

Management of Hyperprolactinemia in Patients Receiving Antipsychotics

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With the broadening of use of antipsychotics - specifically newer atypical neuroleptics -- to treat common psychiatric disorders, including depression, bipolar disease and behavioral disorders, medication-induced hyperprolactinemia is an increasingly common syndrome faced by endocrinologists, primary care physicians and psychiatrists. Despite the high prevalence of hyperprolactinemia in patients taking psychotropic medications, a minority of patients have clinically significant signs and symptoms necessitating treatment. When hyperprolactinemia results in hypogonadism, i.e. amenorrhea and estrogen deficiency in women and testosterone deficiency in men, replacement of gonadal steroids may be the treatment of choice in many psychiatric patients so that effective psychiatric medication regimens do not have to be modified.

Antipsychotic medications cause hyperprolactinemia by blocking D2 dopamine receptors and therefore dopamine action. Because dopamine tonically inhibits prolactin release from the pituitary gland, medications which decrease dopaminergic tone result in elevations of prolactin. Hyperprolactinemia itself has not been demonstrated to directly result in long-term health-related consequences, though it can cause bothersome galactorrhea. However, by inhibiting gonadotropin releasing hormone (GnRH) secretion and in turn gonadotropins (LH and FSH), prolactin may result in gonadal steroid deficiency. This produces estrogen deficiency in women and testosterone deficiency in men, with consequent detrimental effects on skeletal health and other signs and symptoms, as listed in Table 1. That hyperprolactinemia itself is not responsible for bone loss has been clearly demonstrated by Klibanski et al. who reported low bone density in a group of women with hyperprolactinemic amenorrhea in contrast to a group of eumenorrheic women with a similar degree of prolactin elevation (1).

Although hyperprolactinemia commonly occurs with psychotropic medication use, only a minority of patients - typically those with hypogonadism - need to be considered for treatment. Interestingly, the degree of elevation of prolactin does not predict the probability of developing side effects, such that prolactin levels of greater than 100 ng/ml are possible without side effects in some patients, whereas others experience hyperprolactinemic sequelae with minimal prolactin elevations. Studies have demonstrated that the prevalence of hyperprolactinemia varies depending on the specific antipsychotic medication. For example, risperidone use is more commonly associated with hyperprolactinemia than with a number of other atypical antipsychotic medications, including clozapine and olanzapine (2-4). However, it should be noted that the development of diabetes mellitus is a more frequent complication of some anti-psychotic medications that do not commonly elevate prolactin. Despite the high prevalence of hyperprolactinemia in patients receiving antipsychotic medications, the incidence of prolactin-related side effects is low. In patients receiving risperidone, which has a high prevalence of hyperprolactinemia, less than 20% of patients experience any side effects that could be attributed to hyperprolactinemia (2).

Table 1 - Clinical Manifestation of Hyperprolactinemia

Women	Men
Amenorrhea/oligomenorrhea	Decreased libido
Infertility	Erectile dysfunction
Galactorrhea	Infertility
Dyspareunia	Gynecomastia
Acne/hirsutism	Galactorrhea
Osteopenia	Osteopenia

A suggested diagnosis and treatment algorithm is provided in Figure 1. Prolactin measurement is not necessary in all patients taking anti-psychotics. Rather, only patients with galactorrhea or signs or symptoms of hypogonadism -- amenorrhea in women and reduced libido, gynecomastia and/or sexual dysfunction in men -- should be tested. Other causes of hyperprolactinemia should be ruled out, including pregnancy (in women), primary hypothyroidism and renal failure. A decision regarding whether a pituitary MRI is indicated should be based on a clinical assessment of the likelihood of the presence of a pituitary or hypothalamic cause of the prolactin elevation and other symptoms, such as headache. If the signs or symptoms of the endocrinopathy pre-date the initiation of psychotropic medication, the prolactin level is particularly high and therefore cannot be attributed to medication use, or the patient manifests signs or symptoms suggestive of a brain or pituitary tumor, an MRI should be performed.

