

Chapter 29

Growth Hormone Replacement for Normal Aging

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ABSTRACT

The purpose of this paper is to discuss whether or not growth hormone replacement therapy (GHRT) for the treatment of somatopause of normal aging is safe and effective. In order to determine this it is important to learn about GH, the benefits of GHRT, and its side-effects. We also need to discuss whether or not pathological GH deficiency is the same as GH deficiency caused by “normal aging.” The links between GHRT and cancer and insulin resistance are also debated

INTRODUCTION

The purpose of this paper is to discuss whether or not growth hormone replacement therapy (GHRT) for the treatment of somatopause of normal aging is safe and effective. This paper is not going to deal with the basics of GHRT, i.e. doses and optimal delivery techniques. Instead it will address the following important questions:

- What are the benefits of GHRT?
- Is “Normal Aging” GH deficiency the same as “Pathological” GH deficiency?
- Does GHRT increase the risk of cancer?
- Does GHRT cause insulin resistance?
- Are the possible side effects of GHRT manageable nuisances or serious problems?

GROWTH HORMONE, SOMATOPAUSE, AND AGING

Growth hormone (GH) exerts a wide variety of physiological effects on the body. Endogenous peptide ligands such as ghrelin, growth hormone releasing hormone (GHRH), and growth hormone releasing peptide (GHRP) all stimulate the anterior pituitary to release GH. GH migrates to the liver to produce insulin-like growth factor 1 (IGF-1) – 60% of the effects that GH has on the body are exerted via IGF-1. For example, GH’s anabolic effect upon muscle, bone, and cartilage, and its lipolytic effect on fat, are all mediated by IGF-1. GH and IGF-1 can both pass through the blood-brain barrier.

Somatopause signifies the gradual decline in growth hormone production by the pituitary gland. Somatopause can begin anywhere between the ages of 35 and 50, however when it does occur a person’s GH levels will drop significantly. In an article published in *Hormone Research* in 2000, Savine et al concluded that life without growth hormone is poor both in quantity and quality. The emphasis here should be placed on quality as maintaining a good quality of life is the goal. Savine found that GH peaks at puberty and starts decreasing at 21. At the age of 60, most adults have the same 24-hour secretion rate indistinguishable from those hypopituitary patients with organic lesions in the pituitary gland. Thus, a normal 60-year-old is the same as a sick 25-year-old in terms of GH levels. Savine also concluded that if an IGF-1 level of 300 is mean normal for a 20 to 30-year-old, almost everybody over the age of 40 has an IGF-1 deficit.

However, what does GH have to do with aging? The important factor here is inflammation. Chronic inflammation is the cause of many age-related diseases. Thus doing whatever we can to decrease chronic inflammation is important in the quest to stay healthy. A number of things can be done to help combat chronic inflammation. For example: keeping glucose and insulin levels under control, taking regular exercise, and eliminating the visceral abdominal fat. Abdominal fat is a living, throbbing endocrine organ that produces inflammatory cytokines, like IL-6. So carrying extra fat is not just a cosmetic issue. By eliminating visceral abdominal fat the person is also getting rid of a very dangerous inflammatory-producing organ. It is also possible to lower inflammation by controlling the Omega-3 to Omega-6 ratio and eliminating infections – most health professionals are now aware of the connection between heart disease and periodontal disease and chlamydia. Another way of combating inflammation is stress reduction, as stress produces inflammatory cytokines. Control of free radicals, homocysteine

levels, advanced glycation end products, and youthful hormones, such as testosterone, estrogens, growth hormone, IGF-1 all decrease these inflammatory cytokines. Inflammation induces GH insensitivity, however GHRT decreases inflammation. Thus reducing inflammation also improves the body's sensitivity to GH.

