

Hormones and Supplements: Do They Work?

Use of Growth Hormone for Prevention or Treatment of Effects of Aging

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Decreases in growth hormone (GH) and insulin-like growth factor-I, estrogen deficiency in women, diminished testosterone in men, and loss of lean body mass, increased fat, and other changes consistent with hormone deficiencies occur during aging. Treatment of nonelderly GH-deficient adults with recombinant human GH (rhGH) improves body composition, muscle strength, physical function, and bone density, and reduces blood cholesterol and cardiovascular disease risk, but is often accompanied by carpal tunnel syndrome, peripheral edema, joint pain and swelling, gynecomastia, glucose intolerance, and possibly increased cancer risk. Reports that rhGH augments lean body mass and reduces body fat in aged individuals increased use of rhGH to delay aging effects. However, clinically significant functional benefits, prolongation of youth, and life extension have not been demonstrated. Moreover, marketing of rhGH and other hormone supplements largely ignores adverse effects. Until more research has better defined the risk/benefit relationships, treatment of elderly individuals with rhGH should be confined to controlled research studies.

HORMONAL changes during human aging include decreases in growth hormone (GH) secretion and in levels of circulating insulin-like growth factor-I (IGF-I) (1–6), in addition to menopausal estrogen deficiency in women (7–9) and diminished levels of total and bioavailable testosterone (T) in men (10–13). Concomitant with these hormonal changes are decrements in skeletal muscle mass and strength (sarcopenia) (14,15) and bone mass (osteopenia) (16), as well as increases in total and intraabdominal fat (17,18). These undesirable changes in body composition are thought to be precursors of major health problems for the older population, including musculoskeletal frailty and reduced physical function (19), bone fractures (20), insulin resistance, and dyslipidemias, with consequent increased risks of type II diabetes and cardiovascular disease (21–24). The extent to which the hormonal changes listed above contribute to the age-related alterations in body composition and function is unclear. Some observational studies have shown associations in aging humans between endogenous IGF-I or T levels and lean body mass (LBM), muscle strength, bone density, and/or body fat (15,25–28) and some have not (6), but very few randomized controlled trials of recombinant human GH (rhGH) in elderly people have been conducted, and results from such studies are equivocal with regard to clinical benefits.

In contrast, there are numerous observations that nonelderly GH-deficient adults treated with rhGH respond with improvements in body composition, muscle strength, physical function, bone density, and quality of life (29–38).

The publication by Rudman and colleagues in 1990 (39) of the first study in elderly (over age 60) men without overt pituitary disease, reporting that rhGH treatment for 6 months increased LBM and reduced percent body fat, led to considerable interest in both the scientific and lay communities as to whether rhGH treatment might help prevent or reverse important physical and functional concomitants of aging. This interest has, in turn, led to extensive off-label prescription of rhGH for otherwise healthy middle-aged and older persons to prevent or reverse effects of the “somatopause” (40,41). In most publications aimed at laypersons by practitioners of this brand of “anti-aging medicine,” little emphasis is given to actual and potential adverse effects consequent to rhGH administration (42). Nonetheless, it is clear from a report describing continued observation of the Rudman study patients (43) and the observations of others on the effects of rhGH in older adults (43–46) that rhGH treatment commonly produces a variety of adverse effects that have the potential to progress to serious morbidity. These effects include carpal tunnel syndrome, fluid retention with peripheral edema, arthralgias and swelling of joints, gynecomastia, and glucose intolerance. In addition, GH excess in acromegalic patients has been implicated in causation of structural heart disease and cardiomyopathy (47–49) and increased mortality from a variety of causes (50,51). Finally, as reviewed by Holly and colleagues (52), the question of whether rhGH treatment might accelerate neoplasia has been raised by studies in which high normal circulating levels of IGF-I

were associated with significantly increased risks of breast (53), prostate (54,55), and colon (56,57) cancers.

TRIALS OF rhGH IN ELDERLY PEOPLE

The authors recently reported results of a double-masked, placebo-controlled, 26-week study (58) measuring effects of rhGH, with and without sex steroid replacement, on body composition, muscle strength, and cardiovascular fitness in 131 healthy men and women aged older than 65 years. Lean body mass in women increased significantly after administration of rhGH, with or without estrogen/progestin. In men, LBM also increased after administration of rhGH, T, and rhGH + T, in which two hormones showed an additive effect. In women, total fat mass decreased to a similar extent after treatment with rhGH or rhGH+ sex steroids but not with sex steroids alone. In men, fat mass also decreased after administration of rhGH, T, and rhGH + T, but there was a greater decrease after rhGH + T. Total body strength did not change significantly in women. In men, there was a barely significant increase in strength, as measured by the ability to lift a maximum weight one time, in the rhGH + T group. In women, there was no significant increase in maximal oxygen capacity during exercise (VO_2 max/kg body wt, a standard measure of fitness), whereas in men, VO_2 max increased modestly, and significantly only with combined rhGH + T treatment. Changes in LBM were positively related to changes in total body strength and appeared to explain the increases observed in VO_2 max. The findings that rhGH administration significantly increased LBM and decreased total fat mass are consistent with other observations in "somatopausal" elderly individuals (3,39,59,60). The finding in the authors' study of greater GH responsiveness in body composition outcomes in aged men versus aged women is similar to prior reports in GH-deficient younger adults (61,62).

