

## The Effect of Obesity on Growth Hormone Secretion

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Obesity is quickly becoming a major health problem in developed countries with nearly 2/3 of U.S. adults classified as overweight or obese (body mass index (BMI) > 25 kg/m<sup>2</sup>) (1). Excess weight leads to a multitude of health issues, including increased cardiovascular disease and diabetes mellitus. It is not surprising that obesity leads to alterations in other endogenous hormonal systems. This article will examine the effects of increased weight on growth hormone (GH) dynamics and the potential consequences of altered GH concentrations.

Research performed over forty years ago uncovered that growth hormone levels are lower in obese compared to normal weight individuals (2). Careful measurements of this pulsatile hormone with frequent blood sampling over a 24-hour period showed that in men, higher body fat was associated with a decline in pulsatile GH release and faster GH clearance (3). Similarly in women, increased visceral adiposity was associated with a decline in basal and pulsatile GH secretion (4). Because 24-hour secretion profiles are cumbersome to perform, the competency of the GH axis is commonly assessed by performing a stimulation test, such as the arginine-GHRH or insulin tolerance (ITT) test. A study by Bonert et al. of healthy men showed that the peak GH obtained during arginine-GHRH stimulation testing was inversely correlated with BMI (Figure 1). Using a generous (increased sensitivity, decreased specificity) cut-off level, GH deficiency was defined as a failure to stimulate the GH concentration above 9 ng/ml. With this definition, the percentage of subjects meeting criteria for GH deficiency increased relative to BMI (Table 1) (5). A similar inverse correlation of BMI with peak GH was seen when the arginine-GHRH test was performed in women (6) and for the ITT (7). These data have sparked controversy about how to define GH deficiency: Should the cut-off for defining GH deficiency during stimulation testing be lowered (i.e. more stringent) for obese individuals, to prevent misclassification as GH deficient? Alternatively, does obesity produce a state of relative GH deficiency that warrants treatment with GH? The answers to these questions are currently unknown and thus these issues have fueled recent and ongoing research.

IGF-I is often, and sometimes inappropriately, used as an indicator of GH secretory status. While it is a useful clinical marker for defining states of GH excess, it has been well established that IGF-I alone cannot be used to confirm or refute GH deficiency. Factors in addition to the average GH concentration, such as nutritional status and IGF-binding protein concentrations, determine the circulating IGF-I level. For instance, anorexia nervosa is a condition that is associated with high daily production of GH but low IGF-I, likely due to malnutrition effects at the liver. Conversely, in the obese individual, GH levels are low but IGF-I levels have not been consistently shown to be inversely correlated with weight. Thus, IGF-I levels have no current clinical application in defining GH deficiency, or as a grounds for therapy, in the obese population.

It is interesting to consider whether low GH levels, in otherwise-healthy obese individuals, are causative or resulting from increased adiposity. The answer can likely be obtained by examining studies that have included individuals before and after significant weight loss. Most studies have shown an increase in GH levels following weight loss. In a study by Rasmussen et al., 24-hour and stimulated GH secretion were measured in normal weight and obese individuals and then measured again in the obese individuals

Table 1	BMI	Percentage defined as GH deficient (%)
Normal weight	< 25	5
Mildly overweight	25 – 26.9	13
Moderately overweight	27 – 29.9	33
Obese	≥ 30	64

Table 1. Percentage of healthy men who were defined as GH deficient (peak GH < 9 ng/ml) following arginine-GHRH stimulation. Modified from (5). Copyright 2004, The Endocrine Society.

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following massive weight loss. There was significantly lower GH secretion in the obese individuals prior to weight loss compared to the normal weight control subjects. Interestingly, GH secretion increased in obese individuals following weight loss and was no longer significantly different from controls (8). Thus a primary defect in GH secretion is not likely to be the underlying cause of increased weight. Although GH deficiency is not a cause of simple obesity, could it contribute to some of the detrimental outcomes of obesity, such as cardiovascular risk?

Much research has examined the negative effects of GH deficiency in individuals with a history of pituitary disease, primarily due to pituitary tumors or brain radiation. Epidemiological studies have reported that hypopituitarism with growth hormone deficiency increases mortality and that this increased risk is a function of cardiovascular disease (9). Adult-onset GH deficiency is associated with increased fat mass, particularly visceral fat, and decreased lean mass. Moreover, GH replacement in this population decreases visceral fat and increases muscle mass (10). As increased visceral adiposity has been linked to cardiac disease, this improvement in body composition may translate into a decreased risk for future cardiovascular events. Many studies have examined the change in cardiovascular risk markers in individuals with GH deficiency following GH replacement. To date, potential beneficial cardiovascular effects due to GH replacement have been noted via a reduction in LDL cholesterol (11), reduced carotid intima media thickness (12), decreased inflammatory marker concentration (13), and improved cardiac function (14).