We know that a person's C-Reactive Protein (CRP) levels are the strongest predictor of whether or not they are going to have a myocardial infarction or not. CRP is far superior to LDL-cholesterol. Thus, it makes sense to keep CRP levels as low as possible. Where does CRP come from? Interleukin-6, (IL-6) tells the liver to produce CRP. So to keep CRP under control, IL-6 levels also need to be kept at a minimum. Homocysteine raises inflammation – therefore it needs to be kept low. Too much insulin induces inflammation as does tumor necrosis factor- α (TNF- α), as does interleukin-10 (IL-10) – these are all things that need to be kept under control. Inflammation is linked to many chronic illnesses, from heart disease to syndrome X to dementia to depression, cancer, osteoporosis, and autoimmune disease – all have high inflammatory mediators. Maybe the question should be “Why are we so inflammatory?”

Insulin resistance provides us with a good analogy for understanding why the body is prone to inflammation. Insulin resistance was a good thing for our Paleolithic ancestors. If you could store fat and make it through famine, you would live long enough to pass on your DNA. No one lived long enough to develop Type II diabetes and its numerous complications, so that was not a problem. It is the same thing with inflammation. If a person's body is geared towards making inflammatory cytokines, they will get by when a saber tooth tiger bites them. White cells will rush to the infection and their blood will clot. Being prone to inflammation is a bonus when faced with acute trauma and acute infectious disease. As these two things were the main challenge to our ancestors, it is in the genome. We have evolved to be prone to inflammation. Now, since trauma and infection are not such a great threat to most people, and now that we are living significantly longer lives, this inflammatory state is killing us. Just as the insulin resistance is killing us.

Moving back to the original question of GH and aging. We age because our hormones decline, not the other way around. GH is vital in order to live a healthy adult life. Why? GHRT improves quality of life. What other benefits does GHRT have? GHRT is beneficial to the brain, the cardiovascular system, the immune system, aerobic capacity, body composition, and bone.

It is interesting to compare the viewpoints of anti-aging specialists and conventional endocrinologists have on GH. Both groups agree that pathological GH deficiency is a disease that should be treated. Both groups agree that GH secretion declines with age, and both groups agree that GH decline is responsible for part of the clinical syndrome of aging. This is where anti-aging and endocrinology's agreement on GH ends. Anti-aging specialists believe that aging and GH decline is a deficiency disease, which can and should be treated. But the vast majority, if not all, endocrinologists believe that aging and GH decline are normal and should not be treated.

Cappola *et al* carried out a study to investigate what factors were associated with a better quality of life in women aged 70 and over. The results showed that women who had the best quality of life in terms of functional capability – that is walking limitation, mobility, activities of daily living, cognition and so on – had high IGF-1 levels and low IL-6. Thus they had high GH levels and minimal inflammation. The concept is that decreased GH levels and decreased IGF-1 levels lead to frailty. Somatopause is the entry into frailty.

So does GHRT provide us with the long searched for fountain of youth? No, it does not. But we are on a programmed course of destruction and GHRT could help slow it down a little and improve our quality of life. If the benefits outweigh the risks, then something is worth doing. GHRT is a work in progress. It may not be perfect, but it is the best we have at present.

BENEFITS OF GROWTH HORMONE

Growth Hormone and the Brain

GH deficiency is associated with neurocognitive decline, and GHRT improves memory, alertness, and concentration. It is quite amazing that GH can pass through the blood brain barrier, as it is a very large molecule made up from 191 amino acids. The brain needs GH and it needs IGF-1. Many people think that GH is good, whereas IGF-1 is bad, and that we want to increase GH without increasing IGF-1. This is not the case. More than half of the action of GH is exerted through IGF-1, and the general consensus is that both are necessary. So growth hormone improves cognitive capabilities, memory, motivation, and work capacity. There are GH-receptors situated all over the brain. Aleman *et al* correlated

IGF-1 with cognitive function in men – with higher IGF-1 levels being linked to better cognitive function. GH deficiency was correlated with poor emotional and psychosocial functioning.

Growth Hormone and Bone

GH increases the strength and formation of cortical bone. Logobardi linked GH deficiency with reduced bone density, and GHRT with reversal of osteoporosis. Patients who sustain hip fractures tend to have lower IGF-1 levels. GH is synergistic with exercise, thus to get the maximum effect from GHRT it has to be combined with regular exercise. Van der Lely et al treated patients over 75 with hip fractures with GH at the time of fracture for six weeks. The end point was return to pre-fracture living arrangements. Results of the double-blind placebo-controlled trial showed that 94% of patients treated with GH returned to pre-fracture living within just six weeks, compared with 75% of control patients.