In amenorrheic women and hypogonadal men, bone density monitoring is also indicated. The decision as to whether symptomatic hyperprolactinemia warrants a change in psychiatric medication should be carefully assessed from a medical and psychiatric viewpoint, with consideration of the risks and benefits of such a change. Hormone replacement therapy can be safely prescribed in a majority of such patients after consultation with the treating psychiatrist, thus avoiding interruption of a regimen that may be critical to an individual's psychiatric well-being. Treatment of hyperprolactinemia-related hypogonadism in women of reproductive age and men should be strongly considered both to prevent bone loss and enhance compliance with psychiatric medication use, as sexual side effects, particularly, can discourage patients from adhering to their medication regimens. It should be noted that estrogen/progestin treatment will not successfully treat galactorrhea and can worsen it, but explanations and reassurance regarding its etiology is often sufficient. When gonadal steroid replacement is contraindicated, modifying the psychotropic medication regimen can be considered if acceptable to the treating psychiatrist.

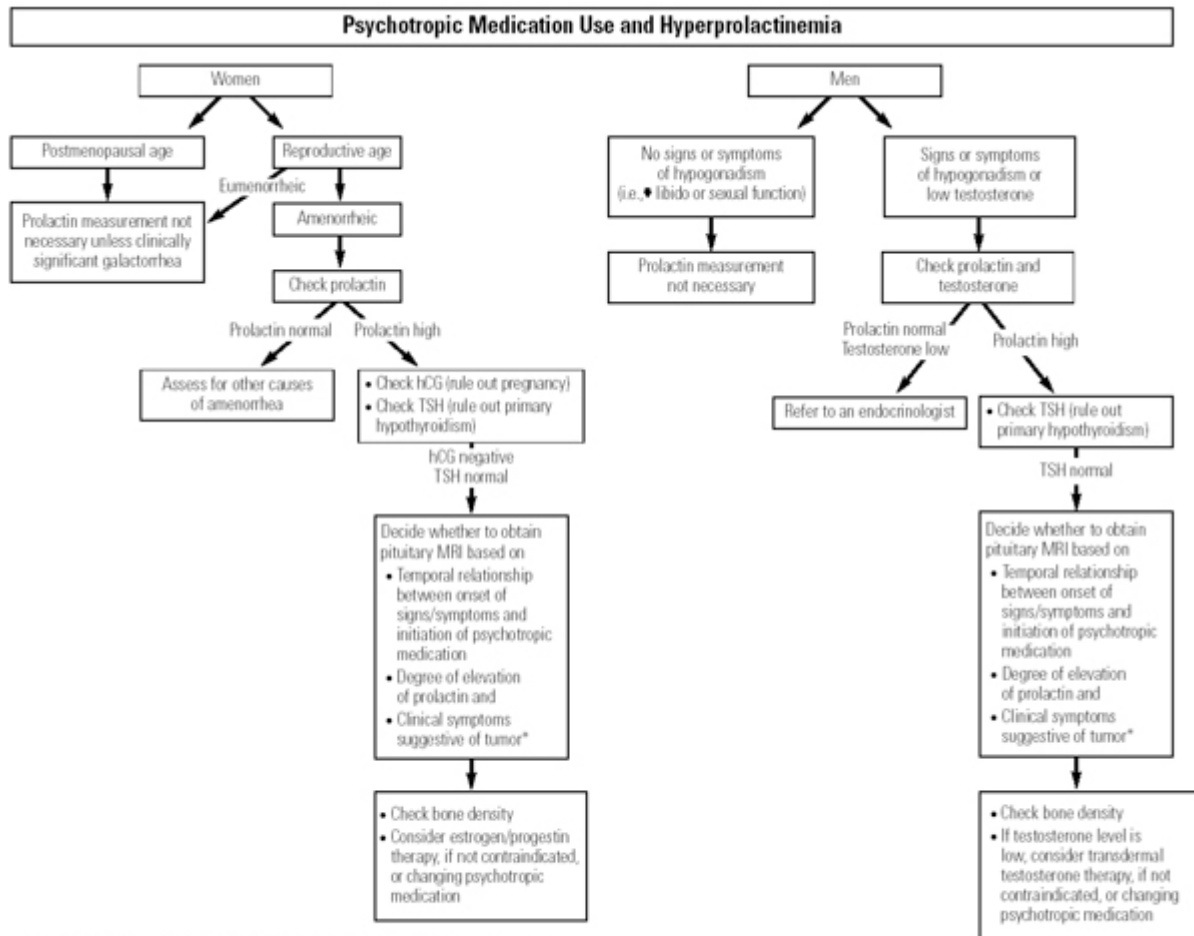
Dopamine agonist therapy is routinely prescribed as first-line therapy for non-medication induced hyperprolactinemia to treat hypogonadism or to reduce the size of a pituitary tumor. However, dopamine agonists should be generally avoided in patients with psychiatric disorders, as psychosis can be precipitated in an occasional case. Dopamine agonists have sometimes been used to lower neuroleptic-induced hyperprolactinemia (5) but should be considered only in patients without histories of psychosis and with extreme caution, and under the supervision of a psychiatrist.