Several studies have addressed the possibility that relative GH deficiency in obese individuals is a maladaptive consequence, by examining the effects of GH treatment on body composition and cardiovascular risk in this population. Due to the known lipolytic effects of GH (15), it was hypothesized that increasing GH concentrations would lead to a decrease in adipose tissue. In studies of men and post-menopausal women, GH treatment reduced fat, primarily in the visceral region, and had a beneficial effect on lipids (16, 17). Additionally, a number of small studies in obesity with relatively short GH treatment duration and with or without caloric restriction have been performed. Results are mixed and while several studies suggest a beneficial effect on body composition, a definitive improvement has not been established (18, 19). Larger studies are needed in obese subjects to elucidate the effects of GH on body composition and to examine the potential benefits with respect to decreasing cardiovascular risk markers.

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Although generally well tolerated, GH replacement may lead to side effects that are particularly detrimental in the obese population. As a hypoglycemic counter-regulatory hormone, GH acutely increases insulin resistance. The effects of chronic treatment with GH on insulin resistance have generally shown an initial worsening of insulin resistance with a gradual improvement over time to baseline levels (20). GH induces sodium retention in the renal tubules leading to water retention and edema (21). Since IGF-I receptor activation has been proposed to play a role in the etiology of polycystic ovarian syndrome (PCOS), therapies that increase IGF-I level may, theoretically, increase the risk of this syndrome in the predisposed obese population (22). These, and potentially other, side effects will need to be addressed prior to any widespread use of GH as a therapeutic in the obese population.

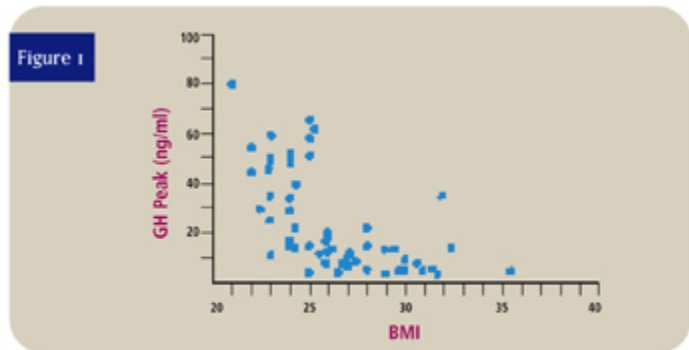


Figure 1. Peak GH response after arginine-GHRH administration correlates with BMI in men. (Pearson  $r = -0.59$ ,  $p < 0.01$ ). Each point represents peak GH response of one subject plotted against the subject's BMI value. Modified from (5). Copyright 2004, The Endocrine Society.

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In summary, it has been established that spontaneous and stimulated secretion of GH is lower in obese relative to normal weight individuals. The underlying cause of reduced GH levels remains unknown. Although beneficial body composition and cardiovascular effects have been noted with GH replacement in individuals with GH deficiency secondary to pituitary or hypothalamic disorders, similar benefits have not been firmly established for GH treatment of relative GH deficiency related to simple obesity. It is important to reiterate that the use of GH in individuals without a history of pituitary or hypothalamic disease or radiation or childhood GH deficiency is currently experimental. Studies underway are attempting to define consequences of obesity-related GH deficiency and to determine whether GH treatment in this population is beneficial and safe.

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## Patient Information:

### Frequently Asked Questions About Radiation Therapy for Pituitary Adenomas

Helen A. Shih, M.D., Jay S. Loeffler, M.D.

**Preface:** *If radiation therapy has been recommended to you for treatment of a pituitary adenoma, you have probably already considered and/or tried other types of medical therapies or surgery with inadequate results. Remember, a tumor is a tissue mass, typically not normally present in the body. It can be either benign or cancerous. Pituitary adenomas are a type of benign tumor with many subtypes. Radiation therapy can be a very effective treatment for both hormonally active (such as Cushing's disease or acromegaly) and inactive ("non-functioning") pituitary adenomas. The decision to use radiation therapy should be balanced with an understanding of its associated risks. Treatment recommendations*

*are tailored by specific type of pituitary tumor, size, boundaries of the tumor if large, response to initial therapies, and other patient health concerns. Compiled here are common questions raised by patients with pituitary adenomas regarding radiation therapy.*

### **1. What is radiation therapy?**

Radiation therapy is the use of ionizing radiation to treat and control benign or cancerous tumors. Ionizing radiation is a form of high energy that can be directed as beams to treat targets. It can effectively reduce or stop excessive tumor growth or activity. The most common form of radiation therapy used is called photon beam. Photon beams can be either generated from machines and are called X-rays or from naturally radioactive substances and are called gamma rays. The photon beams applied in radiation therapy are most often X-rays and are similar to those used for chest X-rays but are of higher energy.