GH increases bone mineral density. Gillberg *et al* treated men with idiopathic osteoporosis with GH. Participants were randomly assigned to treatment with GH, either as continuous treatment with daily injections of 0.4 mg GH or as intermittent treatment with 0.8 mg GH for 14 days every 3 months. All patients were treated with GH for 24 months, with a follow-up period of 12 months. No positive effects of treatment were noted at the 12-month follow-up. But after 12 months there was a continued increase in bone mineral density and no significant adverse effects were reported. After two years of GH treatment significant improvement in bone mineral density were observed in both groups.

Some people say GHRT causes arthritis. This is not true. One of the side effects of GHRT is arthralgia. GH can make joints ache from fluid retention, but it does not cause any pathological damage to joints.

Growth Hormone and the Cardiovascular System

GH deficiency is associated with increased cardiovascular mortality, while GHRT is associated with improved cardiovascular function. Research suggests that GHRT may help to reverse atherosclerosis, improve cardiomyopathy, and reduce carotid intima media thickness.

Pro-inflammatory cytokines contribute to chronic and acute heart failure. Adamopoulos *et al* treated patients with idiopathic dilated cardiomyopathy (IDC) with GH. Results showed that GH treatment led to a significant decrease in both TNF- α and IL-6 levels, and significant improvements in exercise capacity.

GH also corrects endothelial dysfunction. Too much emphasis is placed upon the cholesterol model of atherosclerosis. Inflammation and endothelial dysfunction are very important factors. Cholesterol may be present at the scene of the crime, but it did not trigger the whole process going. GH improves endothelial dysfunction, which plays a significant role in both heart failure and arteriosclerosis.

What about homocysteine? We know that homocysteine is a strong predictor of cardiovascular disease. Sesmilo *et al* randomly assigned 40 men with GH deficiency to treatment with GH or a placebo for a period of 18 months. Homocysteine levels fell significantly in those treated with GH.

What about CRP? Which is the strongest predictor of cardiovascular events that we have. CRP is very high in GH deficiency. With GHRT, CRP decreases and visceral and subcutaneous fat decreases. As we know, visceral fat produces IL-6, which in turn produces CRP.

Thus, the cardiovascular improvements seen with GHRT, appears to be down to its effect upon the inflammatory pathway. IGF-1 is a cardiac hormone. It improves cardiac contractility, stroke volume, and ejection fraction. It improves insulin levels – intracardiac insulin levels – and increases insulin sensitivity. So the heart needs IGF-1. Certainly, after myocardial infarction, IGF-1 is critical in the remodeling of the heart and recovery.

Growth Hormone and the Immune System

When talking about GH and the immune system we have to look at the bigger picture, we have to consider the neuroendocrine-immune system it is all part of one system. IGF-1 is vital for lymphocyte maturation. It will restore age-related thymic involution in rodents. IGF-1 is needed to develop T-cells and B-cells, and the age-related decline in these important cells can be reversed with GHRT.

Growth Hormone, Body Composition, and Obesity

It is a well-documented fact that GHRT can decrease visceral abdominal fat – that cytokine-producing organ – by as much as 50%. According to Christiansen, GH deficiency is linked to:

- Abnormal body composition
- An increase in adipose mass and decrease in muscle mass
- Insulin resistance
- Decreased muscle strength

Long-term GHRT can normalize these abnormalities.

GH secretion is impaired in obesity. Johannsson *et al* studied middle-aged men with low GH and abdominal obesity. After nine months of treatment with GH, abdominal visceral fat decreased by 18%, insulin sensitivity improved, total cholesterol, LDL, and triglyceride levels dropped, and diastolic blood pressure decreased. The men did not make any lifestyle changes during the study. An 18% decrease in visceral abdominal fat without making any life-style alterations is quite impressive.