ADVERSE EFFECTS OF rhGH

In the authors' study, systematic recording of adverse effects revealed significant incidences of edema and arthralgias in rhGH-treated women, and of carpal tunnel symptoms and arthralgias in rhGH-treated men. Mean serum IGF-I level was positively correlated with total number of GH-related adverse effects. These findings are consistent with previously published investigations of rhGH effects in older adults (43–46,63–65), which reported headaches, joint swelling, joint pain, and bloating. An analysis of adverse effects reported in 12 European placebo-controlled trials of rhGH replacement in middle-aged GH-deficient adults (adult GHD), at doses ranging from 4–15 μ g/kg/day, found fluid retention in 37%, arthralgias in 19%, and muscle pains in 16% in the first 6 months of treatment (66). In the latter studies, symptoms tended to disappear over several weeks without any action or were resolved soon after dose reduction. Arthralgias that occur in adult GHD patients during rhGH treatment tend to involve both small and large joints, which rarely exhibit effusion or inflammation. It is unclear whether, if rhGH therapy were continued for years rather than months, these "nuisance" symptoms might evolve into accelerated osteoarthritis or clinically significant carpal tunnel syndrome, such as occur in many acromegalic

patients (67). In the authors' study there was no evidence that coadministration of T or estrogen/progestin either increased or decreased incidence of GH-related soft tissue adverse effects. In the latter investigation, approximately 85% of study subjects with GH-related adverse effects experienced relief after a 25% rhGH dose reduction.

Hypertension is an established clinical concomitant of acromegaly and appears to occur in a susceptible minority of acromegalics (68). The salt and water retention and increased tissue hydration occurring with rhGH treatment (69) are associated with increases in plasma renin activity, but not in elevation of plasma aldosterone concentration (70), and are prevented by blockade of the renin/angiotensin system (71). In some other studies of rhGH treatment of adults, blood pressure did not rise significantly after short-term exposure (58,72) nor after up to 3 years of treatment (73). A possible explanation for the absence of a rise in blood pressure relates to the observation that GH acts directly on vascular endothelium to allow salt and water transudation into the extracellular fluid space, perhaps via activation of nitric oxide synthase (74). The latter would be expected to reduce intravascular volume, thus activating the renin/angiotensin system, leading to edema and compensatory sodium retention without elevation of blood pressure.

Glucose intolerance and diabetes are well-documented complications of acromegaly (75). GH is a counter-regulatory hormone, which causes hyperinsulinemia and impairs the ability of insulin to suppress hepatic glucose production and to stimulate glucose uptake and oxidation (69,76). In the authors' study, groups receiving rhGH exhibited significant increases in mean levels of serum glucose at fasting and 120-minute time points on a standard glucose tolerance test. In women taking rhGH, the rate of new-onset glucose intolerance was not significantly increased and diabetes did not occur, whereas in the corresponding groups of men, glucose intolerance was frequent and several men developed diabetes, all but one of whom were receiving rhGH. These results were consistent with prior observations of glucose intolerance in rhGH-treated older men (43). Also, as reported previously (77), men were more often affected than women. In nonelderly adult GHD patients, short-term (4 months) rhGH replacement therapy led to a reduction in insulin sensitivity, despite favorable changes in body composition (78)—results similar to those we observed. However, in a study of adult GHD patients who had received 4 or more years of rhGH therapy (79), beneficial effects on body composition persisted, and fasting plasma glucose levels and plasma glucose area under the curve during glucose tolerance tests were similar to baseline values. The latter authors concluded that concerns regarding glucose intolerance in patients receiving long-term rhGH therapy were not substantiated. Thus, there may be a biphasic response to rhGH treatment in adults, with an initial period in which the counter-regulatory effects of GH predominate, and a later stage in which the continued beneficial effects of rhGH on body composition improve insulin sensitivity, leading to an overall null, or even a beneficial, effect on glucose and insulin homeostasis. However, to date, we are not aware of any published studies assessing whether

an analogous biphasic sequence of events occurs in rhGH-treated older adults.

Another major concern with regard to hormone replacement in elderly individuals is the potential for causing or accelerating cancer. Various prior reports have linked acromegaly to an increased incidence of neoplasia (80), in particular to colon cancer and polyposis (81), but the relevance of this association to rhGH treatment of adults with the typical doses employed is unknown. Although some early evidence linked GH treatment to leukemia in children, subsequent investigations have mitigated against a causal relationship (82,83). Moreover, observations of GH-deficient children (33,83) and, more recently, adults (33,46) treated with rhGH have not revealed any increase in the incidence of neoplasia.

Of note, however, are several epidemiologic studies in which higher endogenous levels of circulating IGF-I preceded increased incidence rates of prostate (54,55), breast (53), and colon (56,57) cancers. The above data remain associative and equivocal, with no clear evidence of a causal link, although basic studies have provided plausible mechanisms by which IGF-I could accelerate the growth of malignant cells (84,85). To date, no prospective, placebo-controlled trials large enough to clearly define the risk of neoplasia have been completed for rhGH replacement in elderly people. Thus, this risk remains a legitimate concern, but one that is largely theoretical and unproved. The authors' trial was too small and of insufficient duration to elucidate the cancer question. Also of theoretical concern is the potential for stimulation by rhGH, of benign prostatic hyperplasia (BPH) (86). In our study, use of a structured standardized questionnaire (87) revealed no evidence of worsening of BPH symptoms in any of the active hormone groups, and mean serum prostate-specific antigen levels decreased slightly, but significantly, in the GH-treated men and were unchanged in the other groups.