In summary, although hyperprolactinemia is commonly caused by antipsychotic medication use, treatment is only necessary in women of reproductive age and men with resultant hypogonadism - a minority of those with elevations in prolactin. After a work-up to rule out alternative causes of hyperprolactinemia, as indicated, has been completed and bone density measurement performed, gonadal steroid replacement should be considered to preserve skeletal health and maintain compliance with a successful psychiatric medication regimen. Referral to an endocrinologist for work-up and treatment of hyperprolactinemia is appropriate and decisions regarding any change in psychotropic treatment regimen should be made in consultation with the treating psychiatrist.

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Figure 1 (click image for pdf version).



*These include headaches, visual field defects, endocrine dysfunction, and/or hormone hypersecretion.
 N.B. Referral to an endocrinologist is appropriate at any and all stages of work-up of hyperprolactinemia.
 N.B. Dopamine agonists may precipitate psychosis in some patients with psychiatric disorders.

hCG indicates human chorionic gonadotropin; TSH, thyroid-stimulating hormone; MRI, magnetic resonance imaging.

Miller, KK. Effect of antipsychotic treatments on reproductive function. Presented at: 2nd World Congress on Women's Mental Health, March 19, 2004, Washington, D.C.

Pituitary Disease in Multiple Endocrine Neoplasia Type 1

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Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome defined by the presence of pituitary adenomas, pancreatic islet cell tumors, and hyperparathyroidism. Other endocrine tumors (carcinoid and adrenocortical tumors), as well as non-endocrine tumors (lipoma, angiofibroma) may also occur as part of the syndrome (Table 1). MEN1 occurs in 0.02-0.2 per 1000 people, with most cases occurring as part of a familial syndrome, although sporadic cases also occur (1). After a brief overview of the genetics of MEN1, this review will focus on the pituitary manifestations of the syndrome.

Genetics

In 1988, Larsson demonstrated by linkage analysis that the MEN1 gene locus was located on chromosome 11q13 (2). Nine years later, the MEN-1 gene was identified by positional cloning (3). The protein encoded by the MEN1 gene is a 610-amino acid called menin. Menin is a nuclear protein that interacts with several proteins, such as JunD, Smad3, Pem, Nm23, NF-kB, replication protein A, GFAP,

and Vimentin. The exact function of menin is unknown, but it appears to regulate cell growth and has tumor suppressor properties (4).

Heterozygous germ line mutations in the MEN1 gene have been demonstrated in the majority of familial and sporadic cases of MEN1 (3,5,6). The reported mutations include small deletions, insertions, nonsense mutations, missense mutations, and mRNA splicing defects, which predict truncation or absence of the menin protein and the propensity for tumor formation (5-7). Tumors from MEN1 patients reveal loss of the wild-type allele (loss of heterozygosity) or somatic point mutations of the MEN1 gene, supporting Knudsen's two-hit model of tumorigenesis (8,9). Somatic MEN1 mutations have also been found in sporadic tumors, including parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids (7). Although menin RNA and protein is expressed in nearly all tissues, the absence of menin is associated primarily with tumors of the endocrine system (10). The presence of inactivating germline mutations in MEN1 patients, and the observation of loss of heterozygosity or somatic mutations in MEN1 tumors, supports the hypothesis that menin has tumor suppressor properties.