Blackman *et al* studied the effect of treating healthy men and women with sex steroids and GH. The women received HRT, which was Estraderm – transcutaneous estradiol. Plus Provera – this was not a wise choice as Provera increases insulin resistance. The men were given 100 mg of testosterone once every two weeks. One group of men and women were treated only with the sex steroids, while another were also treated with GH at a fixed dose per weight, which is not a good way to treat people with GH in terms of producing side-effects. Anyway, a fixed dose was used and the patients were given GH three times a week. Results showed that visceral abdominal fat decreased by 14% in men treated with GH alone, and 16% in those given GH and testosterone. Interestingly, women who were treated with GH alone did not lose abdominal fat, but when GH was combined with the HRT they did. A second study by the same group was published a year later in 2002. The participants were treated with the same regimen as in the 2001 study. Lean body mass increased in women treated with HRT and GH by an average of 2.1 kg, and in men treated with testosterone and GH by an average of 4.3 kg. Fat mass decreased in both groups of men and women. VO₂ max increased in both men and women, and muscle strength increased by 6.8% in men treated with both GH and testosterone. These changes occurred within six months, and once again, the participants made no life-style changes – imagine what results you could get by also making positive life-style changes. However, not all the results were positive. 38% of women suffered from edema. While 32% of men treated with both GH and testosterone suffered from Carpal Tunnel Syndrome. 41% of men treated with GH suffered from arthralgias. Diabetes or glucose intolerance was noted in 18 men treated with GH, compared with just 7 men who were not treated with GH. Unfortunately, the press picked up on this study and the resulting headline read: “Growth Hormone Replacement Therapy Causes Diabetes.” People who use GH in clinical practice know that this is simply not true. In terms of insulin resistance, GH can make it worse if the patient’s life-style is not managed correctly. If life-style is managed correctly insulin resistance could improve dramatically. The very high rate of side-effects seen with this study might be related to the dosage schedule – the fixed dose per weight, and the three times a week, and not titrating the dose. This side-effect profile is not seen in clinical practice. In clinical practice approximately 10% of patients may suffer from such side-effects, however these are manageable simply by decreasing the dose.

Other Benefits of Growth Hormone

Every study of GH and exercise capacity shows that GH increases VO₂ max. Gibney *et al* found a link between GH deficiency and chronic fatigue and depression. Meanwhile, GHRT was found to improve a person’s sense of well-being and was associated with an improved quality of life. Gilchrist *et al* concluded that GH deficient adults have a poor quality of life, but that this poor quality of life could be altered with GHRT. Gilchrist found that GHRT significantly improved energy levels, vitality, anxiety, depression, well-being, and self-control.

GROWTH HORMONE AND INCREASED MORTALITY IN PATIENTS IN ICU

One study that is often brought up when people talk about GH is a study by Takkala *et al* that was published in the *New England Journal of Medicine* in 1999. In this study critically ill patients – half of them were on ventilators, a lot with acute respiratory distress syndrome – were treated with large doses of GH, sixteen to 24 units per day. The average anti-aging dose can vary from 4 to 12 units a week or 1 unit a day, however these patients were treated with doses of 16 to 24 units a day. The outcome was not good.

Significantly higher numbers of patients treated with GH died. So we can conclude that an overdose of GH is not good. A rebuttal to this study by Bengtsson *et al* in the *Journal of Clinical Endocrinology* looked at a metaanalysis of over 2,000 patient years, none of which was associated with increase in mortality.

GROWTH HORMONE AND CANCER

Why do people feel that GH might increase the risk of cancer? The answer is simple – because it does stimulate cellular replication. But does GHRT increase the risk of cancer? Vance *et al* concluded that there is “No evidence that GHRT affects the risk of cancer or cardiovascular disease.” Meanwhile Molitch concluded: “Although there has been some concern about an increased risk of cancer [with GHRT], reviews of existing, well-maintained databases of treated patients have shown this theoretical risk to be nonexistent.” Shalet *et al* concluded that there is “No evidence of an increased risk of malignancy, recurrent or *de novo*.” On the package insert on GH it says don't use in active malignancy. However, the Growth Hormone Research Society published a paper in the *Journal of Clinical Endocrinology* saying that there is no data to support this labeling, and that current knowledge does not warrant additional warning about cancer risk. They say that this line should be removed from the package insert because no evidence that GH increases cancer recurrence or *de novo* cancer or leukemia.