### **2. How does radiation work?**

Ionizing radiation causes injury to the most actively growing cells. Abnormally growing cells will frequently die over a period of days to months following radiation treatment. Truly normal cells can frequently repair radiation injury.

### **3. What type of radiation therapy is best for me? I've heard of terms such as intensity modulated radiation therapy (IMRT), 3D conformal radiation therapy, stereotactic radiosurgery (SRS), and stereotactic radiotherapy (SRT).**

This is a complex question and requires the training and expertise of your doctor to select the treatment delivery system that is best suited for you. All of these terms refer to radiation treatment techniques. They all use photon radiation. Frequently, there is more than one good choice.

### **4. How do I get treatment? What are the practical things that I need to know for my schedule?**

Radiation therapy comes in many forms but all types of radiation therapy involve a planning process referred to as the "simulation". The first part of the simulation is to establish a reproducible set up position that you will assume for each treatment. A mask or frame for your head will be custom made such that you will be able to get into the same position with great accuracy for each radiation treatment. The simulation session usually takes about one hour to complete and most commonly involves a CT scan or X-ray pictures of your head in the treatment position. These pictures are used to design the appropriate radiation beams for your treatment.

Daily treatments are usually about 10-15 minutes within the treatment room with most of that time allotted to setting you up accurately. Treatments are delivered by radiation therapists, highly skilled technologists who currently go through four years of training to obtain their radiation therapist license. The radiation beams are usually on for 1-2 minutes per day once the patient is in the correct position. Treatments are usually given daily, Monday through Friday, for five treatments per week. The total number of treatments most commonly ranges between 25-30 treatments, meaning a total of 5-6 weeks. Most centers have some amount of waiting time preceding treatment so it is best to be flexible and expect up to an hour's time with each daily visit until you are familiar with your treatment center's pattern.

### **5. Does this treatment hurt? Will I be sick? What does it feel like?**

This treatment does not hurt. In fact, most people do not feel anything and cannot detect when the radiation beam is on. Others can either smell a scent described as ozone or see colors while the radiation beam is on. There are no detectable side effects immediately after treatment. It is not known to make people feel sick.

### **6. What are my daily restrictions if any?**

There are typically no restrictions to your activity or diet.

### **7. What are the common side effects while on radiation therapy?**

While on treatment, you may notice a little fatigue that slowly appears over the weeks of treatment. Sometimes patches of hair loss and skin redness and dryness are experienced. These occur in the

radiation beam paths. Much less common are headaches or nausea. Even less common are neurological symptoms like seizures.

#### **8. What are the risks of me going blind from radiation?**

Risks are individualized so you should ask your radiation oncologist. However, for most people, this risk is very low because it is taken into careful consideration during the planning of your radiation treatment. It is one of the main reasons why the protracted 5-6 week course of radiation is preferred over the single dose of stereotactic radiosurgery. The nerves involved with vision are able to absorb a fair amount of radiation without risk of injury to their function.

#### **9. Am I or my body fluids radioactive?**

For practical purposes, you are not radioactive while you are receiving your radiation treatment. However, for a few minutes immediately after each treatment, there does remain extremely low residual radioactivity in the tissues that have directly received radiation. This is not dangerous to others and no activity restrictions are needed.

#### **10. Can I take medications while receiving radiation therapy?**

Yes, generally there are no changes to medications while on radiation therapy.

#### **11. Can I work during my treatments? If not, when can I return to work?**

This is up to you and your doctor. Some people prefer to relax and may consider returning to work after a few weeks from completion of radiation treatment. Others choose to work while under treatment and are able to do so without difficulty.

#### **12. How fast will the treatment be effective? How do I know if the radiation has worked?**

Treatment response varies. Some patients feel that they begin to have a response even while on radiation treatment, but most experience gradual responses ranging over many months between 2-3 years from the completion of radiation treatment. However, responses do continue to evolve for many years beyond that. Depending upon the nature of your pituitary adenoma, response is measured by imaging the head (MRI or CT), blood or urine tests, and how you feel.