Several studies have reported that rhGH treatment increased the frequencies of headaches in adult GHD patients and of benign intracranial hypertension with papilledema in children (88,89). In the authors' study, there was not a significant increase in headache symptoms in the rhGH-treated participants, nor were changes detected in the optic fundi during monthly ophthalmoscopic examinations.

Gynecomastia due to conversion of T to estrogens is a known complication of T treatment (90), but has also been reported in rhGH-treated men (43). In our study, approximately 10% of men receiving rhGH or rhGH + T, but not T alone, demonstrated mild gynecomastia.

A final concern with regard to rhGH therapy in humans is the theoretical, but intriguing, possibility that it may actually accelerate, rather than retard, the aging process (91). Observations of mice transgenic for overexpression of GH have shown a shortened life span and a number of physiologic and anatomic changes suggestive of accelerated aging (92,93). Consistent with the latter observation, dwarf mice with a genetic deficiency of either pituitary GH secretion (94) or GH receptors (95) have a prolonged life span, compared with their wild-type counterparts. Enzymological investigations in mice with GH excess and dwarf mice with GH deficiency have suggested that GH down-

regulates activity of superoxide dismutase and catalase, enzymes responsible for detoxification of oxygen free radicals (96–98), providing one possible explanation for “accelerated aging” due to GH excess. Another possible mechanism is suggested by the finding that DNA damage to human peripheral blood lymphocytes *in vitro* by bleomycin oxidative stress is amplified by GH and IGF-I upregulation of p53 protein expression (99). In contrast to these observations in rodents is the observation that pathologic GH deficiency in humans is associated with increased mortality (100). Whether rhGH supplementation in elderly people will promote anti-aging or pro-aging effects may be better answered by future clinical studies in which restoration of GH and IGF-I homeostasis is achieved by more physiologic treatment paradigms, such as the use of GH secretagogues.

RISKS AND BENEFITS, CONSIDERATIONS OF DOSE, AND AGE

Although most adverse effects of rhGH treatment appear to be dose dependent, it is unknown whether, and to what extent, use of lower doses of rhGH would eliminate or reduce beneficial effects. During the authors' study, rhGH doses, administered 3 days per week, were reduced from 30 to 20 $\mu\text{g}/\text{kg}$ due to the incidence of adverse events. Doses of rhGH averaged between 9 and 10 $\mu\text{g}/\text{kg}/\text{day}$. A few recent studies of young to middle-aged GH-deficient men and women, in which lower rhGH doses in the range of 3 to 6 $\mu\text{g}/\text{kg}/\text{day}$ were employed and/or doses were increased gradually, have reported lesser incidences of edema, arthralgias, carpal tunnel symptoms, and glucose intolerance (101–103). In studies in older men reported in an abstract (104), few or no adverse effects of low-dose rhGH and an additive effect of T to rhGH similar to that reported in our study (58) were observed. However, middle-aged and older adult participants in the studies using lower doses of rhGH generally demonstrated smaller improvements in body composition and no data regarding physical or psychologic function (fitness, strength, improved activities of daily living, quality of life) were reported. Furthermore, because soft tissue adverse effects are seldom observed in children or young adults treated with relatively high doses of rhGH (33), it is likely that aging increases susceptibility to these adverse effects, a conclusion also suggested by previous investigators (40).

The clinical usefulness of any therapeutic intervention depends in part on the relationship of benefits to risks, which will depend on the population (age, sex, type and severity of illness, and so forth) in which it is assessed, the doses and regimen employed, the severity of adverse effects encountered, and other factors. Clearly, the use of a long-term intervention aimed at attenuating functional loss or improving future function and health outcomes in otherwise healthy aged persons requires a higher standard for assessing risk/benefit relationships and a more favorable balance of these factors than does an acute and potentially lifesaving intervention in the seriously ill. The possible use of hormone replacement therapies to reduce risks of age-related problems such as sarcopenia, osteoporosis, cardiovascular disease, dementia, or the combined loss of functions characteristic of frailty deserve special scrutiny in this regard.

USE OF rhGH IN ANTI-AGING MEDICINE

Despite the caveats expressed herein, treatment of older men and women with rhGH has been widely touted to the public as exerting “anti-aging” properties in books (42,105), on websites, and in other public media. Moreover, rhGH injections have been prescribed for large numbers of middle-aged and older persons, despite the absence of Food and Drug Administration approval for this use and scant data regarding efficacy or long-term safety of rhGH treatment in this population. In addition, a plethora of products alleged to increase endogenous GH secretion, but of uncertain efficacy, are being advertised to the general public.