When the issue of GH and cancer is being discussed, the Chan study is always referenced. Blood was drawn for IGF-1 and IGF binding protein-3 (IGFBP-3), and other studies, on a group of men. The blood was stored, and then 15 years later the investigators followed-up the participants to see which men developed prostate cancer. Men who had the IGF levels in the highest quartile had the most prostate cancer. There are some interesting aspects to this study. Firstly, the blood was stored for 15 years. Secondly, the IGF levels in the highest quartile were between 300 and 500. The average age of the men at the start of the study was 59. Now, it is unlikely people in clinical practice will ever have seen someone of that age with IGF levels of 400 or 500. This is why these study findings seem very unusual.

IGFBP-3 is one of the binding proteins that carries IGF. This seemingly simple system is actually very complex. All the binding proteins are hormones in their own right; they do not just provide storage for the hormones. So the highest quartile had a 2.4 times increased relative risk of prostate cancer. When a patient is treated with GHRT, IGF-1 levels increase and levels of IGFBP-3 also increase. Thus, GH stimulates the production of both IGF and IGFBP-3. In the study by Chang *et al* the men with more IGFBP-3 had a decreased risk of prostate cancer.

IGFBP-3 has been called the guardian of the genome. IGF-1 does have a mitogenic effect – it does cause cellular replication and renewal. However, the mitogenic effect of IGF-1 is balanced by the apoptotic effect of IGFBP-3. IGFBP-3 triggers apoptosis in cancer cells. Thus IGFBP-3 plays an important role in cancer control. However, too much apoptosis would cause cellular aging. So it is important that the body gets the balance just right.

A study of 765 men by Scheafer *et al* found no association with IGF-1 and prostate cancer. However, another study by Baffa *et al* linked low IGF-1 levels with prostate cancer. It is clear that we have conflicting evidence. However, if the Chan study is the one and only reason to link GH with increased risk of cancer, that reason is not valid.

Treating Patients With Cancer or Inactive Past Cancer

Patients who have had cancer can be given GHRT. You must discuss all the issues with them and make sure you have informed consent. What about active cancer? What about your patient with prostate cancer who is 78 years old? He does not want a radical prostatectomy, and he does not want Lupron. He realizes he is 78 and that he is probably going to die of something else first. But he is kind of slowing down. His GH level is low. Would you give him GH? I do not recommend that you should. But I have patients like this, and I do. This is a controversial issue. Giving patients with inactive past cancer GHRT is a little controversial even though all the data says that GH causes no increase in recurrence. In active cancer, it is very controversial because that little package insert says: “Do not do it”. So, I am not telling you to do that by any means. All of this has to be within the patient's comfort zone and your comfort zone.

GROWTH HORMONE REPLACEMENT THERAPY

If you decide that a patient is a candidate for GHRT you should start them off at a dose of about 4 IU (3 IU= 1 mg) a week and gradually increase the dose until you achieve the desired IGF-1 level and clinical results. The average dose to achieve an IGF-1 of 290 in females and 350 in males is 8IU per week. The average female dose is 0.6 mg/day, while the average male dose is 0.4 mg/day – women need higher doses than men in order to achieve the same clinical results. Elderly men often require less GH. In the past, patients were often given GH just two or three times a week. This is not good practice. The old way of doing it was not physiologic and was associated with a high incidence of side effects – both of which we do not want. Patients should be given GH everyday.

Should you take GH at morning or at night? This is a matter of debate; roughly half of people think morning and the other half think night. You make GH during deep sleep so the morning supporters believe that taking GH in the morning will result in less suppression of nighttime secretion. Whilst the night school of thought, is that it is more physiologic to take GH at night because that is when you secrete it. So, it can be taken first thing in the morning or last thing at night before bed. Either way, GH should be avoided after meals when insulin levels are high.