Clinical Characteristics

MEN1 causes combinations of different endocrine tumors. A practical clinical definition of MEN1, as recommended by a recent consensus panel, is the presence of at least two of the three main endocrine tumors (parathyroid, pancreas, pituitary) (11). Primary hyperparathyroidism (HPT) is the most common feature of MEN1, with greater than 90% penetrance by age 50 (1,12). Duodenal or pancreatic neuroendocrine tumors occur in 30-80% of patients with MEN1, whereas the reported prevalence of anterior pituitary tumors is 15-50%, depending on the patient population studied and the method of diagnosis (1,12). Although the clinical presentation in MEN1 is quite variable, a genotype-phenotype correlation has not been reported (6).

Table 1. Expressions of MEN1 with estimated penetrance (in parentheses) at age 40 yr

Endocrine features	Nonendocrine features
Parathyroid adenoma (90%)	Lipomas (30%)
Entero-pancreatic tumor	Facial angiofibromas (85%)
Gastrinoma (40%)	Collagenomas (70%)
Insulinoma (10%)	
NF1 including pancreatic polypeptide (20%)	
Other: glucagonoma, VIPoma, somatostatinoma, etc. (2%)	Rare, maybe innate, endocrine or nonendocrine features
Foregut carcinoid	
Thymic carcinoid NF (2%)	Pheochromocytoma (<1%)
Bronchial carcinoid NF (2%)	Ependymoma (1%)
Gastric enterochromaffin-like tumor	
NF (10%)	
Anterior pituitary tumor	
Prolactinoma (20%)	

Other: GH+ PRL, GH, NF (each 5%)
ACTH (2%), TSH (rare)

Adrenal cortex NF (25%)

1 NF, Nonfunctioning. May synthesize a peptide hormone or other factors (such as small amine), but does not usually oversecrete enough to produce a hormonal expression.

2 Omits nearly 100% prevalence of NF and clinically silent tumors, some of which are detected incidental to pancreatico-duodenal surgery in MEN1.

[Reprinted with permission from The Endocrine Society (11)].

Pituitary adenoma may be the initial presentation of disease in a subset of patients. For example, Verges et al analyzed data from a large series of MEN1 patients (n=334) in France and Belgium and reported that 16.7% of patients presented with pituitary adenoma at initial diagnosis of MEN1. Alternatively, 35.6% of subjects initially presented with HPT and 18.8% presented with pancreatic tumors (13). Pituitary adenomas can occur at any age. In one series, the age of onset of pituitary adenoma in MEN1 ranged from 12-83 years of age, although the majority of patients were diagnosed before 50 years of age (13). The youngest reported MEN1 patient with a pituitary macroadenoma is 5 years of age (14). Pituitary adenomas appear to occur more frequently in women than in men with MEN1 (13). Prolactinomas are the most commonly occurring hormone secreting adenomas in MEN1 patients, although growth hormone and ACTH secreting tumors, as well as nonfunctioning tumors, also occur (13,15,16). As compared with non-MEN1 pituitary adenomas, the age at diagnosis, the female preponderance, and the frequency of the type of pituitary adenoma in MEN1 are similar (13)(Table 2).

The diagnosis of pituitary tumors in MEN1 is based upon medical history, physical exam, biochemical screening tests for pituitary hormones, such as prolactin, and radiologic imaging. The clinical symptoms and signs of pituitary adenoma are similar in patients with MEN1 or sporadic tumors and depend upon the size and type of the adenoma. Headache and visual field abnormalities may be the initial clinical manifestations in those with larger tumors. Symptoms related to prolactin-secreting adenomas include amenorrhea, galactorrhea, and infertility in women, and diminished libido and impotence in men. Patients with GH or ACTH secreting tumors present with typical symptoms and signs of acromegaly or Cushing's syndrome, respectively.