Shortly after the publication of the authors’ report on GH and sex steroid effects in elderly people (58), a counterresponse was published by the American Association of Anti-Aging Medicine (A4M) (106). The latter claimed that prior studies of rhGH in adults have established the effectiveness and safety of rhGH to treat the somatopause in otherwise healthy persons. They further asserted that the adverse effects observed in the authors’ study were due to use of higher doses of rhGH than commonly employed by anti-aging medicine physicians, and that patients given lower doses maintain beneficial effects, while experiencing little or no adverse consequences of treatment. The A4M document cited eight recently published research studies in support of their claims. However, all but one of these studies were conducted in men and women with documented pituitary disease, not the “somatopause.” The exception was the Rudman study (39) in which research participants were men older than age 65. Regarding that study, the A4M document states, “The researchers showed clear benefits to the therapy. Men administered rhGH gained an average of 8.8% in lean body mass and lost 14% in fat (without diet or exercise), improved their skin texture and tone, and increased their bone density.” In fact, in the Rudman study there were no physiologic (strength, VO_2) or functional (quality of life) measures performed, nor was bone density significantly affected by treatment after 6 months. Moreover, that study was discontinued after 1 year due to the accumulation of adverse events in the rhGH-treated men (43), a fact not mentioned in the A4M critique.

In the other seven studies cited by the A4M (103,107–112), patients had pituitary disease and positive criteria for adult GHD, with profound GH deficiency, in most cases, based on provocative testing with insulin, growth hormone-releasing hormone, glucagon, or arginine. Such tests are generally not conducted by anti-aging medicine doctors nor are the criteria for rhGH treatment in most anti-aging clinics well defined. Second, the patients in the reports cited were mainly middle-aged (mean of 44 to 51 years, depending on the study), whereas the participants in our study averaged 72.3 years of age (range 65–88 years). To assert that conclusions based on results obtained in a younger hypopituitary patient population can be generalized to an older somatopausal population is potentially misleading. In fact, in one of the studies cited, the results of treatment in a subset of 258 adult GHD patients older than age 60, compared with younger groups, showed more frequent adverse effects and, importantly, smaller improvements in LBM and body fat mass, which beneficial changes failed to reach statistical significance (108).

The differences between adult GHD and the somatopause are important. It is clear that the great majority of healthy people in their 40s and 50s, without pituitary disease, have physiologically reduced levels of GH secretion and circulating IGF-I that remain in the normal range, and distinctly higher than the corresponding levels in patients with adult GHD. Treating such healthy individuals with rhGH simply replaces their own pituitary GH with injected bioengineered rhGH, (often at a cost of \$10,000 per year or more). It is only in the mid-60s to 70s that substantial numbers (but not all) of otherwise healthy people begin to exhibit significantly decreased levels of GH and IGF-I (1–6). Even these elderly “somatopausal” adults generally exhibit mean GH secretion and IGF-I levels that are higher than those observed in pathologically hypopituitary patients, although there is some overlap of individual values between these two groups (113).

Another issue is dose regimen. It was suggested (106) that the dose of rhGH used in the authors’ study (an average of 9–10 $\mu\text{g}/\text{kg}/\text{day}$ administered as 21–23 $\mu\text{g}/\text{kg}$, 3 times weekly) was too high, and that the administration of lower doses at more frequent intervals avoids the adverse effects we observed, while preserving beneficial effects. However, the doses shown to be effective in adult GHD patients in all but one of the studies cited (106) ranged from 5 to 12.5 $\mu\text{g}/\text{kg}/\text{day}$, not very different from those we employed. Moreover, in the authors’ trial, IGF-I levels were only restored to the normal youthful range and did not exceed the upper limits of normal. In addition, in the majority of the cited reports, significant incidences of the same adverse effects (fluid retention, joint pain, carpal tunnel, glucose intolerance, and diabetes) reported by the authors in their study were also seen. The single apparent exception to the above was an uncontrolled open-label trial in adult GHD patients in which rhGH doses from 1.7 to 3.0 $\mu\text{g}/\text{kg}/\text{day}$ were employed, and in which there were no apparent adverse effects at 3 months, and small but significant improvements in body composition (112). To date, no carefully controlled clinical trial has convincingly demonstrated that frequent administration of low GH doses improves its risk/benefit relationships in somatopausal elders.

Thirdly, there is the question of how “clinical benefit” is defined. In the authors’ study, although both men and women given rhGH increased LBM and decreased fat mass, only the men treated with both rhGH and T demonstrated improvements in muscle strength and $VO_2\text{max}$, and these were small changes unlikely to be of clinical significance. We contend that such changes in body composition are, per se, only cosmetic (however attractive they may be) and cannot justify the use of rhGH unless accompanied by true physiologic and functional changes. We suggest that clinical benefit be defined as measurable improvements in meaningful functions, such as the ability to carry bags of groceries up stairs or walk a mile without undue fatigue, and/or improved quality of life as measured by validated psychological instruments, rather than by anecdotal reports. Increased muscle strength and/or bone density and improved quality of life have been demonstrated in many studies of nonelderly adult GHD patients treated with rhGH (29–38). Although rhGH administration has improved indices of QOL in some (114) but not other (115) studies of aged adult GHD patients, to date there are no reports of similar

benefits in healthy somatopausal individuals. Because of the absence of placebo controls in most of the studies cited by the A4M, a placebo effect cannot be discounted. Finally, there is a legitimate question with regard to serious adverse effects (especially cancer) occurring over the long term, which cannot be evaluated in studies of 2–3 years or less or conducted in relatively small numbers (fewer than 1000) of patients. Thus, determination of the true efficacy, safety, and clinical utility of rhGH supplementation in healthy aged individuals will require successful, properly controlled studies of sufficient size and duration before claims of clinical efficacy for rhGH in elderly persons can be substantiated.

