protein synthesis in the two fiber types *(27)*. Shortened half-life relaxation time and rightward shift of force-frequency relation of quadriceps muscle have been reported in patients with GHD, indicating a greater proportion of fast, fatigable type 2 fibers within the muscle in patients with GHD *(32)*.

Similar to its effect in adipose tissue, GH stimulates amino acid uptake and incorporation into muscle tissue in vivo *(28)*. Short-term administration of GH to growing animals improves nutrient "partitioning" and utilization, by increasing nitrogen retention, improving feed efficiency, and altering carcass composition (reduced fat and increased protein/muscle content) *(29)*. Prolonged treatment with GH increases muscle weight and nitrogen retention, mediated by both indirect effects of hepatic and locally produced IGF-1 and direct effects of GH on utilization of amino acids for either gluconeogenesis or oxidation *(30)*. While it is clear that the GH-IGF axis plays a major role in controlling the growth and differentiation of muscle, it is less clear that GH itself acts directly upon skeletal muscle to stimulate its growth (**Fig. 4**). The presence of GH receptors in muscle is well established, but many investigators have been unable to demonstrate specific binding of GH to muscle or myoblasts in culture. The effects of IGF-1 on muscle growth are somewhat clearer, with IGF-1 stimulating both proliferation and differentiation of myoblasts.

Growth hormone deficiency leads to diminished muscle mass and muscle strength *(31)*. Following cessation of GH therapy, young adults with GHD develop reduced maximal voluntary isometric muscle strength, muscle size, and

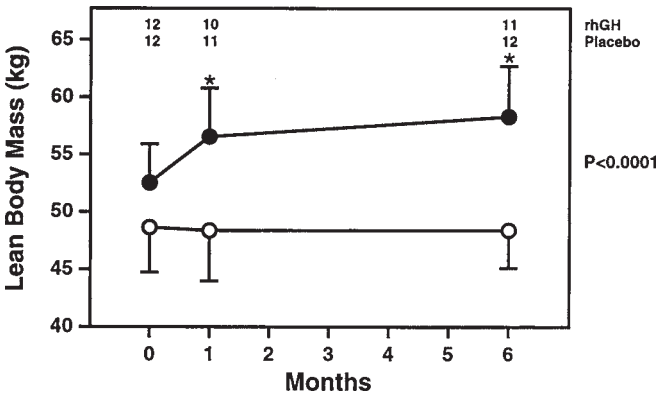

Fig. 4. Effect of GH-replacement therapy (0.07 U/kg body weight) on lean body mass during the administration of GH (●) or placebo (○) in adults with GHD. The number of patients studied at each time in each group appears at the top of the panel. The horizontal bars indicate the standard error for the mean values shown. Lean body mass was estimated using total-body potassium. Reprinted with permission from Salomon, F., et al. (1989). *N. Engl. J. Med.* **321,** 1800. Copyright ©1989 Massachusetts Medical Society. All rights reserved.

muscle fiber area *(32)*. A recent small study ($n = 6$) investigating muscle strength in children with GHD *(33)* revealed that quadriceps strength per thigh muscle mass, estimated by anthropometry, appeared to be normal. However, when both strength and mass of tested muscles were measured *(34)*, patients with GHD demonstrated reduced muscle mass and reduced isometric muscle strength (assessed by dynamomometry, which electronically measures the torque exerted across a joint axis). Some studies have confirmed this reduced quadriceps isometric force in GHD patients compared with that of matched healthy controls *(35,36),* while others have not *(38)*.