Patients with symptoms of Cushing's syndrome require an initial screening evaluation (24-hour urine free cortisol or 1-mg overnight dexamethasone suppression test). When screening is positive, confirmatory tests are performed. MEN1 patients with ACTH-dependent Cushing's syndrome present the clinician with the dilemma of distinguishing pituitary Cushing's disease from ectopic Cushing's syndrome, secondary to an ACTH-secreting carcinoid (bronchial or mediastinal) or pancreatic islet cell tumor, both of which can occur in the MEN1 syndrome. However, as in the general population, a pituitary source of excess ACTH is much more common than ectopic ACTH production, even in MEN1 kindreds (17). For the patient with ACTH-dependent Cushing's syndrome and a normal pituitary MRI scan, the approach to localizing the ACTH production is the same as in non-MEN1 patients. Specifically, bilateral inferior petrosal sinus sampling should distinguish a central source from an ectopic source of ACTH production in the majority of patients.

Therapeutic Considerations

The treatment of pituitary adenomas in MEN1 is similar to the treatment of non-MEN1 pituitary adenomas. The goals of therapy are to reduce tumor volume and thereby eliminate any symptoms of mass effect (headache, visual disturbance) and to decrease hormone hypersecretion, if evident. Treatment modalities can include surgery, radiation therapy, or medical therapy, depending on the size and type of tumor. However, tumor size is larger in MEN1 and successful treatment occurs less frequently (13,15). In the

series of patients with MEN1 reported by Verges et al (13), 136 patients with MEN1-associated pituitary adenoma were compared with 110 patients with non-MEN1 pituitary adenomas. Macroadenomas (tumor size >10 mm), including prolactin-secreting macroadenomas, occurred more frequently in MEN1 (85% vs 42%), regardless of the decade of diagnosis. Using similar treatment modalities, normalization of hormone levels in hormone-secreting tumors occurred in 90% of non-MEN1 tumors, but in only 42% of MEN1 tumors, with a median follow-up interval of 11.4 years (Table 2) (13). Thus, pituitary tumors in MEN1 appear to be more aggressive than non-MEN1 pituitary tumors (13,15,18), although pituitary carcinoma has not been linked to MEN1 (18). Successful treatment occurs more often in patients diagnosed with microadenomas (13), which underscores the importance of early screening and diagnosis in MEN1 kindreds. Even after successful treatment of a pituitary adenoma, annual monitoring should continue in order to detect recurrence (11).

Screening Recommendations

Regular screening for pituitary disease in known carriers of MEN1 is advocated by most investigators (11,12). The MEN1 consensus panel recommended annual biochemical screening of MEN1 carriers for prolactinoma and acromegaly (with assessment of prolactin and IGF-1, respectively) beginning at 5 years of age, the earliest age at which a pituitary tumor has been reported. MRI scanning of the pituitary was recommended at 3-year intervals. Lifetime screening for new pituitary disease is recommended (11), as the onset of pituitary tumors may occur late in some patients.

Table 2. Pituitary adenomas in MEN1 patients and in controls.

	MEN 1 pituitary adenomas (n = 136)	Control (non-MEN1) pituitary adenomas (n = 110)	P
Age (yr)	38.0 ± 15.3	36.2 ± 14.6	NS
Mean follow-up (yr)	11.1 ± 8.7	10.0 ± 6.3	NS
Type of pituitary adenoma:			
PRL	n = 85	n = 68	
GH	n = 12	n = 15	
ACTH	n = 6	n = 7	NS
Cosecreting	n = 13	n = 2	
Nonsecreting	n = 20	n = 18	
Clinical signs related to tumor size	n = 39 (29%)	n = 15 (14%)	P < 0.01
Tumor size			
Microadenoma	n = 19 (14%)	n = 64 (58%)	P < 0.001
Macroadenoma	n = 116 (85%) no data: n = 1 (1%)	n = 46 (42%)	
Outcome			
Normalization of pituitary hypersecretion	n = 49 (42%)	n = 83 (90%)	P < 0.001

For each qualitative data, the number of patients and the percentage of affected patients in each group (MEN1 patients and controls) are given. The results of the statistical comparison between the two groups (MEN1 patients and controls) are shown in the last column. [Reprinted with permission from The Endocrine Society (13)].