CONCLUSIONS

Given the above considerations, we conclude that, while rhGH treatment for middle-aged patients with proven pathological pituitary GH deficiency appears to be effective and safe, there is considerable reason for caution with regard to employing rhGH intervention as a means of reducing or delaying the effects of aging. Although in certain elderly men and women, rhGH or a combination of rhGH and sex steroid replacement may provide significant benefits with regard to body composition, it has not been demonstrated that it is either safe or clinically effective to prescribe rhGH (without or with sex steroid) for such “somatopausal” patients. Therefore, it would appear prudent for physicians and patients to adopt the attitude that further studies are required to determine whether alternative dose rhGH regimens, use of GH secretagogues, longer durations of rhGH or secretagogue treatment, and so forth, might produce a satisfactory risk/benefit relationship. We thus recommend that, until such studies have been reported and an optimal regimen has been developed, treatment of healthy elderly men and women with rhGH, or agents that augment GH and IGF-I levels, should be confined to properly controlled research studies.

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REFERENCES

- Finkelstein J, Roffwarg H, Boyar P, Kream J, Hellman L. Age-related changes in the twenty-four hour spontaneous secretion of growth hormone in normal individuals. *J Clin Endocrinol Metab.* 1972;35:665–670.
- Zadik Z, Chalew SA, McCarter RJ, Meistas M, Kowarski AA. The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. *J Clin Endocrinol Metab.* 1985;60:513–516.
- Corpas E, Harman SM, Blackman MR. Human growth hormone and human aging. *Endocrinol Rev.* 1993;14:20–39.
- Anawalt BD, Merriam GR. Neuroendocrine aging in men. Andropause and somatopause. *Endocrinol Metab Clin N Am.* 2001;30:647–669.
- Yamamoto H, Sohmiya M, Oka N, Kato Y. Effects of aging and sex on plasma insulin-like growth factor I (IGF-I) levels in normal adults. *Acta Endocrinol (Copen).* 1991;124:497–500.
- O'Connor KG, Tobin JD, Harman SM, et al. Serum levels of insulin-like growth factor-I are related to age and not to body composition in healthy women and men. *J Gerontol Med Sci.* 1998;53A:M176–M182.
- Cauley JA, Gutai JP, Kuller LH, Powell JG. Reliability and interrelations among serum sex hormones in postmenopausal women. *Am J Epidemiol.* 1991;133:50–57.
- Rossmannith WG, Scherbaum WA, Lauritzen C. Gonadotropin secretion during aging in postmenopausal women. *Neuroendocrinol.* 1991;54:211–218.
- Miller MM, Franklin KB. Theoretical basis for the benefit of postmenopausal estrogen substitution. *Exp Gerontol.* 1999;34:587–604.
- Bremner WJ, Prinz PN. A loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab.* 1983;56:1278–1281.
- Morley JE, Kaiser FE, Perry HM III, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism.* 1997;46:410–413.
- Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab.* 2001;86:724–731.
- Matsumoto AM. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol Med Sci.* 2002;57A:M76–M99.
- Hughes VA, Frontera WR, Wood M, et al. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. *J Gerontol Biol Sci.* 2001;56A:B209–B217.
- Roy TA, Blackman MR, Harman SM, Tobin JD, Schragger M, Metter EJ. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. *Am J Physiol Endocrinol Metab.* 2002;283:E284–E294.
- Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med.* 1986;314:1676–1686.
- Baumgartner RN, Heymsfield SB, Roche AF, Bernardino M. Abdominal composition quantified by computed tomography. *Am J Clin Nutr.* 1988;48:936–945.
- Shimokata H, Andres R, Coon PJ, Elahi D, Muller DC, Tobin JD. Studies in the distribution of body fat. II. Longitudinal effects of change in weight. *Int J Obes.* 1989;13:455–464.
- Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA.* 1998;279:585–592.
- Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for the prediction of hip fractures. *Lancet.* 1993;341:72–75.
- Cefalu WT, Werbel S, Bell-Farrow AD, et al. Insulin resistance and fat patterning with aging: relationship to metabolic risk factors for cardiovascular disease. *Metabolism.* 1998;47:401–408.
- Zamboni M, Armellini F, Harris T, et al. Effects of age on body fat distribution and cardiovascular risk factors in women. *Am J Clin Nutr.* 1997;66:111–115.
- Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol.* 1996;144:1143–1150.
- Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA.* 1998;280:1843–1848.
- Abbasi AA, Mattson DE, Duthie EH Jr, et al. Predictors of lean body mass and total adipose mass in community-dwelling elderly men and women. *Am J Med Sci.* 1998;315:188–193.
- Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. *J Endocrinol Invest.* 1999;22:110–116.
- Waters DL, Yau CL, Montoya GD, Baumgartner RN. Serum sex hormones, IGF-1, and IGFBP3 exert a sexually dimorphic effect on lean body mass in aging. *J Gerontol Biol Sci Med Sci.* 2003;58A:648–652.
- Gillberg P, Olofsson H, Mallmin H, Blum WF, Ljunghall S, Nilsson AG. Bone mineral density in femoral neck is positively correlated to circulating insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3 in Swedish men. *Calcif Tissue Int.* 2002;70:22–29.
- Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med.* 1989;321:1797–1803.
- Bengtsson BA, Eden S, Lonn L, et al. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab.* 1993;76:309–317.