Given the multiple effects of GH on fat and muscle tissue described above, important changes in body composition would be expected to occur as a result of GH deficiency. Indeed, both adults and children with untreated GHD exhibit abnormal body composition characterized by increased body fat mass, and decreased lean body mass relative to healthy subjects *(38)*. The diminished lean body mass is a critical distinguishing feature from nutritional obesity, in which both fat mass and lean body mass are increased. Fat mass in GHD individuals is concentrated in the intra-abdominal region (visceral fat), and patients exhibit an increased waist to hip ratio *(37)*. GH replacement therapy leads to consistent and substantial reductions in percent body fat in adults and children with GHD *(38)*. This catabolic effect of GH on adipose tissue is accompanied by an anabolic effect on protein metabolism in children and adults *(38–40)*, with or without *(41,42)* GHD. As a result, replacement of GH consistently increases muscle mass in GHD individuals. Cuneo *(34)* demonstrated an increase in thigh volume (+11.2 cm^2) and strength of hip flexors (+1.25 SDS) in GHD patients treated with GH after 6 mo. Several subsequent studies have confirmed these observations *(43)*. However, while effects of GH on muscle mass are relatively easily demonstrated with DEXA or isotope studies, assessing the effect of GH upon muscle strength is more challenging. Some studies using dynamometry have shown GH-treatment-associated gains in muscle strength which parallel increases in muscle volume, while other show that intrinsic muscle strength is not significantly different in patients with GHD, and did not change with GH therapy *(44)*.

Effect of GH on Bone Mineral Density

Continuous bone renewal occurs within microscopic remodeling units in which the resorption of old bone by osteoclasts is followed by the deposition and mineralization of new bone by osteoblasts. These processes are closely coupled and regulated by hormonal systems including: parathyroid, vitamin D, gonadal steroids, thyroxine, cortisol, and GH *(45,46)*. Receptors for both GH and IGF-1 are expressed in various sites in bone *(47)*. With regard to effects on the epiphyseal growth plate, a dual effector theory proposes that GH acts directly to stimulate differentiation of prechondrocytes into early chondrocytes that in turn stimulates production of IGF-1. IGF-1 then stimulates clonal expansion of and maturation of chondrocytes *(48)*. GH effects, however, are not limited to the growth plate, but occur throughout bone tissue. In vitro, cultured human osteoblast-like cells express functional GH receptors and proliferate in response to GH *(49)*, indicating that GH exerts direct effects on bone formation. GH has also been shown to stimulate osteoclast differentiation directly *(50)*. As is the case with longitudinal bone growth, the mechanism of action of GH in other bone sites may be direct and/or indirect, through effects of IGF-1. The "dual effector theory" *(51,52)*, would predict that GH stimulates mesenchymal precursor cell differentiation and then locally produced IGF-1 promotes the clonal expansion of more highly differentiated cells.

GH plays a key role not only in longitudinal bone growth, but in the accretion of bone mass during childhood and adolescence. Studies evaluating BMD using different techniques consistently demonstrate reduced bone mass at various skeletal sites in patients with childhood-onset *(53,54)* as well as adult-onset GHD *(55,56)*. Delayed and/or incomplete replacement of GH is a likely contributing factor to persistent reduced bone mineral content (BMC) and bone mineral density (BMD) observed in adults with childhood-onset GHD. Bone histology in patients with childhood onset GHD is characterized by high trabecular bone volume, increased bone erosion, increased osteoid thickness, and increased mineralization lag time, indicating a delayed bone mineralization process. However, the role of GH in achieving and maintaining peak bone mass after epiphyseal growth plates closure and completion of