Summary and Conclusions

Fifteen to 20 percent of patients with MEN1 will develop pituitary adenomas. Although most patients are identified by 50 years of age, pituitary disease may also be a late manifestation of the syndrome, underscoring the importance of lifelong screening of affected MEN1 kindreds. The clinical presentation of pituitary adenoma is similar in sporadic and MEN1 cases; however, patients with MEN1 tend to have larger tumors that are less responsive to therapy. Treatment is more successful with microadenomas compared with macroadenomas, and therefore, early identification through biochemical screening should improve therapeutic response.

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Physiologic Regulation and Potential Utility of Growth Hormone in HIV Lipodystrophy

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HIV lipodystrophy is a recently described metabolic syndrome characterized by changes in fat distribution and insulin resistance (1) (2) (3). Fat distribution changes are heterogeneous and can include reduced subcutaneous fat as well as increased visceral fat (4). In non-HIV-infected patients, obesity is associated with reduced GH secretion (5). Johannsson et al. (6) have shown that GH administration (0.01 mg/kg/day) to abdominally obese men reduced visceral fat and improved glucose disposal rates. At first glance, such a finding may seem contradictory, because GH is known to increase insulin resistance and antagonize the actions of insulin. However, use of low-dose GH may actually improve insulin resistance in association with reduced visceral adiposity. In such a scenario, the lipolytic effects might, therefore, prevail over the diabetogenic effects of GH.

What is the rationale for the use of GH in HIV-infected patients with fat redistribution? Although the mechanisms of fat redistribution in HIV-infected patients receiving highly active antiretroviral therapy have not been determined, such patients often demonstrate extreme visceral obesity without increases in total body fat. In such patients, excess visceral fat, not total body fat, predicts reduced GH secretion (4). Overnight GH secretion and pulse amplitude are decreased in patients with HIV lipodystrophy (4). The physiologic regulation of growth hormone (GH) is complex, and occurs under the dual influence of growth hormone releasing hormone (GHRH) and somatostatin. More recently, it has been suggested that ghrelin, a nutritionally mediated gut peptide and GH secretagogue (7) may also be an important regulator of GH secretion. Growth hormone is reduced in generalized obesity and recent studies suggest that visceral fat is a critical determinant of GH secretion (8). Increased somatostatin tone is thought to contribute to reduced GH secretion in obesity, but little is known regarding the pattern of GH secretion and regulation of GH by somatostatin, GHRH and ghrelin in lipodystrophic conditions when total fat may be unchanged but fat distribution markedly altered. Increased somatostatin tone, impaired GHRH stimulation of GH by excess free fatty acids and reduced ghrelin were all recently shown to contribute to the altered pattern of GH secretion in HIV lipodystrophy (9) (Figure 1).

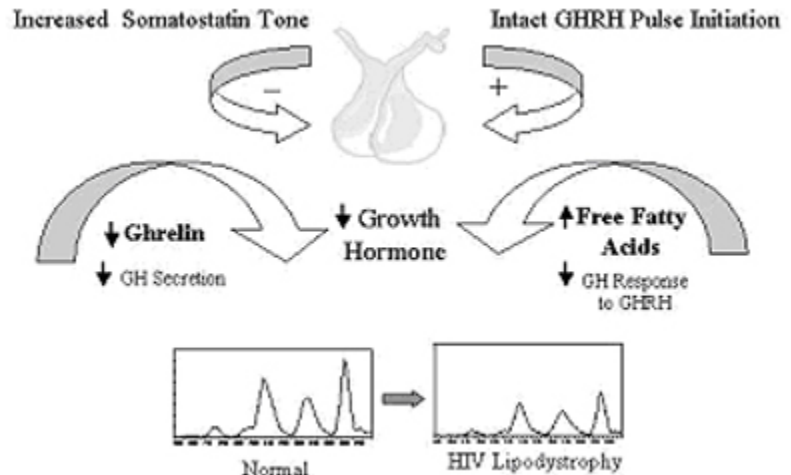


Figure 1. Potential schema for the mechanisms of reduced GH secretion in HIV lipodystrophy. [Reprinted with permission from the American Journal of Physiology (9)].