#### **13. What is stereotactic radiosurgery? How does it differ from other radiation used for pituitary adenomas?**

Stereotactic radiosurgery (SRS) is a type of radiation therapy that delivers high dose radiation in a single treatment. The most commonly used form of SRS for pituitary tumors is known as "gamma-knife". At Massachusetts General Hospital, SRS is given as either "proton beam" or "photon beam" radiation. SRS is a convenient treatment because it takes only one day and is frequently associated with a quicker response than the protracted alternative of daily radiation treatments over several weeks. However, SRS can also be associated with increased risk of side effects, such as injury to the nerves which transmit vision. Risk of injuries varies depending upon the nature of your tumor. Details of the size, shape, and location of your pituitary adenoma determine which form of radiation delivery is best suited for you. If SRS has been recommended, then the risk of serious injury is felt to be very low.

Because a high radiation dose will be given at one setting, the highest precision is very important with SRS. A special head frame is used to keep your head still during treatment. Most people tolerate this treatment very well.

#### **14. What is the chance of the tumor reappearing after radiation treatment?**

There is roughly a 95% chance of controlling your tumor's growth and 60-80% chance of controlling activity of hormonally active tumors although this does vary depending on the details of your tumor. If the tumor is controlled, it is unlikely for it to recur.

#### **15. What are the long-term side effects of radiation treatment?**

Radiation can decrease levels of one or more hormones produced by the pituitary gland. The risk of

hormone deficiencies is very low immediately following radiation, but gradually increases over the years. Some patients develop hormone deficiencies a year or two after radiation, while others may have normal levels for 10 or 20 years and then develop low hormone levels. These deficiencies are treatable with replacement hormones. Because of this, it is important that you continue under close care with your endocrinologist. It is uncommon to develop injury to the brain or vision and even more rare to develop a radiation-induced tumor. All of these unlikely but serious events typically require years to occur.

At MGH, proton radiation is also available and offers unique advantages to photon radiation in some conditions. Some common inquiries about this resource are addressed below:

#### **16. What is proton radiation therapy? How is it different from photon radiation?**

Protons, like photons, are another form of high energy ionizing radiation. Unlike photons, protons are particles with significant mass and a positive charge. These properties of protons make proton beams easier to shape than photon beams during treatment. All radiation beams give off energy as they travel through tissue. Proton beams travel a finite short length. Proton beams are designed to stop in the target so that there is no additional radiation deposited downstream, on the other side of the target. In comparison, photon beams are radiation beams that go on and on like a beam of light and will deposit energy to the tissues beyond the target. This is a lower dose than the dose delivered to the target but sometimes even this low dose can be harmful.

#### **17. Why is proton radiation more appropriate for me?**

When considering options within radiation, protons are often better suited for large pituitary tumors that extend beyond the sella, the bony cup that holds the normal pituitary gland. Larger tumors generally require a wider and larger radiation beam. Proton treatment in this situation will deliver significantly less radiation to the surrounding normal tissues. Small tumors that overproduce hormones (such as in Cushing's or acromegaly) can also be ideal for proton beam treatment. There are some data to suggest that control of hormone overproduction may be faster with stereotactic radiosurgery than with conventional radiation.

#### **18. Will there be any side effects to proton radiation?**

Side effects of radiation associated with photon radiation can also be seen with proton radiation. The risk of most of these side effects is reduced but still include injury to the neighboring brain or other tissues. Sometimes the risk of hair loss and skin irritation is higher with proton radiation.

#### **19. How often will I see my Radiation**

Oncologist after the treatment has been given? Initially, visits are annually, then just as needed. It is very important that head scans (MRI or CTs) be performed regularly. It is essential to see your endocrinologist every 6-12 months to monitor pituitary hormones.

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## **Anorexia Nervosa Increases the Risk for Fractures and Other Medical Complications**

Karen K. Miller, M.D.

Anorexia nervosa is a devastating disease that affects approximately 1% of college-aged women. Although it is a psychiatric illness, the medical sequelae of prolonged starvation in women afflicted with the disease are myriad, serious and the focus of this article. A 5.6% mortality rate per decade – 12 times the rate for healthy young women — has been established, and is at least in part due to an increased risk of suicide in women with anorexia nervosa (1). The cause of death in other women with anorexia nervosa is often not clear, even after autopsy, and may be related to medical issues, particularly cardiac. Medical complications of anorexia nervosa are common and include bone loss, cardiac dysfunction, electrolyte disorders, and bone marrow suppression.

Fewer than 15% of 214 young women with anorexia nervosa – average age 25 years – had normal bone density at all skeletal sites.