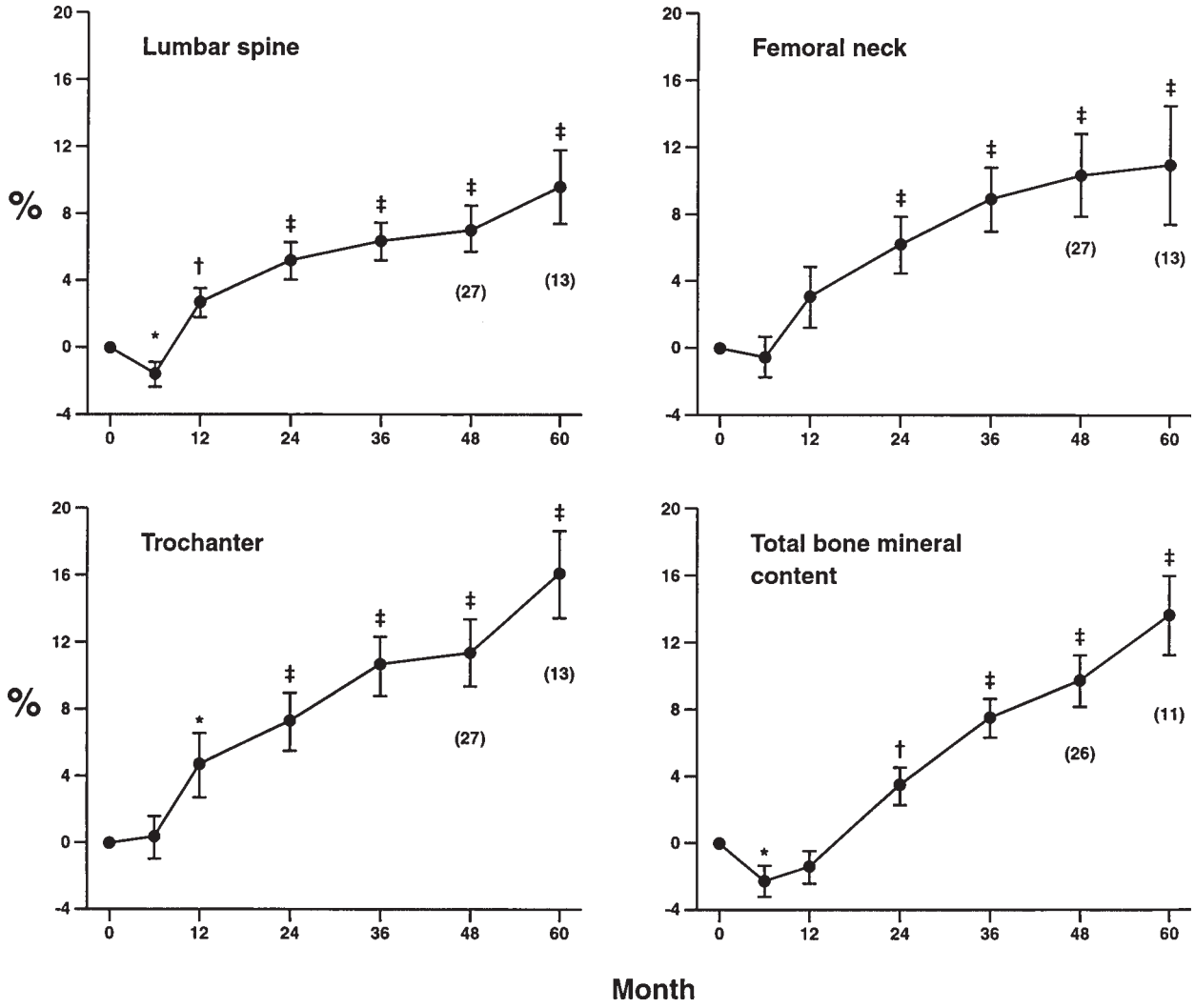

Fig. 5. Mean (±SE) changes in BMD/bone mineral content from baseline values in men with GHD receiving GH for 5 yr. Data are shown for BMD of the spine, femoral neck, and trochanter and for total bone mineral content (measured by dual-energy x-ray absorptiometry). $n = 38$ unless stated otherwise. $^{*}p < 0.052$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$ (for comparison of changes from baseline). Reprinted with permission from JC Ter Maaten, et al. (1999). *J. Clin. Endocrinol. Metab.* **84,** 2373.

linear growth, is still being clarified *(57)*. GH stimulates the proliferation and (in some studies) the differentiation of osteoblasts *(58)*, and increased osteoblastic activity has been demonstrated in children with GHD after therapy with exogenous GH *(59)* (**Fig. 5**). Typical biochemical markers of osteoblastic activity (e.g., osteocalcin), bone turnover (alkaline phosphatase) and collagen synthesis (type 1 procollagen) are increased in children during treatment with GH.

While a low bone mass in adults with childhood-onset GHD results from deficient bone accretion during childhood and early adulthood, patients with adult-onset GHD appear to have decreased bone mass secondary to an imbalance in bone remodeling *(60,61)*. In adults with GHD, markers for both bone resorption and bone formation also increase in response to GH treatment, suggesting that overall, bone remodeling is increased and that the action of GH on bone metabolism is dichotomous: it stimulates both bone resorption and bone formation (**Fig. 6**). Clinical studies utilizing 6-mo trials of GH therapy demonstrate unchanged, or even decreased BMC, while more prolonged trials of GH therapy demonstrated increased BMC after 12–30 mo. Thus, GH appears to have a "biphasic" effect on bone metabolism — an initial phase of increased bone resorption (with concomitant bone loss and increased urinary calcium excretion) followed by a phase of increased bone formation.