31. Verhelst J, Abs R, Vandeweghe M, et al. Two years of replacement therapy in adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1997;47:485–494.
32. Carroll PV, Christ ER, Bengtsson BA, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab*. 1998;83:382–395.
33. Vance ML, Mauras N. Growth hormone therapy in adults and children. *N Engl J Med*. 1999;341:1206–1216. STOP
34. Jorgensen JO, Thuesen L, Muller J, Ovesen P, Skakkebaek NE, Christiansen JS. Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. *Eur J Endocrinol*. 1994;130:224–228.
35. Nass R, Huber RM, Klauss V, Muller OA, Schopohl J, Strasburger CJ. Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. *J Clin Endocrinol Metab*. 1995;80:552–557.
36. Johannsson G, Grimby G, Sunnerhagen KS, Bengtsson B-A. Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. *J Clin Endocrinol Metab*. 1997;82:2877–2884.
37. Johannsson G, Ohlsson C. Growth hormone therapy and fracture risk in the growth hormone-deficient adult. *Baillieres Clin Endocrinol Metab*. 1998;12:233–250.
38. Rodriguez-Armao J, Jabbar A, Fulcher K, Besser GM, Ross RJ. Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. *Clin Endocrinol (Oxf)*. 1999;51:53–60.
39. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med*. 1990;323:1–6.
40. Savine R, Sonksen P. Growth hormone—hormone replacement for the somatopause? *Horm Res*. 2000;53(Suppl 3):37–41.
41. von Werder K. The somatopause is no indication for growth hormone therapy. *J Endocrinol Invest*. 1999;22:137–141.
42. Klatz R. *Grow Young With HGH: The Amazing Medically Proven Plan to Reverse Aging*. New York: Harper and Collins; 1997
43. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. *Clin Endocrinol (Oxf)*. 1993;39:417–425.
44. Holloway L, Butterfield G, Hintz R, Geusundheit N, Marcus R. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. *J Clin Endocrinol Metab*. 1994;79:470–479.
45. Chipman JJ, Attanasio AF, Birkett MA, Bates PC, Webb S, Lamberts SW. The safety profile of GH replacement therapy in adults. *Clin Endocrinol (Oxf)*. 1997;46:473–481.
46. Abs R, Bengtsson BA, Hernberg-Stahl E, et al. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clin Endocrinol (Oxf)*. 1999;50:703–713.
47. Pepine CJ, Aloia J. Heart muscle disease in acromegaly. *Am J Med*. 1970;48:530–534.
48. Fazio S, Cittadini A, Biondi B, et al. Cardiovascular effects of short-term growth hormone hypersecretion. *J Clin Endocrinol Metab*. 2000;85:179–182.
49. Mercuro G, Zoncu S, Colonna P, et al. Cardiac dysfunction in acromegaly: evidence by pulsed wave tissue Doppler imaging. *Eur J Endocrinol*. 2000;143:363–369.
50. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)*. 1980;12:71–79.
51. Bengtsson BA, Eden S, Ernest I, Odén A, Sjögren B. Epidemiology and long-term survival in acromegaly. *Acta Med Scand*. 1988;223:327–335.
52. Holly JM, Gunnell DJ, Davey Smith G. Growth hormone, IGF-I and cancer. Less intervention to avoid cancer? More intervention to prevent cancer? *J Endocrinol*. 1999;162:321–330.
53. Hankinson SE, Willett WC, Manson JE, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*. 1998;351:1393–1396.
54. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*. 1998;279:563–566.
55. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. *J Clin Endocrinol Metab*. 2000;85:4258–4265.
56. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst*. 1999;91:620–625.
57. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr*. 2001;131(11 Suppl):3109S–3120S.
58. Blackman MR, Sorkin JD, Munzer T, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA*. 2002;288:2282–2292.
59. Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. *J Clin Endocrinol Metab*. 1994;79:470–479.
60. Papadakis MA, Grady D, Black D, et al. Growth hormone replacement in healthy older men improves body composition but not functional ability. *Ann Intern Med*. 1996;124:708–716.
61. Johannsson G, Bjarnason R, Brammert M, et al. The individual responsiveness to growth hormone (GH) treatment in GH-deficient adults is dependent on the level of GH-binding protein, body mass index, age, and gender. *J Clin Endocrinol Metab*. 1996;81:1575–1581.
62. Burman P, Johannsson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *J Clin Endocrinol Metab*. 1997;82:550–555.
63. Holmes SJ, Shalet SM. Factors influencing the desire for long-term growth hormone replacement in adults. *Clin Endocrinol (Oxf)*. 1995;43:151–157.
64. Thompson JL, Butterfield GE, Marcus R, et al. The effects of recombinant human insulin-like growth factor-I and growth hormone on body composition in elderly women. *J Clin Endocrinol Metab*. 1995;80:1845–1852.
65. Papadakis M, Grady D, Black D, et al. Growth hormone replacement in healthy older men improves body composition but not functional ability. *Ann Intern Med*. 1996;124:708–716.
66. Mårdh G, Lundin K, Borg G, Jonsson B, Lindeberg A. Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: Combined data from 12 European placebo-controlled trials. *Endocrinol Metab*. 1994;1(Suppl A):43–49.
67. Lieberman SA, Bjorkengren AG, Hoffman AR. Rheumatologic and skeletal changes in acromegaly. *Endocrinol Metab Clin North Am*. 1992;21:615–631.
68. Davies DL, Beastall GH, Connell JM, Fraser R, McCrudden D, Teasdale GM. Body composition, blood pressure and the renin-angiotensin system in acromegaly before and after treatment. *J Hypertens Suppl*. 1985;3(Suppl 3):S413–S415.
69. Ho KK, O'Sullivan AJ, Hoffman DM. Metabolic actions of growth hormone in man. *Endocr J*. 1996;43(Suppl):S57–S63.
70. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sönksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *J Appl Physiol*. 1991;70:688–694.
71. Moller J, Moller N, Frandsen E, Wolthers T, Jorgensen JO, Christiansen JS. Blockade of the renin-angiotensin-aldosterone system prevents growth hormone-induced fluid retention in humans. *Am J Physiol*. 1997;272(5 Pt 1):E803–E808.
72. Hoffman DM, Crampton L, Sernia C, Nguyen TV, Ho KK. Short-term growth hormone (GH) treatment of GH-deficient adults increases body sodium and extracellular water, but not blood pressure. *J Clin Endocrinol Metab*. 1996;81:1123–1128.
73. Thuesen L, Jorgensen JOL, Muller JR, et al. Short and long-term cardiovascular effect of growth hormone therapy in growth hormone deficient adults. *Clin Endocrinol (Oxf)*. 1994;41:615–620.
74. Pagel I, Langenickel T, Hohnel K, et al. Cardiac and renal effects of growth hormone in volume overload-induced heart failure: role of NO. *Hypertension*. 2002;39:57–62.
75. Foss MC, Saad MJ, Paccola GM, Paula FJ, Piccinato CE, Moreira AC. Peripheral glucose metabolism in acromegaly. *J Clin Endocrinol Metab*. 1991;72:1048–1053.
76. Jorgensen JOL, Moller J, George K, et al. Marked effects of sustained low growth hormone (GH) levels on day-to-day fuel metabolism: studies in GH-deficient patients and healthy untreated subjects. *J Clin Endocrinol Metab*. 1993;77:1589–1596.