Side-Effects

The most common side-effects of GHRT are edema, arthralgia, and insulin resistance. Vance *et al* concluded that edema and arthralgia are related to the dose schedule. Patients that are affected by edema or arthralgia are often being treated on a low-frequency, high-dose schedule. They are also associated with mg/kg doses instead of a gradually increasing dose. Both are reversible by simply decreasing the dose.

Another side-effect of GHRT is paresthesia. If a patient complains of paresthesia, or edema, or arthralgia, the best thing to do is stop their treatment for a few days, decrease the dose, and maybe treat them symptomatically with some NSAID's or mild diuretics. Potassium replacement can also help to ameliorate these symptoms. In rare cases, a patient cannot tolerate GH. If their arthralgia, or whatever, keeps coming back, GHRT is not for them and should be discontinued

Insulin Resistance

GHRT can cause insulin resistance. But this can be avoided if the patient is managed correctly. Can you give people with metabolic syndrome GH? Yes, but you have got to manage things. It is vital that the patient eats correctly. We have the Atkins' diet, the Zone diet, and the Paleolithic diet. All three of these diets are pointing towards the same thing – that we need protein, good-quality fats, and that we have to choose our carbohydrates carefully, i.e. obtaining them from vegetables. So before a patient embarks on an anti-aging program, it is vital that they eat properly. Testosterone replacement therapy decreases insulin resistance. And so a patient with borderline insulin resistance who wants to be treated with GHRT may benefit from being treated with testosterone first. Diabetics need to be advised that their insulin requirements could go up or down.

Nam *et al* evaluated the effects of low-dose GH therapy combined with diet restriction on changes in body composition and insulin resistance in newly diagnosed obese type 2 diabetic patients. The findings led them to conclude: "Low-dose GH treatment combined with dietary restriction resulted not only in a decrease of visceral fat but also in an increase of muscle mass with a consequent improvement of the insulin resistance observed in obese type 2 diabetic patients." Remember, obesity is another inflammatory disease. Abdominal fat makes IL-6, and IL-6 causes insulin to go up and store more fat: thus creating one big cycle.

CONCLUDING REMARKS

GHRT is expensive - \$12,000 - \$15,000 a year including lab screening – and is therefore not an option for everyone. It is associated with side effects, one of which is insulin resistance. However, when used properly by a competent physician, GH is safe. GHRT is associated with less morbidity and mortality, less cardiovascular disease, less inflammation, improvements in body composition, improvements in exercise capacity, and a better quality of life. In the word's of Peter Sonksen: "GH is essential for normal adult life, and without it life expectancy is shortened, energy and vitality are reduced, and the quality of this life is impaired. The medical case for GH replacement is now proven beyond any reasonable medical and scientific doubt. "

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ABOUT THE AUTHOR

As a pioneer in the field of Anti-Aging Medicine, Ron Rothenberg, M.D., was one of the first physicians to be recognized for his expertise to become fully board certified in the specialty. Dr. Rothenberg founded the California HealthSpan Institute in Encinitas, California in 1997 with a commitment to transforming our understanding of and finding treatment for aging as a disease. Dr. Rothenberg is dedicated to the belief that the process of aging can be slowed, stopped, or even reversed through existing medical and scientific interventions. Challenging traditional medicine's approach to treating the symptoms of aging, California HealthSpan's mission is to create a paradigm shift in the way we view medicine: treat the cause. He received his MD from Columbia University, College of Physicians and Surgeons in 1970. Dr. Rothenberg performed his residency at Los Angeles County-USC Medical Center and is also board certified in Emergency Medicine. He received academic appointment to the USC School of Medicine Clinical Faculty in 1997 and was promoted to full Clinical Professor of Preventive and Family Medicine in 1989. In addition to his work in the field of Anti-Aging medicine, Dr. Rothenberg is an Attending Physician and Director of Medical Education at Scrips Memorial Hospital in Encinitas, California. Dr. Rothenberg travels extensively to lecture on a variety of topics, which include Anti-Aging Medicine and Emergency Medicine and is the author of *Forever Ageless*. He has recently been featured in the University of California MD TV series in the shows on Anti-Aging Medicine.