Bone loss is nearly universal in women with anorexia nervosa, due to the effects of severe undernutrition on endocrine regulators of skeletal homeostasis, and results in an increased fracture rate. We reported in the Archives of Internal Medicine that less than 15% of 214 young women with anorexia nervosa – average age 25 years — had normal bone density at all skeletal sites tested (2). Thirty-four percent of these women had osteoporosis, defined as having a bone density more than 2.5 standard deviations below the normal healthy mean for young women (T score < -2.5) (Figure 2). Whether this reduction in bone density translates into an increased risk of fractures is an important question. Although we could not investigate this question directly in a cross-sectional study, of note, 30% of the women studied reported histories of fractures (2). In over one-third of these cases, multiple fractures were reported, and in 42% of cases, the fractures were atraumatic, i.e. resulted from minimal trauma that does not usually cause

fractures (2). These rates are much higher than expected for a young healthy population and confirm published data by Rigotti et al, who reported a non-spinal fracture rate seven times higher than for healthy young women without anorexia nervosa (3). Despite the presence of amenorrhea, estrogen therapy is not effective at reversing bone loss in women who have already achieved peak bone mass (4, 5). We are currently studying whether estrogen use during adolescence will counteract the deleterious effects of amenorrhea on peak bone mass accrual. We previously demonstrated that recombinant IGF-I administration increases bone formation and bone density in adult women with anorexia nervosa (5), and studies of other potential therapies are ongoing (see listing of studies elsewhere in this issue for referral information.)

Serious cardiac complications of anorexia nervosa have been reported, including a cardiomyopathy associated with chronic ipecac use, which is usually reversible. Dysrhythmias, some of which are likely due to hypokalemia, have been documented in hospitalized patients, and may be the cause of some of the deaths of unknown etiology in women with anorexia nervosa. We reported bradycardia in 43%, hypotension in 16%, and hypokalemia in 20% of ambulatory women studied (2). Potassium levels were as low as 1.9 mEq/L (2). Although a previous large study reported that hypokalemia occurs only in women who purge, 52% of women with hypokalemia in our study denied purging .

(6). This high rate may reflect reticence in reporting such behaviors, which are perceived as embarrassing by many patients. Nevertheless, given the risk of dysrhythmias conferred by hypokalemia, the implication is clear – all women with anorexia nervosa should be monitored for hypokalemia, regardless of a history of known purging.

Other medical findings in our study included hyponatremia, which was present in seven percent of patients, with one woman reporting a history of hyponatremia-related seizures (2). Additional common laboratory abnormalities included anemia (39%), leukocytopenia (34%), and transaminitis (12%) (2). The clinical sequelae of these abnormal lab results, if any, are unclear.

Therefore, although anorexia nervosa is fundamentally a psychiatric disease, medical complications of chronic starvation are common and can be serious. Medical monitoring is therefore prudent, including

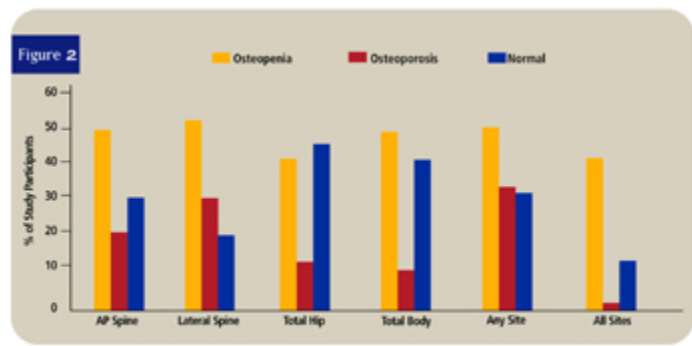


Figure 2. Percentage of study participants with anorexia nervosa who had normal bone density, osteopenia, and osteoporosis. A T score less than -1.0 defines osteopenia and a T score less than -2.5 defines osteoporosis. AP indicates anteroposterior. (2). Copyright© 2005, American Medical Association. All rights reserved.

Figure 2. Percentage of study participants with anorexia nervosa who had normal bone density, osteopenia, and osteoporosis. AT score less than -1.0 defines osteopenia and a T score less than -2.5 defines osteoporosis. AP indicates anteroposterior. (2). Copyright© 2005, American Medical Association. All rights reserved.

measurement of electrolytes and performance of electrocardiograms. Education regarding potential harmful medical complications of anorexia nervosa and associated behaviors, including purging and ipecac use, can be important for patient safety and recovery. Although no effective treatment for bone loss is readily available, measurement of bone density may help some patients understand the concrete deleterious effects of anorexia nervosa and move them a step closer to recovery. Most important for resolution of medical complications, including bone loss, is psychiatric and nutritional recovery, which is most often achieved with a multidisciplinary treatment team approach, including a therapist, nutritionist and primary care provider.

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