The use of GH has been proposed both in the treatment of AIDS wasting to increase lean body and muscle mass, as well as in the HIV lipodystrophy syndrome, to reduce abdominal visceral fat. Use of the same hormone, GH, in these two seemingly disparate conditions, highlights the multiple effects of GH. GH is anabolic, improves nitrogen balance, and increases lean body mass. GH is also lipolytic and may prove useful to decrease visceral fat in patients with HIV lipodystrophy.

Patients with AIDS wasting are undernourished and have significant GH resistance. Clinical trials have investigated the effects of high dose GH on lean body mass in patients with AIDS wasting. A large randomized, placebo-controlled study of patients with advanced HIV disease and weight loss demonstrates a significant 3-kg increase in lean body mass over 12 weeks in response to GH (10). In this study, 178 HIV-infected patients with documented unintentional weight loss of at least 10% or weight less than 90% of the lower limit of ideal body weight were randomly assigned to receive either recombinant human growth hormone, 0.1 mg/kg of body weight per day (average dosage, 6 mg/d) (n = 90) or placebo (n = 88) for 12 weeks. No significant differences were seen between groups in clinical events, progression of AIDS, CD4+ or CD8+ cell counts, or viral burden. Treatment with growth hormone increased body weight, lean body mass, and treadmill work output (10). The dose of GH used, 0.1 mg/kg/day, was quite high (in comparison, GH may be initiated at doses as low as 0.002 mg/kg/day for adults with GH deficiency). Although the extracellular fluid component of fat-free mass increased, functional indices improved, suggesting a true anabolic effect of GH. However, significant side effects occurred in response to high dose GH, including arthralgias, fluid retention and glucose intolerance (10). The Food and Drug Administration (FDA) approved recombinant human growth hormone, for treatment of AIDS-related wasting (11), but caution is generally recommended in prescribing large doses of GH, and this strategy is best employed for patients with severe wasting.

Recently, a number of studies have proposed the use of GH as a lipolytic agent in HIV-infected patients with fat redistribution (12). GH is not approved for this indication and the use of GH for lipodystrophy must be considered experimental. Wanke et al. gave 6 mg of rhGH a day, subcutaneously for 12 weeks to ten HIV-infected patients (seven men, three women) with HIV associated lipodystrophy in order to determine the efficacy of recombinant human GH in the treatment of the fat redistribution syndrome. Short-term treatment improved the alterations in body shape that occur with lipodystrophy in HIV-infected patients (12). However, the dose used, 0.1 mg/kg/day was associated with significant side effects including hyperglycemia.

Engelson et al. investigated GH as a potential treatment for the excess visceral fat in HIV lipodystrophy. A prospective, open-label trial of rhGH 6 mg/d for 24 weeks, followed by 4 mg every other day was conducted. Thirty HIV-positive participants (26 men and 4 women) with visceral adiposity were enrolled. The main outcome measure was change in visceral adipose tissue (VAT) measured by whole-body magnetic resonance imaging scan. Changes in whole-body subcutaneous adipose tissue and skeletal muscle, glucose metabolism, serum lipids, and quality of life were also assessed. Despite stable body weight, VAT decreased an average of 42% with the 6 mg/d dose and by 15% with the 4 mg q.o.d. dose after 12 weeks (Figure 2). Subcutaneous adipose tissue also decreased, but proportionately less and not significantly on the lower dose. Skeletal muscle increased. Joint pain was the most common adverse event, and was reflected in subjective quality of life measurements as an increase in bodily pain. Insulin sensitivity fell, and four participants developed diabetes (13).