77. Hayes FJ, Fiad TM, McKenna TJ. Gender difference in the response of growth hormone (GH)-deficient adults to GH therapy. *Metabolism*. 1999;48:308–313.
78. Rosenfalck AM, Fisker S, Hilsted J, et al. The effect of the deterioration of insulin sensitivity on beta-cell function in growth-hormone-deficient adults following 4-month growth hormone replacement therapy. *Growth Horm IGF Res*. 1999;9:96–105.
79. Johnston DG, Al-Shoumer KA, Chrisoulidou A, Kousta E, Beshyah S, Robinson S. Long-term effects of growth hormone therapy on intermediary metabolism and insulin sensitivity in hypopituitary adults. *J Endocrinol Invest*. 1999;22:37–40.
80. Marek B, Kajdaniuk D, Kos K, et al. Acromegaly and the risk of cancer. *Pathophysiol*. 2001;8:69–75.
81. Fukuda I, Hizuka N, Murakami Y, et al. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. *Intern Med*. 2001;40:987–992.
82. Rapaport R, Oberfield SE, Robison L, et al. Relationship of growth hormone deficiency and leukemia. *J Pediatr*. 1995;126(5 Pt 1):759–761.
83. Allen DB, Rundle AC, Graves DA, Blethen SL. Risk of leukemia in children treated with human growth hormone: review and reanalysis. *J Pediatr*. 1997;131(1 Pt 2):S32–S36.
84. Rosfjord EC, Dickson RB. Growth factors, apoptosis, and survival of mammary epithelial cells. *J Mamm Gland Biol Neoplasia*. 1999;4:229–237.
85. Akagi Y, Liu W, Zebrowski B, Xie K, Ellis LM. Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I. *Cancer Res*. 1998;58:4008–4014.
86. Colao A, Marzullo P, Ferone D, et al. Prostatic hyperplasia: an unknown feature of acromegaly. *J Clin Endocrinol Metab*. 1998;83:775–779.
87. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549–1557;discussion 1564.
88. Salomon F, Cuneo RC, Hesp R, Sönksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med*. 1989;321:1797–1803.
89. Malozowski S, Tanner LA, Wysowski D, Fleming GA. Growth hormone, insulin-like growth factor I, and benign intracranial hypertension. *N Engl J Med*. 1993;329:665–666.
90. Wu FC, Farley TM, Peregoudov A, Waites GM. Effects of testosterone enanthate in normal men: experience from a multicenter contraceptive efficacy study. World Health Organization Task Force on Methods for the Regulation of Male Fertility. *Fertil Steril*. 1996;65:626–636.
91. Bartke A, Brown-Borg HM, Bode AM, Carlson J, Hunter WS, Bronson RT. Does growth hormone prevent or accelerate aging? *Exp Gerontol*. 1998;33:675–687.
92. Steger RW, Bartke A, Cecim M. Premature ageing in transgenic mice expressing different growth hormone genes. *J Reprod Fertil Suppl*. 1993;46:61–75.
93. Wolf E, Kahnt E, Ehrlein J, Hermanns W, Brem G, Wanke R. Effects of long-term elevated serum levels of growth hormone on life expectancy of mice: lessons from transgenic animal models. *Mech Ageing Dev*. 1993;68:71–87.
94. Bartke A, Brown-Borg H, Mattison J, Kinney B, Hauck S, Wright C. Prolonged longevity of hypopituitary dwarf mice. *Exp Gerontol*. 2001;36:21–28.
95. Laron Z. Effects of growth hormone and insulin-like growth factor 1 deficiency on ageing and longevity. *Novartis Found Symp*. 2002;242:125–137;discussion 137–142.
96. Hauck SJ, Bartke A. Effects of growth hormone on hypothalamic catalase and Cu/Zn superoxide dismutase. *Free Radic Biol Med*. 2000;28:970–978.
97. Brown-Borg HM, Rakoczy SG. Catalase expression in delayed and premature aging mouse models. *Exp Gerontol*. 2000;35:199–212.
98. Brown-Borg HM, Rakoczy SG, Romanick MA, Kennedy MA. Effects of growth hormone and insulin-like growth factor-1 on hepatocyte antioxidative enzymes. *Exp Biol Med (Maywood)*. 2002;227:94–104.