In contrast to bone resorption-suppressive medications used in the treatment of osteoporosis, an increase in BMD does not occur during short-term GH treatment and, in fact, declines in BMD may be observed during the first remodeling cycles in response to the increased remodeling fre-

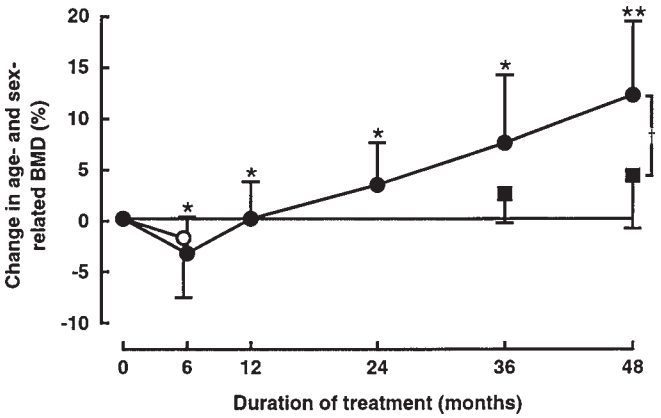

Fig. 6. Change in age- and sex-related bone mineral density (BMD) at the lumbar spine, measured by dual-photon absorptiometry, during 4 yr of treatment with GH. ● GH group; ○ placebo group; filled squares = healthy controls. Results are presented as mean ± SD. *p < 00.5; **p < 0.01 vs baseline (Wilcoxon test); †p < 0.05 vs healthy controls (Student's t-test). Reprinted with permission from Kann, P., et al. (1998). *Clin. Endocrinol.* **48,** 5601.

quency. On the other hand, prolonged GH treatment of adult-onset or childhood-onset GHD-patients results in increased BMC and BMD, primarily in weight-bearing skeletal locations. Patients with the lowest BMD z-scores prior to treatment appear to derive the greatest benefit from GH replacement. Since GH therapy is initially followed by a period of increased bone resorption lasting approx 6 mo, duration of GH therapy is a critical factor in interpreting clinical studies; 12–18 mo may be required to cause a net increase in BMD. Studies examining more than 12 mo of GH therapy have shown increases in BMD of 4–10% above baseline *(54,56,61)*.

In summary, adults and children with GHD have reduced bone mass. Growth hormone is an osteo-anabolic hormone when given to GHD-patients. Treatment with GH appears to have a biphasic effect on BMD; after an initial predominance of bone resorption, stimulation of bone formation leads to a net gain in bone mass after 12–24 mo. Whether these changes in bone metabolism will result in less osteopenia and reduced fracture rate in adults with GHD requires long-term study.

Effect of GH on Energy Expenditure

The factors contributing to the variability in resting metabolic rate (RMR) among individuals are complex and not fully understood. A close positive correlation is found between RMR and fat-free mass (FFM; or lean body mass [LBM]), but gender, age, and familial traits are also important determinants *(62)*. Moreover, energy expenditure is influenced by thyroid hormone levels and sympathetic tone *(63)*, and according to emerging evidence, by GH. Resting energy expenditure (REE) can be assessed through methodologies such as indirect calorimetry, which can provide information about calories consumed as well as substrate utilization. Preference for fat utilization as an energy source is reflected in a reduction of the respiratory quotient (RQ = R/Q = CO_2 produced/O_2 consumed). The RQ normally ranges from 0.7 (strong predominance of fatty acid oxidation) to 1.0 (exclusive oxidation of carbohydrate). In the state of GH insufficiency, energy is preferentially derived from protein, lipogenesis and conservation of adipose tissue is promoted, and LBM declines