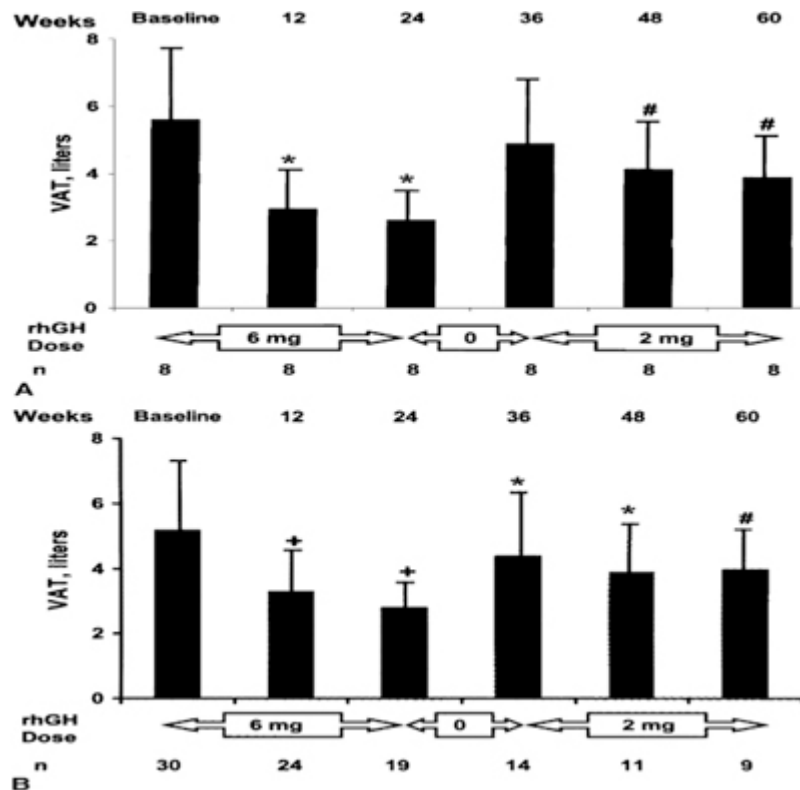


Figure 2. Visceral adipose tissue (VAT) volume estimated by whole body magnetic resonance imaging scans. (A) Results from 8 subjects with evaluable scans for every visit. (B) Results of all evaluable data at each visit. Bars represent the standard deviation. Statistical comparisons are by paired t tests using only subjects with evaluable data at each compared visit. Weeks 12, 24, and 36

Lo et al. (14), conducted an open-label study to evaluate the effects of a lower but still pharmacologic dose of GH (3 mg/d) in eight men with HIV-associated fat

are compared with baseline; weeks 48 and 60 are compared with week 36. #p < .05; * p < .01; +p < .001. [Reprinted with permission from JAIDS (13)].

accumulation. Oral glucose tolerance, insulin sensitivity, and body composition were measured at baseline, and one and six months. Five patients completed six months of GH therapy. Over six months, GH reduced buffalo hump size and excess visceral adipose tissue. Total body fat decreased, primarily in the trunk region and lean body mass increased. One patient with baseline-impaired glucose tolerance but a normal fasting glucose developed fasting hyperglycemia, and an additional patient required a dose reduction for arthralgias and developed diabetes mellitus based on the 2-h glucose level during the oral glucose tolerance test. Insulin sensitivity and glucose tolerance initially worsened, but subsequently improved toward baseline. The dose of GH used by Lo et al. was supraphysiologic and resulted in an increase in IGF-I levels up to three times the upper normal range (14). In contrast to high dose GH, low-dose GH might improve insulin resistance in association with reductions in visceral fat. Normally nourished HIV patients with excess visceral fat demonstrate decreased GH secretion without GH resistance, suggesting that lower doses of GH may be efficacious in this population. Further studies are necessary to address these possibilities.

In conclusion, use of high dose GH increases muscle mass in patients with AIDS wasting. Care should be exercised in utilizing this therapy, which is best reserved for those with severe wasting, refractory to other therapies. The optimal dose is not known and monitoring for side effects is critical. More recent studies suggest the potential use of GH in patients with HIV lipodystrophy and excess visceral fat, in whom GH levels are reduced. GH is effective in reducing visceral fat but may aggravate insulin resistance and hyperglycemia at high doses. GH is not approved for use in HIV lipodystrophy and should not be used in patients with lipodystrophy other than in approved clinical studies with appropriate monitoring. Further studies are needed to define the optimal dose, duration of dosing, and subpopulation of HIV-infected patients most likely to benefit from GH.

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