99. Cianfarani S, Tedeschi B, Germani D, et al. In vitro effects of growth hormone (GH) and insulin-like growth factor I and II (IGF-I and -II) on chromosome fragility and p53 protein expression in human lymphocytes. *Eur J Clin Invest*. 1998;28:41–47.
100. Besson A, Salemi S, Gallati S, et al. Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab*. 2003;88:3664–3667.
101. Kehely A, Bates PC, Frewer P, et al. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. *J Clin Endocrinol Metab*. 2002;87:1974–1979.
102. Yuen K, Ong K, Husbands S, et al. The effects of short-term administration of two low doses versus the standard GH replacement dose on insulin sensitivity and fasting glucose levels in young healthy adults. *J Clin Endocrinol Metab*. 2002;87:1989–1995.
103. Gillberg P, Brammert M, Thoren M, Werner S, Johannsson G. Commencing growth hormone replacement in adults with a fixed low dose. Effects on serum lipoproteins, glucose metabolism, body composition, and cardiovascular function. *Growth Horm IGF Res*. 2001;11:273–281.
104. Giannoulis MG, McMillan CV, Bradley C, et al. Effects of growth hormone administration (by individually tailored dose titration) and/or testosterone on body composition, physical performance and quality of life in health elderly men [Proceedings Abstract]. *Endocrine Society, Annual Meeting*; 2003; Philadelphia, PA: The Endocrine Society; 2003:29.
105. Jamieson J, Marriott V, Dorman LE. *Growth Hormone, the Methuselah Factor*. East Canaan, CT: Safe Goods; 1997
106. Klatz R. On adult growth hormone replacement [A4M Official Response Statement to Blackman, et al.: Growth hormone and sex steroid administration in healthy aged women and men]. Chicago: American Academy of Anti-Aging Medicine (A4M); Nov. 12, 2002. Also available at: http://www.a4minfo.net/id79_.htm
107. Ezzat S, Fear S, Gaillard RC, et al. Gender-specific responses of lean body composition and non-gender-specific cardiac function improvement after GH replacement in GH-deficient adults. *J Clin Endocrinol Metab*. 2002;87:2725–2733.
108. Attanasio AF, Bates PC, Ho KK, et al. Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3-year results from the HypoCCS Database. *J Clin Endocrinol Metab*. 2002;87:1600–1606.
109. Gotherstrom G, Svensson J, Koranyi J, 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;86:4657–4665.
110. Hemberg-Stahl E, Luger A, Abs R, et al. Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency. *J Clin Endocrinol Metab*. 2001;86:5277–5281.
111. Herschbach P, Henrich G, Strasburger CJ, et al. Development and psychometric properties of a disease-specific quality of life questionnaire for adult patients with growth hormone deficiency. *Eur J Endocrinol*. 2001;145:255–265.
112. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clin Endocrinol (Oxf)*. 2001;54:709–717.
113. Toogood AA, O'Neill PA, Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. *J Clin Endocrinol Metab*. 1996;81:460–465.
114. Monson JP, Jonsson P. Aspects of growth hormone (GH) replacement in elderly patients with GH deficiency: data from KIMS. *Horm Res*. 2003;60(Suppl 1):112–120.
115. Li Voon Chong JS, Groves T, Foy P, Wallymahmed ME, MacFarlane IA. Elderly people with hypothalamic-pituitary disease and untreated GH deficiency: clinical outcome, body composition, lipid profiles and quality of life after 2 years compared to controls. *Clin Endocrinol (Oxf)*. 2002;56:175–181.