Since states of GH deficiency and excess are associated with reduced and increased REE respectively *(64,65)*, it was expected that GH therapy would increase energy utilization in GHD-patients. One study of adults with GHD reported a 15% increase in resting metabolic rate and 13% increase in total energy expenditure after GH replacement *(66)*. While conflicting data can be seen depending upon whether REE is expressed absolutely or per lean body mass (LBM), GH replacement in GHD typically results in rapid increases in REE *(64,66)*. Data on the effects of GH on REE in children with GHD is limited (*see* below). In normal *(67)*, obese *(68)*, and in GH-deficient individuals *(69)*, administration of GH leads to preferential oxidation of fat for energy *(70,71)*, a corresponding decrease in RQ, a decrease in fat mass is observed clinically, and increases in previously low RMRs in a dose-dependent manner *(72)*.

Whole body REE is largely determined by LBM *(73)*, and it is attractive to assume that the calorigenic actions of GH are secondary to increases in LBM. Studies in patients with acromegaly and GHD, as well as administration of GH in normal and obese subjects, suggest that GH increases RMR independently of changes in body composition. Restoration of LBM accounts for much of the absolute increase in REE, but when changes are corrected for changes in LBM, significant increases in patients with GHD, normal subjects *(74)*, and obese women *(75)* remain, indicating that direct increases in cellular metabolism are responsible for some of the increased REE *(38)*. Studies have also demonstrated that the calorigenic effect of GH can be demonstrated prior to changes in LBM, and that the calorigenic effect is not mediated by changes in sympathetic activity or leptin secretion *(76)*. In addition, augmentation of REE has been reported after only 5 h of GH infusion in GH-deficient adults *(77)*. While GH is a physiological regulator of thyroid metabolism and of peripheral conversion of thyroxine (T4) to triiodothyronine (T3) in particular, this acute calorigenic effect of GH does not appear to be solely mediated through increased conversion of T4 to T3, and the exact physiological mechanism underlying this immediate effect remains unclear *(69)*. GH therapy in GHD does, however, increase circulating T3 levels in both patients receiving T4 and in euthyroid patients, a change which may contribute to a sustained calorigenic effect of GH.

Table 1
Strength and Agility Testing

	Control group (n = 19) baseline	GH therapy (n = 35) baseline	Control group (n = 19) 12 mo	GH therapy (n = 35) 12 mo
Agility run (s)	10.3 ± 1.8	11.6 ± 0.6	10.6 ± 0.4	9.3 ± 0.3[a]
Broad-jump (in)	17.5 ± 3.7	19.4 ± 2.3	16.5 ± 3.3	22.7 ± 3.0[a]
Sit-ups (in 20 s)	9.1 ± 3.4	9.7 ± 3.1	9.3 ± 3.1	12.7 ± 3.0[a]
Weight lifting (#repetitions)	13.2 ± 2.0	13.1 ± 2.2	12.1 ± 1.9	15.6 ± 1.4[a]
Inspiratory muscle strength (cm/H_2O)	44.8 ± 13.2	45.8 ± 23.4	40.4 ± 13.9	55.7 ± 13.7[a]
Expiratory muscle strength (cm/H_2O)	58.8 ± 22.1	54.6 ± 23.8	46.0 ± 13.3	69.3 ± 20.8[a]

[a] $p < 0.01$, paired t-test pre- and post-GH therapy, compared to either baseline values of treated patients or 12-mo values of nontreated patients.

Clinical Correlation: Effects of GH on Body Composition and Energy Expenditure in Prader–Willi Syndrome.

Prader–Willi syndrome (PWS) is characterized by obesity, hypotonia, short stature, hypogonadism, and behavioral abnormalities, resulting from a functional deletion of the paternal allele of chromosome 15 *(78)*. Obesity results from hyperphagia, and is amplified by decreased energy expenditure and reduced physical activity. The body composition of PWS patients, characterized by reduced lean body mass and increased fat mass, resembles GHD-individuals *(79)*, more than those with obesity due to overnutrition. It has been proposed that diminished GH effect contributes to abnormal body composition, energy expenditure, linear growth, muscle strength, pulmonary function, and carbohydrate and lipid metabolism in PWS.

Diminished GH secretion is a frequent finding in children with PWS *(80,81)*. However, GH secretion is often suppressed in non-GHD-obese individuals, and is partly reversed by weight loss *(82,83)*. The reason for this effect unclear, although negative feedback by IGF-1 levels sustained by the overnourished state has been proposed *(84)*. In addition, most individuals with PWS demonstrate low IGF-1, adding further support of GHD. Consequently, while PWS children frequently display low secretion of GH following provocation, identification of physical manifestations of GH deficiency and correction of these with GH treatment are also needed to support a causative role of GH insufficiency in the pathogenesis of the PWS phenotype. The combination of abnormally diminished LBM and increased fat mass characteristic of PWS suggests that: (1) diminished GH secretion is a primary etiologic factor, and not secondary to the obese state itself; and (2) associated hypotonia and limited exercise tolerance might be improved by treatment with GH.

Recent controlled studies *(70,85–87)* demonstrate that GH treatment of children with PWS can markedly change body composition by decreasing total and truncal fat, increasing LBM, and increasing bone mineral density (**Fig. 7**). Linear growth and blood lipid profiles are also improved. Perhaps most importantly, one study showed improvements in muscle strength, physical agility, and respiratory muscle function in children with PWS treated with GH for 12 mo *(70)* (**Table 1**). These beneficial effects were sustained during a subsequent 12-mo treatment period, but only LBM and BMD showed further improvements during this time *(88)*. Adverse changes in carbohydrate metabolism and scoliosis progression were not observed. Confirmation of these observations would support GH therapy as an intervention of significant value in reducing some disabilities associated with this syndrome.

Conclusions

Growth hormone has many important physiologic roles in addition to promotion of linear growth, and these additional effects of GH appear to have importance throughout life. Deficiency of GH secretion and/or action leads to characteristic abnormalities in body composition and reduced physical strength and performance, bone mineral density, and energy expenditure. In adults and children with GHD, GH therapy improves body composition by promoting growth of lean body mass (muscle mass), reducing fat mass, and increasing fat oxidation and energy expenditure. Beneficial effects of GH on bone mineral density in GHD patients occur following a short period of increased bone resorption. Children with PWS, in whom body composition alterations resemble the GH-deficient state, respond to GH therapy with improvements in body composition and BMD, increased fat oxidation and energy expenditure,

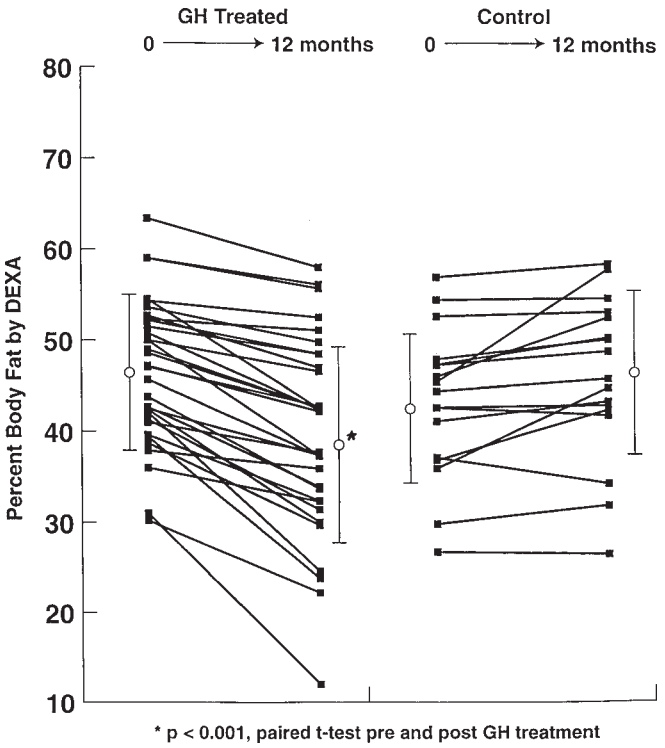

Fig. 7. Percent body fat in PWS.

and improved physical strength and agility which are sustained over a 24-mo treatment period.

Acknowledgements

This work is supported, in part, by NIH M01 RR03186-13S1, to Dr. Carrel.

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